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Valuing health states of people with type 2 diabetes: Analyses of the nationwide representative linked databases

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ABSTRACT

Aims/Introduction: To estimate preference-based measures of health-related quality of life associated with sociodemographic and clinical characteristics in type 2 diabetes patients.

Materials and Methods: Individuals with EuroQol-5 dimensions-3 levels data were identified from Taiwan's National Health Interview Survey in 2009 and 2013. Status of diabetes, comorbidities, complications and treatments were ascertained through data linkage to Taiwan's National Health Insurance Research Database. Multivariable ordinary least squares, Tobit and median regression analyses were used to estimate the coefficients that represented independent impacts of patients' characteristics on health-related quality of life.

Results: The mean health utility score for 2,104 participants was 0.838. Being female, aging, divorced/widowed, never worked or underweight, or having a lower monthly household income, injectable glucose-lowering therapy, comorbid connective tissue disease or depression were associated with lower health utilities. Having an amputation led to the largest reduction by 0.288 in health utilities, followed by debilitating stroke (0.266), heart failure (0.237), other coronary heart disease (0.185), kidney dialysis/transplant (0.148), coronary revascularizations (0.093), transient ischemic attack/stroke (0.078), diabetic neuropathy (0.062), polyneuropathy (0.055) and other neuropathy (0.043).

Conclusions: Major vascular complications, connective tissue disease and depression are associated with considerably worse health-related quality of life. These health utility estimates can facilitate health economic evaluations to determine cost-effective strategies for diabetes management.

INTRODUCTION

As highlighted by the American Diabetes Association's recommendations for diabetes care, achieving optimal health-related quality of life (HRQoL) is recognized as one of the desired goals in diabetes management and should be measured in routine clinical care[1]. HRQoL is considered as an essential component for evaluating the overall treatment outcomes in the health technology assessment of new treatments[2,3]. To support the increasing adoption of the quality-adjusted life year metric in diabetes health economic research, which is determined as the health utility value associated with a given health state multiplied by the years lived in that health state, several preference-based measures of HRQoL instruments have been used to estimate health utility scores associated with sociodemographic and clinical characteristics of people with diabetes[4–6].

Several studies have used statistical modeling analyses to estimate the independent influences of diabetes-related complications on patients' HRQoL, which are expressed as health utility decrements or penalties to be adopted in diabetes health economic simulation models for cost-utility analyses[4–6]. However, health utility values for health states are sensitive to country settings, because preference weights could be affected by the cultural norms, availability of medical technologies, and

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affordability and accessibility of medical services[7,8]. Health utility data that were primarily collected from Western countries and white populations[9–15] could differ from those in Asian countries and populations[16–23]. Only one study[16] focused on health utilities for type 2 diabetes and its complications in the Taiwanese population, whereas a few other studies[17–20] are for Chinese populations. Furthermore, the applicability of results derived from previous Asian studies[16–20] has been a concern for diabetes health economic research in Taiwan owing to the following reasons: (i) reliability of data is uncertain, because only the marginal (crude) health utility estimates of diabetes-related complications were provided, without consideration and adjustment for the contributions from other patient characteristics or co-existing comorbidities (e.g., depression) or complications in the analyses[16]; (ii) generalizability of results is limited, because the sample size was small or the study cohorts were recruited from local hospitals in certain regions[16–18]; and (iii) health states were analyzed only at the aggregate levels, with no consideration of subtypes of clinical conditions[16–20]. Hence, evidence remains scarce on reliable, comprehensive and country-/population-specific health utility estimates of type 2 diabetes and its heterogeneous clinical conditions in Asian populations.

Against this background, we estimated Taiwan population-specific health utility scores for an array of patient sociodemographic characteristics, comorbidities, diabetes-related complications and treatments in patients with type 2 diabetes by utilizing two large nationwide representative databases to provide empirical HRQoL data for facilitating health economic studies, as well as clinical and health policy decisions.

METHODS

Data sources

Data in the present study came from two nationally representative data sources in Taiwan, namely the National Health Interview Survey (NHIS) and the National Health Insurance Research Database (NHIRD). The NHIS is a cross-sectional survey of a representative sample from each county or municipality in Taiwan obtained using a stratified multistage systematic sampling procedure. Within each county or municipality, samples were selected step-by-step in the order following the stratum of district, township, village and neighborhood with a probability proportional to the population size of the individual stratums[24]. Additionally, the population density, the number of individuals aged ≥65 years, the number of individuals with an education level of high school or above, the number of physicians, and the number of workers in agriculture and animal husbandry in a county or municipality were considered in the sampling process.

