Health Care Costs Associated With Macrovascular, Microvascular, and Metabolic Complications of Type 2 Diabetes Across Time: Estimates From a Population-Based Cohort of More Than 0.8 Million Individuals With Up to 15 Years of Follow-up

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OBJECTIVE

Developing country-specific unit-cost catalogs is a key area for advancing economic research to improve medical and policy decisions. However, little is known about how health care costs vary by type 2 diabetes (T2D) complications across time in Asian countries. We sought to quantify the economic burden of various T2D complications in Taiwan.

RESEARCH DESIGN AND METHODS

A nationwide, population-based, longitudinal study was conducted to analyze 802,429 adults with newly diagnosed T2D identified during 1999–2010 and followed up until death or 31 December 2013. Annual health care costs associated with T2D complications were estimated, with multivariable generalized estimating equation models adjusted for individual characteristics.

RESULTS

The mean annual health care cost was $281 and $298 (2017 U.S. dollars) for a male and female, respectively, diagnosed with T2D at age <50 years, with diabetes duration of <5 years, and without comorbidities, antidiabetic treatments, and complications. Depression was the costliest comorbidity, increasing costs by 64–82%. Antidiabetic treatments increased costs by 72–126%. For nonfatal complications, costs increased from 36% (retinopathy) to 202% (stroke) in the event year and from 13% (retinopathy or neuropathy) to 49% (heart failure) in subsequent years. Costs for the five leading costly nonfatal subtype complications increased by 201–599% (end-stage renal disease with dialysis), 37–376% (hemorrhagic/ischemic stroke), and 13–279% (upper-/lower-extremity amputation). For fatal complications, costs increased by 1,784–2,001% and 1,285–1,584% for cardiovascular and other-cause deaths, respectively.

CONCLUSIONS

The cost estimates from this study are crucial for parameterizing diabetes economic simulation models to quantify the economic impact of clinical outcomes and determine cost-effective interventions.

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Diabetes is a global issue that not only causes a serious health burden but also imposes a significant economic impact for individuals, health care systems, and countries (1). In 2017, ~2 million people in Taiwan, or 10.9% of adults aged 20–79 years, had diabetes, which is higher than the global average of 8.8% (1). Diabetes is among the top five causes of death in Taiwan (2). In 2017, diabetes was the third most expensive disease, with an annual health care expenditure of more than US$850 million, accounting for ~4% of the total national health care expenditure reimbursed by the Taiwan National Health Insurance (NHI) program (3). Type 2 diabetes (T2D), which accounts for >99% of the diabetes population in Taiwan, contributed to the majority of the health and economic burden attributable to diabetes (4).

Considering the substantial economic burden of T2D, the parameterization of cost components associated with diabetes progression and management is important for quantifying the cost impact of T2D and serving as the cost data input in economic simulation modeling studies (5–8). The results of cost-effectiveness studies vary with respect to the sources from which unit costs are derived, which compromises comparability. The development of country-specific unit-cost catalogs has been recognized by the Second Panel on Cost-Effectiveness in Health and Medicine (9–11) as a key area for future exploration in cost-effectiveness research because it is valuable to standardize cost inputs, reduce the cost data collection burden, and facilitate the comparison of studies within and across countries. A few studies have analyzed the medical costs of diabetes-related complications in Asian countries (12–19), with only one study in Taiwan (12). Nevertheless, none of these studies fulfill all the requirements for the complete cost parameterization in a diabetes economic simulation model. Specifically, they used restrictive and underrepresentative study cohorts (12–17), considered a limited number of complications or just a single complication (13,14,16–19), excluded fatal complications (15–17,19), had short-term follow-up or did not even account for the temporal distribution and change of costs (12,13,15–17,19), did not distinguish between type 1 diabetes (T1D) and T2D (13,15), or did not consider other potential cost drivers, such as comorbidities and antidiabetic treatments (12,13,15,16,18,19).

Against this background, the current study used Taiwan's NHI claims data from a nationwide, population-based cohort of >0.8 million adults with T2D for up to 15 years of follow-up to comprehensively and systematically estimate the health care costs associated with a wide range of diabetes-related macrovascular, microvascular, and metabolic complications in the event year and subsequent follow-up years, with adjustment for various patient characteristics. These estimates are useful not only for decision makers to quantify and differentiate the economic burden of T2D but also for simulation modelers to parameterize the cost data in diabetes economic simulation models (5–8).

RESEARCH DESIGN AND METHODS

This study was approved by the institutional review board of National Cheng Kung University Hospital (B-EX-103-015).

Data Source

This was a retrospective study that used the Longitudinal Cohort of Diabetes Patients (LHDB) data set for 1996–2013 from Taiwan's NHI Research Database (NHIRD). The NHIRD is a population-based database derived from health claims data of Taiwan's NHI program, which is a mandatory-enrollment, single-payment system that covers >99% of Taiwan's population (20). The LHDB is a nationally representative data set for the population with diabetes in Taiwan and has been validated for research purposes (21). This data set consists of longitudinal health data from a random sample of 120,000 deidentified patients with incident diabetes from each calendar year since 1999 who can be tracked back to 1 January 1996 and followed up to 31 December 2013.

