A New Type 2 Diabetes Microsimulation Model to Estimate Long-Term Health Outcomes, Costs, and Cost-Effectiveness

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Abstract

Objectives: This study aimed to develop a microsimulation model to estimate the health effects, costs, and cost-effectiveness of public health and clinical interventions for preventing/managing type 2 diabetes.

Methods: We combined newly developed equations for complications, mortality, risk factor progression, patient utility, and cost—all based on US studies—in a microsimulation model. We performed internal and external validation of the model. To demonstrate the model's utility, we predicted remaining life-years, quality-adjusted life-years (QALYs), and lifetime medical cost for a representative cohort of 10 000 US adults with type 2 diabetes. We then estimated the cost-effectiveness of reducing hemoglobin A1c from 9% to 7% among adults with type 2 diabetes, using low-cost, generic, oral medications.

Results: The model performed well in internal validation; the average absolute difference between simulated and observed incidence for 17 complications was < 8%. In external validation, the model was better at predicting outcomes in clinical trials than in observational studies. The cohort of US adults with type 2 diabetes was projected to have an average of 19.95 remaining life-years (from mean age 61), incur $187 729 in discounted medical costs, and accrue 8.79 discounted QALYs. The intervention to reduce hemoglobin A1c increased medical costs by $1256 and QALYs by 0.39, yielding an incremental cost-effectiveness ratio of $9103 per QALY.

Conclusions: Using equations exclusively derived from US studies, this new microsimulation model achieves good prediction accuracy in US populations. The model can be used to estimate the long-term health impact, costs, and cost-effectiveness of interventions for type 2 diabetes in the United States.

Introduction

Diabetes is a common chronic disease that causes serious health complications and contributes to as many as 293 000 deaths and $370 billion in economic costs annually in the United States.[1–3] Type 2 diabetes accounts for 90% to 95% of all diabetes.[4] Interventions to prevent the complications of type 2 diabetes can ease the burden of the disease and lower costs, but these benefits may accrue gradually over years or even decades, whereas the interventions usually incur upfront costs. Therefore, it may be difficult for policy makers to compare the benefits and costs of an intervention before it is implemented.

Type 2 diabetes simulation models that project long-term health effects, costs, and cost-effectiveness of interventions can help policy makers make informed decisions that improve efficiency. Several type 2 diabetes simulation models exist.[5–11] Most of these models apply risk equations to predict the development of diabetes-related complications that were derived from the United Kingdom Prospective Diabetes Study (UKPDS).[7] These risk equations benefit from the long-term follow-up (up to 30 years; median follow-up of 17.6 years) of UKPDS. Nevertheless, the study began in the late 1970s; since then, the management of diabetes patients has changed, with new treatment goals for A1c, blood pressure, and lipids, and new medications and treatment devices have been introduced. Most importantly, trials conducted after 2000 often focused on a more intensive glycemic control than UKPDS did, bringing new evidence on the association between blood glucose and complication risks. In addition, advancements in rescue therapy and improved efficiency of the healthcare delivery system have significantly changed the survival pattern from acute events (eg, myocardial infarction [MI]).[12] Furthermore, the UKPDS was limited to newly diagnosed patients in the United Kingdom and may be less applicable to individuals with established type 2 diabetes or to countries such as the United States that have a different racial and ethnic composition. Costs of managing type 2 diabetes and its complications also differ widely between countries and are generally higher in the United States than in other countries.

In this article, we present a new type 2 diabetes microsimulation model focused on the US setting. Development of complications in the model is based on risk equations estimated using data from type 2 diabetes patients in 2 recent US clinical trials with large, diverse study populations and long-term follow-ups. Health utility equations were developed with data collected from the same study population and with a consistent definition of complications. Cost estimates of managing diabetes complications were developed using longitudinal design and one of the largest private insurance data sets.

Methods

Modeling Approach and Simulation Flow

The implemented model is a discrete time microsimulation with a 1-year time step. All risk, complication, and mortality equations are executed for each person every time step until that individual dies or the specified model stopping condition is satisfied. A microsimulation provides an efficient mechanism of implementing complication equations that not only take a variety of time-varying risk factors as input but also depend on an individual's disease history. Time-lagged and time-varying risk factors are required to update most complication equations in the model. The historical presence of certain complications or their occurrence in the current time step are further time-dependent inputs necessary to update most equations. A discrete time step of 1 year approximates the gradual development of complications over time in persons with type 2 diabetes and provides a reasonable time frame to capture the accumulation of diabetes-relevant complications that an individual may experience.

Figure 1 provides an overview of the model and its simulation flow. Users first specify the target population, including the number (N) of individuals and demographic variables, risk factors, and previous history of complication variables for the population to be simulated. Based on these specifications, the model generates the profiles of the N individuals. The default data source for characteristics is adults with diabetes in the National Health and Nutrition Examination Survey (NHANES) from 2009–2010 to 2015–2016, but the user can supply input data for individuals or population statistics from other data sources.