According to the 2013 NHIS report, in each country or municipality, there were no differences in the age and sex distributions between the overall and the survey-sampled population[25]. The NHIS has been carried out every 4 years in Taiwan since 2001. Since 2009, the EuroQol-5 dimensions-3 levels (EQ-5D-3L) survey has been included together with the 36-Item Short-Form Health Survey in the NHIS for assessing people's HRQoL. The NHIS data in 2009 and 2013 were utilized in the present study. The NHIRD comprises sizeable individual longitudinal medical records from almost 23 million beneficiaries in Taiwan's National Health Insurance program, including claims data for outpatient visits, inpatient admissions, emergency department visits, prescription drugs and medical supplies[26]. The NHIRD data could be tracked back to 1 January 2002, and followed up to 31 December 2013. In other words, the individual-level patient data were compiled from the earliest year of the NHIRD available (i.e., 2002) to the end of the survey years of the NHIS (i.e., 2009 and 2013). The individual-level data from the NHIS and NHIRD were linked by the individual, encrypted, de-identified numbers from the Health and Welfare Data Science Center (Figure 1). Few patients (n = 3) responded to both the 2009 and 2013 surveys, and their 2013 NHIS data were used in the present study.

Cohort identification

Study participants were patients who met the following criteria: (i) aged ≥18 years at type 2 diabetes diagnosis; and (ii) had EQ-5D-3L data in the NHIS. Specifically, cases of type 2 diabetes were confirmed in the NHIRD if the patients had at least one inpatient record with a diagnosis of type 2 diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification codes: 250.x0, 250.x2, x = 0–9), at least two outpatient records with a diagnosis of type 2 diabetes, or one outpatient record with a diagnosis of type 2 diabetes and one prescription refill record for a glucose-lowering agent (GLA) in the same year. Patients' incidence year was determined based on the date of their first diagnosis of type 2 diabetes. Incident diabetes cases were defined as those diagnosed with diabetes and without a medical history of diabetes or GLA use in the preceding year. Descriptions of the study variables, data linking and study cohort identification are provided in Figure 1.

The study was approved by the institutional review board of National Cheng Kung University Hospital (A-EX-106-013).

Study variables

Health utility data were collected using the EQ-5D-3L survey in the NHIS. The EQ-5D-3L is a widely used instrument for measuring people's health status. In Taiwan, the validity of the EQ-5D-3L assessment has been carried out for patients with a range of disease conditions[27,28]. The EQ-5D-3L comprises two parts. The first part assesses people's health status in five dimensions, namely mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each of which is rated on three levels; namely, 'no problems', 'some/moderate problems' and 'extreme problems/unable to do'. A total of 243 health states, from '11111' to '33333', are generated and can be weighted to produce a single summary EQ-5D-3L index score as a health utility value by using the value sets derived from the valuation techniques (e.g., time trade-off). In the present study, we used a Taiwanese norm value set to estimate the EQ-5D-3L index

