Patient Health Utility Equations for a Type 2 Diabetes Model

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OBJECTIVE

To estimate the health utility impact of diabetes-related complications in a large, longitudinal U.S. sample of people with type 2 diabetes.

RESEARCH DESIGN AND METHODS

We combined Health Utilities Index Mark 3 data on patients with type 2 diabetes from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Look AHEAD (Action for Health in Diabetes) trials and their follow-on studies. Complications were classified as events if they occurred in the year preceding the utility measurement; otherwise, they were classified as a history of the complication. We estimated utility decrements associated with complications using a fixed-effects regression model.

RESULTS

Our sample included 15,252 persons with an average follow-up of 8.2 years and a total of 128,873 person-visit observations. The largest, statistically significant ($P < 0.05$) health utility decrements were for stroke (event, −0.109; history, −0.051), amputation (event, −0.092; history, −0.150), congestive heart failure (event, −0.051; history, −0.041), dialysis (event, −0.039), estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (event, −0.043; history, −0.025), angina (history, −0.028), and myocardial infarction (MI) (event, −0.028). There were smaller effects for laser photocoagulation and eGFR <60 mL/min/1.73 m^2. Decrements for dialysis history, angina event, MI history, revascularization event, revascularization history, laser photocoagulation event, and hypoglycemia were not significant ($P \geq 0.05$).

CONCLUSIONS

With use of a large study sample and a longitudinal design, our estimated health utility scores are expected to be largely unbiased. Estimates can be used to describe the health utility impact of diabetes complications, improve cost-effectiveness models, and inform diabetes policies.

Cost-effectiveness analysis (CEA) and simulation modeling play critical roles in resource-allocation decisions across interventions to prevent or treat type 2 diabetes. For instance, CEA can help policy makers balance the potential health benefits of screening for prediabetes (1) or gestational diabetes mellitus (2) against the additional costs compared with no screening. Modeling analyses are also used to evaluate prevention interventions, such as the Diabetes Prevention Program (3); improved adherence to guidelines for treating hypertension in people with diabetes (4); and new treatments available to patients such as bariatric surgery (5).

The quality-adjusted life-year (QALY), a measure that combines the length and quality of life, continues to be an essential component of CEA (6,7). Underlying the

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QALY are health utility values, which reflect a person's health-related quality of life. Health complications and ongoing disability from these complications are reflected in lower health utility values, and thus lower QALYs, when summarized over time. Because diabetes increases the risk of multiple macrovascular and microvascular complications, accurately modeling the effect of these complications on health utility is critical to evaluations of diabetes screening and treatment programs.

To improve the accuracy and validity of health utility estimates used in decision modeling, we sought out a longitudinal data set that was substantially larger than previously analyzed data sets. Using longitudinal data to estimate the health utility effects of complications is preferred to using cross-sectional data because it allows us to distinguish the health utility effects from complication event years and postevent years for the same person. The longitudinal analysis allows us to control for individual-specific characteristics that affect utility in every period. Additionally, we wanted the data set to be U.S. based so that the results would be most applicable to U.S. health policy. We combined data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the ACCORD Follow-on (ACCORDION) study, and the Look AHEAD (Action for Health in Diabetes) trial, with data through January 2016, to create a health utility data set with 128,873 person-visit observations—more than three times as many as the next largest study (8).

The objective of our study is to leverage this large U.S. sample to generate improved health utility estimates for diabetes-related complications. By using longitudinal data, we can track diabetes-related events and ongoing complications as they occur over time. We can therefore associate changes in health utility values with diabetes-related complications such as a stroke and the ongoing disability caused by the stroke in future years. Using longitudinal data also allows us to consider fixed effects (FE) and random effects (RE) models to isolate the utility effect of a complication from unobserved, patient-level differences in health utility that do not vary over time (9). In the following sections, we describe our analysis approach, present our study results, discuss the implications of the results for modelers and policy makers, and compare findings with a wide range of results from the literature.

