The Impact of Diabetic Retinopathy and Diabetic Macular Edema on Health-Related Quality of Life in Type 1 and Type 2 Diabetes

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Purpose. To assess the impact of diabetic retinopathy (DR) and diabetic macular edema (DME) on health-related quality of life (HRQoL) in type 1 and type 2 diabetes using the EuroQoL EQ-5D generic multi-attribute utility instrument (MAUI).

Methods. In this cross-sectional study, 577 patients with diabetes were recruited from specialized eye clinics in Melbourne, Australia. Each patient underwent clinical, biochemical, and anthropometric assessments. The severity of combined DR and DME (no DR/DME; mild NPDR [nonproliferative DR (NPDR)] and/or mild DME; moderate NPDR and/or moderate DME; and vision-threatening DR (VTDR) (severe NPDR or PDR and/or severe DME) in the worse eye was calculated. EQ-5D utility measures were the main outcome. Because the distribution of the utility measures was skewed, independent associations were explored using multivariate quantile regression models (five quintiles, namely 15th, 30th, 45th, 60th, 75th) ranging from poorest to highest HRQoL.

Results. Median age of the participants was 66 years (range, 26–90 years). Of the 577 participants, 223 (38.7%) had no DR/DME, 35 (6.1%) had mild NPDR/DME, 127 (22.0%) had moderate NPDR/DME, and 192 (33.3%) had VTDR. In adjusted models, neither presence nor severity of DR/DME was significantly associated with any quantile of the EQ-5D. In contrast, the presence of diabetic complications (other than DR) ($\beta = -0.153$; SE = 0.052; $P < 0.001$), other nonocular comorbidities ($\beta = -0.115$; SE = 0.038; $P < 0.01$), and higher body mass index ($\beta = -0.007$; SE = 0.002; $P < 0.001$) were all associated with worse HRQoL.

Conclusions. Using a generic MAUI, the EQ-5D, the authors found that the presence or severity of DR/DME and concomitant vision loss were not associated with any quantile of HRQoL. These findings suggest that the EQ-5D lacks sensitivity in assessing the impact of the severity of DR/DME on HRQoL parameters and that condition-specific instruments may better capture the full impact of the association. (*Invest Ophthalmol Vis Sci.* 2012;53:677–684) DOI:10.1167/iovs.11-8992

Diabetic retinopathy (DR) is a common microvascular complication of diabetes.[1] In its early nonproliferative stages there are few visual symptoms; however, as the disease progresses to vision-threatening stages (severe nonproliferative DR [NPDR] and proliferative DR [PDR]), significant vision loss can occur. Diabetic macular edema (DME), which can occur at any stage, affects central visual acuity.[2] After 20 years of living with diabetes, most patients will have some degree of DR.[2,3]

As shown by our group, the impact of DR and associated vision impairment on health-related quality of life (HRQoL) is considerable.[4,5] One common way of assessing HRQoL for economic evaluation is through the estimation of utility measures for the calculation of quality-adjusted life years (QALYs). Utility measures have typically been generated by using elicitation methods, such as the time tradeoff (TTO) and standard gamble (SG), directly with patient cohorts. Studies using TTO and SG have shown that utility tends to decrease steadily with worsening visual acuity resulting from DR.[6–14] However, there are limitations associated with TTO and SG elicitation methods. For example, utility values can be influenced by time preference and duration effects in TTO methodology, whereas SG utility values may be affected by patients' attitudes to risk.[15] An alternative method for generating utility measures for the calculation of QALYs is to use a multi-attribute utility instrument (MAUI) for measuring and valuing HRQoL, such as the EuroQol EQ-5D.[16] MAUIs (including the EQ-5D) consist of two main elements: a descriptive system composed of several attributes describing HRQoL with associated levels of increasing severity and a scoring algorithm for assigning utility values to each health state described by the instrument.[17]

Research into the impact of DR on HRQoL using the EQ-5D, however, has produced inconsistent findings. These discrepancies may be due to differing sample populations, exposure variables, or generic utility measures lacking sensitivity to evaluate the specific burden of DR-induced vision loss.[18] Inconsistent findings could also be associated with the use of inappropriate statistical methods (i.e., linear regression models) to analyze utility data that are generally skewed and have ceiling effects. In contrast, quantile regression models, which are based on minimizing least absolute deviations and its estimates, are more robust.[19] Quantile regression analyzes the similarity or dissimilarity of regression coefficients at different points in

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the distribution of the dependent variable, which in this case is represented by the EQ-5D utilities.

