Cost-effectiveness of alternative thresholds of the fasting plasma glucose test to identify the target population for type 2 diabetes prevention in adults aged ≥45 years

Appendix: Technical Report

I. Simulation design

Our simulation model is a deterministic Markov-based model, in which the progression of type 2 diabetes were simulated based on annual transition probabilities from a person's diagnosis to death. In the simulation, we started with a nationally representative cohort of one million non-diabetic individuals aged ≥ 45 years. To ensure the sample to be nationally representative, we specified the distribution of age, sex, race/ethnicity, smoking status, hypertension, and hyperlipidemia, based on data from the National Health and Nutrition Examination survey (NHANES) 2006-2010. Because it is a deterministic process, no first-order random variation was built in the model. We addressed the uncertainty of the simulation using probabilistic sensitivity analysis (described below in VII).

Figure A1 shows the basic design of the simulation process. In the simulation, individuals underwent a one-time fasting plasma glucose test. People who were identified to have elevated fasting glucose were assumed to be referred to a lifestyle intervention program and annual screening test for diabetes. The intervention and screening continued annually until individuals develop diabetes or die. People who were test negative in the test developed type 2 diabetes based on the incidence rates observed in the ARIC study.

People with impaired fasting glucose (IFG) may also develop diabetes-related complications and comorbid conditions before they develop diabetes. The incidence of hypertension and dyslipidemia were modeled based on data from the Diabetes Prevention Program[1] The development of coronary heart disease during IFG was simulated based on data from the Framingham Heart Study.[2] Levitzky and colleagues found that IFG was associated with increased risk of coronary heart disease. The progression of stroke during IFG was based on a meta-analysis.[3] Based on a systematic review, Lee and colleagues found that IFG was associated with an increased risk of stroke even after adjustment for established cardiovascular risk factors. The transition probabilities are shown in Table A1.

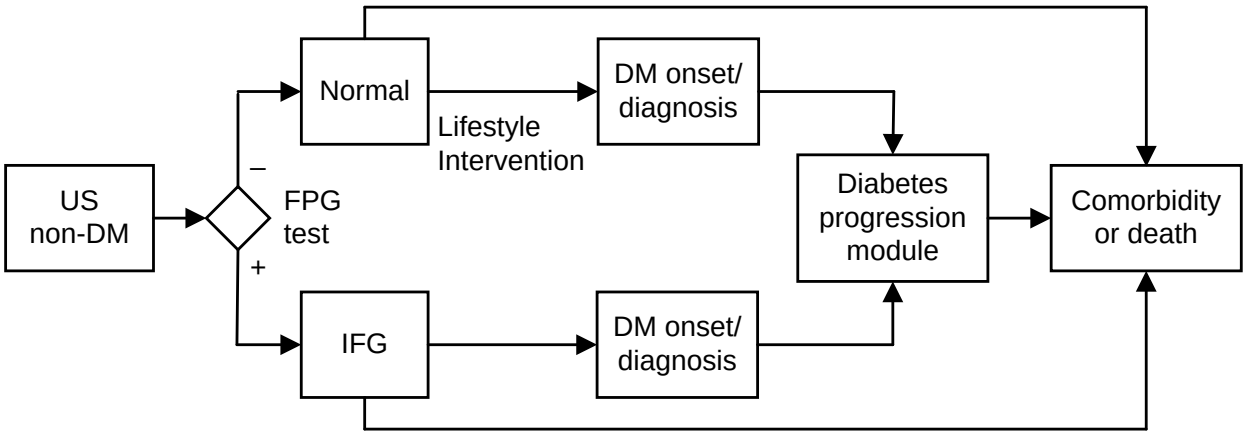


Figure A1. Basic structure of the Markov Simulation Model

Abbreviations: DM diabetes mellitus; FPG fasting plasma glucose; IFG impaired fasting glucose

Note: Normal: Adults with FPG < cutoff; IFG: Adults with FPG ≥ cutoff.

Table A1. Disease progression parameters during IFG

Disease progression during prediabetes	Parameter	Source
Comorbid conditions		
Hypertension hazard rates	0.0506	DPP
High cholesterol hazard rates	0.0375	DPP
COMPLICATIONS		
Coronary heart disease: FPG (mg/dl)[a]		Levitzky et al.
Women		
≤ 99	0.8	
100 to 109	1.3	
110 to 125	2.3	
Men		
≤ 99	2.9	
100 to 109	2.9	
110 to 125	3.0	
Stroke:	1.21	Lee et al.

[a] Adjusted hazard ratios, HbA1c 5.0% to <5.5% as ref
DPP, Diabetes Prevention Program

After the diagnosis of diabetes, the development of diabetes complications in both groups was based on the observations of the United Kingdom Prospective Diabetes Study (UKPDS).[3] Briefly, the model simulates the development of five major diabetic complications, including nephropathy, neuropathy, retinopathy, coronary heart disease, and stroke. Individuals progress simultaneously on five different disease paths. Disease paths and disease states in each path are as follows:

(1) Nephropathy (shown in Figure A2)
- Normal (n_1)
- Low microalbuminuria/high microalbuminuria (n_2)
- Clinical nephropathy (n_3)
- End stage renal disease (ESRD) (n_4)
- ESRD death (n_D)

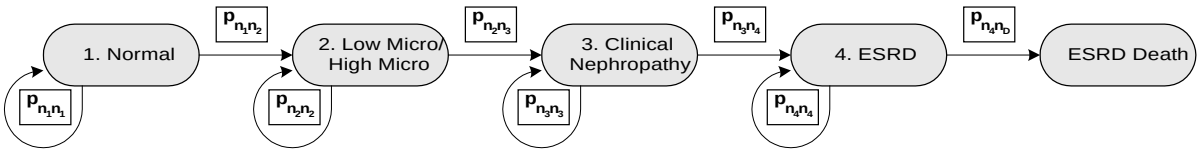


Figure A2. States and Transition Probabilities: Nephropathy

Table A2 shows the baseline hazard rates for nephropathy. The microalbuminuria and clinical nephropathy rates are derived from the transition probabilities reported in Figure 1 in UKPDS 64. We converted the probabilities reported in the figure into hazard rates using Equation (1). Calculation of the clinical nephropathy rates was more complicated, because we needed hazard rates conditional on having had microalbuminuria. We first simulated the number of patients who had progressed to microalbuminuria at each year. We then calculated the clinical nephropathy transition probability necessary to yield the number of patients who had progressed to nephropathy by the end of the study period. Finally, we converted this transition probability into a hazard rate.

Table A2. Baseline Hazard Rates: Nephropathy

Years Since Diagnosis	Normal to Microalbuminuria (No Hypertension)	Normal to Microalbuminuria (Hypertension)	Microalbuminuria to Clinical Nephropathy (No Hypertension)	Microalbuminuria to Clinical Nephropathy (Hypertension)	Clinical Nephropathy to ESRD
0–11	0.0202	0.0202	0.0284	0.0284	0.02327
12–19	0.0202	0.0202	0.0284	0.0284	0.02327
20+	0.0202	0.0202	0.0284	0.0284	0.02327

The hazard rates for ESRD were estimated by Eastman et al. using data reported in Humphrey et al. (1989). The same rates are applied to both nonhypertensive and hypertensive patients.