Study Population

Study patients extracted from the LHDB were newly diagnosed with T2D (ICD-9, Clinical Modification [ICD-9-CM], codes 250.x0 and 250.x2, where x = 0–9) at age ≥18 years during 1999–2010. We excluded those with any macrovascular or microvascular diseases in the year before or at T2D diagnosis, undefined sex, or zero medical expenses throughout the entire study period. Selection of the study cohort is described in detail in Supplementary Fig. 1. A total of 802,429 patients were included in this study.

Identification of Study Variables

Diabetes-Related Complications, Comorbidities, and Death

Each patient was followed up from T2D diagnosis to death or the end of 2013, whichever came first. Diabetes-related complications of interest included macro- and microvascular complications and metabolic complications. We also identified the subtype of diseases within each major complication (e.g., stroke included ischemic or hemorrhagic stroke or transient ischemic attack). Comorbidities included hypertension, hyperlipidemia, liver disease, cancer, and depression. Complications and comorbidities were identified using ICD-9-CM codes. Macrovascular and metabolic complications were identified using the emergency department/inpatient files of the NHIRD, and microvascular complications and comorbidities were based on the outpatient and emergency department/inpatient files of the NHIRD. The coding details for complications and comorbidities are provided in Supplementary Tables 1 and 2. The accuracy of identifying disease conditions on the basis of ICD-9-CM coding in the NHIRD has been validated and published elsewhere (22). For example, the positive predictive value for the diagnosis of myocardial infarction, ischemic stroke, and heart failure is as high as 93%, 94%, and 98%, respectively. In addition, death events comprised a composite of fatal cardiovascular diseases (CVDs) (including death as a result of stroke, myocardial infarction, ischemic heart disease, or heart failure) and other-cause death. The operational definitions of confirming mortality status using the inpatient files of the NHIRD have been validated (23). We further used the disenrollment records from the NHIRD registration files of beneficiaries to confirm mortality (24).

Health Care Costs

This economic analysis was conducted from the perspective of the health care sector. The health care costs comprised two aspects of medical costs from the formal health care sector: costs paid by the third-party payer (reimbursement costs by Taiwan's NHI program) and out-of-pocket costs paid by individual beneficiaries (copayments by patients). Cost components in the NHIRD claims reimbursed by the NHI program included the fees of diagnosis,

treatments (i.e., examinations, procedures, special materials), pharmaceutical services, and medications. Costs were adjusted on the basis of the medical consumer price index and are expressed in 2017 U.S. dollars.

Exposure to Antidiabetic Drugs

Medication utilization was identified using drug identification numbers, linked to the World Health Organization Anatomical Therapeutic Chemical Classification System, to define active ingredients of antidiabetic drugs. Patients were classified into four groups on the basis of the status of their antidiabetic drug exposure: *1*) none (diet, exercise control), *2*) only use of oral drugs, *3*) only use of injectable drugs, or *4*) combined use of oral and injectable drugs. Further, the annual medication possession ratio (MPR) for antidiabetic treatments was measured to quantify the amount of antidiabetic drug exposure.

Statistical Analyses

Statistical analyses were initiated in early 2018 and finalized in mid-2019. Descriptive analyses were performed for patient characteristics. Means and SDs were used for continuous variables, and percentages and frequencies were applied for dichotomized and categorical variables. The event rates for diabetes-related complications and comorbidities during the follow-up are presented as the number of events per 100 person-years. The antidiabetic treatments during the follow-up are presented as the number of antidiabetic drug exposures per 100 person-years. The death rate is presented as the number of events per 100 people.

Crude Health Care Costs for Diabetes-Related Complications

The costs of diabetes-related complications were estimated as event-year costs and annual state-year costs. Event-year costs were the costs associated with medical management of an acute care episode (initial management in emergency department, inpatient, or outpatient care settings) and any subsequent care provided within the first year following the acute episode. State-year costs reflected the annual resource use required beyond the first year for the ongoing medical management while a given health state/chronic event is present for the remainder of the patient's life.

Cost Multipliers of Annual Health Care Costs Associated With Patient Demographics, Comorbidities, Complications, Antidiabetic Treatments, and Death

Our primary interest was to quantify the impact associated with a wide range of patient demographic and clinical characteristics (i.e., age, sex, diabetes duration, comorbidities, complications, antidiabetic treatments) on health care costs. We applied the generalized estimating equation (GEE) model with a log-link function to estimate the log-transformed annual health care costs as a function of patient demographics, comorbidities, complications, and antidiabetic treatments. The coefficients and 95% CIs from the GEE model were then back-transformed to the ordinal scale using an exponential function to form the cost multipliers. The GEE accounts for the nonindependence of yearly repeated-measured cost data within each subject during the follow-up. In the multivariable modeling analysis, unless indicated otherwise, patient demographics (age at T2D diagnosis and sex) and death status were the time-invariant variables, whereas diabetes duration, comorbidities, diabetes-related complications, and antidiabetic drug exposure were treated as time-varying variables, which were measured each year during the follow-up. We examined the collinearity among the variables in the GEE model by using a variance inflation factor; no significant collinearity problems (supported by variance inflation factor <10) were found.