RESEARCH DESIGN AND METHODS

Data Source

We combined non-public-use data collected in ACCORD, ACCORDION, and Look AHEAD. ACCORD recruited participants with type 2 diabetes who were at high risk of cardiovascular events (10), whereas the Look AHEAD participants were individuals with type 2 diabetes who were overweight or had obesity (11,12). Both trials were multicenter, randomized controlled trials in a cohort of individuals diagnosed with diabetes. All participants still living at the end of each study were invited to join the follow-up observational studies (ACCORDION and Look AHEAD). Because of the recruitment strategies of ACCORD and Look AHEAD, minority and underserved populations were adequately represented in each trial sample. At randomization, participants were age 45–76 years in Look AHEAD and age 40–79 years in ACCORD.

Each trial tracked complications, including stroke, amputation, dialysis, myocardial infarction (MI), congestive heart failure (CHF), hospitalizations for angina, chronic kidney disease defined as estimated glomerular filtration rate (eGFR) $<$60 mL/min/1.73 m^2 or eGFR $<$30 mL/min/1.73 m^2, revascularization (e.g., angioplasty), laser photocoagulation, and hypoglycemia events requiring any assistance. ACCORD and its follow-up study, ACCORDION, also included data on foot ulcers, blindness, neuropathy, and hypoglycemia events requiring medical assistance; however, these data were not collected in Look AHEAD with the same frequency or instruments and thus could not be included in the combined study sample. In ACCORD, angina, CHF, and revascularization events were not adjudicated by a centralized committee or process as they were in Look AHEAD, but both studies collected this information using similar forms and criteria. Other complication definitions were also consistent between the trials with only minor differences.

Health Utility Measurement

The Health Utilities Index Mark 3 (HUI-3) instrument was used to measure health utility in each of the trial data sets. The HUI-3 consists of a survey to classify a person's health status and a scoring algorithm used to translate survey responses into a health utility value on a scale of 0.00 (death) to 1.00 (perfect health). Health status in the HUI-3 considers eight attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain), each with five or six levels of health. For instance, for the pain attribute, respondents can be "free of pain and discomfort" (level 1) or they can have "severe pain that prevents most activities" (level 5). The 15-question, multiattribute survey classifies individuals into 1 of 972,000 different health states (13). With a validated scoring algorithm, the responses are translated into a single health utility value (14). The scoring algorithm reflects community preferences for each health state based on a visual analog scale or standard gamble elicitation technique and has been validated in a wide range of medical conditions and countries (15).

Diabetes complications are not directly included in the HUI-3 survey. However, to the extent that a complication affects attributes that are measured in the survey, the complication will be associated with a change in the person's utility value. We examine this relationship in our study.

ACCORD administered the HUI-3 instrument at baseline, 12 months, 36 months, 48 months, and study exit. During the follow-on ACCORDION study, the HUI-3 was measured up to three times during posttrial follow-up exams from year 5 to year 13. The Look AHEAD trial administered the HUI-3 at baseline, 3 months, 6 months, 9 months, and 12 months; every 6 months thereafter during the main Look AHEAD trial through 10 years; and once during years 10–13 in Look AHEAD. Although the Look AHEAD trial had fewer participants, it contributed more observations to our analysis because the HUI-3 was measured more frequently. Measurements of the HUI-3 $\leq$1 year after the onset of a complication were classified as measuring an incident complication in the "event" year, which represents the 1st-year health utility effects of the complication. In a few cases, utility was measured more than once during the 1-year period following an event. Thus, some events are used twice in the utility estimation. Meanwhile, measurements $>$1 year after the onset of a complication were classified as a history of the complication, representing the ongoing

disability associated with the complication. By defining complications this way, we are differentiating between the acute, initial impact of a complication in the year that it occurs and the long-term effects in subsequent years. For example, the negative health utility effect of a stroke is generally larger in the year immediately following the stroke compared with later years after the patient has had time to rehabilitate. After at least 1 year has passed since the stroke, health utility data from the combined data set are used to estimate the effect of having a history of stroke instead of the more acute stroke "event" year. These definitions are also convenient for use in simulation models that track each patient's event history and quality of life over time. Recurrent complications during the trial period were not tracked in the combined data set. However, study participants with a history of a complication at baseline could experience that complication as an "event" during the trial and follow-up period.