Projected disease progression for each individual in each year is determined by a set of 17 risk equations for complications that depend on the individual's characteristics. For each complication, the model draws a random number from a uniform distribution (0–1) and compares it with the probability from the risk equation. If the draw is less than the probability, the individual incurs the complication. After going through all the complication equations, the model evaluates risk equations for mortality that project whether the individual dies during that cycle. The complications and mortality risk equations are derived from pooled longitudinal data on US participants in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial, which continued in the ACCORD Follow-On Study, and the Action for Health in Diabetes[13] clinical trial and follow-on study. Estimation of the risk equations for complications and mortality are described below and in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.05.013.

After all individuals progress through the complication and mortality equations, the risk factors and complication histories for surviving individuals are updated using risk factor equations derived from the pooled ACCORD and Look AHEAD data. The individuals advance to the next year, where the simulation process repeats itself. The simulation continues until there are no individuals alive or the specified time horizon for the analysis is reached. Complications and life-years are summed across individuals and over time, yielding the cumulative cases per complication and remaining life-years.

Costs and patient utility in each year are based on incident complications in the year and previous complications. These complications enter an annual type 2 diabetes cost equation derived using longitudinal data from the Optum de-identified Normative Health Information database[14] and a patient utility equation derived from pooled ACCORD and Look AHEAD Health Utility Index Mark III measurements.[13] Costs and patient utility are then summed across individuals and over time. Summing patient utility over time produces quality-adjusted life-years (QALYs).

Interventions may change risk factors or directly affect the probability that a complication occurs. The model includes interventions for glycemic control, hypertension control, cholesterol reduction, and smoking cessation, and users can specify other interventions that affect risk factors or apply risk reductions to complication risk equations.

To evaluate the projected effects of an intervention, each individual is run through the model twice, once with no intervention (ie, the status quo) and once with the intervention. Costs and QALYs summed across all individuals in the intervention arm are compared with costs and QALYs summed across all individuals in the no-intervention arm. These comparisons generate the incremental costs and the incremental QALYs for the intervention, which can then be combined to calculate the incremental cost-effectiveness ratio for the intervention.

The model addresses stochastic uncertainty by allowing the user to increase the population size to reduce random variation in outcomes. Parameter uncertainty is addressed through probabilistic sensitivity analysis (PSA), repeatedly drawing sets of key model parameters from appropriate distributions, and simulating results for each set of parameters.

The components of the model are described in greater detail in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.05.013.

Risk Equations for Complications and Mortality

We estimated multivariate, parametric, Weibull hazards models to predict absolute and relative risk associated with 17 diabetes-related complications, including 2 alternative measures of hypoglycemia (Table 1). The Weibull specification allows risk to increase, stay the same, or decrease over time, other factors being equal. To make the risk equations more dynamic, we included time-varying covariates as explanatory variables to assess how the risk of a complication changes as risk factors and previous complications change over time.

We estimated 3 mortality equations, depending on whether the person has a history of previous cardiovascular disease (CVD) or a CVD event during the period. This approach reflects that mortality risk is high immediately after a CVD event and higher for persons with a history of CVD than for persons with no history of CVD. Equation 1 includes individuals who do not have a history of CVD; they remain in the equation until they die, have a qualifying CVD event, or are lost to follow-up. Once these individuals have a qualifying CVD event, they are moved into the second equation. Equation 2 includes individuals who have a qualifying CVD event (MI, stroke, congestive heart failure, angina, revascularization) during the study. This equation includes but is not limited to individuals

with a fatal MI or stroke who die on the same day as their event. Equation 3 includes individuals with a baseline history of CVD events or who had a CVD event during the trial and survived >1 year after the event. Each mortality equation estimates deaths from all causes, not just those from diabetes-related conditions.

Equations 1 and 3 are estimated as Gompertz hazard models, where the analytic time variable is age. Age is used as the analytic time variable because general population mortality rates increase with age. Equation 2 is a logistic equation where all observations within a year of a CVD event are collapsed down to a single observation per person. Equations 2 and 3 include the type of CVD event in the current year (equation 2) or previous years (equation 3).

Further details on estimation of the risk equations and the parameter estimates are presented in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.05.013.

Programming, Performance, and Code

The model is programmed in Python (Python Software Foundation) and runs on any operating platform as long as Python (version 3.8+) is installed. A single iteration (including the no-intervention and intervention arms) with a basic glycemic intervention, a population of 1000 individuals, and a time horizon of 30 years takes 1.4 seconds on a MacBook Pro laptop with the M1 pro CPU and 16GB of RAM. The same iteration with 10 000 and 100 000 individuals takes 113 and 114.8 seconds, respectively. This roughly linear scaling implies that n iterations of a particular simulation will take n * time(single run). Two areas are most promising for performance gains: (1) parallel processing the model and (2) minimizing input/output operations (Appendix 2, Section 7, in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.05.013).