Table A3 shows the baseline transition probabilities for nephropathy. These numbers can be compared to the hazard rates in Table 7a to show the differences between hazard rates and transition probabilities in the nephropathy disease path. For example, the baseline hazard rate for microalbuminuria 0 to 11 years after diagnosis for persons without hypertension is 0.03253, while the corresponding transition probability is 0.03201. Because the hazard rate in this case is close to zero, its difference from the corresponding transition probability is small. The baseline hazard rate for clinical nephropathy 0 to 11 years after diagnosis for persons with hypertension is 0.1505, while the corresponding transition probability is 0.1397. The difference between the hazard rate and the transition probability is greater in this case because the hazard rate is larger to begin with.

Table A3. Baseline Transition Probabilities: Nephropathy

Years Since Diagnosis	Normal to Microalbuminuria (No Hypertension)	Normal to Microalbuminuria (Hypertension)	Microalbuminuria to Clinical Nephropathy (No Hypertension)	Microalbuminuria to Clinical Nephropathy (Hypertension)	Clinical Nephropathy to ESRD
0–11	0.02	0.02	0.019	0.019	0.022
12–19	0.02	0.02	0.019	0.019	0.022
20+	0.02	0.02	0.019	0.019	0.022

(2) Neuropathy (shown in Figure A3)
- Normal
- Peripheral neuropathy (u_2)
- History of LEA (u_3)
- LEA death (u_D)

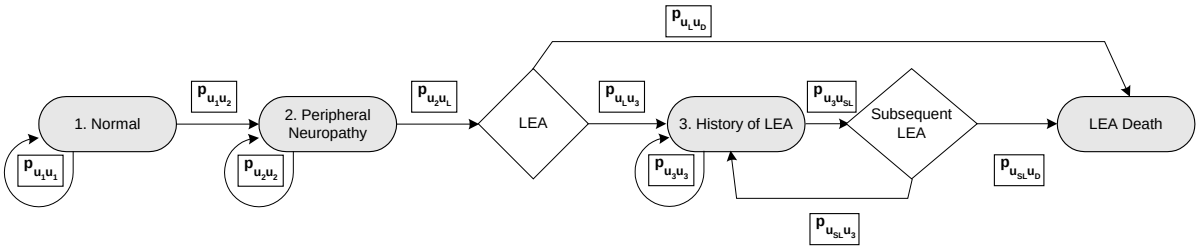


Figure A3. States and Transition Probabilities: Neuropathy

Our neuropathy path includes the four states and two intermediate events that are shown in Figure 2. An individual who begins in the Normal state may progress to peripheral neuropathy with probability P_{u1u2} or may remain in the Normal state with probability P_{u1u1}. An individual with peripheral neuropathy may experience an LEA with probability P_{u2uL}. At this point, the individual enters the bridge model and—within the time period—either dies and moves to LEA Death with probability P_{uLuD} or survives and moves to the History of LEA state with probability P_{uLu3}. Once an individual reaches the History of LEA state, she will remain there (P_{u3u3}) unless she experiences a subsequent LEA event. The individual will enter the subsequent LEA bridge model with probability P_{u3uSL}. At this point, the individual either dies and moves to LEA Death with probability P_{uSLuD} or survives and returns to the History of LEA with probability P_{uSLu3}.

Table A4 shows the baseline hazard rates for neuropathy. The hazard rate for peripheral neuropathy is derived from the 9-year value in Figure 8 in UKPDS 33 (1998) using Equation (1). The probability for a subsequent LEA and the mortality rate for LEA come from Tables 18.8 and 18.10, respectively, in Reiber, Boyko, and Smith (1995). Separate hazard rates for persons with hypertension are not available from the UKPDS hypertension study; therefore, we apply the same rates to persons with and without hypertension.

Table A4. Baseline Hazard Rates: Neuropathy

Years Since Diagnosis	Normal to Peripheral Neuropathy	Peripheral Neuropathy to LEA	History of LEA to Subsequent LEA(s) (Transition Probability)	Death from LEA (Transition Probability)	Probability of Foot Ulcers (States of Neuropathy and History of LEA)
0–14	0.03600	0.00672	0.11	0.105	0.04

We estimated the conditional hazard rate of 0.00672 using the following cumulative incidence rates taken from Humphrey et al. (1994): 1.6 percent at 8 years, 3.2 percent at 13 years, 5.5 percent at 19 years, and 11 percent at 25 years.

Individuals in the neuropathy and History of LEA states are also assumed to face a 4 percent annual incidence of diabetic foot ulcers. This incidence rate is assumed to be independent of past history of foot ulcers. Estimates of the incidence of diabetic foot ulcers for the entire type 2 population include 2.6 percent for 1 year (Moss, Klein, and Klein, 1992) and 5.8 percent cumulative incidence for 3 years (Ramsey et al., 1999). Most (78 percent) foot ulcers occur among persons with neuropathy (Reiber, Boyko, and Smith, 1995). Assuming that the annual incidence rate for all persons with type 2 diabetes is 2 percent, persons with neuropathy account for 80 percent of foot ulcers, and about 40 percent of persons with type 2 diabetes have neuropathy yields an estimated annual incidence of 4 percent for persons with neuropathy.

Table A5 shows the baseline transition probabilities for neuropathy. A comparison of these numbers to Table 8a shows the differences between hazard rates and transition probabilities in the neuropathy disease path. For example, the baseline hazard rate for peripheral neuropathy 0 to 7 years after diagnosis is 0.03600, while the corresponding transition probability is 0.03536. Because the hazard rate is close to zero, its difference from the corresponding transition probability is small. Likewise, the baseline hazard rate for LEA is 0.00642, while the corresponding transition probability is 0.0067.

Table A5. Transition Probabilities for Neuropathy

Years Since Diagnosis	Normal to Peripheral Neuropathy	Peripheral Neuropathy to LEA	History of LEA to Subsequent LEA(s)	Death from LEA	Probability of Foot Ulcers (States of Neuropathy and History of LEA)
0–14	0.03536	0.0067	0.11	0.105	0.04

(3) Retinopathy (shown in Figure A4)
- Normal (r_1)
- Photocoagulation (r_2)
- Blind (r_3)

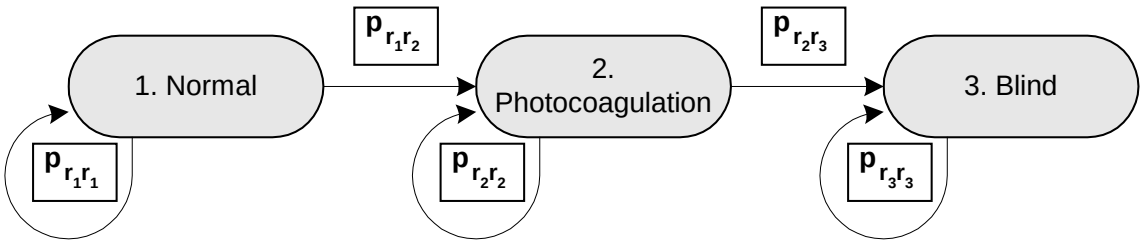


Figure A4. States and Transition Probabilities: Retinopathy

Table A6 shows the baseline hazard rates for retinopathy. The photocoagulation rate for persons with no hypertension is taken directly from Figure 5 in UKPDS 33 (1998), while the rate for persons with hypertension is taken directly from Figure 8 in UKPDS 38 (1998). Data from Figure 5 in UKPDS 38 were also used to derive the hazard rate for blindness, conditional on photocoagulation. We combined data from persons with intensive glycemic control and conventional glycemic control in the calculation, under the assumption that the hazard rate for blindness—conditional on photocoagulation—is the same for both groups. We also assumed that this rate was the same for persons with and without hypertension. We first simulated the number of patients who had progressed to photocoagulation at each year. We then calculated the blindness transition probability necessary to yield the number of patients who had progressed to blindness by the end of the study period. Finally, we converted this transition probability into a hazard rate.