Statistical Approach

By combining the ACCORD/ACCORDION and Look AHEAD data, we created a data set with repeated observations for each study participant over time, allowing us to account for individual heterogeneity in our modeling approach. We considered ordinary least squares (OLS), FE, and RE models and two diagnostic tests to determine the most appropriate model. First, the Breusch-Pagan Lagrange multiplier test was run with RE model results to determine whether the variance between individuals is zero. If the variance is zero, then OLS may be preferred. Otherwise, an RE model is preferred. Next, the Hausman test is run after estimates from an RE model and an FE model are saved for determination of whether the errors for each individual and the explanatory variables are related. If they are, then the null hypothesis is rejected and an FE model is more appropriate than an RE model. Essentially, these diagnostic tests help us determine the need to account for unobserved, systematic differences in patients who experience diabetes-related complications. These differences can be a source of bias that results in the overestimation of the utility effects, unless they are accounted for using an FE model.

We included key confounding variables that could impact health utility, such as BMI, duration of diabetes, and current smoking status. Each of these control variables is time varying and was included in the FE model. Because everyone included in these data already had type 2 diabetes at baseline, the variable for duration of diabetes incorporates the effects of increasing age and diabetes duration, each of which is expected to negatively affect health utility, as seen in previous analyses (8,9,16,17). When testing OLS and RE models, we also included time-invariant confounding factors that were observed, such as age at diagnosis of diabetes, sex, race/ethnicity, and education level (some college or higher); in the FE model, these variables are incorporated within each individual's fixed effect. In the OLS model, we allowed for the clustering of error terms by study participant.

Individuals with multiple complications will have their health utility reduced by the sum of all complications that occur in the current period as well as decrements for the history of all complications occurring in previous periods. Decrements for dialysis should generally be summed with history of eGFR $<$30 mL/min/1.73 m^2 and history of eGFR $<$60 mL/min/1.73 m^2 because nearly everyone on dialysis will have these disease histories as well. Similarly, someone with eGFR $<$30 mL/min/1.73 m^2 will also have a history of eGFR $<$60 mL/min/1.73 m^2; thus, these decrements should also be summed for applying these results in a simulation model or CEA.

RESULTS

For both diagnostic tests (Breusch-Pagan Lagrange multiplier test and the Hausman test), the null hypothesis was rejected, indicating that an FE model is preferred over the OLS or RE model. Our combined FE estimation sample included 128,873 person-visit observations (ACCORD/ACCORDION, 53,746; Look AHEAD, 75,127), representing 15,252 unique persons (ACCORD/ACCORDION, 10,149; Look AHEAD, 5,103) with an average follow-up of 8.2 years. The maximum follow-up time was 13.7 years.

At baseline, the average age in the combined sample was 51.6 years, and 45.6% of the sample was female (Table 1). The average HUI-3 score at baseline was 0.74 (interquartile range 0.62–0.92). Most study participants identified as non-Hispanic White (62.7%). The remaining race/ethnicity groups were black (18.0%), Hispanic (9.2%), and a combination of other race/ethnicities (Asian, American Indian, other race [10.2%]). At baseline, 31.2% of the study sample had at least some college education, and 10.7% were current smokers. The average BMI was 33.5 kg/m^2, and the average duration of diabetes was 9.5 years. Individuals with a history of dialysis or eGFR $<$30 mL/min/1.73 m^2 were rarely observed at baseline due to trial exclusion criteria related to serious illnesses like kidney failure. Baseline history of other important diabetes-related outcomes is also shown for CHF, stroke, history of laser photocoagulation, hospitalizations for angina, eGFR $<$60 mL/min/1.73 m^2, MI, and revascularization (Table 1). Study participants with a history of serious complications at baseline were largely from ACCORD.

The combined study sample allowed us to observe a relatively large number of complications. Table 2 shows the number of person-visit observations with an event, such as stroke, or with a history of that event. Amputations (59 observations), dialysis (261 observations), CHF (349 observations), and stroke (358 observations) were the rarest events.