The code for the model is available in a publicly accessible repository (https://github.com/RTIInternational/diabetes-sim-backend-only; a github account is required).

Validation of the Model

To validate how well the model predicts disease progression, we performed a series of internal and external validation exercises. Internal validation examines how well the model predicts the outcomes in the data set used to derive the equations in the model. External validation considers how well the model predicts outcomes in data sets that were not used to derive the equations in the model.

Internal validation

We simulated outcomes using an input data set consisting of baseline demographic, risk factors, and complication history for the 14 811 participants with complete data in the ACCORD and Look AHEAD public-use data sets. We then simulated the development of complications yearly for 13 years (the last year with a large number of observations within the study data) using the risk equations, applying the mortality equations and updating risk factors and previous complications at the end of each year.

To compare the observed and simulated values, we performed separate Kaplan-Meier[15] (KM) estimates on the observed and simulated results for each complication. The KM approach accounts for differences in sample size. We then compared the simulated KM estimates with the observed KM estimates at 13 years. We calculated the average ratio of simulated KM to observed KM cumulative incidence across complications. Values close to one suggest that, on average, the simulation model produces estimates that are close to the observed values. We also calculated the mean absolute deviation between the simulated and observed KM values. Values close to zero indicate that the deviations are small on average.

External validation

We performed external validation of the type 2 diabetes simulation model using aggregate, cohort-level data for 6 studies: Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE),[16] Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN), Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction (DECLARE) 58,[17] Veterans Affairs Diabetes Trial (VADT),[18] Jackson Health Study (JHS), and Multi-ethnic Study of Atherosclerosis (MESA).[16–21]

ADVANCE, ASPEN, DECLARE, and VADT were clinical trials that included separate control and intervention arms and only included people with diabetes, whereas JHS and MESA were observational cohort studies that included people with and without diabetes at baseline. Our external validation focused on JHS and MESA participants with diabetes at baseline.

For each study arm, we created an input data set of N individuals. Each individual was assigned baseline demographic, risk factor, and previous complication history variables drawn from distributions for the percentage or mean and SD for the variable in the study population. If published data for some of the variables were not available for a study, we applied statistics from ACCORD, Look AHEAD, or NHANES type 2 diabetes participants, depending on which data set's population was most comparable with the study's population. We ran the model for the integer number of years closest to the median number of years in the study and used the intervention screens to incorporate the changes in risk factors in each study arm.

We then compared the simulated number of complications and events in the model with the observed number of complications and events in the study arm. To account for differences between the integer number of years simulated in the model and the median follow-up in the study, we converted the simulated and observed events to rates per 100 life-years. We plotted the simulated versus observed rates by study across all complications and by individual complications across studies. Observed data for some complications were not available for all studies, and in some cases, the reported complications were defined differently from how the model complications were defined.

Simulating the Lifetime Health and Medical Cost of the US Population With Type 2 Diabetes (Application 1)

We used the model to predict the cumulative incidence of complications, costs, and QALYs for a population of 10 000 US representative adults with type 2 diabetes. To generate the simulation population, we entered the mean and SDs for demographic variables, risk factors, and baseline history of complications for adult participants with diabetes in 4 NHANES waves (Appendix 2, A2 Table 3, in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.05.013). We performed a PSA, running 100 iterations of 10 000 individuals while drawing complication costs and disutility values for each iteration based on their mean and standard error (SE). We ran the model until all individuals reached the end of life or 100 years of age.

Simulating the Cost-Effectiveness of an Intervention (Application 2)

To demonstrate the effect of an intervention in the model, we analyze a simple glycemic intervention that lowers hemoglobin A1c (HbA1c). We performed a PSA, running 100 iterations of 10 000 individuals with the intervention effects on HbA1c distributed normally (mean = 2%, 95% confidence interval bound by 0) and intervention costs distributed uniformly (mean = $361.50 per year ±25%); complication costs and disutility values were varied as in application 1. The effects and costs are based on taking 2 low-cost generic drugs: metformin and either a sulfonylurea or thiazolidine-dione, which each reduce HbA1c by 1% and cost $40 and $321.50 based on median annual prices for the generics on the Federal Fee Schedule. The intervention is applied to individuals aged 61 years with diabetes duration of 1 year who have an initial HbA1c of 9%. All other baseline variables are set equal to the mean values in the NHANES population with diagnosed diabetes. We assume that the intervention lasts for the individual's remaining lifetime or until the age of 100 years.