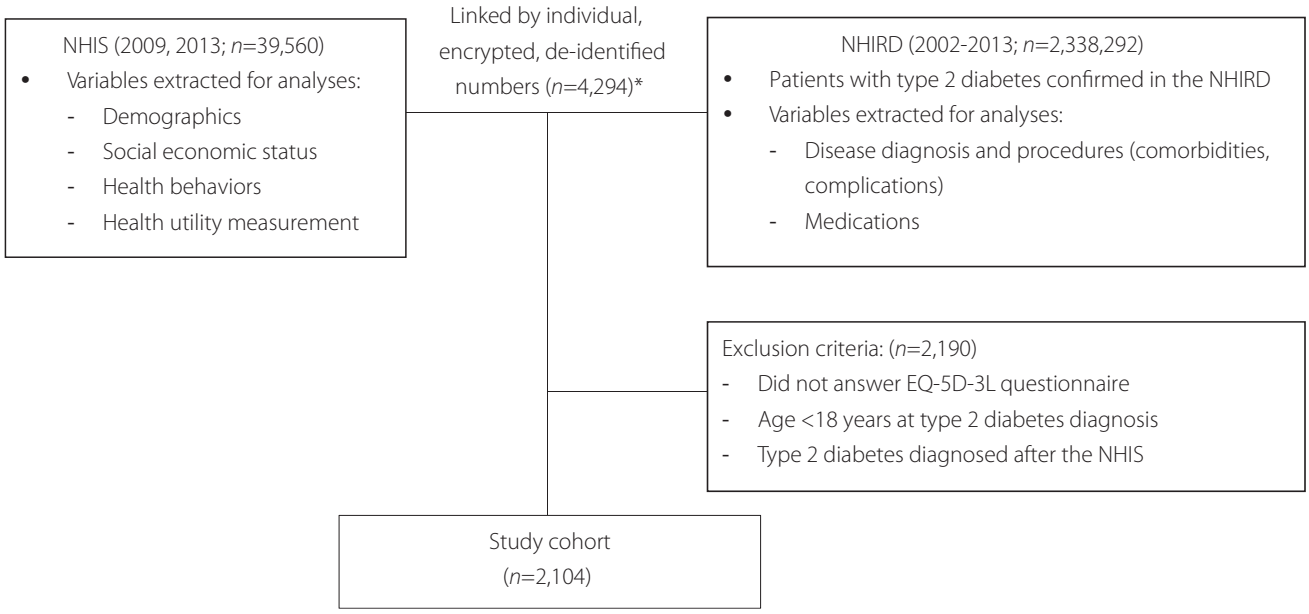

Figure 1 | Illustration of the database linking and study cohort identification. *The National Health Insurance Survey (NHIS) examines health status, health behaviors and healthcare utilization in a nationally representative sample of the entire population in Taiwan every 4 years since 2001. The National Health Insurance Research Database (NHIRD) comprises individual longitudinal medical records and claims from almost 23 million beneficiaries in Taiwan's National Health Insurance program. The estimated prevalence of diagnosed type 2 diabetes in people aged 20–79 years during 2009–2014 in Taiwan was approximately 8.4–10.1% (*J Formos Med Assoc* 2019;118[Suppl 2]:S66–S73). EQ-5D-3L, EuroQol-5 dimensions-3 levels.

scores[29]. According to the Taiwanese value set, the range of health utility scores is from −0.674 to 1.000, with higher scores representing better health states. Additionally, patient demographics (age, sex), socioeconomic status (education level, marital status, employment status, monthly household income), height and weight, and health behaviors (drinking and smoking history) were also ascertained from the NHIS. The body mass index (BMI) was estimated based on the given height and weight information.

Disease conditions, treatment procedures and medication utilization of study participants were measured from the NHIRD. Diabetes-related complications and comorbidities were identified from the date of type 2 diabetes diagnosis to the year of the NHIS. Macro- and microvascular complications were measured in a broad, major category, such as cerebrovascular disease, coronary heart disease, nephropathy, retinopathy, neuropathy and peripheral vascular disease. The detailed subtypes within each major complication category were also measured. Comorbidities of interest were hypertension, hyperlipidemia, liver disease, depression, cancer, chronic obstructive pulmonary disease and connective tissue disease. All disease conditions were identified based on International Classification of Diseases, Ninth Revision, Clinical Modification disease or procedure codes (Table S1) from the NHIRD. Microvascular complications and comorbidities were measured from the outpatient visit, inpatient admission and emergency department visit files of the NHIRD, and macrovascular diseases were determined from the inpatient admission and emergency department visit files. The GLA use was confirmed from the prescription records in the NHIRD and classified into individual therapeutic categories according to the World Health Organization Anatomical Therapeutic Chemical Classification System. The patterns of GLA use were classified into three types; namely, none, oral medication only, and a combination of oral and injectable medications. Study variables are listed in Tables 1 and S2.

Statistical analysis

Means and standard deviations were used to present continuous variables, and frequencies and percentages were reported for dichotomous and categorical variables. The marginal health utility scores were calculated to represent the crude average health utility scores for patients overall and patient subgroups based on sociodemographic and clinical characteristics.