Given the new treatment modalities for DR such as antivascular endothelial growth factor (VEGF) therapy, clinical trials will be needed to evaluate them against traditional methods of treatment, not only in terms of clinical outcomes but also from the patient's perspective and from a cost-effectiveness viewpoint. Using the EQ-5D, we assessed the impact of the presence and severity of DR and DME and associated vision loss on HRQoL. To overcome some of the shortcomings of previous studies, we recruited a large clinical sample of patients across the spectrum of DR and applied a robust statistical technique—quantile regression analysis—to analyze our EQ-5D data.

METHODS

Study Design and Participants

English speaking adults with diabetes were recruited into the Diabetes Management Project (DMP), a large longitudinal study conducted in Melbourne, Australia, from March 2009 to December 2010. Cross-sectional data from the baseline phase are presented here. The methodology of DMP has been described previously.[20] In brief, participants were recruited primarily from general and specialized eye clinics at the Royal Victorian Eye and Ear Hospital (RVEEH). Eligible participants included those who were 18 years or older, free of significant hearing and cognitive impairment, and living independently. Each participant provided written informed consent. Ethical approval for the DMP was provided by the RVEEH Human Research and Ethics Committee (08/815H), and the DMP protocol adhered to the tenets of the Declaration of Helsinki.

Assessment of Health-Related Quality of Life

General HRQoL was measured using the EQ-5D MAUI.[16] The EQ-5D is a descriptive system that covers five dimensions of self-reported health: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has three response categories: no problems, some problems, and extreme problems. For example, a result of 11222 indicates no problems with mobility and self-care but some problems with the other three dimensions. The 243 health states defined by the EQ-5D responses were translated to EQ-5D utility scores using available values sets that have been derived from large population-based surveys.[21,22] The scale of the utility index ranges between 0.0 and 1.0, where 0.0 represents death and 1.0 represents full health. States that are considered worse than death are represented by negative utility values. Given that no publicly available value set exists for the Australian population, we conducted two analyses, the first using the United Kingdom value set[21] (TTO valuation method) and the second using the New Zealand value set[22] (visual analog scale (VAS) valuation method). Because the findings were similar, only data using utility values derived from the UK value set are reported in this study.

Assessment of Diabetic Retinopathy and Vision Impairment

DR and DME were assessed using dilated fundus photography. Right and left macular and optic disc fields (45° view) for each participant were imaged using a nonmydriatic retinal camera (CR6–45NM; Canon, Tokyo, Japan). Using the worse eye, we categorized the severity of DR using the ETDRS definition as no DR = 13–15, mild NPDR = 20, moderate NPDR = 31–41, severe NPDR = 51, and PDR = 60–80; the severity of DME using the American Academy of Ophthalmology classification[23] as no DME = 10/20, mild DME = 30, moderate DME = 40, and severe DME = 50; and the severity of combined DR/DME as no DR and no DME, mild NPDR and/or mild DME, moderate NPDR and/or moderate DME, and VTDR (severe NPDR, PDR, and/or severe DME. Given that the results for the severity of DR and DME separately were similar to the combined DR/DME categorization, we report data for the latter group only. Ungradable fundus photographs attributed to poor image quality or opacity in the media were excluded from the analysis.

Presenting distance uniocular and binocular visual acuity were assessed using a 3-m LogMAR chart. We collapsed presenting visual acuity (better eye) into two categories: 6/12 or better representing no vision impairment and worse than 6/12 representing vision impairment. Although this is a reasonably crude division, it allowed us a basic understanding of the association between vision impairment and EQ-5D utility score. We also examined the relationship between presenting visual acuity as a continuous variable and the EQ-5D utility score (data not shown) to ensure we were not overlooking an important association; however, the results were nonsignificant and did not improve the model fit.

Assessment of Other Risk Factors

Participants underwent a comprehensive assessment that included a range of clinical, biochemical, and anthropometric measures and questionnaires on lifestyle, psychosocial factors and quality of life. The main outcome was EQ-5D utility as an indicator of HRQoL. Key covariables included age (years), sex, duration of diabetes (years), insulin use, presence of one or more general comorbidities, presence of diabetic complications other than DR/DME (including diabetic neuropathy, diabetic nephropathy, and peripheral vascular disease), educational attainment, household income, marital status, HbA_{1c} (%), fasting plasma glucose (mg/dL), HDL cholesterol (mg/dL), systolic and diastolic blood pressure (SBP and DBP; mm Hg), body mass index (BMI; kg/m^2), and smoking status.

Statistical Analysis

Statistical analyses were undertaken (Stata/SE 11; StataCorp LP, College Station, TX). Initially, the descriptive data from the EQ-5D questionnaire were converted to utilities using the scoring algorithms provided by the EuroQoL group for the United Kingdom and the New Zealand general population groups, respectively. Normality of the variables was examined using box plots, Kolmogorov-Smirnov test, and Shapiro-Wilks test. Clinical and sociodemographic characteristics of the study participants were summarized using mean and SD for normally distributed variables, median and interquartile range (IQR) for nonnormally distributed and count variables, and proportions for categorical variables. The χ^2 statistical test was used to analyze differences in proportions between groups. Comparisons of mean and median values were conducted using an independent samples *t*-test or two-sample Wilcoxon rank-sum (Mann-Whitney *U*) test.