In the GEE models, the base case was determined as the annual health care costs for a male diagnosed with T2D at age <50 years, with a diabetes duration of <5 years, and without comorbidities, complications, and antidiabetic treatments. The GEE models were multiplicative. That is, to determine the relative impact on health care costs for a given patient with characteristics other than those of the base case patient, we can multiply the health care costs for the base case patient (baseline cost) by the product of the cost multipliers (or multiplicative factors) calculated for each demographic and clinical condition applied to that patient.

In the primary analysis, we considered 14 fatal or nonfatal complications in the multivariable model. A series of sensitivity analyses were conducted. First, we examined a total of 29 fatal or nonfatal subtypes of complications (sensitivity analysis 1). Second, we considered the status of comorbidities measured in the year before or at T2D diagnosis and treated them as the time-invariant variables in the analysis (sensitivity analysis 2). Third, we modeled the annual MPR of antidiabetic drugs as a time-varying variable in the analysis (sensitivity analysis 3). The annual MPR during the follow-up was calculated by summing days supply from the first to the last antidiabetic prescription in a year divided by 365 days (25). A cutoff point for MPR of 0.8 (25) was applied to determine low (MPR <0.8) and high (MPR ≥ 0.8) exposure/adherence to antidiabetic drugs. SAS 9.4 software (SAS Institute, Cary, NC) was used for all statistical analyses.

RESULTS

Table 1 describes the baseline patient characteristics. The study population of 802,429 individuals had a mean age of 54.2 years and 46.3% females. Prevalent comorbidities were present from 2.8 to 37.0% of the study population; hypertension, hyperlipidemia, cancer, and depression were more frequent in females. Most individuals (55.5%) were treated with oral antidiabetic drugs only.

Supplementary Table 3 shows the event rates of comorbidities, incidence rates of diabetes-related complications, antidiabetic drug exposure rates, and death rates during the follow-up. The average follow-up duration was 6.9 years. Hyperlipidemia and hypertension were the two most common comorbid conditions. Nonfatal microvascular complications were the most frequent, followed by nonfatal macrovascular and metabolic complications. About 57% of patients had exposure to antidiabetic drugs during the follow-up. A total of 55,193 (6.9%) patients died during the follow-up period, with 0.9% as a result of fatal CVD and 6.0% as a result of other causes.

Table 2 presents the crude health care costs of diabetes-related complications in the event year and subsequent years. The mean time from T2D diagnosis to the development of the first complication event ranged from 4.0 to 7.3 years. The average event-year cost of complications was from $1,772 for proteinuria to $17,652 for fatal ischemic heart disease. The average annual state-year cost of complications ranged from $1,798 for other retinopathy to $16,404 for

Table 1—Patient characteristics in the year before or at T2D diagnosis stratified by sex

Characteristic	Total population	Male	Female
Cohort size, *n* (%)	802,429 (100.0)	430,799 (53.7)	371,630 (46.3)
Age at T2D diagnosis (years), mean (SD)	54.16 (13.69)	53.28 (13.46)	55.18 (13.89)
Comorbidity, %			
Hypertension	36.97	34.92	39.35
Hyperlipidemia	30.85	29.75	32.13
Liver disease	19.47	21.58	17.03
Cancer	10.64	8.05	13.64
Depression	2.80	2.15	3.56
Antidiabetic drug exposure, %			
None	39.95	36.60	43.84
Only oral	55.45	58.06	52.44
Only injectable	0.73	0.77	0.69
Oral + injectable	3.86	4.58	3.09

Injectable antidiabetic drugs included insulin and glucagon-like peptide 1 receptor agonists.

end-stage renal disease (ESRD) with dialysis. Supplementary Fig. 2 shows the annual health care costs before, during, and after the occurrence of 10 nonfatal major macrovascular, microvascular, and metabolic complications. The event-year costs were relatively high for macrovascular complications, and the cost decline in the subsequent years was relatively slow for microvascular complications. Supplementary Figs. 3–14 illustrate the crude annual event- and state-year health care costs of diabetes-related complications (as a composite outcome or by subtype of diseases) and other-cause death. For nonfatal complications, the event-year cost was the highest for lower-extremity amputation ($12,989) followed by hemorrhagic stroke ($12,304) and myocardial infarction ($11,103). The annual state-year cost for most of the complications increased gradually over time. ESRD with chronic dialysis or kidney transplant was the costliest followed by lower-extremity amputation and heart failure. For death cases, the event-year cost was the highest for deaths associated with ischemic heart disease.