Multivariable ordinary least squares (OLS) regression models were carried out to estimate the independent impacts of a wide range of patients' characteristics, including sociodemographics, presence of comorbidities and diabetes-related complications, and utilization of glucose-lowering treatments, on the HRQoL. All patients' characteristics were initially considered as the independent variables in the regression models. The coefficients of independent variables were estimated from the models to represent the reduction or penalty associated with each patient

Table 1 | Characteristics of 2,104 study patients and their marginal EuroQol-5 dimensions-3 levels health utility scores

	Mean (SD) or no. patients (%)	EQ-5D-3L, mean (SD)
Type 2 diabetes duration, years[†]	4.54 (2.84)	
Age at type 2 diabetes diagnosis (years)	57.48 (13.48)	
Sex		
Male	1,076 (51.14)	0.875 (0.254)
Female	1,028 (48.86)	0.800 (0.303)
Education level		
Primary or below	1,148 (54.56)	0.818 (0.295)
High school	437 (20.77)	0.901 (0.211)
College/university or above	504 (23.95)	0.831 (0.294)
Unknown	15 (0.71)	0.805 (0.331)
Marital status		
Single	134 (6.37)	0.889 (0.235)
Married	1,474 (70.06)	0.862 (0.256)
Divorced	119 (5.66)	0.830 (0.250)
Widowed	372 (17.68)	0.730 (0.362)
Unknown	5 (0.24)	0.676 (0.460)
Employment status		
Never worked	124 (5.89)	0.688 (0.352)
Ever/currently employed	1,980 (94.11)	0.847 (0.274)
Monthly household income		
≥NT$70,000	367 (17.44)	0.916 (0.185)
NT$30,000–69,000	677 (32.18)	0.875 (0.242)
<NT$30,000	681 (32.37)	0.769 (0.331)
Unknown	379 (18.01)	0.821 (0.297)
Drinking history		
Never	1,153 (54.80)	0.807 (0.302)
Ever	951 (45.20)	0.876 (0.250)
Smoking history		
Never	1,356 (64.45)	0.825 (0.286)
Ever	748 (35.55)	0.862 (0.271)
Betel nut chewing history		
Never	1,614 (76.71)	0.832 (0.284)
Ever	490 (23.29)	0.858 (0.271)
BMI (kg/m^2)		
Underweight (BMI <18.5)	39 (1.85)	0.669 (0.437)
Normal (18.5 ≤ BMI < 24)	649 (30.84)	0.850 (0.269)
Overweight (24 ≤ BMI < 27)	624 (29.66)	0.853 (0.278)
Obesity I (27 ≤ BMI < 30)	408 (19.39)	0.849 (0.258)
Obesity II (30 ≤ BMI < 35)	221 (10.50)	0.861 (0.237)
Obesity III (BMI ≥35)	64 (3.04)	0.768 (0.311)
Unknown	99 (4.71)	0.684 (0.384)
Hypertension		
No	539 (25.62)	0.912 (0.188)
Yes	1,565 (74.38)	0.813 (0.303)
Dyslipidemia		
No	497 (23.62)	0.824 (0.299)
Yes	1,607 (76.38)	0.842 (0.276)
Liver disease		
No	1,135 (53.94)	0.834 (0.282)
Yes	969 (46.06)	0.843 (0.281)
Depression		
No	1,818 (86.41)	0.857 (0.261)
Yes	286 (13.59)	0.719 (0.363)
Cancer		
No	1,191 (56.61)	0.842 (0.276)
Yes	913 (43.39)	0.833 (0.289)
Chronic obstructive pulmonary disease		
No	1,379 (65.54)	0.865 (0.254)
Yes	725 (34.46)	0.786 (0.321)
Connective tissue disease		
No	1,898 (90.21)	0.846 (0.275)
Yes	206 (9.79)	0.762 (0.330)
Glucose-lowering agents		
None	832 (39.54)	0.905 (0.183)
Oral only	1,046 (49.71)	0.902 (0.191)
Oral + injectable	226 (10.74)	0.803 (0.297)

BMI, body mass index; EQ-5D-3L, EuroQol-5 dimensions-3 levels; NT$, New Taiwan dollar; SD, standard deviation. [†]The duration of type 2 diabetes was calculated as the difference in time between the calendar year of patients filling out the survey and the year when their type 2 diabetes was diagnosed.

characteristic in the HRQoL. During the model fitting process, independent variables were omitted from the models in the consideration that the corresponding coefficient estimates were greater than zero – implying that the given characteristics were not associated with a reduction or penalty in the patients' HRQoL, statistically insignificant (P-value >0.05) or clinically unimportant (the absolute value of a coefficient estimate <0.03)[30]. The final multivariable regression model included the variables that produced either statistically or clinically significant penalties in the patients' HRQoL. Subtracting the penalties corresponding to the independent variables in the final regression model from the intercept coefficient of the model formed an additive model to explain the health utility estimates impacted by any combination of patients' sociodemographics, disease conditions and glucose-lowering treatments.