Results

Internal Validation

Results of the internal validation are shown in Figure 2, which plots simulated and observed incidence for individual complications based on the 13-year KM results. If the model predicts observed data perfectly, the points for each complication would fall along a 45-degree line with slope = 1 and intercept = 0. The dotted line in the graph represents the simple regression slope for the complication points. Its slope (1.0509) is a little > 1, and its intercept (0.0015) is close to 0.

The average ratio of simulated to observed cumulative incidence for the 17 complications was 1.047, indicating that the estimates are reasonably close to the observed values on average (see the Validation Report Supplemental Materials, Appendix 3, A3 Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.05.013). The mean absolute deviation was 0.079, indicating that the average absolute deviation is < 8%. The Validation Report also includes figures showing the simulation and observed KM survival curves for each complication for every year through year 13. In general, the simulation and observed survival curves are closely aligned.

External Validation

Figure 3 plots the predicted versus observed complication rates per 100 person-years across control and intervention arms of the ASPEN, ADVANCE, DECLARE, and VADT clinical trials and the single arms of the JHS and MESA observational studies. Many of the pairs cluster close to the 45-degree line, where the predicted and observed complication rates are equal, but there are obvious deviations from this relationship.

The Validation Report (Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.05.013) shows the results separately for the 4 trials and the 2 observational studies. Overall, the model predications appear closer to the observed rates for the clinical trials than for the observational studies. The Validation Report also shows predicted versus observed results for individual complications and mortality. For mortality, the model appears to underpredict mortality in several of the external validation exercises.

Application 1: Simulating the Lifetime Health and Medical Cost of the US Population With Type 2 Diabetes

The first 2 columns of Table 2 show the remaining life-years, costs, QALYs, and cumulative incidence of complications for the simulation of 100 iterations of 10 000 individuals with baseline characteristics derived from participants with diagnosed diabetes in 4 NHANES waves. On average, the remaining life expectancy is 19.95 (SE = 0.01) years, costs are $187 729 (SE = $1038), and QALYs are 8.79 (SE = 0.006) per person, when costs and QALYs are discounted at a 3% annual rate.

Neuropathy, microalbuminuria, and hypoglycemia requiring medical attention are among the most common complications. Among more severe complications, amputation and dialysis are relatively rare (< 1000 cases), blindness is relatively common (2865 cases), and CVD events range from stroke (900 cases) to revascularization (2723 cases), with angina (1223 cases), MI (1565 cases), and congestive heart failure (1755 cases) between these extremes.

Application 2: Simulating the Cost-Effectiveness of an Intervention

The glycemic intervention increases cost by $1256 (SE = $249) per person and results in increases of 0.98 (SE = 0.04) life-years and 0.39 (SE = 0.02) QALYs per person (the last 6 columns of Table 2). The incremental cost-effectiveness ratio is $9103 (SE = $4762) per QALY. The intervention reduces all complications except neuropathy, with the percentage reduction in a complication depending on the size of the hazard ratio for HbA1c in the complication's risk equation and its interplay with the history of other complications.

Conclusions

We developed a new diabetes simulation model to estimate the long-term health impacts, costs, and cost-effectiveness of interventions for preventing/managing type 2 diabetes. The key components in the model—risk equations, patient utility, and complication costs—are based on recent US studies, making the model especially relevant for US applications. The model accounts for US racial/ethnic groups, current US healthcare costs, and current US treatment patterns. Moreover, the modeling framework is flexible, allowing researchers

using the model to specify the effectiveness and costs of interventions, incorporate new complications, and change model parameters including complication costs and disutilities and discount factors.

We provided 2 applications to demonstrate the model's utility. The model can be used to predict remaining life-years, costs, and QALYs for different cohorts of adults with type 2 diabetes. In application 1, we presented the predictions for a representative cohort of adults with type 2 diabetes in the United States. Policy makers can also use the model to estimate the long-term outcomes and cost-effectiveness of interventions such as glycemic control (application 2). Users can choose from a list of interventions and vary the magnitude of intervention effects.

Results from the extensive internal and external validations showed our new model performed well. For internal validation, the predicted complications were close to the observed complications, and the average deviation between predicted and observed complications was < 10%. For external validation, we compared model predictions with outcomes from 2 observational studies and the treatment and control arms of 4 clinical trials. The model appeared to better estimate outcomes from the clinical trials than from the observational studies. The model appears more likely to underestimate the observed rates in the observational studies. There are at least 2 possible explanations for this result. First, participants in clinical trials may be healthier than the general population recruited for an observational study. Our risk equations were derived from ACCORD and Look AHEAD, and participants in those trials and 4 external validation clinical trials might have been healthier than the participants in the observational JHS and MESA studies, even after controlling for participant characteristics. Second, although ACCORD and Look AHEAD included significant numbers of white, black, and Hispanic people, we cannot fully rule out differences related to race/ethnicity or location.