Table 3 shows the cost multipliers from the primary analysis. The baseline cost of $281 represents the mean annual health care cost for the base case patient, who is a male diagnosed with T2D at age <50 years, with diabetes duration of <5 years, and without complications, comorbidities, and antidiabetic treatments. If a patient has any characteristics other than those for the base case, the mean annual health care cost is estimated by multiplying the baseline cost by the product of the cost multipliers for each characteristic of that patient. For instance, the mean annual health care cost for a patient aged 70 years is 1.68 times that of a patient aged <50 years, that for a patient with T2D duration of 5 years is 0.85 times that of a patient with a T2D duration of <5 years, that for a female is 1.06 times that of a male, that for a patient with a comorbidity is 0.98–1.81 times that of a patient without comorbidities, and that for a patient treated with oral antidiabetic drugs is 1.78 times that of a patient without oral treatments. Having nonfatal complications increases the cost by 1.37–2.95 times in the event year and 1.13–1.49 times in subsequent years. Patients who died as a result of CVD have an increased cost in the year of death by 20.49 times. For a female patient aged 50 years, with a T2D duration of 5 years, treated with oral antidiabetic drugs, and developing stroke, the estimated mean annual health care cost in the event year is $1,583 ($281.21 × 1.06 × 1.19 × 0.85 × 1.78 × 2.95).

Table 4 shows the results when we considered subtypes of complications in the GEE analysis. Hemorrhagic or ischemic stroke, upper- or lower-extremity amputation, ESRD with dialysis, ischemic heart disease, and proliferative retinopathy are the leading cost drivers for the event- and state-year costs. Supplementary Table 4 shows the results when we considered the baseline comorbidity status in the GEE analysis. Compared with the primary analysis results, depression is still the costliest comorbidity. Supplementary Table 5 presents the results when we used the MPR to examine the cost impact of adherence to antidiabetic treatments. Higher adherence to oral or injectable treatments was associated with increased costs.

CONCLUSIONS

This study provides a comprehensive view of the real-world economic impact associated with each of the 29 incident fatal or nonfatal diabetes-related complications, independently of the effects of patient demographics, comorbidities, antidiabetic treatments, and other-cause death among patients with T2D in Taiwan. We found that the health care costs of T2D varied by patient demographics, clinical characteristics, and cause of death. Fatal complications generally had a higher economic impact than nonfatal complications. Mortality as a result of a composite of CVD events (fatal CVD) was the costliest event, which increased the event-year health care costs by 1,784–2,001%, followed by other-cause death (1,285–1,584%), nonfatal stroke (195–202%), and myocardial infarction (145–154%). When the subtypes of complications were assessed, among fatal complications, other-cause death was the costliest event, which increased the event-year health care costs by 1,285%, followed by ischemic or hemorrhagic stroke (613–728%) and heart failure (447%). Among nonfatal complications, ischemic or hemorrhagic stroke, ESRD with dialysis, upper- or lower-extremity amputation, and coronary heart disease (e.g., ischemic heart disease, myocardial infarction, heart failure) were among the most significant cost drivers, increasing the event-year and annual state-year health care costs by 103–376% and 13–599%, respectively.

Some of cost estimates in our study are different from those reported in the four most relevant and recently published studies from Germany (26), Taiwan (12), Hong Kong (15), and the U.K. (27). The discrepancy is likely due to differences in the health care setting or system (e.g., a mixture of public and private providers [15] vs. universal coverage [12,26]), definition of complication events (e.g., mixed prevalent and incident events [12,15,26,27]), inclusion of cost components for estimating health care costs (e.g., health care

Table 2—Crude event-year and annual state-year health care costs of diabetes-related complications