Additionally, we acknowledged that: (i) health utility scores are continuous variables, upper bounded by 1.0 (the score for full health), and often skewed; and (ii) in the EQ-5D instrument, it is common for a considerable proportion of respondents to rate themselves in a full health state with a score of 1.0[10,31–33]. With this regard, sensitivity analyses were carried out with the use of two alternative regression analyses as the Tobit model[31,33–36] and median regression[31,34–36] for comparison with results from the OLS regression analysis[31,34–36]. All statistical analyses were carried out using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

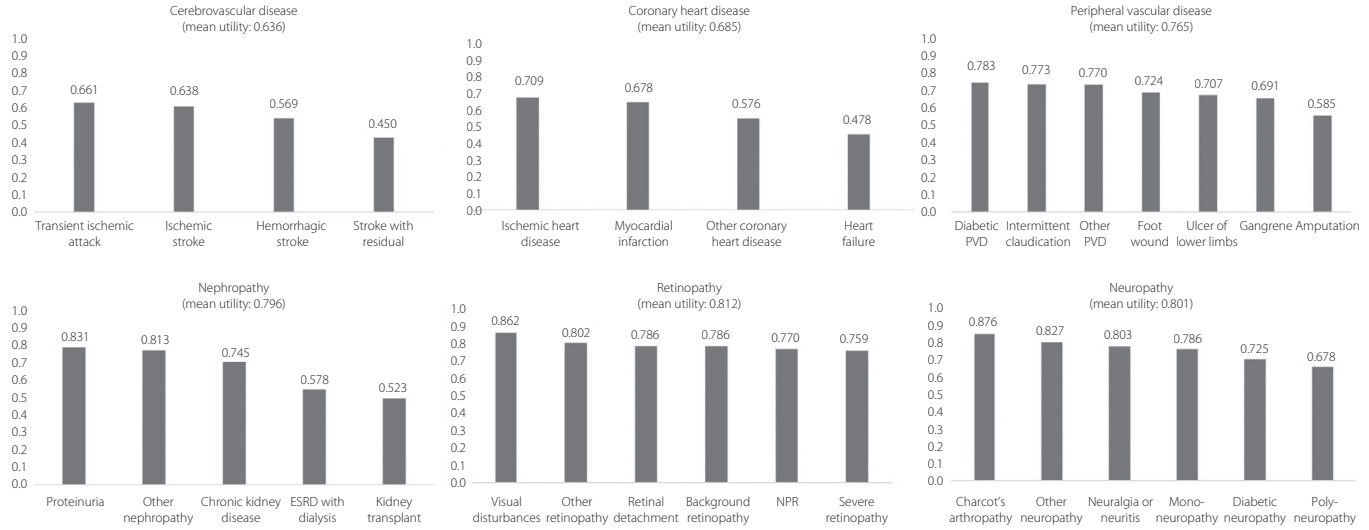

Figure 2 | Marginal EuroQol-5 dimensions-3 levels health utility scores stratified by subtype of diabetes-related complications. ESRD, end-stage renal disease; NPR, non-proliferative retinopathy; PVD, peripheral vascular disease.

RESULTS

A total of 2,104 patients (51.14% male) were included in the present study, with an average age of 57.48 years at type 2 diabetes diagnosis and a mean duration of 4.54 years from type 2 diabetes diagnosis to the survey year (Table 1). The majority of study participants had a BMI of between 18.5 and 26.9 kg/m^2, the prevalence of comorbidities ranged from 9.79% (connective tissue disease) to 76.38% (dyslipidemia), and 89.25% of participants were either without any glucose-lowering treatments or with only oral medications. The mean health utility scores stratified by patient characteristic are presented in Table 1. The patients who were male, single and employed, and had higher education levels, higher monthly household income levels and no or only oral glucose-lowering treatments generally had higher health utilities compared with their counterparties.