For mortality, the model appears to underpredict mortality in several of the external validation exercises. Because underprediction of mortality could affect estimated costs, QALYs, and cost-effectiveness ratios in analyses with a long time horizon, we recommend calibrating mortality for analyses with time horizons > 10 years. Mortality calibration is discussed in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.05.013.

Our model has limitations, many of which are inherent to all disease simulation models. First, the data sources for the risk equations that drive disease progression in the model are clinical trials, ACCORD, and Look AHEAD, and their trial participants may not be representative of all US adults with type 2 diabetes. ACCORD focused on individuals with established diabetes and previous/high risk of CVD. Look AHEAD included some individuals with newly diagnosed diabetes but focused on individuals who were overweight or had obesity. Participants in clinical trials may also receive better care than the typical diabetes patient. Balanced against these limitations are the following strengths: ACCORD and Look AHEAD focus on US diabetes patients, measure complications regularly, have relatively long follow-ups, and have enough complications to support estimation of risk equations.

Second, the model can only directly predict the impact of interventions on a complication through the intervention's effect on risk factors that enter the risk equation for that complication. For example, if 2 medications each lower HbA1c by 1% and have no other effects on risk factors, the model will predict that the interventions have the same effect on complications. Recent clinical trials for newer diabetes medications appear to show larger-than-predicted risk reductions for CVD or renal outcomes.[17,22–25] Our model would not predict these effects prospectively. Nevertheless, once risk reductions have been identified, we can incorporate the risk reductions directly into the model to evaluate the medications' effects on outcomes and costs.

Third, simulation models often extrapolate outcomes observed in clinical studies to longer time horizons, different age groups, or different populations, and these extrapolations are not always validated. The longest follow-up in the ACCORD and Look AHEAD data that we analyzed was 13 years, which is longer than the follow-up in most studies of type 2 diabetes except UKPDS. ACCORD and Look AHEAD covered participants aged 45 to 75 years at baseline and included a large share of participants who had diabetes for > 10 years. We believe that the model may accurately represent older adults with diabetes. The model has not been validated for people with type 2 diabetes in their 20s and 30s or for people outside the United States, and care should be taken when applying the model to these populations.

The purpose of the model is to inform policy makers about the benefits and costs of public health policies and clinical interventions for preventing/managing type 2 diabetes. These impacts are difficult to compare without a simulation model because of the difference in timing between the costs and benefits of an intervention. Choosing between interventions based on long-term benefits and costs can reduce the burden of diabetes and lead to more efficient use of healthcare resources.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Cowie CC, Casagrande SS, Menke A et al. Diabetes in America. 3rd ed. Bethesda, MD: National Institutes of Health; 2018.

2. Alva ML, Hoerger TJ, Zhang P, Cheng YJ. State-level diabetes-attributable mortality and years of life lost in the United States. Ann Epidemiol. 2018;28(11):790–795. [PubMed: 30245053]

3. American diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care. 2018;41(5):917–928. [PubMed: 29567642]

4. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2020. https://www.cdc.gov/diabetes/pdfe/data/statistics/national-diabetes-statistics-report.pdf. Accessed January 31, 2023.

5. Brown JB, Russell A, Chan W, Pedula K, Aickin M. The global diabetes model: user friendly version 3.0. Diabetes Res Clin Pract. 2000;50(suppl 3):S15–S46. [PubMed: 11080561]

6. The CDC Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA. 2002;287(19):2542–2551. [PubMed: 12020335]

7. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30-year United Kingdom 18. Prospective Diabetes Study: UKPDS 82. Diabetologia. 2013;56(9):1925–1933. [PubMed: 23793713]

8. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE diabetes model. Value Health. 2014;17(6):714–724. [PubMed: 25236995]

9. Shao H, Fonseca V, Stoecker C, Liu S, Shi L Novel risk engine for diabetes progression and mortality in USA: building, relating, assessing, and validating outcomes (BRAVO). Pharmacoeconomics. 2018;36(9):1125–1134. [PubMed: 29725871]

10. Willis M, Asseburg C, He J. Validation of economic and health outcomes simulation model of type 2 diabetes mellitus (ECHO-T2DM). J Med Econ. 2013;16(8):1007–1021. [PubMed: 23718682]

11. Ye W, Brandle M, Brown MB, Herman WH. The Michigan model for coronary heart disease in Type 2 diabetes: development and validation. Diabetes Technol Ther. 2015;17(10):701–711. [PubMed: 26222704]

12. Chatterjee P, Joynt Maddox KE. US national trends in mortality from acute myocardial infarction and heart failure: policy success or failure? JAMA Cardiol. 2018;3(4):336–340. [PubMed: 29541764]