Event	Patients with event, *n*	Time to the first event (years), mean (SD)	Event-year cost (US$), mean (SD)	Average annual state-year cost (US$), mean (SD)
Stroke	59,543	5.21 (3.55)	7,166.06 (12,868.20)	3,572.20 (7,789.74)
Ischemic stroke	43,663	5.36 (3.59)	6,790.06 (12,032.49)	3,654.47 (7,738.86)
Hemorrhagic stroke	12,162	5.10 (3.56)	12,304.31 (18,946.12)	4,181.91 (10,159.10)
Transient ischemic attack	13,137	5.59 (3.59)	4,559.47 (7,391.18)	3,215.62 (6,644.44)
Myocardial infarction	14,942	5.76 (3.63)	11,103.10 (12,788.41)	3,968.37 (7,724.08)
Ischemic heart disease	62,218	5.35 (3.53)	7,186.14 (10,786.39)	3,490.74 (7,054.18)
Heart failure	29,077	5.94 (3.73)	10,070.83 (15,839.95)	5,691.68 (10,222.44)
Arteriosclerotic CVD	388	5.22 (3.45)	7,750.24 (12,037.88)	3,972.51 (8,470.16)
Arrhythmia	32,617	5.57 (3.66)	8,101.12 (15,216.45)	3,586.78 (8,284.03)
Nephropathy	228,983	4.73 (3.49)	3,158.42 (7,987.84)	2,544.21 (5,623.36)
CKD with or without short-term dialysis	47,441	6.31 (3.90)	3,894.18 (8,336.73)	2,349.70 (4,940.97)
ESRD with dialysis	8,990	6.52 (3.56)	9,846.21 (12,071.96)	16,403.68 (11,295.76)
Proteinuria	36,146	5.16 (3.56)	1,772.43 (4,274.87)	2,193.31 (5,188.79)
Kidney transplant	95	7.32 (3.11)	10,866.27 (4,427.81)	11,123.23 (6,402.39)
Other nephropathy	142,307	4.78 (3.53)	3,159.59 (8,395.77)	1,868.30 (4,276.29)
Retinopathy	296,940	4.29 (3.22)	1,972.96 (3,763.25)	2,042.24 (4,343.47)
Proliferative retinopathy	26,569	6.22 (3.82)	3,548.15 (5,082.46)	4,687.43 (7,841.06)
Blindness	1,342	5.01 (3.44)	4,394.43 (7,143.49)	3,025.47 (6,211.11)
Other retinopathy	269,144	4.27 (3.20)	1,885.07 (3,696.92)	1,797.51 (3,809.84)
Neuropathy	249,533	4.10 (3.10)	2,212.41 (4,341.18)	2,072.20 (4,510.40)
Peripheral vascular disease	130,957	4.65 (3.36)	3,444.45 (7,594.15)	2,490.97 (5,295.28)
Diabetes foot ulcer	21,354	5.32 (3.60)	4,701.95 (8,150.95)	3,284.20 (6,700.11)
Upper-extremity amputation	601	4.93 (3.44)	8,335.78 (12,434.98)	3,067.11 (6,019.06)
Lower-extremity amputation	4,441	6.03 (3.81)	12,988.73 (13,761.50)	5,777.34 (10,361.16)
Other peripheral vascular disease	106,991	4.66 (3.36)	3,119.31 (7,299.63)	2,262.14 (4,796.40)
Hospitalized diabetic ketoacidosis	17,049	4.01 (3.48)	5,401.15 (9,323.16)	NA
Hospitalized HHS	13,388	4.51 (3.81)	7,557.12 (13,550.72)	NA
Hospitalized hypoglycemia	44,808	6.14 (3.91)	6,881.47 (11,491.43)	NA
All-cause death	55,193	5.82 (3.82)	13,079.68 (13,938.41)	NA
Fatal CVD	7,488	5.49 (3.71)	14,542.10 (15,581.51)	NA
Fatal stroke	4,034	5.94 (3.74)	14,329.33 (15,251.66)	NA
Fatal myocardial infarction	2,220	6.79 (3.80)	14,963.03 (16,070.27)	NA
Fatal ischemic heart disease	2,255	6.04 (3.83)	17,651.55 (17,798.79)	NA
Fatal heart failure	3,722	6.26 (3.81)	16,883.87 (17,182.75)	NA
Other-cause death	47,705	5.87 (3.83)	12,850.14 (13,648.53)	NA

CKD, chronic kidney disease; HHS, hyperosmolar hyperglycemic syndrome; NA, not applicable.

sector costs [12,26] vs. mixed public and private medical costs [15,27]), inclusion of covariates in the modeling analysis (e.g., without considering comorbidities [12,15,26,27]), and study design and analytical approaches (e.g., cross-sectional [12,15] vs. longitudinal [15,26,27]). Even with similar health care systems, studies from different countries may yield different results. For example, in a previous study from Germany (26), which has the statutory national health insurance program as Taiwan, the top three costly complications are ESRD, fatal ischemic heart disease, and amputation, which are different from what is found in this study (i.e., other-cause death, fatal stroke, ESRD with dialysis). Despite these differences, however, our study and previous studies (12,15,26,27) consistently revealed that fatal CVD as well as nonfatal stroke, ESRD, amputation, and coronary heart disease have a high impact on the health care costs of T2D. These results highlight the importance of early effective prevention of vascular complications and their associated deaths to restrain the considerable economic burden incurred in the T2D population.

