



A Patient-Level Model to Estimate Lifetime Health Outcomes of Patients With Type 1 Diabetes

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OBJECTIVE

To develop a patient-level simulation model for predicting lifetime health outcomes of patients with type 1 diabetes and as a tool for economic evaluation of type 1 diabetes treatment based on data from a large, longitudinal cohort.

RESEARCH DESIGN AND METHODS

Data for model development were obtained from the Swedish National Diabetes Register. We derived parametric proportional hazards models predicting the absolute risk of diabetes complications and death based on a wide range of clinical variables and history of complications. We used linear regression models to predict risk factor progression. Internal validation was performed, estimates of life expectancies for different age-sex strata were computed, and the impact of key risk factors on life expectancy was assessed.

RESULTS

The study population consisted of 27,841 patients with type 1 diabetes with a mean duration of follow-up of 7 years. Internal validation showed good agreement between the predicted and observed cumulative incidence of death and 10 complications. Simulated life expectancy was ~13 years lower than that of the sex- and age-matched general population, and patients with type 1 diabetes could expect to live with one or more complications for ~40% of their remaining life. Sensitivity analysis showed the importance of preventing renal dysfunction, hypoglycemia, and hyperglycemia as well as lowering HbA_{1c} in reducing the risk of complications and death.

CONCLUSIONS

Our model was able to simulate risk factor progression and event histories that closely match the observed outcomes and to project events occurring over patients' lifetimes. The model can serve as a tool to estimate the impact of changing clinical risk factors on health outcomes to inform economic evaluations of interventions in type 1 diabetes.

Simulation models are now being widely used for predicting the progression of diabetes and its complications, particularly when evaluating the long-term clinical and economic benefits of interventions (1). These models have many applications. For example, the UK Prospective Diabetes Study (UKPDS) outcomes model for type 2 diabetes (2) was used to develop life expectancy tables stratified by combined levels of risk factors (3), which can assist clinicians and patients in making decisions on strategies to improve modifiable risk factors. Models that predict health outcomes in chronic diseases are also essential for optimizing health policies because it can take many years to observe the impact of new

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interventions on patient outcomes. These simulated outcomes, when combined with the associated quality of life and costs, can facilitate the quantification of quality-adjusted life years (QALYs) and total lifetime costs, which constitute the foundations of modern health technology assessment.

There are currently more than a dozen published simulation models for type 1 diabetes (4), but most of them were built by synthesizing inconsistent data from clinical trials involving cohorts with different characteristics and using equations from populations without type 1 diabetes, such as the Framingham equation (5) and those from the UKPDS model (6), to predict macrovascular events. Patients with type 1 diabetes have higher risk of cardiovascular disease (CVD) compared with the general population (7), but the current tools for absolute CVD risk assessment fail to provide reasonable estimates of CVD risk in patients with type 1 diabetes. For example, the Framingham equation developed for the general adult population (5) and the UKPDS model developed for type 2 diabetes (6) have been shown to poorly predict CVD risk in type 1 diabetes (8).

It has long been recognized that there is a need to develop risk stratification models specifically for patients with type 1 diabetes. There have been several efforts to develop calculators for CVD risk in type 1 diabetes (9,10), but there is currently no integrated set of equations like those that have been developed for type 2 diabetes (2,11) to predict the occurrence of a range of complications in type 1 diabetes.

The lack of an appropriate simulation model based entirely on large clinical data from patients with type 1 diabetes has been a major gap in the current literature to assess the cost-effectiveness of interventions for this disease. To address this, we developed a comprehensive simulation model for lifetime health outcomes of patients with type 1 diabetes based on a nationally representative population. This model is envisaged to serve as a tool for economic evaluation of new interventions for type 1 diabetes.

RESEARCH DESIGN AND METHODS

Data Sources and Study Population

We used data from the Swedish National Diabetes Register (NDR) for adults, which contains longitudinal data since 1996 from patient visits to the registered

primary health care centers (PHCs) and hospital outpatient clinics (HOCs) across Sweden (12,13). It is estimated that up to 95% of PHCs and 100% of HOCs reported to the NDR. In brief, the NDR includes demographic variables, date of diagnosis, diabetes duration, treatment modalities, and various risk factors measured at least annually for ~97% of patients with type 1 diabetes (12,14). To capture the occurrence of diabetes-related complications and deaths, the NDR was confidentially linked to the Swedish National Inpatient Register (15) and the Swedish Cause of Death Register (16) by using the Swedish personal identity numbers that are assigned to all Swedes at birth or at the time of immigration (15,17).

Because data on blood lipids were first recorded in the NDR in 2002, we set the time window of analysis between 1 January 2002 and the time we first compiled the data (31 December 2011) and included patients with a diagnosis of type 1 diabetes within this time window. To minimize the risk of including patients with type 2 diabetes in our analyses, we included only patients who were younger than 30 years old at the time of the type 1 diabetes diagnosis and, during the follow-up period, had at least one prescription for insulin annually and no prescriptions for metformin. The latter criterion was based on the fact that metformin is not indicated in Sweden and is seldom used in practice for type 1 diabetes. The prescription records were obtained from the Swedish Prescribed Drug Register, which includes information on dispensed substances and dates of prescribing and was linked to the NDR (18). The flowchart for study cohort selection is provided in Supplementary Fig. 1. Approval for our study was obtained from the Regional Ethical and Review Board in Sweden.