13. Neuwahl SJ, Zhang P, Chen H, et al. Patient health utility equations for a type 2 diabetes model. Diabetes Care. 2021;44(2):381–389. [PubMed: 33277301]

14. Yang W, Cintina I, Hoerger T, et al. Estimating costs of diabetes complications in people <65years in the U.S. using panel data. J Diabetes Complications. 2020:34:107735. [PubMed: 32962890]

15. Look AHEAD Research Group, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369(2):145–154 [published correction appears in N Engl J Med. 2014;370(19):1866]. [PubMed: 23796131]

16. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of coronary heart disease endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care. 2006;29(7):1478–1485. [PubMed: 16801565]

17. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–357. [PubMed: 30415602]

18. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129–139 [published correction appears in N Engl J Med. 2009 Sep 3;361(10):1028 [published correction appears in N Engl J Med. 2009;361(10):1024–1025]. [PubMed: 19092145]

19. ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560–2572. [PubMed: 18539916]

20. Taylor HA Jr Wilson JG, Jones DW, et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. Ethn Dis. 2005;15(4 suppl 6):S6–4–S17.

21. Bild DE, Bluemke DA Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002;156(9):871–881. [PubMed: 12397006]

22. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311–322. [PubMed: 27295427]

23. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–657. [PubMed: 28605608]

24. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22): 2117–2128. [PubMed: 26378978]

25. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–1844. [PubMed: 27633186]
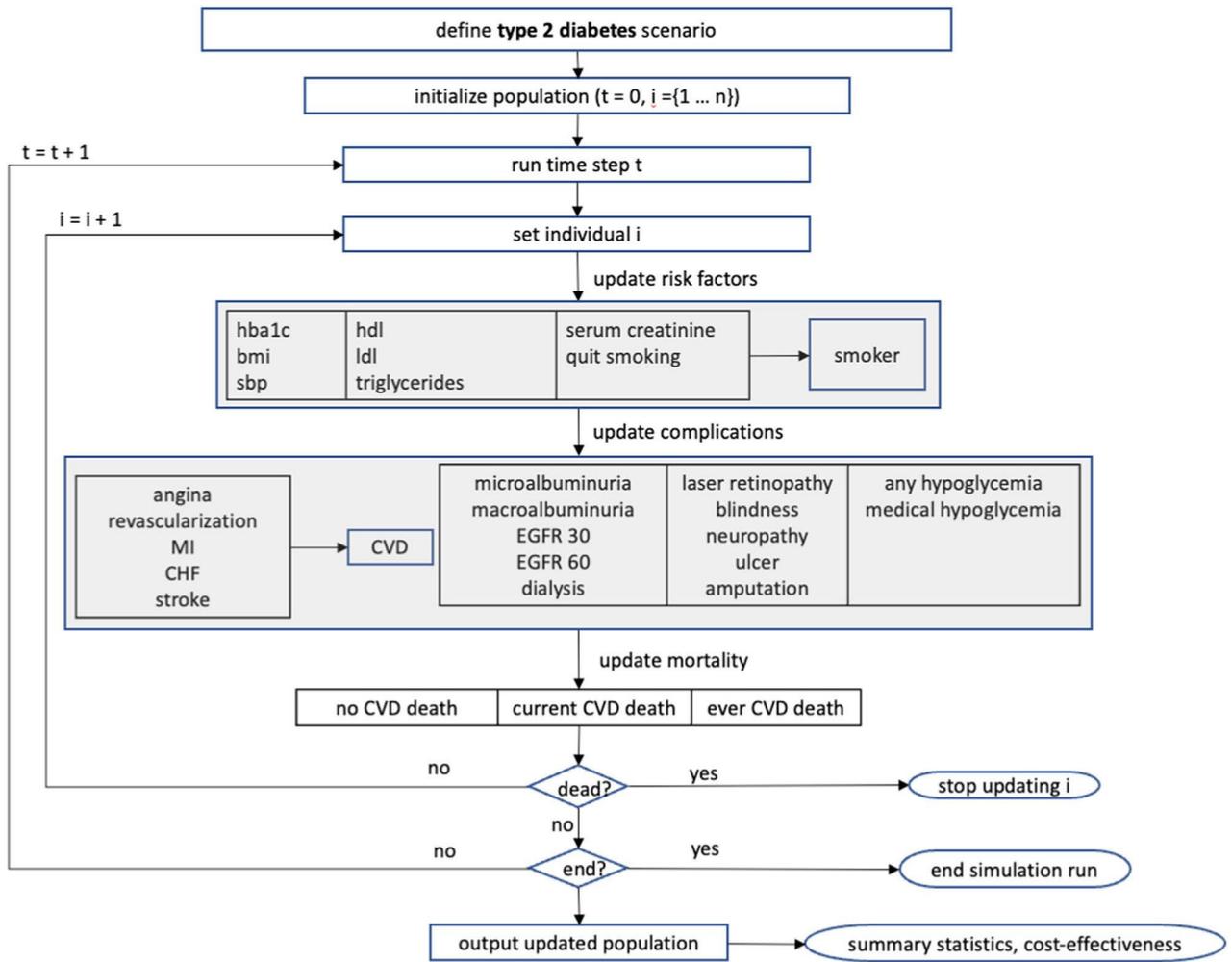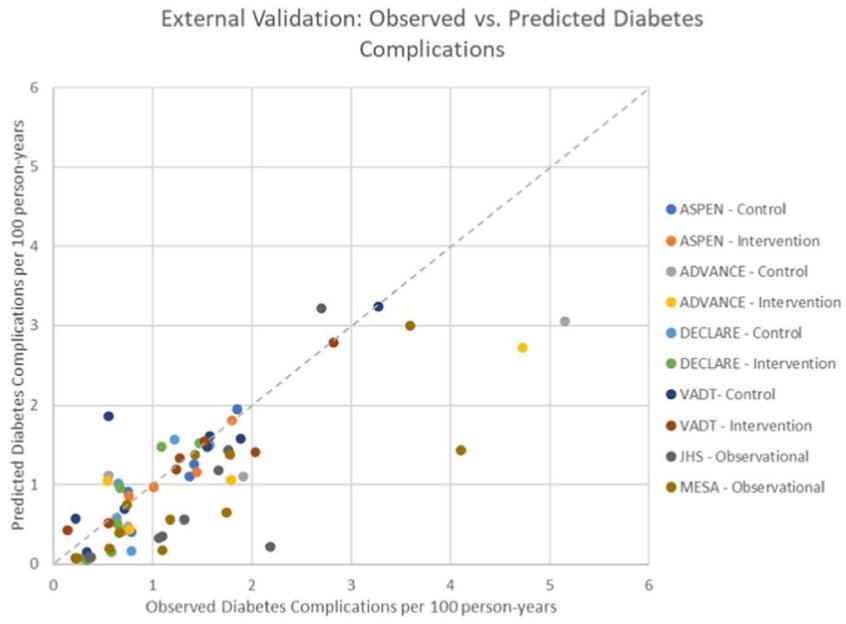
Figure 1.
Overview of the model and simulation flow. Once a scenario has been defined, the input population is initialized at t = 0. During initialization, baseline values for all risk factors and complication histories are calculated and any selected basic intervention is applied. After initialization, the simulation runs t time steps of the model and loops over all living individuals (i) every time step (t). Within each time step, risk factors are updated first in random order except for the update to an individual's smoking state, which is always updated last. The update of risk factors at t = 1 accounts for baseline values of the risk factors. Next, all previous history of complication variables are updated, again in random order except for CVD. CVD state is updated after the set of macrovascular complications has been updated. Mortality is updated last, depending on the CVD state of an individual. Not shown in the figure are time-invariant risk factors: age at entry, diabetes duration at entry, accord, postsecondary education status. Black, Hispanic, other race.
bmi indicates body mass index; CHF, congestive heart failure; CVD, cardiovascular disease; EGFR 30 (60), estimate glomerular filtration rate < 30(60) mL/min/1.73m^2; hba1c, glycated hemoglobin A1c; hdl, HDL cholesterol; ldl, LDL cholesterol; MI, myocardial infarction; sbp, systolic blood pressure.
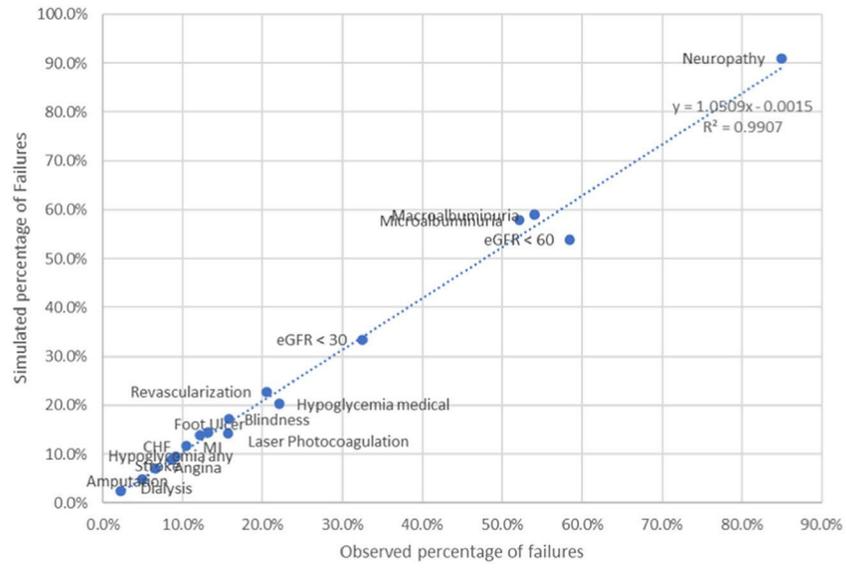
Figure 2.
Simulated versus observed complications at year 13 (internal validation).