With use of an FE model, all complication events and complication history indicators negatively affected health utility (Table 2). The largest health utility decrements were observed for stroke (event, −0.109; history, −0.051), amputation (event, −0.092; history, −0.150), CHF (event, −0.051; history, −0.041), dialysis (event, −0.039), eGFR $<$30 mL/min/1.73 m^2 (event, −0.043; history, −0.025), angina (history, −0.028), and MI (event, −0.028) ($P < 0.05$). More modest effects were observed for laser photocoagulation (history, −0.014), and eGFR $<$60 mL/min/1.73 m^2 (event, −0.014; history, −0.015) ($P < 0.05$). Decrements for history of dialysis, history of MI, revascularization event, history of revascularization, laser photocoagulation event, and hypoglycemia (any assistance) event were not statistically significant. There were some differences in utility effects when the two trial samples were analyzed separately, but results were generally similar (Supplementary Table 2). Health utility decrements from the FE model were consistently smaller than decrements from the OLS model estimated during model specification tests. Results from the OLS model and RE model are shown in Supplementary Table 1.

Table 1—Characteristics for combined study sample at baseline

	Combined (N = 15,252)	ACCORD (N = 10,149)	Look AHEAD (N = 5,103)
HUI-3 score	0.74 (0.62–0.92)	0.71 (0.57–0.92)	0.79 (0.69–0.95)
Age at diagnosis	51.6 (46.0–58.0)	51.4 (46.0–58.0)	51.9 (46.0–58.0)
Female sex	45.6	38.6	59.5
Black race	18.0	19.0	15.8
Hispanic	9.2	7.2	13.2
White race	62.7	62.4	63.3
Other races	10.2	11.4	7.7
College education	31.2	26.1	41.7
Smoker	10.7	13.9	4.4
BMI (kg/m^2)	33.5 (29.3–37.2)	32.2 (28.2–35.9)	35.9 (31.5–39.4)
Duration of diabetes (years)	9.5 (4.0–13.0)	10.9 (5.0–15.0)	6.8 (2.0–10.0)
History of stroke	5.0	6.1	2.7
History of amputation	1.3	1.8	0.4
History of dialysis	<0.1	0.0	0.1
History of MI	12.5	15.5	6.4
History of CHF	3.4	4.8	0.7
History of angina†	7.6	11.4	0.0
History of eGFR <30 mL/min/1.73 m^2	<0.1	<0.1	<0.1
History of eGFR <60 mL/min/1.73 m^2	8.5	10.3	4.9
History of revascularization	18.1	22.4	9.7
History of laser photocoagulation	6.8	8.7	2.9

Data are percentages or mean (interquartile range). †The Look AHEAD trial did not report history of hospitalizations for angina at baseline. ACCORD did report these hospitalizations.

CONCLUSIONS

This combined analysis of the ACCORD, ACCORDION, and Look AHEAD studies uses the largest and most recent source of U.S. data on individuals with type 2 diabetes to estimate the impacts of diabetes-related complications on health-related quality of life. Previously, U.S. policy makers had to rely on cost-effectiveness analyses that used health utility estimates from non-U.S. samples, smaller sample sizes, or samples without longitudinal measurements—each of which can potentially bias estimates. An analysis by Alva et al. (9) of health utility data from the UK Prospective Diabetes Study (UKPDS) highlighted the importance of using longitudinal data to control for patient heterogeneity. Alva et al. demonstrated the potential for estimator bias by estimating the effect of six complications of diabetes with and without an FE model. The health utility effect of major complications, such as MI, was reduced substantially in an FE model compared with an OLS model. The smaller health utility effects in the FE model were attributed to its ability to account for unobserved, systematic differences in patients who experience diabetes-related complications. This FE approach is only possible in a longitudinal data set with repeated measurements for each individual.