As anticipated, the distribution of the EQ-5D utility scores was positively skewed, and a ceiling effect was evident, with 28% of participants scoring full health (1.0) (Fig. 1). As indicated earlier, this is not an uncommon finding with application of the EQ-5D[24,25]; however, it means that the true variation in HRQoL among those scoring full health may not adequately be captured. This is because traditional regression analysis focuses on the mean, in which the relationship between the outcome (EQ-5D) and predictors (e.g., age, sex, DR) are summarized by describing the mean of the outcome (EQ-5D) for each fixed value of the predictors. However, traditional regression analysis has inherent limitations. First, when summarizing the responses for fixed values of predictor variables, a traditional regression model cannot be readily extended to noncentral locations, which is precisely where the interests of social science research often reside. For instance, studies using the EQ-5D have intrinsic interest in the poorer outcomes (lower tail), and traditional regression analysis cannot address these questions efficiently and may even miss the point of the research altogether. Second, the model assumptions are not always met in the real world, which results in biased and inappropriate estimates. Third, traditional regression analysis cannot reflect how changes in the predictor variables affect the underlying shape of the distribution of the outcome (EQ-5D).[26]

Because the distribution of the EQ-5D was skewed in our study (Fig. 2), it cannot be adequately approximated by the usual parametric

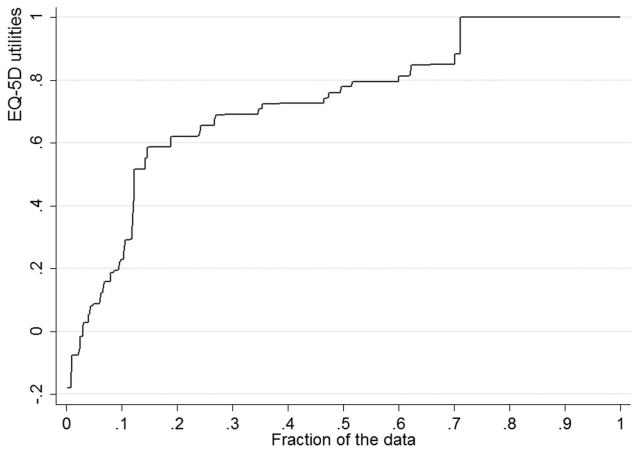

FIGURE 1. Nonnormal distribution of the EQ-5D utility scores. The distribution of the EQ-5D is skewed, with >28% of participants having an EQ-5D score of 1.

distribution functions. Therefore, using an ordinal least squares model or indeed other models such as the Tobit or CLAD model, which have also been used in EQ-5D related research,[24,27,28] would be problematic because these models all assume that the residuals are normally distributed. Moreover, the Tobit and CLAD models use an underlying latent variable with a normal or other distribution, and this has been criticized because these assumptions are unrealistic and cause a biased estimation.

Quantile regression, on the other hand, is a statistical technique that aims to estimate and conduct inference about conditional quantile functions. Quantile regression methods offer a mechanism for estimating models for the conditional median function and the full range of other conditional quantile functions. Given that multiple quantiles can be modeled, it is possible to achieve a more complete understanding of how the response distribution is affected by predictors, including information about shape change. A set of equally spaced conditional quantiles (e.g., every 5% or 1% of the population) can characterize the shape of the conditional distribution in addition to its central location. By supplementing the estimation of conditional mean functions with techniques for estimating an entire family of conditional quantile functions, quantile regression is capable of providing a more complete statistical analysis of the stochastic relationships among random variables. Unlike linear regression, quantile regression is not limited to explaining the mean of the EQ-5D, and it can be used to explain the determinants of the EQ-5D at any point in its distribution.[29]

Therefore, the relationships among presence and severity of DR and DME, vision impairment, and other sociodemographic and clinical covariates and HRQoL were examined using a multivariate quantile regression model. The EQ-5D utility scores were categorized into five quintiles of HRQoL—15th, 30th, 45th, 60th, and 75th—ranging from poorest to highest HRQoL. The choice of percentiles largely depends on the research question and the distribution of the outcome. For example, research interested in the very lowest spectrum may choose to look at, for example, the 5th, 10th, and 15th quantiles for a fine-grained analysis at the area of interest. We chose to use the 15th, 30th, 45th , and so on, quantiles because these best fit the distribution of the data.