Table S2 lists the marginal health utility scores for the overall study patients and those stratified by diabetes-related complication. The mean health utility score for the overall study participants was 0.838. Retinopathy was the most prevalent complication (n = 1,161; 55.18% of total participants), followed by neuropathy (n = 1,036; 49.24%) and nephropathy (n = 739; 35.12%). The average health utility scores for patients with macrovascular complications were generally lower than those for patients with microvascular complications. The range of mean health utility scores in macrovascular complications was between 0.450 (stroke with residual deficits) and 0.744 (angina pectoris), and that in microvascular complications was between 0.523 (kidney transplant) and 0.876 (Charcot's arthropathy). Figure 2 presents the marginal health utility scores stratified by subtype of complications in the corresponding broad complication category.

Table 2 summarizes the results of the primary regression (OLS) and two additional regression (Tobit model and median regression) modeling analyses for health utility scores. The health utility can be decreased due to the penalty functions associated with patient demographics, comorbidities, complications and treatments in the models. From the OLS regression analyses, being female, aging, divorced or widowed, never worked, underweight, with injectable glucose-lowering therapy, or having a lower monthly household income was associated with a lower health utility score. Among comorbidities, connective tissue disease and depression were associated with a reduction in the health utility score by a decrement of 0.067 and 0.101, respectively. Among diabetes-related complications, amputation led to the largest reduction by 0.288 in the health utility score, and stroke with residual deficits, heart failure, other coronary heart disease and kidney dialysis or transplant were also associated with a substantial reduction by >0.100 in the health utility score. Compared with the OLS regression analyses, the Tobit model analyses produced the larger estimated coefficients and standard errors consistently for patient characteristics, whereas the median regression analyses produced the insignificant estimated coefficients and larger standard errors for many of patient characteristics.

Based on the OLS regression analysis results in Table 2, the intercept value of 0.983 can be interpreted as the mean health utility score for the 62-year men with type 2 diabetes, a monthly household income of ≥NT$70,000, a BMI of ≥18.5 and being single/married, ever/currently worked, treated with none/only oral glucose-lowering therapy, and without comorbidities or macrovascular, neuropathic or microvascular complications. A patient's health utility score can be estimated by subtracting the penalties associated with sociodemographic and clinical characteristics from such a base-case type 2 diabetes patient. For example, the estimated health utility score of a 62-year married, employed woman with type 2 diabetes, a

Table 2 | Estimated coefficients (penalties) from three regression analyses: Ordinary least squares, Tobit and median regression models

Patient characteristics	OLS		Tobit model		Median regression	
	Estimated coefficients	Standard errors	Estimated coefficients	Standard errors	Estimated coefficients	Standard errors
Intercept	0.983	0.014	1.642	0.047	1.000	0.139
Sex (ref: male)						
Female	−0.038	0.012	−0.156	0.037	0.000	0.042
Age, years (per year greater; centered at 62)	−0.002	0.001	−0.008	0.001	0.000	0.002
Marital status (ref.: single/married)						
Divorced	−0.034	0.025	−0.185	0.070	0.000	0.098
Widowed	−0.039	0.018	−0.065	0.049	0.000	0.102
Employment status (ref: ever/currently employed)						
Never worked	−0.043	0.028	−0.101	0.072	−0.167	0.110
Monthly household income (ref.: ≥NT$70,000)						
NT$30,000–NT$69,000	−0.023	0.016	−0.094	0.050	0.000	0.062
<NT$30,000	−0.074	0.016	−0.234	0.050	0.000	0.061
BMI, kg/m^2 (ref.: BMI ≥18.5)						
Underweight (BMI <18.5)	−0.184	0.041	-0.363	0.107	0.000	0.128
Comorbidities (ref.: no comorbidity)						
Depression	−0.101	0.017	−0.234	0.046	0.000	0.099
Connective tissue disease	−0.067	0.020	−0.154	0.055	0.000	0.113
Diabetes-related complications (ref.: no complication)						
Cerebrovascular disease						
TIA or stroke	−0.078	0.022	−0.153	0.057	0.000	0.092
Stroke with residual deficits	−0.266	0.041	−0.447	0.102	−0.393	0.127
Coronary heart disease						
PTCA or CABG	−0.093	0.048	−0.195	0.123	−0.156	0.248
Other coronary heart disease	−0.185	0.076	−0.327	0.188	−0.393	0.199
Heart failure	−0.237	0.030	−0.366	0.075	−0.391	0.081
Neuropathy						
Other neuropathy	−0.043	0.026	−0.136	0.074	0.000	0.108
Polyneuropathy	−0.055	0.033	−0.105	0.088	0.000	0.116
Diabetic neuropathy	−0.062	0.018	−0.133	0.049	0.000	0.053
ESRD with dialysis/kidney transplant	−0.148	0.050	−0.300	0.126	−0.038	0.262
Amputation	−0.288	0.079	−0.574	0.200	−0.339	0.392
Diabetes treatment (ref.: none or oral therapy only)						
Injectable therapy	−0.058	0.020	−0.109	0.056	0.000	0.073