Since this comparison analysis by Alva et al., other prominent analyses of diabetes-related complications and health utility data have used an FE approach under similar rationale. Analyzing utility data from the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, researchers used an FE model to account for patient-specific differences across 20 countries (8). More recently, Shao et al. (16) estimated an FE model and an OLS model from the ACCORD trial sample. They noted that results from the FE model are preferred for estimating the impact of a diabetes-related complication, independent of individual characteristics. Shao et al. (16) were the first to publish an analysis of longitudinal U.S. health utility data among people with diabetes. Our analysis uses a larger data set by adding data from ACCORDION and Look AHEAD. By combining data, we also achieve a sample that is representative of a broader population with low (Look AHEAD) and high (ACCORD, ACCORDION) cardiovascular disease risk levels.

All complications negatively impacted health utility. For procedures such as dialysis, revascularization, amputations, and laser photocoagulation, we do not believe that the procedure itself lowers utility. The estimates for these procedures reflect at least two effects: the worsening health condition and utility that lead to the procedure and the improvement in health and utility associated with the procedure. We cannot disentangle the two effects because we do not observe patient utility immediately before and shortly after the procedure and because we do not observe what would have happened in the absence of the procedure. For most complications, including stroke, MI, CHF, eGFR <30 mL/min/1.73 m^2, and dialysis, the impact of the complication on health utility was larger in the event year than in the subsequent years. Someone who has an average health utility value of 0.74 before experiencing a stroke will decrease to 0.63 in the year of their stroke (utility decrement of −0.109). The stroke event decrement only applies in the year of the event. As the patient rehabilitates from the stroke, the patient's health utility increases, on average. In subsequent years their health utility will return

Table 2—Health utility decrements for complications of diabetes: FE model results

Covariate	Number of complication events or history of a complication	Coefficient	SE	*P* value
Current smoker	7,887	−0.006	0.005	0.275
BMI (1-unit increase)	n/a*	−0.003	0.000	0.000
Duration of diabetes in years (time varying)	n/a*	−0.008	0.000	0.000
Stroke event	358	−0.109	0.015	0.000
History of stroke	5,848	−0.051	0.014	0.000
Amputation event	59	−0.092	0.027	0.001
History of amputation	1,248	−0.150	0.034	0.000
Dialysis event†	261	−0.039	0.015	0.009
History of dialysis†	917	−0.015	0.013	0.243
MI event	876	−0.028	0.009	0.002
History of MI	14,626	−0.006	0.008	0.509
CHF event¶	349	−0.051	0.014	0.000
History of CHF	3,579	−0.041	0.014	0.003
Angina event¶	839	−0.015	0.009	0.101
History of angina	8,558	−0.028	0.008	0.000
eGFR <30 mL/min/1.73 m^2 event§	691	−0.043	0.010	0.000
History of eGFR <30 mL/min/1.73 m^2§	1,282	−0.025	0.010	0.009
eGFR <60 mL/min/1.73 m^2 event§	6,039	−0.014	0.003	0.000
History of eGFR <60 mL/min/1.73 m^2§	23,310	−0.015	0.003	0.000
Revascularization event	1,722	0.005	0.006	0.452
History of revascularization	22,244	−0.001	0.007	0.923
Laser photocoagulation event	1,630	−0.011	0.007	0.079
History of laser photocoagulation	10,274	−0.014	0.006	0.025
Hypoglycemia (any assistance)	1,247	−0.001	0.006	0.861
Constant‡		0.935	0.012	0.000