Because quantile regression is an extension of the linear regression model, we used an a priori sample size calculator for multiple regression to estimate the sample size for the regression at different quantiles using the formula

$$\text{Cohen's } f^2 \text{ effect size } = f^2 = \frac{R^2}{1-R^2} \text{ of } 0.07$$

Thus, at the 15th percentile, we needed 165 patients to detect an anticipated effect size of 0.07 at 80% power and at the 0.05 significant level. At the 30th percentile, the required sample was 314. At the 45th percentile, the required sample size was 245; at the 60th percentile, the required sample size was 190; and at the 75th percentile, the required sample size was 249. Given that our sample size was 577, these power calculations indicated that we had enough power to detect the association for each quintile.

Regression coefficients for each quantile are provided and represent the change in EQ-5D utility score per unit change of each covariate for that particular level of HRQoL (see Tables 3, 4). Instead of having a *single* regression coefficient for the mean change in outcome, as in ordinal least squares models, there is a regression coefficient for each particular quantile of HRQoL. Thus, the change in utility score per unit change of each covariate alters, depending on which quantile of HRQoL is being considered. This allows the association between exposure and outcome to be explored across the spectrum of HRQoL.

To examine risk factors associated with utility measures, we adjusted for the variables found to be significantly associated with EQ-5D utility measures in univariate analyses. Despite not being significantly associated with the EQ-5D in univariate analyses, age was also included in the models because it is known to be associated with HRQoL. Model 1 adjusted for DR/DME presence and severity, age, income, general comorbidity, and diabetic complications. Model 2 adjusted for all the variables in model 1 plus duration of diabetes, insulin use, HDL cholesterol, and BMI. Two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

A total of 577 patients (379 men; 65.7%) 26 to 90 years of age (median, 66 years) were included in this analysis. Given that data for type 1 and type 2 diabetes were almost identical, we present the results as a combined group. Two-hundred twenty-three (38.7%) participants had no DR/DME, 35 (6.1%) had mild NPDR/mild DME, 127 (22.0%) had moderate NPDR/moderate DME, and 192 (33.3%) had VTDR. Most participants ($n = 482$; 83.5%) reported having type 2 diabetes, and 71 (12.3%) reported having type 1 diabetes (Table 1). The DR/DME group had higher proportions of men ($n = 254$; 71.8%; $P < 0.001$) and insulin users ($n = 194$; 55.0%; $P < 0.001$), more diabetic complications (≥1 complications: $n = 140$; 39.6%; $P < 0.001$), and longer median duration of diabetes (18.0; IQR 12.0 years; $P < 0.001$), and they were significantly younger (63.0 ± 11.1

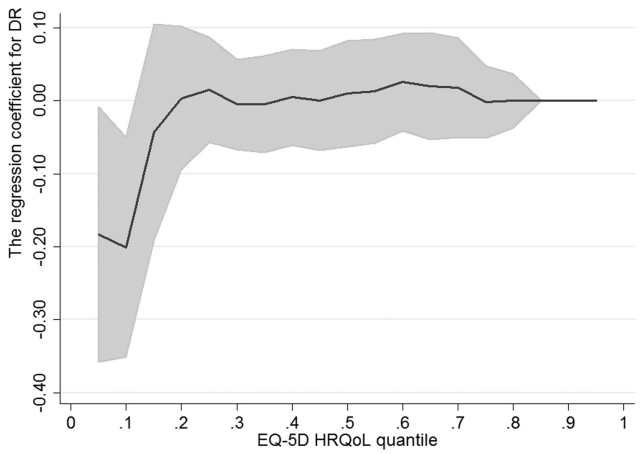

FIGURE 2. This figure clearly indicates that the regression coefficients varied at different quantiles of the EQ-5D and proves that applying traditional statistical models based on an underlying normal distribution would be inappropriate. Quantile regression, in contrast, which does not rely on a normally distributed sample, would be a better approach to study the association between DR/DME and EQ-5D utility scores.

TABLE 1. Participants' Sociodemographic and Clinical Characteristics by DR Status (n = 577)

	Without DR (n = 223)		With DR* (n = 354)		
	n	***%***	***n***	***%***	***P***
Male	125	56.1	254	71.8	**<0.001**
Income					
<$30,000	147	71.4	224	66.5	0.24
≥$30,000	59	28.6	113	33.5	
Marital status					
Never married	18	11.1	38	13.6	0.45
Married/de facto/divorced/separated/widowed	144	88.9	242	86.4	
Education					
Primary school or below	34	15.6	46	13.3	
Secondary school	113	51.8	207	59.7	0.19
14 years or more	71	32.6	94	27.1	
Current/past smoker (yes)	125	56.8	193	54.8	0.73
Diabetes type†					
1	19	8.5	52	14.7	0.09
2	194	87.0	288	81.4	
Insulin use (yes)	45	20.4	194	55.0	**<0.001**
Number of comorbidities‡					
0	24	10.8	54	15.3	0.12
≥1	199	89.2	300	84.8	
Diabetic complications§					
0	175	78.5	214	60.5	**<0.001**
≥1	48	21.5	140	39.6	
Vision impairment (yes)	70	35.6	212	62.7	**<0.001**