Figure 3.
Observed versus predicted diabetes complication rates by study.

Table 1.

Risk equations estimated for type 2 diabetes complications using pooled data from ACCORD and Look AHEAD.

Complication	Description	Notes
Myocardial infarction	Fatal and nonfatal	
Stroke	Fatal and nonfatal	
Angina	Hospitalization for angina	
Congestive heart failure	Fatal and nonfatal	
Revascularization	Procedure	
Microalbuminuria	Albumin/creatinine ratio (ACR) ≥ 30 mg/g	
Microalbuminuria to macroalbuminuria	ACR > 300 mg/g	Estimated only for those with microalbuminuria
Chronic kidney disease (CKD) stage 3	Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2	
CKD stage 4	eGFR< 30 mL/min/1.73 m^2	Estimated only for those with CKD stage 3
Dialysis	Event	
Laser photocoagulation	Procedure	
Impaired vision/blindness	Snellen fraction < 20/200	
Neuropathy	Michigan Neuropathy Screening Instrument score > 2 (based on exam)	ACCORD/ACCORDION data only
Foot ulcer	Based on foot exam	ACCORD/ACCORDION data only
Amputation	Lower extremity amputation	ACCORD/ACCORDION data only
Hypoglycemia—any assistance	Event requiring assistance of another person	ACCORD but not ACCORDION, Look AHEAD data
Hypoglycemic event needing medical assistance	Event requiring medical assistance	ACCORD/ACCORDION data only

ACCORD indicates Action to Control Cardiovascular Risk in Diabetes; ACCORDION, Action to Control Cardiovascular Risk in Diabetes Follow-On Study.

Table 2.

Remaining life-years, costs, QALYs, and cumulative complications for application 1 and application 2 simulations.

Outcome	Application 1: representative sample of 10 000 individuals with type 2 diabetes		Application 2: glycemic control intervention reducing HbA1c from 9% to 7% (N = 10 000, age = 61, time horizon = lifetime)					
	No intervention		Intervention		No intervention		Incremental	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Per person								
Remaining life-years (undiscounted)	19.9552	0.0134	21.4212	0.0397	20.4416	0.0108	0.9796	0.0398
Costs (discounted)	$187 729	$1038	$151 689	$1151	$150 433	$1030	$1256	$249
QALYs (discounted)	8.7947	0.0060	10.7658	0.0159	10.3747	0.0058	0.3911	0.0158
ICER ($/QALY)	NA	NA	NA	NA	NA	NA	$9103	$4762
Cumulative cases								
Amputation	368	1.52	201	3.30	287	1.71	−86	3.54
Angina	1223	3.45	1575	6.42	1719	3.56	−144	6.01
Blindness	2865	4.59	3029	6.17	3130	4.50	−101	5.65
CHF	1755	3.68	1508	8.62	1710	3.67	−202	8.82
Dialysis	940	2.90	589	3.14	659	2.47	−70	3.51
eGFR < 30	1604	3.36	1004	4.56	1071	2.83	−68	4.94
eGFR < 60	3407	4.41	3814	5.67	3888	4.35	−74	5.70
Hypoglycemia, medical	3737	7.07	3965	17.58	4402	7.64	−437	17.96
Laser retinopathy	3197	4.76	2628	11.70	2916	4.45	−287	12.84
Macroalbuminuria	3805	4.59	3314	24.69	3941	4.69	−626	25.35
MI	1565	4.60	1986	10.94	2258	4.51	−272	10.70
Microalbuminuria	5245	4.29	5992	14.65	6315	5.15	−323	13.70
Neuropathy	8695	3.59	9415	2.61	9403	2.56	12	3.10
Revascularization	2723	6.60	3495	21.80	3971	7.81	−477	20.65
Stroke	900	3.30	1222	8.44	1413	4.13	−191	8.29
Foot ulcer	2913	6.39	3333	10.35	3546	6.43	−213	9.63

Note. Mean and SE are based on 100 iterations of 10000 individuals per iteration. Costs and QALYs are discounted at a 3% annual rate. Remaining life-years are not discounted. CHF indicates congestive heart failure; eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio; HbA1c, hemoglobin A1c; MI, myocardial infarction; NA, not available; QALY, quality-adjusted life-year; SE, standard error.