Total person-visit observations, $N = 128,873$; Total individuals, $N = 15,252$. *Not applicable. All observations (128,873) from the estimation sample had a BMI and diabetes duration variable present. Coefficients are shown for a 1-unit change in these variables. †Typically, someone with dialysis or a history of dialysis also has a history of eGFR <30 mL/min/1.73 m^2 and a history of eGFR <60 mL/min/1.73 m^2. Thus, these coefficients should be added together for someone with a dialysis event or a history of dialysis. For example, someone who started dialysis in the past year has a decline in utility of ~0.079 relative to someone with eGFR ≥60 mL/min/1.73 m^2. Someone who started dialysis >1 year ago has a decline in utility of ~0.055 relative to someone with eGFR ≥60 mL/min/1.73 m^2. ¶Angina and CHF events represent hospitalization events for these two complications. §By definition, someone with eGFR <30 mL/min/1.73 m^2 also has history of eGFR <60 mL/min/1.73 m^2, so these two coefficients should be combined for someone with eGFR <30 mL/min/1.73 m^2. Similarly, someone with a history of eGFR <30 mL/min/1.73 m^2 also has history of eGFR <60 mL/min/1.73 m^2. Again, the coefficients should be combined. ‡The constant term here incorporates the average FE. This can be used in modeling as a base utility value for a hypothetical person with no complications, no duration of diabetes, and a BMI of 0. With mean characteristics for BMI (33.5 kg/m^2) and duration of diabetes (9.5 years), a person's expected health utility is ~0.76.

to 0.69 (history of stroke decrement of −0.051), lower than their original health utility due to the long-term effects of a stroke but higher than their health utility in the year of the stroke event. Similarly, for dialysis, patients experience a lower health utility in the year they begin dialysis; however, in subsequent years there is no effect on health utility, as treatment with dialysis maintains or may even improve their health utility compared with someone progressing from stage 4 renal disease to end-stage renal disease in their initial year of dialysis. In comparison, for angina and amputations, the health utility decrement for the subsequent years was larger. For angina, this result is likely due to the chronic and progressive nature of the complication. Also, in these data, angina events are defined by hospitalizations for the complication. Thus, the smaller decrement for angina events may reflect an earlier, less severe stage of these chronic conditions. For amputations, issues of mobility may worsen over time. However, the amputation and history of amputation coefficients have the largest SEs, indicating that the differences between these two coefficients may not be statistically significant.

We compared our utility estimates based on the FE model with results from several previous studies, including published data from ADVANCE (8), the Translating Research Into Action for Diabetes (TRIAD) study (18), the UKPDS (9,17), the Cost of Diabetes in Europe – Type 2 (CODE-2) study (19), a meta-analysis study (20), and a recent analysis of ACCORD data (16) (Table 3). Each of the studies included in Table 3 presents a slightly different approach or data source. The most common model type was the FE model, and most studies relied on longitudinal trial data. However, a couple of studies (18,19) used cross-sectional data from a survey of individuals with diabetes and thus may be limited by the effects of unobserved, systematic differences that are correlated with diabetes complications.

Some complication decrements show substantial variation across studies. Although Hayes et al. (8) estimated an FE model like ours, the authors did not include history of variables, which ignores the important ongoing effects of many complications in the years after the event. The ADVANCE analysis also had a non-U.S.