	Without DR (n = 223)		With DR* (n = 354)		
	Median or Mean	**IQR or SD**	**Median or Mean**	**IQR or SD**	***P***
Age, y	67.1	12.1	63.0	11.1	**<0.001**
Systolic blood pressure, mm Hg	137.2	18.1	141.1	19.0	0.99
Diastolic blood pressure, mm Hg	91.3	27.8	93.7	32.7	0.82
Duration of diabetes, y	8.0	9.1	18.0	12.0	**<0.001**
BMI, kg/m^2	30.6	6.4	31.0	6.0	0.74
Fasting plasma glucose, mg/dL	7.2	2.4	8.4	4.4	**<0.001**
HbA_{1c}, %	7.0	1.4	7.9	1.9	**<0.001**
HDL cholesterol, mg/dL	1.36	0.55	1.27	0.51	**0.006**

Data are shown as medians or IQR for skewed data and mean (SD) for normally distributed data. Some variables have missing data. Bold values indicate significant results.

* Includes any DR and/or DME.

† Twenty-four patients with unknown type of diabetes.

‡ Includes hypertension, heart attack/angina, irregular heartbeat, stroke, high cholesterol, asthma, anemia, migraine, arthritis, and osteoporosis.

§ Includes nephropathy, peripheral vascular disease, and neuropathy.

years; $P < 0.001$) than participants without DR/DME (Table 1). The DR/DME group also had a significantly higher proportion of persons who were vision impaired and persons who had higher levels HbA_{1c}, fasting plasma glucose, and HDL cholesterol (all $P < 0.05$).

Compared with those with no DR/DME, participants with any DR/DME had a lower EQ-5D utility value (0.80 vs. 0.76; $P = 0.04$) in univariate analysis (Table 2). Higher income and higher HDL cholesterol were significantly associated with higher EQ-5D utility values, whereas insulin use, presence of comorbidity, longer duration of diabetes, and higher BMI were all associated with lower utility values (all $P < 0.05$). Vision impairment and severity of DR were not associated with EQ-5D utility (Table 2).

Because the results from model 1 (presence of any DR/DME, age, income, presence of comorbidity, and presence of another diabetic complication) were very similar to those from model 2 (all the variables in model 1 plus duration of diabetes, insulin use, HDL cholesterol, and BMI), we report here only on the best-fitting model (model 2). After adjusting for all variables in model 2, we found that the presence of any DR/DME was no longer significantly associated with any quantile of HRQoL (all $P > 0.05$; Table 3).

In contrast, the presence of one or more other diabetic complications ($\beta = -0.153 \pm 0.052$, $P < 0.001$ in the 75th quantile), at least one other nonocular comorbidity (β -0.115 ± 0.038, $P < 0.01$ in the 60th quantile) and higher BMI (β -0.007 ± 0.002, $P < 0.001$ in the 60th quantile) were all independently associated with worse HRQoL across various quantiles. Longer duration of diabetes was also independently related with poorer HRQoL in the lowest quantile and higher income was associated with better HRQoL in the highest quantile (Table 3).

We investigated whether severity of DR/DME had a significant impact on HRQoL (Table 4) and found that after adjustment for all covariables (model 2), severity of DR/DME was not

TABLE 2. Association between EQ-5D Utility Values and Sociodemographic and Clinical Variables

	EQ-5D Utility Values		
	Median	**IQR**	***P***
Sex			
Male	0.80	0.34	0.10
Female	0.73	0.19	
Income			
<$30,000	0.73	0.26	**<0.001**
≥$30,000	0.81	0.31	
Marital status			
Never married	0.79	0.31	0.33
Married/de facto/divorced/separated/ widowed	0.77	0.38	
Education			
Primary school or below	0.73	0.23	0.35
Secondary school	0.78	0.31	
14 years or more	0.80	0.38	
Smoking			
Nonsmoker	0.80	0.31	0.19
Current/past smoker	0.76	0.38	
Diabetes type*			
1	0.76	0.38	0.56
2	0.78	0.34	
Insulin use			
No	0.80	0.31	**0.012**
Yes	0.73	0.26	
Number of comorbidities†			
0	0.85	0.23	**<0.001**
≥1	0.73	0.38	
Diabetic complications‡			
0	0.80	0.31	**<0.001**
≥1	0.73	0.23	
Vision impairment			
No	0.78	0.31	0.27
Yes (>0.3 LogMAR)	0.76	0.35	
Presence of DR§			
No	0.80	0.31	**0.04**
Any DR	0.76	0.34	
Severity of DR			
No DR or DME	0.80	0.31	0.24
Mild NPDR, mild DME, or both	0.80	0.48	
Moderate NPDR, moderate DME, or both	0.76	0.31	
Vision-threatening DR	0.73	0.38	