Table A6. Baseline Hazard Rates: Retinopathy

Years Since Diagnosis	Normal to Photocoagulation (No Hypertension)	Normal to Photocoagulation (Hypertension)	Photocoagulation to Blindness
All years	0.01100	0.01660	0.10650

Table A7 shows the baseline transition probabilities for retinopathy. These can be compared to the hazard rates in Table A6 to show the differences between hazard rates and transition probabilities.

Table A7. Transition Probabilities for Retinopathy

Years Since Diagnosis	Normal to Photocoagulation (No Hypertension)	Normal to Photocoagulation (Hypertension)	Photocoagulation to Blindness
All years	0.01094	0.01646	0.1010

(4) Coronary Heart Disease (CHD) (an abbreviated version is shown in Figure A5)
- Normal (c_1)
- Angina (c_2)
- History of Cardiac Arrest (CA)/Myocardial Infarction (MI) (c_3)
- CHD death (c_d)

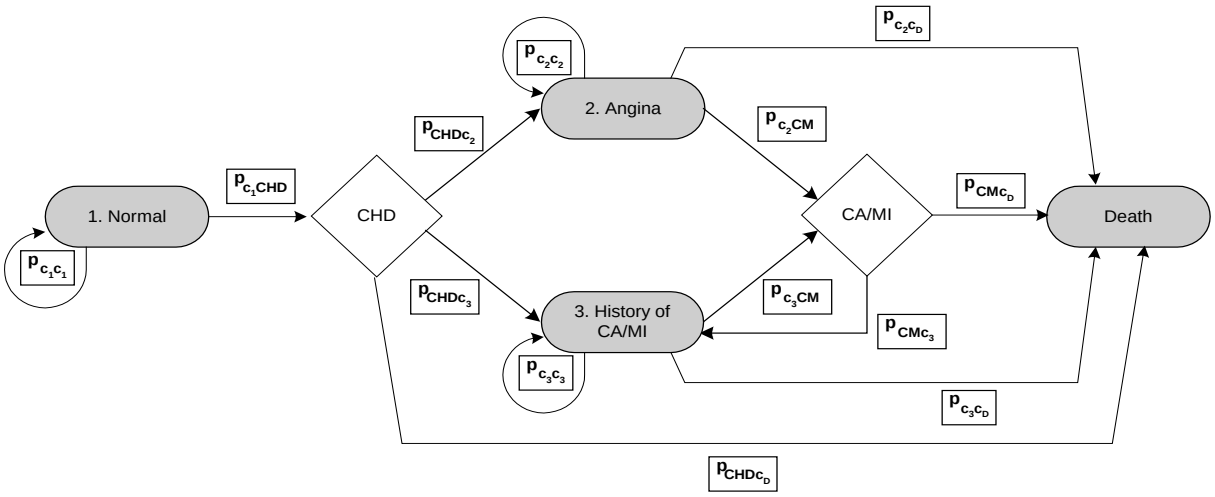


Figure A5. States and Transition Probabilities: Coronary Heart Disease

The CHD component of our model is an abbreviated version of the Coronary Heart Disease Policy Model developed at Harvard University by Weinstein et al. (1987). The complete version of the Coronary Heart Disease Policy Model has 12 CHD states. We simplified the model by eliminating the states associated with coronary artery bypass graft surgery and by combining the CA and MI states into a single state. As a result, our model includes four CHD states: Normal, Angina, History of CA or MI, and Death. Due to the very low survival rates associated with CA, the transition probabilities given a history of CA/MI are those given a history of MI; however, mortality rates associated with CA are incorporated as appropriate. Most of the probabilities in the model are derived from the probabilities outlined by Weinstein et al. (1987) and its updated version in Hunink et al. (1997).

The basic structure for the CHD component is shown in Figure A6. The states labeled A (Normal), B (Angina), C (History of CA/MI), and D (Death) represent the states where individuals end up at the end of each year; these are the actual states that are programmed in the model. The remaining diamonds and arrows show what happens to the individual within the course of each year as they move between states (hence the shading for "First Year Events" and "Within Year Events"). These events are incorporated within the model's transition probabilities, as described below.

Consider an individual beginning at A in the Normal state. With probability P_1, the individual may experience a CHD event. Otherwise, the individual either dies from a non-CHD event or remains in the Normal state. This part of our model corresponds to the Demographic–Epidemiologic model component of the Coronary Heart Disease Policy Model, so named because P_1 depends on demographic and epidemiologic factors such as age, sex, blood pressure, and cholesterol levels. Unlike the Coronary Heart Disease Policy Model, the P_1 in our model includes a variable for the presence of diabetes. P_1 is calculated from Framingham data using estimation equations developed by Anderson et al. (1990).

Following the Coronary Heart Disease Policy Model, we carefully model what happens to an individual in the first 30 days following their first CHD event. This corresponds to the bridge model component of the Coronary Heart Disease Policy Model. If an individual experiences a first CHD event, the event may be either angina with probability P_2 or CA/MI with combined probability P_3. If the first event is angina, there is a cost associated with the immediate treatment of angina but no immediate other events. If the first event is CA or MI, the individual may either die within 30 days with probability P_{12} or survive to move to the new History of CA/MI box with probability P_{13}.

The Coronary Heart Disease Policy Model allows surviving individuals to incur a second CHD event during the remainder of the year (11 months) following the first 30 days of the first CHD event (this is part of the model's Disease History model component), and we have also incorporated this possibility within our model. Thus, an individual whose first event is angina may either die from angina-related causes (with probability P_4), experience a CA/MI (P_6), or continue on with angina (P_8) during the remainder of the year following the first CHD event. If they experience a CA/MI, they may either die within 30 days (P_{10}) or survive (P_{11}). An individual who survives an initial CA/MI may experience a second CA/MI (P_{15}), die from chronic conditions related to MI (P_{14}), or continue on with no

further events (P_{16}). An individual who experiences a second CA/MI will either die within 30 days (P_{17}) or survive (P_{18}).