Measurement of Risk Factors and Health Outcomes

All HbA_{1c} (19) values were converted to standard levels according to the U.S. National Glycohemoglobin Standardization Program (20). In addition to the current HbA_{1c}, a variable representing the time-weighted mean of past HbA_{1c} measures was also created to capture the legacy effect or “metabolic memory” of past HbA_{1c} control. The theory of metabolic memory is based on evidence that patients who underwent early glycemic control or intensive treatment have

significantly fewer vascular complications compared with patients receiving standard treatment, despite no difference in the current glycemic control between the two patient groups (21). To estimate the time-weighted mean of past HbA_{1c}, we assigned a weight for each HbA_{1c} measure as the duration between that measure and the immediately preceding HbA_{1c} measure (or the diagnosis of type 1 diabetes for the first HbA_{1c} measure). The time-weighted mean HbA_{1c} was calculated by averaging all previous HbA_{1c} measures using the above-mentioned weights.

Microalbuminuria and macroalbuminuria were defined as occurrence of positive results in two of three consecutive tests within a year. A positive test for microalbuminuria indicates an albumin-to-creatinine ratio (ACR) between 3 and 30 mg/mmol or a urinary albumin excretion rate (UAE) between 20 and 200 μ g/min or between 20 and 300 mg/L; and for macroalbuminuria, an ACR >30 mg/mmol or a UAE >200 μ g/min or >300 mg/L. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (22).

Major complications were identified using the *International Classification of Diseases-Ninth Revision* and ICD-10 codes for the following events and procedures: fatal and nonfatal myocardial infarction (MI), fatal and nonfatal stroke, heart failure, peripheral vascular disease (PVD), severe hypoglycemia and hyperglycemia (i.e., those events leading to hospitalization), amputation, end-stage renal disease (ESRD), percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) (see Supplementary Table 1 for specific codes).

Estimation of Risk Equations for Complications and Mortality

In our simulation model, we captured the history of events that influence risk of mortality and other events (see section MODEL SIMULATION below for details). To increase the generalizability of the model, we defined a CVD event as a composite outcome of MI, PCI, and CABG because the proportion of patients with the same risk factors who undergo PCI or CABG varies across health care systems. As such, for each of the five acute complications (CVD, stroke, amputation, severe hypoglycemia, and severe hyperglycemia), we

developed two separate risk equations for first and second events. For each of the three chronic conditions (heart failure, PVD, and ESRD), we developed one risk equation predicting the beginning of the condition. We used the multivariable parametric proportional hazards (PHs) models to develop these risk equations. Conditional on the occurrence of a CVD event, a multinomial logit model was developed to determine whether the event was MI, PCI, or CABG. The set of candidate covariates for each equation included time-independent factors (e.g., sex), time-varying risk factors (e.g., time-weighted mean HbA_{1c}), and time-varying complications (e.g., history of stroke). We used MI, PCI, and CABG instead of CVD as potential predictors of other events. Because a BMI that is too low or too high has a harmful effect on survival (23,24), we treated BMI as a categorical variable in the risk models based on the following ranges (in kg/m²): 22.51–25.00 (BMI_category [cat]1, reference), ≤20.00 (BMI_cat2), 20.01–22.50 (BMI_cat3), 25.01–27.50 (BMI_cat4), 27.51–30.00 (BMI_cat5), and >30.0 (BMI_cat6). We compared this approach with using a continuous BMI covariate by examining the impact of changes in BMI on the simulated life expectancy.

A risk equation for all-cause mortality was developed using a Gompertz PHs model with time to death determined as the duration between the first visit to a PHC or HOC after 1 January 2002 and death or last data collection, whichever came first. We used age as a time scale to allow extrapolation beyond ages at the end of the follow-up period, where the age at the first visit to a PHC or HOC after 1 January 2002 was treated as left censored.

Significant covariates in the models for complications and death were selected in a backward stepwise regression at $P < 0.05$. The selection of a distribution, being exponential, Weibull, or Gompertz for a complication risk model was based on the log-cumulative hazard plot (25) and the Akaike information criterion. The PHs assumption was tested by examination of Schoenfeld residuals (26) in comparable Cox models, and the model fit was examined using the cumulative hazard plot of the Cox–Snell residuals (27). A full description of covariates considered in the model selection is presented in Supplementary Table 2.

Estimation of Equations for Risk Factor Progression

As risk factors influence the occurrence of events, it is essential to model the progression of risk factors. Because continuous risk factors (HbA_{1c}, BMI, systolic blood pressure [SBP], triglycerides, HDL cholesterol, LDL cholesterol, and eGFR) changed considerably with age and the patients entered the first clinic after 2002 (baseline) at different ages (17–93 years), we used age as a time scale to model the progression of these risk factors, which is consistent with the use of age as time scale in survival analysis of the events. We found a moderate to strong correlation between two adjacent measures of a risk factor and therefore included the 1-year lagged value as a potential predictor. Plots of continuous risk factors against age for individual patients showed both linear and quadratic patterns, and the magnitudes of changes over time were strongly governed by the baseline values. Therefore, the baseline value of the modeled risk factor, sex, age, age squared, and the 1-year lagged value of the modeled risk factor were included as potential predictors in the full linear regression model for each continuous risk factor, and backward stepwise procedures were performed to select the final set of predictors. We did not include history of complications in the models for risk factors because this resulted in poor agreement between observed and simulated changes in risk factors over time (see Supplementary Fig. 3).