	***ρ*¶**	**SE**	***P***
Age, y	0.01	0.04	0.87
Systolic blood pressure, mm Hg	−0.02	0.04	0.66
Diastolic blood pressure, mm Hg	0.07	0.04	0.08
Duration of diabetes, y	−0.13	0.04	**0.001**
BMI, kg/m^2	−0.22	0.04	**<0.001**
Fasting plasma glucose, mg/dL	−0.06	0.04	0.15
HbA_{1c}, %	−0.07	0.04	0.09
HDL cholesterol, mg/dL	0.13	0.04	**0.002**

Bold values indicate significant results.

* Twenty-four patients with unknown type of diabetes.

† Includes hypertension, heart attack/angina, irregular heartbeat, stroke, high cholesterol, asthma, anemia, migraine, arthritis, and osteoporosis.

‡ Includes nephropathy, peripheral vascular disease, and neuropathy.

§ Includes any DR, DME, or both.

¶ Spearman's rank correlation coefficient.

independently associated with any HRQoL quantile (all $P < 0.05$). The association between poorer HRQoL and presence of any diabetic complication other than DR, any nonocular comorbidities, and higher BMI maintained their previous significant trends, as did the association between higher income and better HRQoL.

DISCUSSION

Using a robust statistical modeling method, we investigated the relationship between the presence and severity of DR, DME, and combined DR/DME, associated vision impairment, and HRQoL using EQ-5D utility values elicited from a large clinical sample of adults with type 1 and type 2 diabetes. Data were almost identical for the three categorizations, and we report here on the combined DR and DME classification. Our findings show that neither the presence nor severity of DR/DME or vision impairment was independently associated with HRQoL after adjusting for relevant sociodemographic, medical, and biochemical parameters. In contrast, higher BMI, presence of comorbidity, and diabetic complications (other than DR) were significantly associated with worse HRQoL across several quantiles of HRQoL. Higher income was also consistently associated with better HRQoL in the top spectrum of HRQoL states. Our findings indicate that the EQ-5D is not suitable for assessing the impact of the severity of DR/DME and associated vision loss, and other instruments are needed to provide better assessment of the impact of this condition on general health parameters.

Our current findings support those from existing studies showing minimal, nonsignificant differences in EQ-5D utility values,[30–32] 15D utility values,[33] and SF-6D utility values[32] for diabetic patients with and without DR/DME and pre- and post-anti-VEGF treatment for DME.[34] Our findings are also similar to those found in other ocular conditions. Espallargues et al., for example,[35] found that the EQ-5D was less sensitive to the HRQoL burden associated with AMD and related vision loss than other utility values containing vision-related content. However, our findings differ from those of previous studies reporting small but significant decrements in utility values in patients with DR[36] or blindness caused by DR[24] and studies showing a clear association between declining levels of visual acuity and reduced utility values.[14,37] For instance, Smith et al.[37] found that the doubling of the visual angle resulted in a modest but statistically significant loss in utility score of 0.03 in a large sample of patients with type 2 diabetes ($n = 154$ with visual acuity worse than 6/12). In addition, our findings do not echo the comprehensive reductions in QoL caused by to DR-related vision impairment seen in studies using vision-specific TTO and SG utility scores.[6–9]

There are several plausible factors to explain why our findings differ from those of some previous reports. First, we believe it is likely that generic instruments, such as the EQ-5D, that do not include a vision-specific dimension in the descriptive system are not sensitive enough to evaluate the specific burden of DR-induced vision loss and therefore result in underreporting of the impact of the disease. Second, the small sample sizes of most previous studies, especially with regard to the more severe spectrum of DR,[14,37] could have contributed to spurious results; our study, in contrast, had a rich clinical sample of patients with both mild DR and VTDR. Unlike many other studies, we were able to adjust for important clinical and sociodemographic variables, thus ensuring that the association between DR-related vision impairment and utility score was not confounded by known factors. Indeed, our application of quantile regression models to the skewed data enhances the validity of our results and offers a novel and relevant approach to the field of cost-effectiveness and cost-utility analysis.