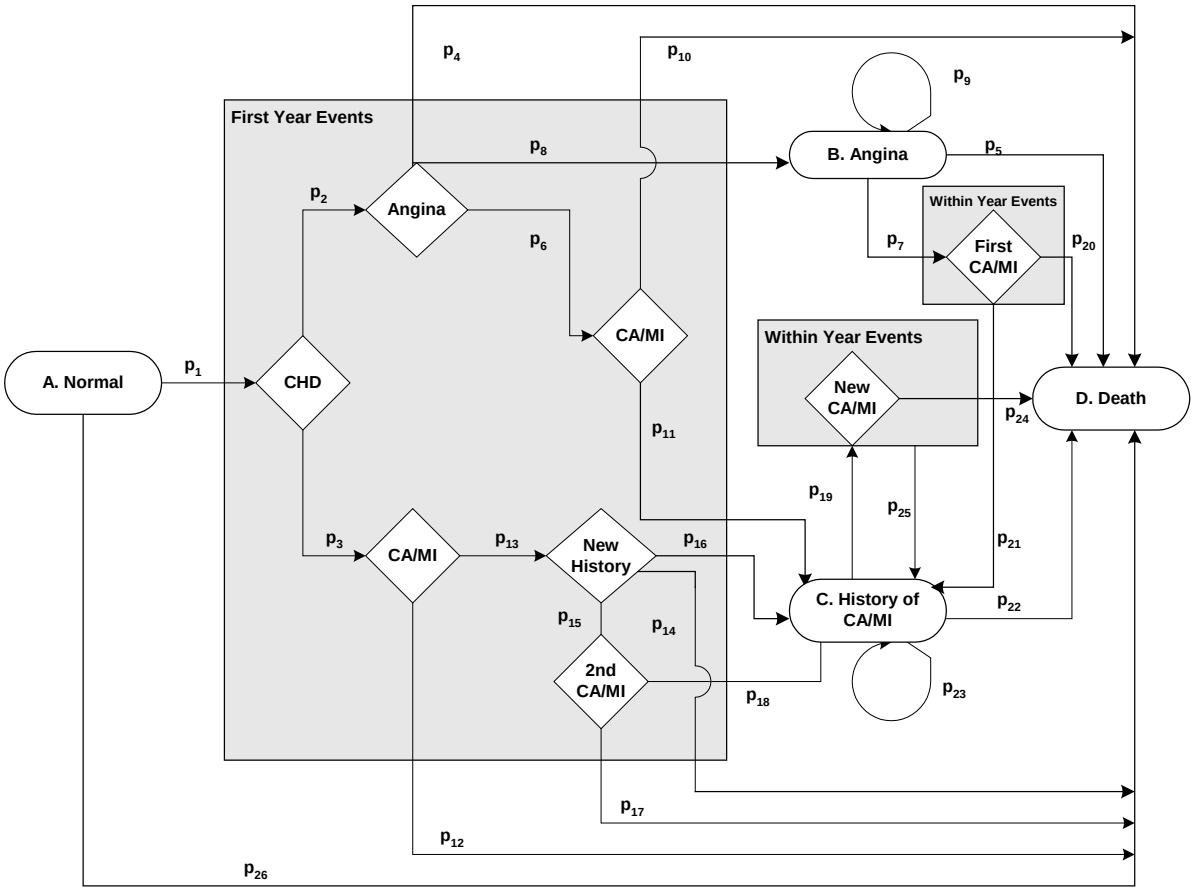


Figure A6. States and Transition Probabilities: Coronary Heart Disease, Detailed View

Thus, at the end of the first year, patients either remain at the Normal state, have angina, have a history of CA/MI, or are dead. The process repeats itself for patients in the Normal state. Patients in the Angina and History of CA/MI states can experience one additional CHD event in the following period. Angina patients can experience a first CA/MI event (P_7), with subsequent probabilities of death (P_{20}) or survival (P_{21}). Alternatively, they may die from angina-related causes (P_5) or continue with angina (P_9). Patients with a history of CA/MI can experience a new CA/MI event (P_{19}), with subsequent probabilities of death (P_{24}) or survival (P_{25}). Alternatively, they may die from chronic conditions related to MI (P_{22}) or survive with no additional CHD event (P_{23}). Naturally, patients in the death state experience no new events.

Below, we describe the derivation and source for each of the probabilities shown in Figure A6.

The model offers two options for calculating P1, the probability of moving from the Normal state to CHD; P2, the probability that the CHD event is angina; and P3, the probability that the CHD event is a CA/MI. The two options are the Framingham equation or the UKPDS Risk Engine. The Framingham equation is discussed below and the UKPDS Risk Engine in Section 1.2.3.

Framingham equation.

Calculating the value of P1. From Anderson et al. the probability of a new case of CHD at period t is given by

$$CHD(t) = [F(t) - F(t-1)] / [1 - F(t-1)], \text{ where}$$

$F(t) = 1 - \exp(-\exp\{[\ln(t) - \mu(t)] / t\})$

(the Weibull function)

$\mu = 15.5305 + 28.4441 \times \text{female} - 1.4792 \times \ln[\text{age}(t)] - 14.4588 \times \ln[\text{age}(t)] \times \text{female} + 1.8515 \times \ln[\text{age}(t)]2 \times \text{female} - 0.9119 \times \ln[\text{sbp}(t)] - 0.2767 \times \text{smoker}(t) - 0.7181 \times \ln[\text{totalc}(t) / \text{HDL}(t)] - 0.1759 \times \text{diagnosed diabetic} - 0.1999 \times \text{diabetic} \times \text{female} - 0.5865 \times \text{LVH}(t, \text{gender})$

sbp = systolic blood pressure

totalc = total cholesterol level

HDL = high density lipoprotein cholesterol level

LVH = left ventricular hypertrophy

Note: In the current model, t was set equal to 8, to estimate an average annual mortality based on the valid range of follow-up (4 to 12 years).

Calculating the value of P_2.

$P_2 = P(\text{Angina} \mid \text{CHD}) = 1 - P(\text{CA/MI} \mid \text{CHD}) = 1 - P3.$

See P_3 below.

Source: Hunink et al.

Calculating the value of P_3.

$P_3 = P(\text{CA/MI} \mid \text{CHD}) = P(\text{CA} \mid \text{CHD}) + P(\text{MI} \mid \text{CHD})$

See Table 10.

Source: Hunink et al.

Table A8. Probability that Initial Coronary Heart Disease Event is Cardiac Arrest or Myocardial Infarction

Age (years)	Probability (CA | CHD)		Probability (MI | CHD)	
	Male	Female	Male	Female
35–44	0.1024	0.0803	0.6171	0.5864
45–54	0.1070	0.0917	0.5440	0.4942
55–64	0.1085	0.0852	0.4739	0.4199
65–74	0.1297	0.0998	0.4929	0.4916
75+	0.1527	0.1793	0.5101	0.4983

Source: Hunink et al.

- $P_4 = P(\text{Death} \mid \text{History of Angina}) * (11/12)$
  See Table 11. Source: Weinstein et al.

Table A9. Probability of Death Given a History of Angina

Age (years)	Probability (Death | History of Angina)	
	Male	Female
35–44	0.00460	0.00249
45–54	0.01070	0.00618
55–64	0.01841	0.01196
65–74	0.03267	0.02507
75+	0.10591	0.09638

Source: Weinstein et al.