To predict initiation and cessation of smoking and development and remission of microalbuminuria and macroalbuminuria, we used logistic regression models with independent variables being sex, age, and continuous risk factors, selected based on backward stepwise procedures. For both continuous and binary risk factors, we did not include history of complications as predictors because this resulted in poor agreement between observed and simulated cumulative incidence of complications and risk factor progression (see section FACE AND INTERNAL VALIDATION below). Statistical analyses were performed using Stata (28) and R (29) software.

Model Simulation

The estimated equations for risk of events and risk factor progression were integrated into a discrete-time simulation model with

annual cycles. Model inputs included baseline characteristics (demographic variables, clinical risk factors, and complication history) of the individual patients in the study population. The simulation involved using the risk equations to estimate the probability of each complication and death for each patient, which was compared with a random number drawn from the standard uniform distribution to determine whether the event occurred. If the model predicted that an individual died, time to death and time free of complications was calculated; if the individual survived the cycle, age, diabetes duration, event histories, and risk factor values (including time-weighted HbA_{1c}) were updated. Then, this patient entered the next cycle, with their updated risk factors and event histories being used to predict the occurrence of events and changes in risk factors in that cycle. Model outputs included annual incidence of complications and death, time to events, and changes in risk factors over the simulation time. Half-cycle correction was applied in the calculation of life expectancy. The model was developed in Stata (28).

Simulated Outcomes and Uncertainty Analysis

The simulated outcomes of interest were life expectancy (i.e., time between the current age and age at death) and complication-free survival time (i.e., time between the current age and age at the first occurrence of any of the complications after the current age), stratified by sex and into 10-year age groups. We included all patients irrespective of the prior complication status before the current age in the calculation of mean complication-free survival time. We minimized the first-order uncertainty (i.e., uncertainty due to patient variability) by performing Monte Carlo simulations with increasing number of replications until the mean survival time in each age-sex stratum was stable (i.e., changes in the mean survival time were <0.05 years regardless of any further increase in the number of replications) (30). Second-order uncertainty (i.e., uncertainty due to variation in parameter estimates) was addressed by bootstrapping (i.e., sampling with replacement) the patients in the study population and, for each sample, reestimating all equations to derive a set of fully correlated regression coefficients (30). From 1,000 bootstrap replications, distributions and 95% CIs of

the expected outcomes were derived. This approach conforms to the American Diabetes Association guidelines on simulation modeling in diabetes (1).

Sensitivity Analysis

In the sensitivity analysis, we examined the effects on life expectancy and complication-free survival time of 1) increasing and decreasing the baseline value of each continuous risk factor for each person by 1 SD of the cohort values at baseline, and 2) increasing and decreasing the estimated probability of each of the complications within each model cycle by 20%.

Face and Internal Validation

Face validity was assessed by having the model structure, equations for risk factor progression and events, and dependencies between events reviewed by experts in simulation modeling, internal medicine, statistics, and epidemiology represented within the authorship group and through presentation to and feedback from global diabetes modeling experts at both the Eighth (2016) and Ninth (2018) Mount Hood Challenges (31). We performed internal validation of the model by simulating outcomes for each patient in the study population to predict the occurrence of complications and death over the follow-up period given the observed baseline risk factors and then comparing the simulated with the observed cumulative incidence of each event. We also internally validated the equations for risk factor progression by comparing the changes in mean risk factors over time within each quartile of baseline risk values between the simulated and observed values of risk factors. To examine whether the model behaved appropriately (referred to as stress tests), we ran the simulation with a wide range of values for seven risk factors and checked whether the simulated life expectancy met the expectation. For example, life expectancy of a patient with type 1 diabetes should be about 9–13 years lower than that of an age- and sex-matched person from the general population, and higher HbA_{1c} levels or lower eGFR should be associated with lower life expectancy.

RESULTS

Descriptive Statistics and Simulated Outcomes

The study population consisted of 27,841 patients (55.6% male) with type 1 diabetes

with a mean follow-up time of 7.0 years. Mean age (SD) at onset and baseline (i.e., first visit to a clinic after 1 January 2002) was 15.1 (7.6) and 37.0 (14.9) years, respectively (see baseline descriptive statistics in Supplementary Table 3). There were 2,018 deaths during the follow-up period, which translated to an annual probability of 0.0104. Acute events that occurred at the highest rates included third amputation and third MI, and hospitalizations of chronic conditions that occurred at the highest rates included third and second ESRD, third heart failure, and third PVD, where time at risk for the first event started from the first clinic visit and for the second and third event from the first and second event, respectively (see numbers of events and annual event rates observed during the follow-up period in Supplementary Table 4).

Figure 1 shows the dependencies between events and the estimated hazard ratios for significant risk factors. The arrows in the figure indicate the direction of event-related dependencies. The large number of arrows indicates that the occurrence of many complications increased the risk of others in subsequent years. Functional forms and coefficients of the risk equations are provided in Supplementary Table 5. For coefficients in the models for continuous and binary risk factors, see Supplementary Tables 6 and 7, respectively.