Moreover, we found that the economic impact of depression in the T2D population cannot be neglected because it was the costliest comorbidity, increasing the annual health care costs by 64–82%. This finding supports the recent guidelines emphasizing the importance of assessing, preventing, and managing coexistent mental illnesses in patients with diabetes (28). Furthermore, consistent with previous studies (29,30), we found that the use of antidiabetic treatments contributes to the cost burden, increasing health care costs by 76–86%. Beyond this, we further showed that higher use/exposure of antidiabetic treatments (MPR $\geq$0.8) yielded a higher cost impact compared with that for lower use/exposure (MPR $<$0.8). This may suggest a trade-off when enhancing an antidiabetic therapy; more exposure/adherence to antidiabetic treatments increases upfront

Table 3—Cost multipliers and associated 95% CIs for patient demographics, comorbidities, diabetes-related complications, antidiabetic drug exposure, and death: primary analysis

Variable	Multiplier	95% CI	
Baseline annual health care cost (2017 U.S. $), mean (95% CI)	281.21	279.25	283.21
Age at T2D diagnosis (years) (ref. <50)			
50–59	1.19	1.19	1.20
60–69	1.43	1.42	1.44
≥70	1.68	1.67	1.69
Diabetes duration (years) (ref. 1–4)			
≥5	0.85	0.84	0.85
Female (ref. male)	1.06	1.06	1.06
Comorbidity (ref. none)			
Hypertension	1.21	1.21	1.22
Hyperlipidemia	1.07	1.06	1.07
Liver disease	0.98	0.98	0.98
Cancer	1.04	1.04	1.05
Depression	1.81	1.80	1.82
Oral antidiabetic drug exposure (ref. none)	1.78	1.78	1.79
Injectable antidiabetic drug exposure (ref. none)	1.83	1.82	1.84
Complication (event year) (ref. none)			
Stroke	2.95	2.92	2.98
Myocardial infarction	2.53	2.48	2.58
Ischemic heart disease	2.51	2.49	2.53
Heart failure	2.24	2.21	2.27
Arteriosclerotic CVD	1.80	1.62	2.01
Arrhythmia	2.04	2.01	2.06
Nephropathy	1.49	1.48	1.50
Retinopathy	1.37	1.36	1.37
Neuropathy	1.41	1.40	1.41
Peripheral vascular disease	1.55	1.54	1.56
Hospitalized diabetic ketoacidosis	1.90	1.87	1.93
Hospitalized HHS	1.72	1.69	1.76
Hospitalized hypoglycemia	1.90	1.88	1.92
Complication (state year) (ref. none)			
Stroke	1.44	1.43	1.45
Myocardial infarction	1.18	1.16	1.20
Ischemic heart disease	1.32	1.31	1.33
Heart failure	1.49	1.47	1.51
Arteriosclerotic CVD	1.15	1.04	1.26
Arrhythmia	1.14	1.13	1.15
Nephropathy	1.18	1.18	1.19
Retinopathy	1.13	1.13	1.13
Neuropathy	1.13	1.13	1.13
Peripheral vascular disease	1.14	1.14	1.15
Death (ref. none)			
Fatal CVD	20.49	19.93	21.05
Other-cause death	16.42	16.20	16.64

All variables in the model were statistically significant at $P < 0.05$. Injectable antidiabetic drugs included insulin and glucagon-like peptide 1 receptor agonists. Fatal CVD was a composite end point of death as a result of stroke, myocardial infarction, ischemic heart disease, or heart failure. All variables were treated as time-dependent variables in the model, except age and sex. Hypertension, hyperlipidemia, liver disease, and cancer were considered as chronic diseases and assumed to be irreversible once they occurred, so the status of these comorbidities remained in the subsequent follow-up years. Depression status could be in and out, depending on whether patients had a diagnosis in a given year. HHS, hyperosmolar hyperglycemic syndrome; ref., reference.

costs that are due to high drug acquisition costs, but these costs could be offset given that intensive antidiabetic treatments may decrease the risks of developing costly vascular complications, which might thus lead to lower downstream complication costs and overall health care costs (31,32). Further studies are warranted to examine the association of intensive medication therapies/adherence with the complication and all-cause medical costs in diabetes.

Compared with existing studies on the economic burden of T2D, this study has several strengths. First, by using the individual-level data from the NHI claims covering all medical utilization and costs, this study used the largest nationally representative T2D study cohort with the longest follow-up period to estimate the health care costs associated with a wide range of diabetes-related complications. This study addresses several limitations in previous studies, including that the analyses were based on restrictive/underrepresentative or ancient study cohorts (13–19,27,29,30,33); included only a limited number of study patients for severe/chronic complication events (12,19,26); assessed only a few diabetes-related complications, only nonfatal complications, or just a single complication (12–19,27,29,30,33); or were cross-sectional or conducted with only a short-term follow-up (12,15–19,29,30). Importantly, the large sample size in our study ensured statistical power for assessing relatively rare complication events and differentiating them into subtypes (e.g., hemorrhagic stroke, blindness, amputation, deaths). The long-term follow-up allowed us to measure chronic events (e.g., ESRD with dialysis or kidney transplant, death), and the longitudinal nature of the data allowed us to explore the costs in both the event year and subsequent years. The differences between costs in the event year and those in subsequent years can be substantial. This is also observed in previous studies (12,15,26,27). In addition, with the large study cohort with a long-term follow-up, this study included sufficient numbers of individuals with T2D with diverse demographic and clinical characteristics to allow a comprehensive assessment of the independent cost impact associated with diabetes-related complications.