P5 = P(Death | History of Angina)
See Table A9. Source: Weinstein et al.

- P6 = P(CA/MI | Angina) * (11/12) * AgeRisk1
  The age-relative risk of CA or MI given a History of Angina was assumed to be equal to AgeRisk1, the age-relative risk of CA or MI given a History of CHD (Table A10). Source: Hunink et al.

Table A10. Relative Risk of Cardiac Arrest or Myocardial Infarction Given a History of Angina (AgeRisk1)

Age (years)	Relative Risk
35–44	0.261
45–54	0.630
55–64	1.000
65–74	1.371
75+	1.826

Source: Hunink et al.

- P_7 = P(CA/MI | Angina) * AgeRisk1
  P(CA/MI | Angina) = 0.0303 for males, 0.0120 for females
- $P_8 = 1 - P_6 - P_4$
- $P_9 = 1 - P_5 - P_7$
- P_{10} = P(Death | 1st CA/MI) =
  P(Death | CA) * P(CA | CA/MI) + P(Death | 1st MI) * P(MI | CA/MI)
  P(CA | CA/MI) = 0.2 P(MI | CA/MI) = 0.8
  P(Death | CA) = 1 – [P(Survival to Admission) * P(Survival to Discharge)]
  See Table 13.

Table A11. Probability of Death Given Cardiac Arrest

Age (years)	Probability		
	Survival to Hospital Admission	Survival to Discharge	Death Given CA
35–44	0.3885	0.6446	0.7496
45–54	0.3316	0.5837	0.8064
55–64	0.2747	0.4974	0.8634
65–74	0.2178	0.3661	0.9203
75+	0.1609	0.1419	0.9772

Table A12. Probability of Death Given the First Myocardial Infarction

Age (years)	Probability (Death | 1st MI)	
	Male	Female
35–44	0.0154	0.0154
45–54	0.0336	0.0336
55–64	0.0730	0.0730
65–74	0.1587	0.1587
75+	0.2953	0.2953

Source: Hunink et al.

- $P_{11} = 1 - P_{10}$
- $P_{12} = P_{10}$
- $P_{13} = 1 - P_{12}$
- P_{14} = P(MI Chronic Death) * (11/12)

See Table A13.

- P_{15} = P(Recurrent CA/MI in year of first MI | 1st MI)
  = [P(CA | History of CA/MI) + P(MI | History of CA/MI)]
  * (11/12) * AgeRisk1

P(CA | History of CA/MI) = 0.01432 for males, 0.01132 for females

Table A13. Probability of Death from Chronic Myocardial Infarction

Age (years)	Probability (MI Chronic Death)	
	Male	Female
35–44	0.00460	0.00249
45–54	0.01070	0.00618
55–64	0.01841	0.01196
65–74	0.03267	0.02507
75+	0.10591	0.09638

Source: Weinstein et al

P(MI | History of CA/MI) = 0.0573 for males, 0.0453 for females
Source: Hunink et al
The age-relative risk of MI given a History of CA/MI is assumed to be equal to AgeRisk1, the age-relative risk of CA or MI given a History of CHD (Table 11).

- $P_{16} = 1 - P_{14} - P_{15}$
- P_{17} = P(CA | CA/MI) * P(Death | CA) +
  P(MI | CA/MI) * P(Death | Recurrent MI)
  P(CA | CA/MI) = 0.2
  P(MI | CA/MI) = 0.8
  P(Death | CA) = 1 – [P(Survival to Admission) * P(Survival to Discharge)]
  See Table 13.
  See Table 16 for probability of death given recurrent MI.

Table A14. Death Rates After Recurrent Myocardial Infarction

Age (years)	Probability (Death | Recurrent MI)	
	Male	Female
35–44	0.0867	0.0867
45–54	0.1120	0.1120
55–64	0.1446	0.1446
65–74	0.1867	0.1867
75+	0.2953	0.2953

See Table A13 for probability of death given the first MI.

- $P_{18} = 1 - P17$
- P_{19} = P(CA/MI | History of CA/MI) * AgeRisk1 = [P(CA | History of CA/MI) + P(MI | History of CA/MI)] * AgeRisk1
  P(CA | History of CA/MI) = 0.01432 for males, 0.01132 for females
  P(MI | History of CA/MI) = 0.0573 for males, 0.0453 for females

Source: Hunink et al.
The age-relative risk given a History of CA/MI was set equal to AgeRisk1, relative risk of MI or CA given a History of CHD (Table 12).
See Table 14 for probability of death given the first MI.

- $P_{20} = P_{10}$
- $P_{21} = 1 - P_{20}$

- P_{22} = P(MI Chronic Death)

See Table A13.
Source: Weinstein et al.

$P_{23} = 1 - P_{19} - P_{22}$

- $P_{24} = P_{17}$
- $P_{25} = 1 - P_{17}$

Finally, there is the chance of death from all other causes, represented by P_{26}, the transition probability from Normal to Death. This probability is incorporated into the overall model as a separate calculation done after all other transitions have taken place for the year.

These transition probabilities are based on the general population rather than on people with diabetes. In order to account for the increased risk of CHD among people with diabetes, we have adjusted the transition probabilities by multiplying them by the relative risk of CHD in a person with diabetes versus a healthy person. Relative risks are shown in Table A15. The relative risk of incurring an initial CHD event is already incorporated into P_1 in the form of the coefficients for diabetes.

Table A15. Relative Risk of Coronary Heart Disease Events Among People with Diabetes

Event	Relative Risk		Probabilities Affected
	Male	Female	
Death within 30 days after CA/MI	1.58[a]	2.60[a]	P_{10}, P_{12}, P_{17}, P_{20}, P_{24}
Death within 1 year after CA/MI	1.97[a]	4.17[a]	P_{14}, P_{22}
Second CA/MI	2.00[b]	2.00[b]	P_{15}, P_{19}

[a]Table 3 in Miettinen et al.

[b]Table 19.8 in Wingard and Barrett-Connor

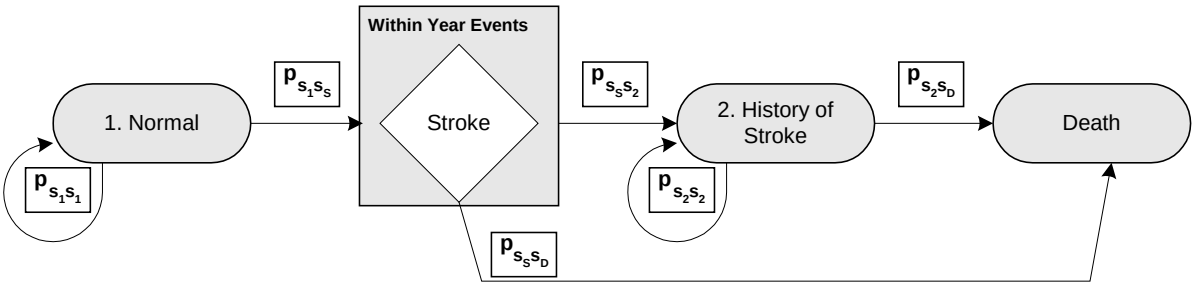
To calculate the transition probabilities between the lettered states in the computer model, the probabilities of movement between each state must be multiplied together along every possible path between any two lettered states. The transition probability is then the sum of these products (Table A16).