Among 2,104 patients, 446 people were excluded from the regression analysis due to missing values in some variables listed in Table 1. BMI, body mass index; CABG, coronary artery bypass graft; ESRD, end-stage renal disease; NT$, New Taiwan dollar; OLS, ordinary least squares; PTCA, percutaneous transluminal coronary angioplasty; ref., reference; TIA, transient ischemic attack.

monthly household income of NT$70,000, a BMI of 18, having had transient ischemic attack and receiving injectable glucose-lowering treatment is 0.625 (=0.983 − 0.038 − 0.184 − 0.078 − 0.058).

DISCUSSION

This is the first nationwide, population-representative study that assesses the health utility scores using three different types of regression modeling analyses (OLS, Tobit model, median regression) as a function of a variety of patient demographics, comorbidities, diabetes-related complications and glucose-lowering treatments in a Taiwanese population with type 2 diabetes. The comprehensive assessment would enable the present study to provide an overall picture of the independent impacts of diabetes-related complications on the HRQoL of a type 2 diabetes population. Our results not only quantify the humanistic burden attributable to various comorbidities and diabetes-related complications, but also facilitate the parameterization in further diabetes health economic evaluations for determining cost-effective interventions. With consideration and adjustment for a wide range of patient sociodemographic and clinical characteristics, most of the major diabetes-related complications still had a substantial impact on patients' HRQoL, such as amputation, stroke with residual deficits, heart failure and kidney dialysis/transplant, which can cause numerous burdens in patients' and caregivers' daily life. Additionally, we found that the impacts of comorbid depression and connective tissue disease on patients' HRQoL were compelling, although these comorbid conditions were not commonly evaluated in previous studies[9,10,17,19,20,37,38].

Some consistent patterns have been found in the results between the present study and previous studies. First, using EQ-5D as the instrument to estimate health utility scores, the results from our and previous studies showed that the average health utility scores in Asian populations (0.84 in the present study; 0.85–0.90 in previous studies)[11,17,19,37] are higher than those from studies on mainly white populations (0.77–0.82)[10,11,37,38]. Second, consistent with a cross-sectional interview-administered survey carried out in the clinics of a hospital in northern Taiwan[16], we found that study participants with blindness, amputation, end-stage renal disease with dialysis or stroke complications had lower marginal health utility scores compared with those of patients with other complications. Third, similar to previous modeling studies carried out in the USA and the UK[9–11], the complications with the greatest independent impact on diabetes patients' HRQoL were amputation, stroke with sequelae and heart failure. However, as addressed earlier, the applicability of these previous studies to a Taiwanese population with type 2 diabetes would be questionable, because they were mainly from white populations or limited to local hospitals/settings, or they reported only the marginal health utility estimates in a broad category level of diabetes-related complications.