Second, this study was based on NHI claims data, which are recognized as the most suitable source because of the large sample size, wide coverage, detailed longitudinal cost data, and elimination of self-report bias (i.e., recall and social desirability biases), unlike previous studies, which used data from either patient surveys or a chart review (29,30,34). Third, to avoid misclassification and ensure result applicability to patients with T2D, we applied valid procedures to define the study cohort and assess clinical characteristics and events; these

Table 4—Cost multipliers and associated 95% CIs for patient demographics, comorbidities, diabetes-related complications, antidiabetic drug exposure, and death: sensitivity analysis 1 (subtypes of diseases)

Variable	Multiplier	95% CI	
Baseline annual health care cost (2017 U.S. $), mean (95% CI)	293.04	290.99	295.10
Age at T2D diagnosis (years) (ref. <50)			
50–59	1.20	1.19	1.20
60–69	1.45	1.44	1.45
≥70	1.73	1.72	1.74
Diabetes duration, years (ref. 1–4)			
≥5	0.86	0.86	0.86
Female (ref. male)	1.06	1.06	1.07
Comorbidity (ref. none)			
Hypertension	1.19	1.19	1.20
Hyperlipidemia	1.06	1.05	1.06
Liver disease	0.97	0.96	0.97
Cancer	1.04	1.03	1.04
Depression	1.82	1.81	1.83
Oral antidiabetic drug exposure (ref. none)	1.80	1.79	1.80
Injectable antidiabetic drug exposure (ref. none)	1.76	1.75	1.77
Complication (event year) (ref. none)			
Stroke			
Ischemic stroke	2.57	2.54	2.59
Hemorrhagic stroke	4.76	4.66	4.87
Transient ischemic attack	1.46	1.44	1.49
Myocardial infarction	2.45	2.41	2.50
Ischemic heart disease	2.50	2.48	2.52
Heart failure	2.03	2.00	2.06
Arteriosclerotic CVD	1.87	1.68	2.07
Arrhythmia	2.03	2.01	2.06
Nephropathy			
CKD with or without short-term dialysis	1.54	1.53	1.56
ESRD with dialysis	3.01	2.94	3.09
Proteinuria	1.20	1.19	1.21
Kidney transplant	2.29	1.94	2.72
Other nephropathy	1.48	1.47	1.50
Retinopathy			
Proliferative retinopathy	1.80	1.78	1.82
Blindness	1.66	1.57	1.75
Other retinopathy	1.34	1.34	1.35
Neuropathy	1.41	1.41	1.42
Peripheral vascular disease			
Diabetes foot ulcer	1.67	1.65	1.69
Upper-extremity amputation	3.79	3.49	4.11
Lower-extremity amputation	3.22	3.11	3.33
Other peripheral vascular disease	1.46	1.45	1.46
Hospitalized diabetic ketoacidosis	1.94	1.91	1.98
Hospitalized HHS	1.73	1.69	1.76
Hospitalized hypoglycemia	1.73	1.71	1.74
Complication (state year) (ref. none)			
Stroke			
Ischemic stroke	1.37	1.36	1.38
Hemorrhagic stroke	1.48	1.45	1.51
Transient ischemic attack	1.03	1.02	1.05
Myocardial infarction	1.16	1.14	1.18
Ischemic heart disease	1.31	1.30	1.32
Heart failure	1.24	1.22	1.25
Arteriosclerotic CVD	1.17	1.08	1.28
Arrhythmia	1.17	1.16	1.18
Nephropathy			
CKD with or without short-term dialysis	1.09	1.08	1.10
ESRD with dialysis	6.99	6.82	7.17
Proteinuria	1.03	1.02	1.04
Kidney transplant	1.04	0.89	1.21

Continued on p. 1739

procedures are documented elsewhere (18,35–38). In contrast, previous studies did not differentiate T1D from T2D (13,15,39,40) or did not document the validity of the approaches used for outcome identification (13,15,40–42). In addition, we analyzed incident diabetes-related complications on the basis of the study cohort without any history of vascular complications by T2D diagnosis, unlike previous studies, which either did not distinguish between prevalent and incident complication events (29,30) or simply applied multivariable regression analyses to adjust for the history of complication events (12,15,26,27). Using a complication-free cohort design allows for the exclusion of potential influence of prior complication events on the future events of interest, and thus, one could argue that analyses that are based on a complication-free cohort may provide more reliable and valid cost estimates of complication events that can be attributed to diabetes itself.