Table A16. Transition Probabilities Between Coronary Heart Disease States

	A	B	C	D
A	$1 - P_1$	$P_1 * P_2 * P_8$	$P_1 * P_2 * P_6 * P_{11} + P_1 * P_3 * P_{13} * P_{16} + P_1 * P_3 * P_{13} * P_{15} * P_{18}$	$P_1 * P_2 * P_4 + P_1 * P_2 * P_6 * P_{10} + P_1 * P_3 * P_{12} + P_1 * P_3 * P_{13} * P_{14} + P_1 * P_3 * P_{13} * P_{15} * P_{17}$
B	0	P_9	$P_7 * P_{21}$	$P_7 * P_{20} + P_5$
C	0	0	$P_{23} + P_{19} * P_{25}$	$P_{19} * P_{24} + P_{22}$
D	0	0	0	1

(5) Stroke (shown in Figure A6)
- Normal (s_1)
- History of Stroke (s_2)
- Stroke death (s_D)

Figure A6. States and Transition Probabilities: Stroke



The stroke component of our model has three states: Normal, History of Stroke, and Death (see Figure A6). All individuals begin in the Normal state. The probability of experiencing a stroke is P_{S_S}. The probability of dying from the stroke within the period is given by $P_{S_SS_D}$. If the individual survives the stroke, she progresses to History of Stroke. Thus, at the end of 1 year, individuals may be in the Normal, History of Stroke, or Death states. Once an individual reaches the History of Stroke state, she may remain there ($P_{S_2S_2}$) or may die ($P_{S_2S_D}$).

The user has two options for calculating the transition probability from Normal to Stroke: the Framingham equation (Anderson et al., 1990) and the UKPDS Risk Engine (Kothari et al., 2002); the Framingham equation is discussed below and the UKPDS Risk Engine in Section 1.2.3. The other transition probabilities come from the literature (Table 19).

Letting s_1 = Normal, s_2 = History of Stroke, and s_D = Death, the equations for the transition probabilities from Normal to History of Stroke and Normal to Death follow:

Starting with the individuals in s_1

- the proportion who experience a stroke and die immediately (within 6 months)
  = P(s) * P(Stroke to Death, immediate)
- the proportion who experience a stroke but do not die immediately
  = P(s) * [1 – P(Stroke to Death, immediate)]
- all others remain in the Normal state.

For individuals with a history of stroke (s_2)

- the percentage who die
  = P(History of Stroke to Death; 1 year)
- all others remain in the History of Stroke state.

Death is an absorbing state. The total number of individuals who have had a stroke are those who pass into state s_2 plus those who transition to death due to stroke with Equation (2).

Table A17. Transition Probabilities: Stroke

Transition	Probability	Source	Notes
Normal to Stroke	P(S)	Anderson et al. (1990) Kothari et al. (2002)	See Table 1. Diabetes is included as a risk factor in the Anderson et al. model. See text.
Stroke to Death History of Stroke to Death	Immediate (0–6 months): 0.1420 One-year: 0.0915	Sacco et al. (1994)	Sacco et al. include the 1-month, 1-year, and 5-year transition probabilities. Those were converted to hazard rates from which 6-month and 1-year transition probabilities were calculated. Since this study found that history of diabetes was not a significant predictor of stroke recurrence, we chose to use the transition probabilities for the entire cohort. Alternatively, we might have used the admission glucose >140 mg/dl as a proxy for diabetes, as that was found to be a significant predictor of stroke recurrence at p< 0.05. However, the rest of the model's parameters are for diagnosed diabetes; therefore, using admission glucose as a proxy would be inconsistent.

If the Framingham equation is applied, the probability of a new case of stroke at period t is given by

$$\text{Prob}(S[t]) = [F(t) - F(t\,!\,1)] / [1 - F(t\,!\,1)]$$

where

$$F(t) = 1 - \exp(-\exp\{[\ln(t) - \mu(t)] / t\}) \text{ (the Weibull function)}$$

$$\mu = 26.5116 + 0.2019 \times \text{female} - 2.3741 \times \ln[\text{age}(t)] - 2.4643 \times \ln[\text{sbp}(t)] - 0.3914\ \text{smoker}(t) - 0.0229 \times \ln[\text{totalc}(t) / \text{HDL}(t)] - 0.3087 \times \text{diagnosed diabetic} - 0.2627 \times \text{diabetic} \times \text{female} - 0.2355 \times \text{LVH}$$

This is the equation used for P(s) above.

Note: In the current model, t was set equal to 8, to estimate an average annual mortality based on the valid range of follow-up (4 to 12 years).

UKPDS Risk Engine

The UKPDS Risk Engine can be applied to calculate the risk of a myocardial infarction or the risk of having a stroke event. The Risk Engine calculations are based on individuals with type 2 diabetes participating in the UKPDS study. In this paper, we apply the UKPDS Risk Engines rather than the Framingham equation for calculating the risk of all CVD events.

Myocardial Infarction. The UKPDS Risk Engine calculates the probability of a myocardial infarction, whereas the Framingham equation computes the probability of angina or CA/MI. Because our model also incorporates angina as a state of CHD, we will keep the same ratio of angina to CA/MI as with the Framingham equation. Instead of calculating the probability of a CA/MI event or angina conditional upon a CHD event, we calculate the probability of moving from normal to CA/MI or angina in one step.

*Calculating the value of **p** using the UKPDS Risk Engine.* From UKPDS 56, the probability of a first myocardial infarction at period t is given by

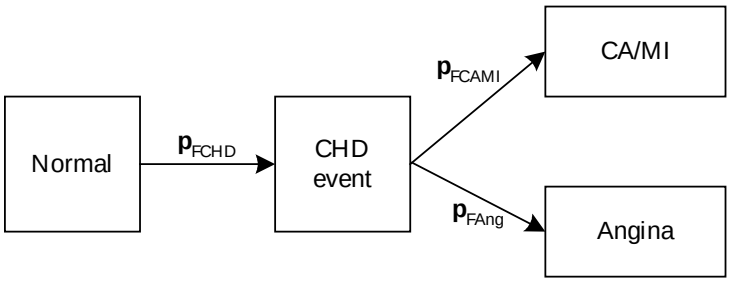
$$MI(t) = 1 - \exp(-qd^{t-1})$$

where

$$Q = q_0\beta_1^{\text{AGE-55}}\beta_2^{\text{SEX}}\beta_3^{\text{AC}}\beta_4^{\text{SMOK}}\beta_5^{\text{h-6.72}}\beta_6^{(\text{SBP-135.7})/10}\beta_7^{\ln(\text{LR})-1.59}$$

and

Framingham equation



UKPDS Risk Engine

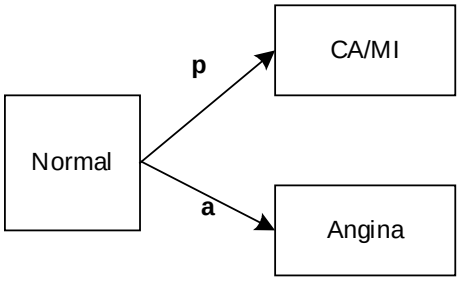


Figure A8. Progression to Initial CHD Event Using the Framingham Equation and the UKPDS Risk Engine