The magnitude of the humanistic burden of diabetes-related complications found in the present study was larger than that shown in previous studies. Clarke *et al.*[10] estimated the EQ-5D health utility scores in type 2 diabetes patients who participated in the United Kingdom Prospective Diabetes Study, and reported that the health penalty scores for complications ranged from 0.055 (myocardial infarction) to 0.280 (amputation). Zhang *et al.*[11] derived the EQ-5D health utility scores of patient demographic and clinical characteristics using the data collected in a large-scale observational study of type 2 diabetes patients from seven regions of the USA. The estimated health penalty scores for individual complications ranged from 0.012 (peripheral vascular disease) to 0.108 (amputation). Luk *et al.*[19] utilized the EQ-5D data collected in the Joint Asia Diabetes Evaluation program to evaluate the clinical features correlated with the health utilities in type 2 diabetes patients, and reported the health penalty scores for various clinical characteristics in a range of 0.007 (obesity) to 0.063 (sensory neuropathy). In the present analysis, the diabetes-related complications with the least and greatest impacts on patients' HRQoL were neuropathy and amputation, with a health penalty score of 0.043 and 0.288, respectively.

The variations of health utility penalties associated with diabetes-related complications in the present study compared with those in previous studies[10,11,19] could be explained by several reasons: (i) the preference weights for each health state that might be influenced by different cultural norms; (ii) the modeling approaches with differences in including covariates in the analyses; and (iii) the differences in cultures and attitudes toward life in the Taiwanese population[39]. For some patients, the greatest fear related to developing diabetes-related complications is the burden caused by these complications on daily life and activities, instead of the physical discomfort that the complications might cause. In a previous study of a Taiwanese population with type 2 diabetes[16], participants with blindness, amputation, end-stage renal disease or stroke complications had an average standard gamble-derived preference score of lower than zero, implying that a considerable proportion of study participants might view these complications as a worse health state than death. Therefore, a much greater extent of health utility penalty scores associated with diabetes-related complications in a Taiwanese population could be expected. The variations in the humanistic burden attributable to diabetes-related complications caused by cultural differences have highlighted the significance of the present study to existing evidence.

In addition to diabetes-related complications, we also identified comorbid depression and connective tissue disease in the analyses, which have been reported to affect the HRQoL of diabetes patients[11,18,40,41] but were rarely considered in previous studies[9,10,17,19,20,37,38]. In the present study, these two comorbidities significantly reduced the HRQoL of patients, independent of other patient sociodemographic characteristics and diabetes-related complications. The impacts of these comorbidities on patients' HRQoL were even more substantial than those of

certain diabetes-related vascular complications (Table 2). These results suggest the importance of effective intervention strategies that aim to improve the HRQoL of diabetes patients in averting not only diabetes-related complications, but also these comorbidities.

Compared with the Tobit model and median regression analyses, the applicability of results from the OLS regression analysis in the present study would be preferred for several reasons. First, the OLS regression analysis has been used in the majority of the applications that analyzed HRQoL and quality-adjusted life years[32]. Second, the OLS regression analysis produced a better model goodness-of-fit for the data and the robust estimates of coefficients. Studies using the simulation-based approach[31] and empirical data analyses[36] have found the OLS regression approach to be superior to the Tobit model and median regression methods, which might yield biased estimates. Third, choosing between these regression modeling approaches should not be based on statistical considerations alone. Important issues considering how various responses are from different patients and what plausible impacts can be expected from empirical data should be aggregated to estimate the overall effect associated with a clinical condition. The theoretically correct method has been argued to calculate the mean health utility regardless of the degree of skewness, given a principle that the strength of all individuals' preferences should count[10].

Some limitations of the present study should be acknowledged. First, severe complications, such as blindness, were not selected into the final multivariable regression model due to a lack of statistical or clinical significance. This would be probably owing to the limited number of these events in our cohort. Second, the health utility data were self-reported by patients, and thus there might have been a recall or social desirability bias. Third, health utility penalties could be greatest in a few days or months immediately after the event, but might decrease or further increase with increasing time since the event[6,13]. However, due to the nature of a cross-sectional design for the health utility survey, the present study could not differentiate the initial impact of the complication event from its successive impact on the health utility.

To conclude, the present study quantifies the magnitude of the independent impacts of various patient sociodemographic characteristics, comorbid conditions, diabetes-related complications and glucose-lowering treatments on the health utilities of a population with type 2 diabetes in Taiwan. These results can facilitate the implementation and parameterization of diabetes health economic evaluations to determine cost-effective prevention and control strategies for advancing diabetes care.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | International Classification of Diseases, Ninth Revision, Clinical Modification disease or procedure codes of diabetes-related complications and comorbidities.

Table S2 | Marginal EuroQol-5 dimensions-3 levels health utility scores stratified by diabetes-related complication.