Fourth, this study used a wide spectrum of analyses. We assessed a wide range of diabetes-related complications considered as the composite outcome or by subtype, considered a number of important comorbidities as the time-varying covariates in all analyses and further performed a sensitivity analysis to assess their effects as the baseline time-invariant covariates, and considered antidiabetic treatments as the time-varying covariates in all analyses and conducted a sensitivity analysis to further assess the effects by the level of medication exposure/adherence. In contrast, previous studies focused on either aggregate-level complications (i.e., incremental cost burden of people with diabetes relative to those without diabetes [43–46]) or only a single complication (e.g., death [13], severe hypoglycemia [14]). In addition, the potential economic impact of comorbidities was neglected in previous studies (12,26,27,33). The cost impact of antidiabetic treatments was either not considered (12,26,27,33) or only analyzed at an aggregated level as exposure versus nonexposure to antidiabetic treatments (29,30,34,40). Finally, to ensure the validity of study results, we adopted rigorous analyses to systematically quantify the crude cost burden of individual diabetes-related complications at their initial occurrences (event-year costs) and in subsequent years (state-year

Table 4—Continued

Variable	Multiplier	95% CI	
Other nephropathy	1.07	1.07	1.08
Retinopathy			
Proliferative retinopathy	1.27	1.26	1.29
Blindness	1.08	1.03	1.13
Other retinopathy	1.10	1.09	1.10
Neuropathy	1.13	1.13	1.14
Peripheral vascular disease			
Diabetes foot ulcer	1.10	1.09	1.12
Upper-extremity amputation	1.16	1.08	1.25
Lower-extremity amputation	1.13	1.09	1.16
Other peripheral vascular disease	1.11	1.10	1.11
Death (ref. none)			
Fatal CVD			
Fatal ischemic stroke	8.28	7.75	8.84
Fatal hemorrhagic stroke	7.13	6.63	7.68
Fatal myocardial infarction	2.99	2.77	3.22
Fatal ischemic heart disease	4.21	3.90	4.55
Fatal heart failure	5.47	5.17	5.79
Other-cause death	13.85	13.66	14.04

In sensitivity analysis 1, stroke, nephropathy, retinopathy, peripheral vascular disease, and fatal CVD were divided into subtypes of diseases. All variables in the model were statistically significant at $P < 0.05$, except kidney transplant (state year) ($P = 0.521$). Injectable antidiabetic drugs included insulin and glucagon-like peptide 1 receptor agonists. Fatal CVD was a composite end point of death as a result of stroke, myocardial infarction, ischemic heart disease, or heart failure. All variables were treated as time-dependent variables in the model, except age and sex. Hypertension, hyperlipidemia, liver disease, and cancer were considered as chronic diseases and assumed to be irreversible once they occurred, so the status of these comorbidities remained in the subsequent follow-up years. Depression status could be in and out, depending on whether patients had a diagnosis in a given year. CKD, chronic kidney disease; HHS, hyperosmolar hyperglycemic syndrome; ref., reference.

costs) and model their cost impacts with adjustment for a wide range of potential confounders, including patient demographics, comorbidities, and antidiabetic treatments. Some previous studies only analyzed the crude costs of diabetes-related complication events (42,47). Moreover, the cost estimates in this study are presented as the adjusted cost multipliers, which represent the independent cost impact of specific variables in the regression analyses. The multipliers would be easier to interpret from different perspectives and by different stakeholders and are not tied to actual monetary cost values that would vary by time.

Several limitations should be acknowledged. First, we used health claims data as the primary study data source, where clinical biomarkers (e.g., HbA_{1c} for determining the severity and control level of diabetes) are typically lacking, which might affect clinical events and costs. However, we carefully measured diabetes duration, diabetes-related complications, comorbidities, and antidiabetic treatments, which could be surrogate proxies for diabetes severity and control. We adjusted all these variables in the analyses to minimize the potential unmeasured confounding effects. Second, socioeconomic data (e.g., income, education) are not collected in the health claims database. However, these variables have been found to have no significant impact and were not considered in previous studies (12,15,26,27,29,30). Third, our cost measures considered medical costs from the formal health care sector. The costs from the informal health care sector (e.g., patient time costs, unpaid caregiver time costs, transportation costs) and non–health care sectors (e.g., cost of unpaid lost productivity as a result of illness [9]) were not included because of data unavailability. Finally, the absolute crude medical costs may be limited to country-specific cost estimates (i.e., a Taiwanese population with T2D under a universal health care coverage setting). However, the adjusted cost multipliers, instead of absolute dollar values, reflect the magnitude of the economic impact according to the given individual characteristics and would be more appropriate for international comparisons.

In summary, among a T2D population of >0.8 million individuals with up to 15 years of follow-up in Taiwan, the economic burden of incident vascular complications and death is found to be compelling over time. The cost impact attributable to depression and intensive antidiabetic treatments cannot be ignored. The cost estimates provide a Taiwan-specific cost catalog of T2D and are useful for facilitating the parameterization of diabetes economic simulation models to quantify the economic impact of clinical outcomes, determine cost-effective interventions, and inform clinical and policy efforts of improving diabetes care.

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