Figure 2 shows the simulated and observed cumulative incidences for each complication and all-cause mortality from age 18 years. The predicted values in all cases were generally within the 95% CIs of the observed cumulative incidence. We also obtained a good agreement between observed and simulated progression of mean risk factors (see Supplementary Fig. 2).

All outputs from the stress tests met our expectation. For example, an increase in HbA_{1c} resulted in a decrease in life expectancy, and patients with a normal BMI of 25 kg/m² lived longer than those with a lower BMI (<20 kg/m²) or higher BMI (>30 kg/m²), holding other risk factors constant. In contrast, when BMI was treated as a continuous variable in the risk models (see Supplementary Table 8 for coefficients), the simulated life expectancy in patients with a higher BMI was higher than that in patients with a lower BMI, regardless of the baseline BMI. These observations supported the use of BMI as a categorical variable in our main

analyses. Table 1 reports the mean life expectancy and complication-free survival time of the patients with type 1 diabetes in different age and sex groups. Within each age group, men and women had similar mean baseline age, but life expectancies of women were longer than those of men, with the difference of 2.9 years for the age-group 20.0–29.9 years and 0.7 years for the age-group 80.0–89.9 years. Similarly, complication-free survival times of women in all but the oldest age groups were longer than those of men, with the difference of 1.2 years for the age-group 20.0–29.9 years and 0.8 years for the age-group 70.0–79.9 years.

Sensitivity Analysis

The tornado plots of the impact of each risk factor considered in our model on predicting life expectancy and complication-free survival time (Fig. 3A and B, respectively) show the importance of BMI, renal function (represented by eGFR), and HbA_{1c} in predicting the outcomes.

The tornado plots of the impact of changes in risks of major complications on the outcomes (Fig. 3C and D, respectively) show the importance of the risk of the first CVD event (MI, PCI, or CABG) and hypoglycemia and hyperglycemia in predicting life expectancy as well as complication-free survival time.

CONCLUSIONS

Using a nationwide cohort of patients with type 1 diabetes, we developed a comprehensive, face-valid and internally valid simulation model for occurrence of major complications and mortality in these patients, which can be used to support economic evaluation of type 1 diabetes treatment. The model can predict risk factor progression, impact of risk factors on the occurrence of an event, and the dependencies between the occurrences of events. Our model is the first to incorporate the impact of hypoglycemic events on the occurrence of other complications such as ESRD, stroke, amputation, and death. The model has been developed according to best modeling practice following international guidelines (1,32).

Using this model, we quantified the life expectancy for different patient subgroups, and supported the hypothesis that patients with type 1 diabetes have a much lower life expectancy compared with the general population. Specifically,