Our finding that BMI, comorbidity, and income level are independently associated with HRQoL status is well supported by previous studies.[38–40] For example, in a state-wide US study, Jia et al.[41] found that obesity/overweight and low in-

Table 3. Association between the Presence of any DR/DME and HRQoL Using Quantile Regression Models for Five Different Quintiles of HRQoL

	15th Quantile		30th Quantile		45th Quantile		60th Quantile		75th Quantile	
Model 2 (n = 341)	***b***	**SE**	***b***	**SE**	***b***	**SE**	***b***	**SE**	***b***	**SE**
Presence of any DR or DME	−0.043	0.075	−0.007	0.030	−0.003	0.028	0.018	0.033	−0.000	0.027
Age, y	0.006	0.004	0.001	0.002	0.000	0.001	0.001	0.001	0.000	0.001
Income (<30,000, ≥30,000)	0.117	0.085	0.049	0.030	0.034	0.029	0.064	0.030	**0.024**	**0.037**
Comorbidities (yes, no)*	**−0.142**	**0.072**	**−0.093**	**0.035**	−0.092	0.047	**−0.115**	**0.038**	−0.009	0.025
Diabetic complications†	−0.213	0.118	**−0.077**	**0.030**	**−0.066**	**0.024**	−0.059	0.032	**−0.153**	**0.052**
Duration of diabetes, years	**−0.011**	**0.005**	−0.003	0.002	−0.001	0.001	−0.002	0.002	0.000	0.001
Insulin use (yes, no)	0.081	0.087	0.022	0.030	0.023	0.024	−0.012	0.029	0.000	0.025
BMI, kg/m^2	−0.006	0.004	**−0.004**	**0.002**	***−0.006***	***0.002***	***−0.007***	***0.002***	−0.003	0.003
HDL-C, mmol/L	−0.051	0.051	−0.027	0.038	0.012	0.034	0.013	0.033	−0.009	0.024

Coefficient (*b*) and standard error (SE) were reported for 15%, 30%, 45%, 60%, and 75%. Coefficients significant at the 5% level are bold; those at the 1% level are bold and underlined; and those at the 0.1% level are bold, underlined, and italic. Standard errors are obtained using 1000 bootstrap replications.

* Comorbidities include hypertension, heart attack/angina, irregular heart beat, stroke, high cholesterol, asthma, anemia, migraine, arthritis, and osteoporosis.

† Diabetic complications include nephropathy, peripheral vascular disease, and neuropathy.

come contributed up to 13.8% and 39.9% of explainable quality-adjusted life years lost, respectively, calculated using EQ-5D utility scores. Similarly, Solli et al.,[42] investigating the association between diabetic complications and EQ-5D, found that patients with complications from type 2 diabetes had significantly lower utility scores than those without any complication (0.73 vs. 0.85, respectively). Given that the EQ-5D is designed to assess general HRQoL, it is not surprising that these fundamental health-related and sociodemographic variables are found to be significantly associated with utility score.

The strengths of our study include a large clinical sample of people with diabetes with differing levels of DR and DME, especially VTDR, the use of dilated fundus photography and standardized grading, the use of novel statistical modeling, and the comprehensive range of demographic and clinical parameters included in the analysis. Potential limitations include the higher proportion of men than women in our sample and the potential selection biases stemming from our focused recruitment from specialized retinal clinics. In particular, because DMP participants were primarily recruited from a single source (the RVEEH), it is possible that the results are not representative of a general diabetic population. However, because the DMP sample approximates sociodemographic and clinical characteristics (e.g., HbA_{1c} level, duration of diabetes, and blood pressure) found in population-based studies,[20] potential bias is minimized.

Because the DMP study criteria excluded patients with hearing and cognitive impairment and those who did not live independently (i.e., those who were likely to have significant impairment), this might have reduced the sensitivity of the EQ-5D to measure disutility related to DR/DME. However, the clinical nature of our study, the extensive testing protocol, and logistic and financial constraints did not allow us to adequately address these issues. There are also certain limitations associated with quantile regression. For example, QALYS cannot be calculated because they rely on mean utility scores, which are not provided by quantile regression, and this limits the applicability of the findings. In addition, quantile regression is more complex than other statistical methods because it requires bootstrapping methods to produce a large number of estimates of standard errors of the coefficients. Similarly, the study findings may be more difficult to interpret because of the large number of regression coefficients produced.

Table 4. Association between Severity of DR/DME and HRQoL Using Quantile Regression Models for Five Different Quintiles of HRQoL