Table 3—Comparison of estimated utility decrements to other published result

	ACCORD and Look AHEAD, HUI-3: FE model	ACCORD, HUI-3 (Shao et al. [16])		ADVANCE, EQ-5D (Hayes et al. [8]): FE model	TRIAD, EQ-5D (Zhang et al. [18]): OLS model	UKPDS, EQ-5D (Clarke et al. [17]): Tobit model	UKPDS, EQ-5D (Alva et al. [9]): FE model	CODE-2, EQ-5D (Bagust and Beale [19]): OLS model	Various sources, instruments (Beaudet et al. [20]): model varies
		OLS model	FE model						
Complication decrements									
Smoker	−0.006	−0.054	n/a	n/a	−0.018	n/a	n/a	n/a	n/a
BMI (each unit)	−0.003	−0.007[a]	n/a	n/a	n/a	n/a	n/a	−0.006[c]	−0.006[c]
Duration of diabetes (time varying)	−0.008	−0.005	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Stroke event	−0.109	−0.204	−0.202	−0.099	−0.094	−0.181	−0.165	−0.115	−0.164
History of stroke	−0.051	−0.101	n/a	n/a	n/a	−0.269	n/a	n/a	n/a
Amputation event	−0.092	n/a	n/a	−0.122	n/a	−0.538	−0.172	−0.272	n/a
History of amputation	−0.150	n/a	n/a	n/a	−0.108	−0.412	n/a	n/a	−0.280
Dialysis event	−0.039	−0.024	−0.029	−0.049	−0.060	n/a	n/a	−0.175	−0.164
History of dialysis	−0.015	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
MI event	−0.028	−0.042	−0.018	−0.026	−0.019[b]	−0.129	−0.065	−0.028[d]	−0.055
History of MI	−0.006	−0.011	n/a	n/a	n/a	−0.078	0.008	n/a	n/a
CHF event	−0.051	−0.089	−0.067	−0.045	−0.042	−0.121	−0.101	n/a	−0.108
History of CHF	−0.041	−0.041	n/a	n/a	n/a	−0.181	n/a	n/a	n/a
Angina event	−0.015	−0.010	0.043	n/a	n/a	n/a	n/a	−0.028[d]	n/a
History of angina	−0.028	−0.032	n/a	n/a	n/a	n/a	n/a	n/a	n/a
eGFR <30 mL/min/1.73 m^2 event	−0.043	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
History of eGFR <30 mL/min/1.73 m^2	−0.025	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
eGFR <60 mL/min/1.73 m^2 event	−0.014	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
History of eGFR <60 mL/min/1.73 m^2	−0.015	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Revascularization event	−0.005	−0.038	−0.013	n/a	n/a	n/a	n/a	n/a	n/a
History of revascularization	−0.001	−0.016	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Laser photocoagulation event	−0.011	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
History of laser photocoagulation	−0.014	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Hypoglycemia (any assistance)	−0.001	n/a	0.016	n/a	n/a	n/a	n/a	n/a	−0.047
Sample size									
Total person-visit observations	128,873	21,045	21,045	39,857	Not shown	n/a	11,614	4,183	Varies
Total unique persons	15,252	8,713	8,713	11,130	7,327	3,192	3,380	4,183	Varies
Example patient 1: BMI 33.5 kg/m^2, diabetes duration 9.5 years, nonsmoker, with a stroke event and an angina event									
Complication decrement	−0.124	−0.214	−0.159	−0.099	−0.094	−0.181	−0.165	−0.143	−0.164
BMI and duration decrement	−0.177	−0.058	0.000	0.000	0.000	0.000	0.000	−0.051	−0.051

Continued on p. 7

Table 3—Continued

	ACCORD and Look AHEAD, HUI-3: FE model	ACCORD, HUI-3 (Shao et al. [16])		ADVANCE, EQ-5D (Hayes et al. [8]): FE model	TRIAD, EQ-5D (Zhang et al. [18]): OLS model	UKPDS, EQ-5D (Clarke et al. [17]): Tobit model	UKPDS, EQ-5D (Alva et al. [9]): FE model	CODE-2, EQ-5D (Bagust and Beale [19]): OLS model	Various sources, instruments (Beaudet et al. [20]): model varies
		OLS model	FE model						
Example patient 2: BMI 27 kg/m^2, diabetes duration 5 years, nonsmoker, with an MI event, history of eGFR <60 mL/min/1.73 m^2, and history of laser photocoagulation									
Complication decrement	−0.054	−0.042	−0.018	−0.026	−0.019	−0.129	−0.065	−0.028	−0.055
BMI and duration decrement	−0.121	0.010	0.000	0.000	0.000	0.000	0.000	−0.012	−0.012

n/a, not available. [a]The coefficient only applies to each additional BMI unit >32 kg/m^2. [b]"Other heart diseases" was used for MI in the study by Zhang et al. (18). These excluded CHF. [c]The coefficient only applies to each additional BMI unit >25 kg/m^2. [d]The health utility effect of coronary heart disease from the study by Bagust and Beale (19) was listed in the comparison table for MI events and angina events.

sample, used a different utility instrument (EuroQol-5D [EQ-5D]), and included a different set of complications. Despite these differences, quality of life decrements for key complications (stroke, MI, and CHF events) from our study were very similar to findings of Hayes et al. These similarities indicate that using results from our study in non-U.S. models would not result in drastic differences in cost-effectiveness results. Nevertheless, caution is warranted in applying our study estimates to non-U.S. policy questions.