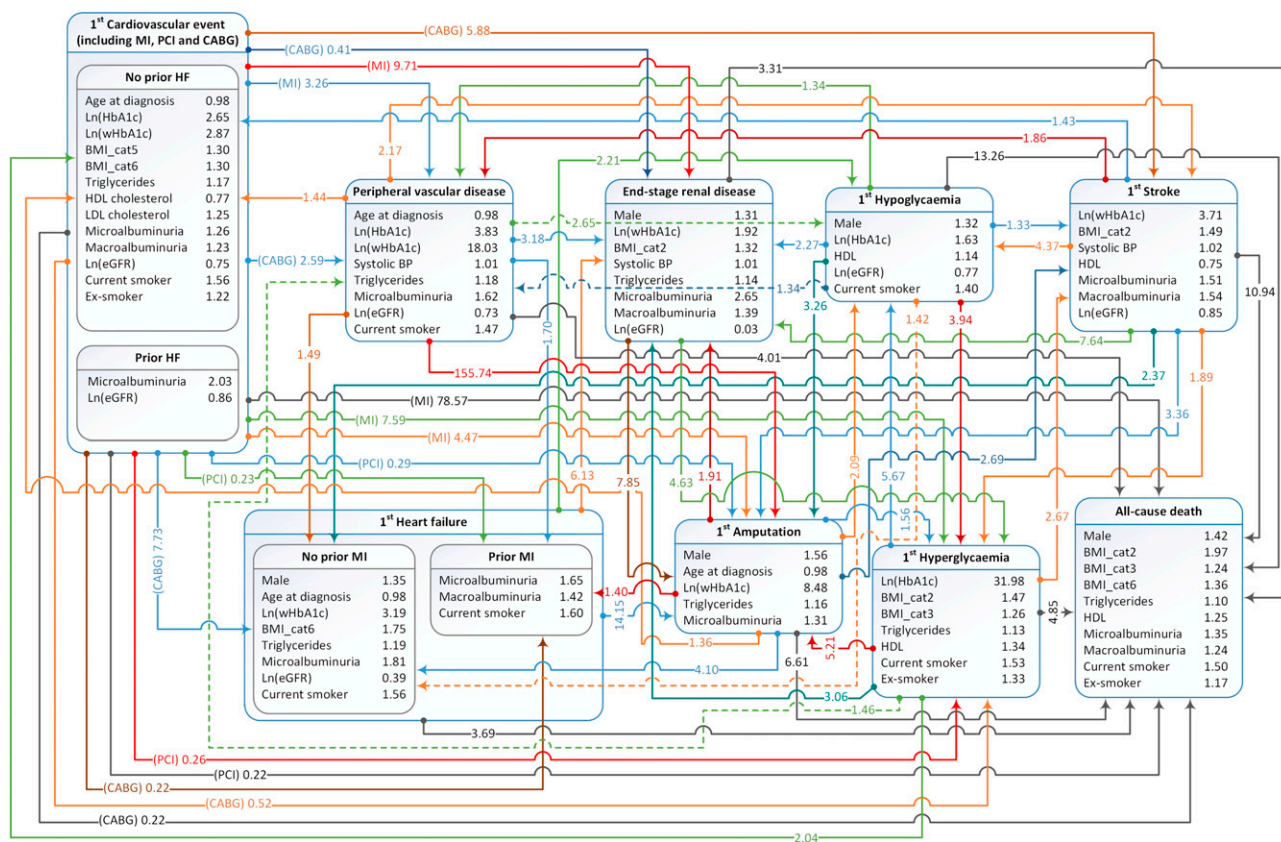


Figure 1—Summary of model equations showing major risk factors and the interdependencies between events. The top part of each box indicates the event predicted by the risk factors in the body of the box, each of which is associated with the hazard ratio next to it. Each arrow indicates that the occurrence of the root event influences the subsequent occurrence of the target event. The numerical figure on each arrow indicates the hazard ratio of the target event (complication or death) in patients with a history of the root event compared with patients without a history of such an event. The reference category of BMI (kg/m^2) represents BMI between 22.51 and 25.00, BMI_cat2 ($\text{BMI} \leq 20.00$), BMI_cat3 (20.01–22.50), BMI_cat5 (27.51–30.00), BMI_cat6 ($\text{BMI} > 30$). BP, blood pressure; HF, heart failure; wHbA_{1c} , time-weighted mean HbA_{1c} of past HbA_{1c} measures.

mean life expectancy of the Swedish patients with type 1 diabetes was ~13 years lower compared with the sex- and age-matched general population (33). For example, the predicted mean life expectancy in the base-case analysis for the age-group 20.0–29.9 years (mean age, 24) was 46.4 (95% CI, 45.9–46.9) years for women and 43.5 (95% CI, 43.1–44) years for men, against the life expectancy estimates of 59.4 years for 24-year-old women and 55.5 years for 24-year-old men in the general population in 2007 (the middle year of the follow-up period in our study cohort). The predicted mean complication-free survival times for the age-group 20.0–29.9 years (mean age, 24) were 28.3 (95% CI, 27.7–28.9) years for women and 27.1 (95% CI, 26.6–27.6) years for men, or ~17 years below the predicted mean life expectancy. This indicates that patients with type 1 diabetes could expect to live with one or more complications for ~40% of their remaining life. Sensitivity

analysis of the impact of risk factors confirmed the importance of renal function and classic risk factors such as HbA_{1c} as determinants of life expectancy, with major implications for optimal renal screening and treatment strategies such as control of blood pressure and glycemic levels. In line with the results from previous analyses using the NDR (34), our study showed that triglycerides had a greater impact on life expectancy compared with LDL or HDL cholesterol in this population with type 1 diabetes.

In the sensitivity analysis, we note that the impact of increasing BMI of each individual by 1 SD ($3.7 \text{ kg}/\text{m}^2$) in the population on the mean survival time is influenced by two opposing effects: increasing survival time in patients with a lower BMI category ($\leq 22.50 \text{ kg}/\text{m}^2$) shifted to a middle category (between 20.01 and 27.00 kg/m^2), and decreasing survival time in patients with a BMI category of 27.5–30 kg/m^2 shifted to the highest BMI category ($> 30 \text{ kg}/\text{m}^2$) (see

Supplementary Table 5 for coefficient associated with each BMI category). Similarly, the impact of decreasing BMI of each individual by 1 SD is also influenced by two opposing effects: decreasing survival time in patients with a middle BMI category shifted to a lower BMI category, and increasing survival time in patients with a highest BMI category shifted to a lower BMI category. As a consequence, the effect of changing BMI of each individual on the mean survival time depends on the distribution of BMI and the hazard ratios associated with different BMI categories.

This model has identified a large number of relationships between risk factors, complications history, and development of complications. There is a need to use evidence from large clinical and epidemiological studies to confirm whether these are causal relationships or are simply statistical correlations. Interestingly, triglycerides were more of a driver of life expectancy than HDL and LDL