	15th Quantile		30th Quantile		45th Quantile		60th Quantile		75th Quantile	
Model 2 (n = 341)	***b***	**SE**	***b***	**SE**	***b***	**SE**	***b***	**SE**	***b***	**SE**
Mild NPDR/mild DME (yes, no)	−0.116	0.185	−0.017	0.141	−0.008	0.077	0.034	0.051	−0.007	0.035
Moderate NPDR/moderate DME (yes, no)	0.020	0.129	0.016	0.038	0.017	0.032	0.007	0.041	0.011	0.032
VTDR (yes, no)	−0.062	0.076	−0.008	0.034	−0.010	0.033	0.009	0.037	0.001	0.035
Age, y	0.005	0.003	0.000	0.002	0.000	0.001	0.001	0.001	0.001	0.001
Income (<30,000, ≥30,000)	0.128	0.082	0.049	0.031	0.041	0.029	**0.073**	**0.033**	0.022	0.034
Comorbidities (yes, no)*	−0.109	0.069	**−0.087**	**0.040**	**−0.092**	**0.046**	−0.109	0.038	−0.009	0.026
Diabetic complications†	−0.221	0.119	**−0.080**	**0.031**	**−0.071**	**0.023**	−0.052	0.033	**−0.154**	**0.049**
Duration of diabetes, y	−0.008	0.005	−0.002	0.002	−0.001	0.001	−0.002	0.002	−0.000	0.001
Insulin use (yes, no)	0.055	0.083	0.018	0.029	0.020	0.025	−0.028	0.026	0.001	−0.001
BMI, kg/m^2	−0.005	0.004	−0.003	0.002	***−0.006***	***0.002***	***−0.007***	***0.002***	−0.003	0.003
HDL-C, mmol/L	−0.042	0.043	−0.012	0.041	0.015	0.037	0.004	0.033	−0.009	0.027

Coefficient (*b*) and standard error (SE) were reported for 15%, 30%, 45%, 60%, and 75% quantiles. Coefficients significant at the 5% level are bold; those at the 1% level are bold and underlined; and those at the 0.1% level are bold, underlined, and italic. Standard errors are obtained using 1000 bootstrap replications.

* Comorbidities include hypertension, heart attack/angina, irregular heartbeat, stroke, high cholesterol, asthma, anemia, migraine, arthritis, and osteoporosis.

† Diabetic complications include nephropathy, peripheral vascular disease, and neuropathy.

Another limitation might have been our analysis of type 1 and type 2 diabetes together. However, we did conduct separate analyses for our type 2 diabetic sample, and the results were similar to those of the combined analysis. Our use of United Kingdom population data to derive EQ-5D utility scores for an Australian population might also have had an unpredictable effect on the results. However, the fact that we were able to replicate our findings using a New Zealand population set validates our conclusions.

Our findings have important implications for clinicians and researchers. We have clearly demonstrated that using generic HRQoL measures such as the EQ-5D to assess the impact of vision-related impairment or treatment interventions for ocular diseases is inappropriate. This is because generic instruments are developed by drawing items from populations typically with major medical conditions such as cardiac disease, respiratory disease, and cancer; consequently, they contain very little or no vision-related content. This is extremely important because one cannot measure vision-related QoL without vision-related content. Moreover, any impact of vision impairment or ocular conditions on generic HRQoL will be lost in the "noise" of other non-vision–related impacts on QoL in the overall score.[18,43] Recent studies have demonstrated empirically that some generic instruments cannot capture the impact of vision-specific impairment and should not be used for this purpose.[4,32,44–46]

These findings are now extremely relevant to the field of DR research, in which novel treatment therapies such as anti-VEGF are emerging. Such novel therapies will have to be compared with traditional treatments, such as laser photocoagulation and surgical vitrectomy, in terms of both clinical and patient-centered outcomes. Similarly, the cost-effectiveness of new treatments may have to be evaluated by policy planners using quality- and disability-adjusted life years (QALYs and DALYs), which are calculated from utility values. Therefore, a utility value that can capture both the impact of DR/DME and the changes after interventions will be invaluable. Our findings suggest that the EQ-5D may not be suitable for use in clinical trials evaluating new DR or DME treatments or for the calculation of QALYs within cost-effectiveness studies. It is possible, however, that other generic instruments with greater discriminative ability and a richer descriptive system, including vision-related impairment such as the 15D,[47] the AQOL-7D[48,49] and the HUI-3,[50] may be more sensitive to the specific effects of DR.[32]

Indeed, we are exploring whether the VisQoL,[51,52] a vision-specific MAUI, can more successfully detect the impact of DR, DME, and associated vision impairment on vision-related QoL. The VisQoL was developed and validated specifically for vision-impaired populations and covers six dimensions of self-reported VRQoL: physical well-being, independence, social well-being, self-actualization, planning, and organization. As such, the VisQoL, or any condition-specific MAUI with similar parameters assessing relevant QoL issues, is likely to better elucidate the relationship between DR/DME and patient QoL.

In conclusion, we found that variation in EQ-5D utility values could not be attributed to the presence or severity of DR/DME or vision impairment. Rather, general nonocular morbidities were significantly associated with lower utility values and thus poorer HRQoL. These findings endorse the use of generic health-related outcome measures by clinicians, researchers, and policy planners to capture the impact of general social and health-related factors on QoL in patients with diabetes but not to assess the impact of impairment specifically related to DR, DME, and related vision loss.

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