In comparison of our results with the preferred health utility decrements from a systematic review by Beaudet et al. (20), only a handful of complications could be directly compared (MI, CHF, and stroke). Making these comparisons showed that our FE results were generally lower than the meta-analysis results (except for hypoglycemia events). However, our health utility decrements were always higher than those in at least one of the individual studies included in the review for each complication. Most of the studies included in the meta-analysis did not use U.S. data, used the EQ-5D instrument instead of the HUI-3, and used a wide range of statistical models to estimate utility decrements. Many of the studies included in the meta-analysis used OLS or presented unadjusted results, likely because of the cross-sectional nature of many of the data sources. Our more conservative results are attributable to our use of a large, longitudinal data set and a modeling approach that *1*) specified event and history of variables for each complication and *2*) accounted for individual heterogeneity using an FE model.

At the bottom of Table 3, we include utility decrements for a couple of example patients. We separated the utility decrement associated with diabetes complications from the effect of BMI and diabetes duration because the latter variables are used differently in each model and can be difficult to compare. The effect of BMI in our model is the largest because our model uses each unit of the BMI value to calculate the effect of BMI, while others center BMI on a threshold value (see Table 3 legend). Models that exclude BMI or center it on a threshold value typically have lower intercept values or larger fixed effects.

Our study has some limitations. First, even with the rich data in the combined study sample, some important diabetes-related events and history of variables may be omitted from our model. For example, we did not observe neuropathy or foot ulcers in Look AHEAD trial data (only in ACCORD data) and therefore did not include these in the combined study sample. The potential impact of these omitted variables is shown in Supplementary Table 4 where we compare an FE model using the ACCORD-only sample with an FE model using the full, combined data set. Smaller health utility decrements for amputation are likely due to the inclusion of additional complications that were available in the ACCORD data that were also correlated with amputation like foot ulcer events and history of foot ulcer—both of which had statistically significant health utility decrements. Additional variables available in the ACCORD-only results included neuropathy, foot ulcer, severe vision loss, and hypoglycemia requiring medical assistance.

Second, our decision to define an "event" year effect and a "history of" effect for each complication may not identify distinct stages of each complication as accurately as other intervals. For example, stroke utility decrements may be better modeled in three stages: 0–3 months, 4–12 months, and >12 months. We did not pursue shorter intervals due to the small sample size of utility values measured within shorter intervals. Also, for models designed around an annual cycle, utility effects from shorter intervals (e.g., 0–3 months) would overestimate the impact of an incident complication.

Third, because the results of this study are based on the HUI-3 instrument, they may not be comparable with results of previous models, which often used utility effects from other instruments such as the Short-Form Six-Dimension (SF-6D) or the EQ-5D. We used the HUI-3 data for this study because the SF-6D was only administered to approximately one-fifth of the ACCORD sample and was not administered during ACCORDION. Also, the HUI-3 had been used in a previous analysis of ACCORD data (16) and would therefore allow for better comparison and cross validation. The HUI-3 instrument may be more sensitive to changes in health utility than other instruments such as the SF-6D. In comparing the SF-6D, HUI-2, and HUI-3 and the "feeling thermometer" for a subset of the ACCORD sample, Raisch et al. (21) found that the HUI-3 produces a wider range of scores than the SF-6D does, suggesting that the SF-6D might produce smaller decrements for complications than the HUI-3. Although Raisch et al. did not examine all the complications included in our analysis, the complications that they did examine, using data collected at baseline only, had smaller coefficients with use of the SF-6D instrument.

Conclusion

The health utility decrements estimated in this study provide a new, U.S.-based source for modeling the quality of life impact of diabetes-related complications. The combined study sample is larger than any previous analysis of health utility in diabetes, and the applied FE analysis approach best fits the purpose of obtaining unbiased estimates required for modeling incremental health effects. Cost-effectiveness researchers can use these health utility estimates to improve U.S.-based models and better inform policy-making around issues related to the benefits, costs, and cost-effectiveness of type 2 diabetes screening, prevention, and treatment programs.

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