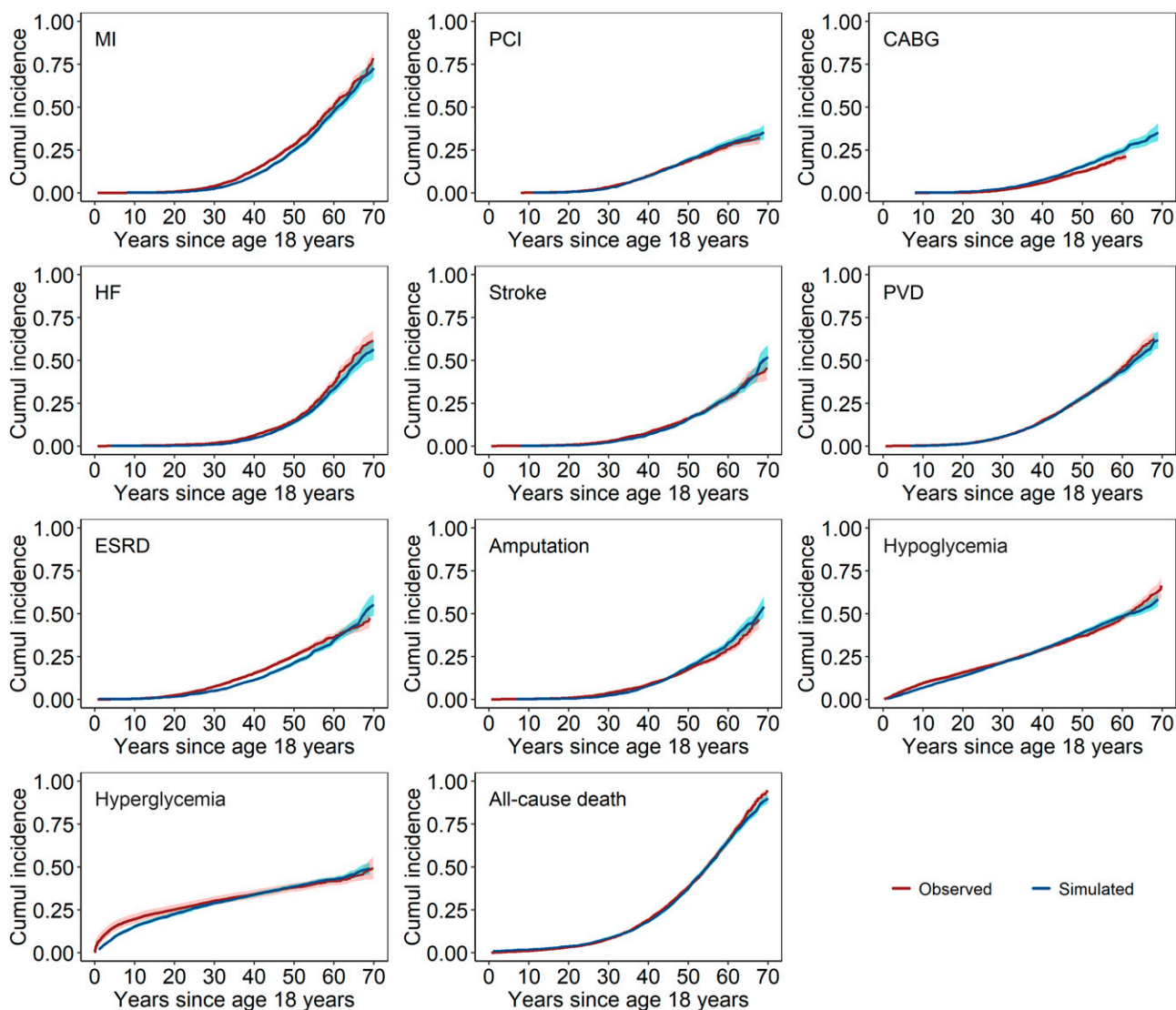


Figure 2—Observed and simulated cumulative incidence of each of 10 major diabetes-related complications and of all-cause mortality. The shaded areas in red and blue represent 95% confidence regions of the observed and simulated values, respectively. The curves were generated using Kaplan-Meier methods with a cumulative failure estimator. CV, cardiovascular; HF, heart failure.

cholesterol in this population, possibly through their impact on multiple complications, including ESRD, MI, heart failure, PVD, hyperglycemia, amputation, and death. BMI was also found to have a greater impact on outcomes than SBP and HDL and LDL cholesterol. This can be explained by the larger hazard ratios for BMI_cat2, BMI_cat3, BMI_cat5, and BMI_cat6 compared with those for SBP, HDL and LDL cholesterol in the equations predicting the risk of CVD, ESRD, stroke, and death (see Fig. 1), and a change by 1 SD (3.7 kg/m²) in BMI leading to a large shift in terms of the number of patients in different BMI categories. Sensitivity analysis of the effect of complication risk suggests that among eight complications, reducing the risk of CVD and

hypoglycemia has the greatest impact on improving life expectancy and complication-free survival time, respectively.

Our model is a major advance over existing published type 1 diabetes simulation models. A recent review of simulation models for type 1 diabetes identified 13 models (4), and there are other models for type 1 diabetes that were not captured in this review (9,35–39). All of these previously published models relied primarily on data from the Diabetes Control and Complications Trial (DCCT), which included only 1,441 patients with type 1 diabetes, and on its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) (40) for most of their inputs, supplemented by a variety of type 2 diabetes data from other studies to fill data

gaps. In contrast to most of these existing type 1 diabetes models (4,9,35–39), all equations for risk factor progression and complications in our model were derived solely from one cohort that included almost all of the patients diagnosed with type 1 diabetes in Sweden. We also captured the effect of metabolic memory on the occurrence of complications. The approach we used to calculate the time-weighted average HbA_{1c} represented a pooled effect of the glycemic control in the past. We realized that there are different methods for quantifying the metabolic memory, one of which is the integration of glycemic burden as the area under the HbA_{1c} curve >7% (41). While we found a strong correlation between this glycemic burden indicator

Table 1—Survival time of female and male patients in different baseline age groups