q_0 = Intercept = 0.0112
β_1 = Risk ratio for one year of age at diagnosis of diabetes = 1.059
β_2 = Risk ratio for female sex = 0.525
β_3 = Risk ratio for Afro-Caribbean ethnicity = 0.390
β_4 = Risk ratio for smoking = 1.350
β_5 = Risk ratio for 1% increase in HbA1c = 1.183
β_6 = Risk ratio for 10 mmHg increase in systolic BP = 1.088
β_7 = Risk ratio for unit increase in logarithm of lipid ratio = 3.845
d = Risk ratio for each year increase in duration of diagnosed diabetes = 1.078
and
AGE = Age (yrs) at diagnosis of diabetes
SEX = Individual's sex
1 = female, 0 = male
AC = Indicator of Afro-Caribbean race
1 = Afro-Caribbean,
0 = Caucasian or Asian-Indian
(By default, set to represent African-American)
SMOK = Indicator of smoking status
1 = current smoker at diagnosis of diabetes,
0 = non-smoker at diagnosis of diabetes
H = HbA1c (%), mean of values at years 1 and 2
SBP = Systolic BP, mean of values at years 1 and 2
LR = Total cholesterol/HDL cholesterol ratio, mean of values at years 1 and 2
T = Years since diagnosis
Notes: Regression dilution adjustments were not made; therefore, assuming that HbA1c is the mean of 2 values, systolic blood pressure is the mean of 6 values (two groups of three values), and total and HDL cholesterol are each

the mean of 2 values. By default, the Afro-Caribbean risk factor in the UKPDS Risk Engine will be applied to African American cohorts. The user may turn off this assumption; in that case, the Afro-Caribbean risk factor is not applied to any cohorts.

*Calculating the value of **a** using the Framingham Equation.*

Let p_{FCHD} = Framingham probability of CHD event,
p_{FCAMI} = P(CA/MI | CHD)
p_{FAng} = P(Angina | CHD)
p = UKPDS Risk Engine probability of MI
m = P(CA/MI| Normal)
a = P(Angina| Normal)

Then $p_{FCAMI} + p_{FAng} = 1$
$m = p_{FCHD} * p_{FCAMI}$
$a = p_{FCHD} * p_{Fang}$
$a = m * p_{FAng} / p_{FCAMI}$, when using either risk model, based on keeping the rate of angina relative to CA/MI the same
m = p (ignoring the CA-MI distinction)

So, $a = p * p_{FAng} / p_{FCAMI}$,
if $p_{FCAMI} > 0$ and $p * p_{FAng} / p_{FCAMI} <= 1 – p$
$a = 1 – p$, if $p_{FCAMI} = 0$ or $p * p_{FAng} / p_{FCAMI} > 1 – p$

We use one of these two equations to compute the probability of moving from the normal state to the angina state when using the UKPDS risk model. We expect $p_{FCAMI} > 0$ generally, so the second equation will usually be used only when the first equation gives a value that makes the sum (p + a) larger than 1.

Using this calculation strategy, P_1 is never explicitly defined. We assume, though, that $P_1 * P_2 = a$ and $P_1 * P_3 = m$.

Stroke. UKPDS Risk Engine uses the method outlined in UKPDS 60 to calculate the probability of a first stroke (P(s)) during period t. This calculation involves the same equation used to calculate the risk of CHD, except that the value of q is calculated using a slightly different formula and different coefficients.

$Stroke(t) = 1 – \exp(-qd^{t-1})$

where

$$q=q_0\beta_1^{AGE-55}\beta_2^{SEX}\beta_4^{SMOK}\beta_5^{h-6.72}\beta_6^{(SBP-135.5)/10}\beta_7^{LR-5.11}\beta_8^{AF}$$

and

q_0 = Intercept = 0.00186
β_1 = Risk ratio for one year of age at diagnosis of diabetes = 1.092
β_2 = Risk ratio for female sex = 0.700
β_4 = Risk ratio for smoking = 1.547
β_6 = Risk ratio for 10 mmHg increase in systolic BP = 1.122
β_7 = Risk ratio for unit increase in lipid ratio = 1.138
β_8 = Risk ratio for atrial fibrillation = 8.554
d = Risk ratio for each year increase in duration of diagnosed diabetes = 1.145

and

AF Atrial fibrillation at diagnosis of diabetes, 1 = yes, 2 = no

The definitions for AGE, SEX, SMOK, SBP, LR and T are defined in above in the Risk Engine calculations for myocardial infarction.

At the end of any period, the cohort occupies one state on each of the disease paths. For the simulation, transitions between states take place at discrete time intervals 1 year apart. Thus, at the end of each 1-year period, portions of the cohort can move from one disease state to another or stay in the same disease state. The simulation program determines what proportion of the cohort will move from one state to another based on the transition probability.

In several cases, an individual can experience a complication event that the patient either dies from or survives during the period. On the neuropathy path, a patient with neuropathy can undergo an LEA and either die or survive. Similarly, a person with a history of LEA may undergo an additional LEA and either die or survive. On the CHD path, patients can experience a CHD event (angina, CA/MI, or recurrent CA/MI). Finally, on the stroke path, patients can either survive or die from a stroke suffered within a period.

Such events are incorporated within the overall Markov model by bridge models (Weinstein et al., 1987). Each bridge model covers the incidence and probabilities of death and survival from the event within one period. These values are incorporated into the transition probabilities between model states. The events themselves are not model states, though they are closely related. To see the distinction, consider a patient who is in the peripheral neuropathy state on the neuropathy path at time t. During the next period, the patient may experience an LEA. If the patient survives the LEA, he or she progresses to the state History of LEA at time t+1. Alternatively, if the patient dies from the LEA, he or she progresses to the Death state at t+1. The Markov model keeps track of the number of patients who are in each state in each period. It also keeps track of the cumulative incidence of patients who have undergone complication events such as LEA, angina, CA/MI, and stroke. In the diagrams, events within the bridge models are represented by diamonds, and the states are numbered and represented by ovals.

We specify the mathematical model based on the Markov model using transition probabilities. The transition probability $p_{i,j}(t)$ is the probability that the patient in state i at time t will be in state j at time t+1. The hazard rates and hence the transition probabilities are dependent on a variety of variables including the following:

- time since diagnosis of diabetes,
- time between onset of diabetes and diagnosis,
- age,
- sex,
- race/ethnicity,
- glycemic levels,
- smoking,
- cholesterol levels, and
- hypertension.

In the model, age, sex, smoking, and cholesterol level affect only the transition probabilities associated with CHD and stroke. The time between onset of diabetes and diagnosis affects only the glycemic level at the time of diagnosis. Time since diagnosis of diabetes, glycemic level, and hypertension affect all of the transition probabilities. The impact of race/ethnicity affects glycemic levels and death probabilities. Glycemic level has a multiplicative effect on the baseline hazard rates, which in turn determine the transition probabilities used in the model.