Baseline age-group	Age, mean (SD), years	N	Diabetes duration, mean (SD), years	Survival time, mean (95% CI),* years	
				Life expectancy†	Complication-free‡
Female					
20.0–29.9	24.1 (3.0)	2,887	11.8 (6.8)	46.4 (45.9–46.9)	28.3 (27.7–28.9)
30.0–39.9	34.5 (2.9)	2,514	20.2 (8.6)	37.3 (36.9–37.8)	23.3 (22.7–23.8)
40.0–49.9	44.3 (2.9)	1,974	29.8 (7.9)	28.7 (28.1–29.2)	17.3 (16.8–17.9)
50.0–59.9	54.3 (2.8)	1,646	38.6 (8.0)	21.1 (20.6–21.6)	12.3 (11.8–12.7)
60.0–69.9	63.6 (2.8)	824	47.0 (7.7)	14.7 (14.1–15.3)	8.5 (8–9)
70.0–79.9	73.4 (2.7)	260	55.2 (8.0)	9.9 (9.1–10.7)	6.2 (5.5–6.9)
80.0–89.9	81.7 (2.4)	30	63.1 (6.7)	5.9 (4.5–7.3)	3.3 (2.3–4.2)
Male					
20.0–29.9	24.3 (3.0)	3,706	10.7 (6.9)	43.5 (43.1–44)	27.1 (26.6–27.6)
30.0–39.9	34.5 (2.9)	3,185	19.1 (8.5)	35.4 (34.9–35.8)	22.3 (21.9–22.8)
40.0–49.9	44.3 (2.9)	2,487	28.2 (8.2)	26.5 (26.1–27)	15.6 (15.2–16.1)
50.0–59.9	54.3 (2.8)	1,951	37.6 (8.2)	19.1 (18.7–19.6)	10.6 (10.2–11)
60.0–69.9	63.6 (2.7)	954	46.5 (7.9)	14.1 (13.6–14.6)	7.7 (7.3–8.1)
70.0–79.9	73.3 (2.6)	239	53.7 (7.1)	9.5 (8.8–10.3)	5.4 (4.9–6)
80.0–89.9	82.3 (2.6)	26	63.5 (8.7)	5.2 (3.8–6.7)	3.5 (2.1–4.8)

*The 95% CI of the survival times were calculated based on data obtained from the second-order uncertainty analysis. †Defined as, for each individual, the number of years of life remaining from the age at baseline. ‡Defined as, for each individual, the difference in years between the age at the occurrence of the first complication after the baseline age or occurrence of death, whichever came first, and the age at baseline.

and our time-weighted average HbA_{1c} (Pearson correlation coefficient >0.7), a future study examining whether the former indicator improves the prediction

of the complications is warranted. With all hospitalizations and mortality recorded over a long follow-up period, we were able to adjust the survival models for

multiple complications and death, as well as capture the interdependency in the occurrence of the events. In addition, while the uncertainty in the model outcomes

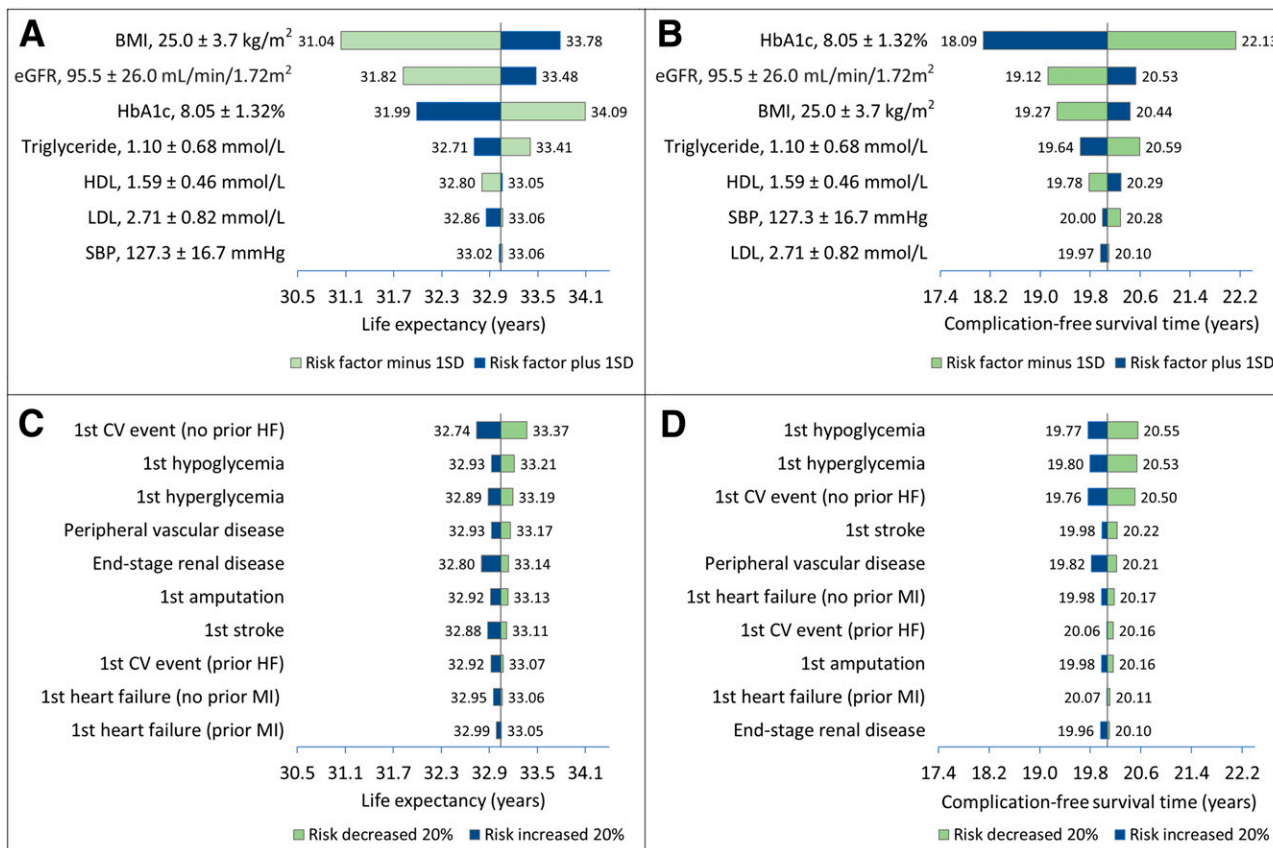


Figure 3—Tornado plots show the impact of changing one risk factor at a time by 1 SD on life expectancy (A) and complication-free survival time (B), and the impact of changing the annual probability of one major complication at a time by 20% on life expectancy (C) and complication-free survival time (D). The cardiovascular (CV) event is a composite end point including MI, PCI, and CABG. HF, heart failure.

due to patient variability and parameter uncertainty were accounted for only in a few of the existing type 1 diabetes models, we thoroughly addressed and minimized the first-order uncertainty by using large numbers of Monte Carlo replications until the projected outcomes stabilized and appropriately captured the second-order uncertainty by using probabilistic sensitivity analysis through bootstrapping the entire the study cohort.

The authors of the above-mentioned systematic review (4) recommended that a “best in class” type 1 diabetes model would use microsimulation methods to simulate micro- and macrovascular events, costs, and QALYs over a lifetime horizon, accounting for parameter uncertainty. While fulfilling most of these criteria, our model, however, requires further work, including determination of complication-related costs and health utility values and incorporation of these inputs into the model to enable its use as a fully functional tool for cost-utility analyses. Because the NDR captured only complications leading to hospitalization, events that occurred outside the hospital were not incorporated in our model. Although we captured a large number of events, the model does not predict occurrence of angina and mild hypoglycemia/hyperglycemia. While none of the existing simulation models for diabetes provides risk equations for all diabetes-related complications, we acknowledged that incorporating more events into a model may enhance its applications. Currently, it is unclear whether the occurrence of mild events, such as angina, substantially affect the incremental health outcome and cost of a new intervention, and this is an objective for our future research.

Possible changes in insulin treatment patterns during the follow-up period, including the introduction of insulin analogs, may have additional impacts on the occurrence of complications. Although we did not directly include drug therapies in the model, we have illustrated how the model could be used to capture the effects of changes in the risk of complications (Fig. 3C and D). This shows that our model can be adapted to account for complex and multifaceted effects of some therapies. However, this requires the user of the model to specify the effects of the treatment on risk factors and any addition of effects not captured in the model. The Real-World Progression in Diabetes (RAPIDs)

model for type 2 diabetes illustrated how these effects could be measured in a real-world setting (42), and this approach should be explored for type 1 diabetes in future work.

Validation using external data sets, such as the DCCT/EDIC (40), Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (43), and the Pittsburgh Epidemiology of Diabetes Complications Study (44), as well as cross-comparisons with other type 1 diabetes models (45–48), is also needed. Past validation efforts in type 2 diabetes suggest that testing a model against a variety of different external data sets provides an understanding of the model generalizability. Because we used data from patients aged 17 years and/or older, validation of our equations in children is also necessary. Despite these limitations, we would envisage that our model will provide an important tool for the economic evaluation of interventions for type 1 diabetes.

The development of this model is timely given the emergence of new technologies, such as hybrid closed-loop insulin pump systems (49), and interest in the potential role for oral agents, such as sodium–glucose cotransporter 2 inhibitors (50), for patients with type 1 diabetes. In many countries, access to new technologies requires a demonstration that these interventions represent value for money, and this will require increasing use of simulation models to quantify the benefits of interventions in terms of relevant outcomes such as QALYs.

Another limitation of our model involves the use of stepwise procedures to select variables in the regression models. Our equations might not contain all clinically important determinants of the occurrence of the complications and progression of risk factors. However, given that our model was primarily designed as a prediction rather than an explanation tool and that the number of potential covariates was very large, the stepwise procedures should be acceptable. Because we focused on the predictive power of the statistical models, there might be a risk of overfitting (i.e., our models fit well to the NDR data but they might not fit well to another data set). Therefore, external validation of our equations is needed in future research.

In conclusion, we have developed the first outcome model for type 1 diabetes that is based entirely on a nationwide

population and can be used to project the occurrence of major complications over the lifetime of the patients and to estimate life expectancy as well as complication-free survival time of the patients. Our face-valid and internally valid model offers an important tool to assist economic evaluations of and inform decisions on treatment strategies for type 1 diabetes.

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Author Contributions. All authors contributed to the study conception and design. A.T.-D. designed data visualization and created the figures. A.T.-D., J.K., D.P., T.W.C.L., and P.M.C. contributed to model development and data analyses. A.T.-D., A.J.P., D.P., B.E., A.-M.S., and P.M.C. contributed to acquisition of data. All authors participated in drafting the article and revising it critically for important intellectual content. All authors gave final approval of the version to be submitted. A.T.-D. and P.M.C. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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