In this report, we distinguish between the related terms “hazard rates” and “transition probabilities.” Hazard rate shows the rate at which individuals change from one state to the next; this rate can take values between 0 and ∞. Transition probability is the probability that an individual patient makes the transition between states during one period. The transition probability has a range between 0 and 1. The relationship between the hazard rate (r) and the transition probability (p) for time period t is given by

$$p = 1 - e^{-rt}. \qquad (1)$$

Although p and r are fairly close when r is near zero (as is the case for most of the hazard rates in the tables), they are not equal.

II. Diabetes Preventive Interventions

Two types of intervention scenarios were assumed in the base-case analysis and sensitivity analysis, respectively: a theory-driven, highly effective, and resource-intensive lifestyle intervention as implemented in the DPP (Diabetes Prevention Program),[5] and a community-based lifestyle intervention with lower cost and a lower level of effectiveness as implemented in the Promoting a Lifestyle of Activity and Nutrition for Working to Alter the Risk of Diabetes (PLAN4WARD).[6]

The details of the DPP lifestyle intervention can be seen elsewhere.[5] Briefly, the lifestyle intervention included a healthy, low-calorie, low-fat diet, and moderate physical activity. It included a 16-lesson core curriculum taught on an individual basis, followed by monthly individual and group sessions. Compared to controls, this intervention achieved loss and maintenance of 7% of baseline body weight and reduced the incidence of diabetes by 55.8%.[7] The cost of the lifestyle intervention was estimated to be $1803 in Year 1, $875 in Year 2, and $905 in Year 3.[7] The cost of the third year was applied to the years beyond the trial period.

PLAN4WARD is a preventive intervention program aimed to translate the DPP lifestyle intervention to the community setting. It incorporated the rationale and experience of the DPP with modifications to enhance sustainability and community accessibility. The program involved the same 16 core-curriculum lessons as the DPP, but the lessons are delivered in groups of 10–12 participants and are held over just 16 weeks. Because the DPP showed that weight reduction was the primary mediator of diabetes risk reduction,[8] PLAN4WARD was designed to demonstrate that a new model that delivers the program at a lower cost can achieve similar weight-loss results.

The program reduced the participants' body weight by 4.0% in the first year,[6] compared to the 7.0% weight loss in the DPP in the first 3 years. Hamman[8] showed that, on average, a 7% weight reduction in DPP predicted a 58% reduction in diabetes incidence, which translates to about an 8% reduction in incidence for each percentage of weight loss. Accordingly, the lifestyle intervention through PLAN4FORWARD was assumed to reduce the risk of diabetes by 32%. DPP also showed that a majority of the participants gradually regained their weight after the trial period. To account for the weight gain, the risk reduction was then adjusted to an even lower level of 25%. In the PLAN4FORWARD program, the total cost for supplies, labor time, and administration during Year 1 was estimated to be $275–$325 per participant.[9] It was assumed that the medical costs would be the same for years afterwards.

III. Health Utilities and Costs Associated with IFG and Type 2 Diabetes

Table A18 shows the annual medical cost of IFG and type 2 diabetes. An estimate was made of the medical cost of treating type 2 diabetes using the data from the UKPDS. The details are provided in another paper,[11] which describes the diabetes module of the model.

To estimate health utility scores associated with type 2 diabetes, an additive prediction model was applied to estimate health utility scores according to demographic, treatment, and disease state variables. [10] Table A18 shows the health utility scores in type 2 diabetes. The baseline health utility score of 0.69 is the health utility score for a non-obese man with type 2 diabetes who is treated with diet and exercise and who has no cardiovascular risk factors or microvascular, neuropathic, or cardiovascular complications. The penalty scores represent the decrement in the health utility score associated with treatments, cardiovascular risk factors, and complications.

Table A18 Annual medical cost of IFG and type 2 diabetes

Annual direct medical costs of IFG, $[a]	
Baseline cost	1671
Cost multiplier	
Female	1.14
African-American	0.82
BMI >30	1.01
Annual direct medical cost of type 2 diabetes, $[c]	
Baseline cost	2171
Cost multiplier	
Female	1.25
African-American	0.82
BMI, every unit >30.0	1.01
Oral anti-diabetic agents	1.1
Insulin	1.59
Microalbuminuria	1.17
Nephropathy	1.3
ESRD with dialysis	10.53
History of stroke	1.3
Angina	1.73
History of CA/MI	1.9
Peripheral vascular disease	1.31
Hypertension (treated)	1.24

a Annual direct medical cost of IFG is the baseline cost ($1671) multiplied by the multipliers for the gender, race/ethnicity, and body weight. For each variable, only the multiplier associated with the most-severe level should be used. The baseline cost represents the median annual direct medical cost for a diet-controlled white man with prediabetes and BMI <30. Source: DPP data.

b Annual direct medical cost of type 2 diabetes is the baseline cost ($2171) multiplied by the multipliers for the combination of characteristics, treatments, and complications. For each variable, only the multiplier associated with the most-severe level should be used. The baseline cost represents the median annual direct medical cost for a diet-controlled white man with type 2 diabetes, BMI of 30, and without microvascular, neuropathic, or cardiovascular risk factors or complications. Source: Brandle et al.2003

CA/MI, cardiac arrest/myocardial infarction; ESRD, end-stage renal disease

Table A19. Treatment costs of type 2 diabetes and health utilities associated with type 2 diabetes and IFG

	Base-case	Probabilistic sensitivity analysis	
		Distribution assumption[a]	**Data source**
Health utility score associated with IFG[b]	0.730	Normal (0.713 to 0.748)	DPP data
HEALTH UTILITY ASSOCIATED WITH TYPE 2 DIABETES[b]			
Baseline score	0.689	Normal (0.662 to 0.716)	Coffey (2002)[10]
Penalty score			
Female	–0.038	Normal (–0.052 to –0.024)	Coffey (2002)[10]
Hypertension	–0.011	Normal (–0.025 to 0.000)	Coffey (2002)[10]
Blindness	–0.170	Normal (–0.192 to –0.148)	Coffey (2002)[10]
Nephropathy	–0.011	Normal (–0.029 to 0.000)	Coffey (2002)[10]
ESRD	–0.078	Normal (–0.129 to –0.027)	Coffey (2002)[10]
Peripheral neuropathy	–0.065	Normal (–0.081 to –0.049)	Coffey (2002)[10]
Foot ulcer	–0.099	Normal (–0.124 to –0.074)	Coffey (2002)[10]
Lower-extremity amputation	–0.105	Normal (–0.144 to –0.066)	Coffey (2002)[10]
History of cardiac arrest or myocardial infarction	–0.052	Normal (–0.074 to –0.030)	Coffey (2002)[10]
Stroke	–0.072	Normal (–0.103 to –0.041)	Coffey (2002)[10]
BMI ≥30.0	–0.021	Normal (–0.035 to –0.007)	Coffey (2002)[10]
COSTS OF TYPE 2 DIABETES DIAGNOSIS AND TREATMENTS ($)			
Oral glucose tolerance test	18	Not varied	
Lifestyle + Metformin therapy when A1c <7%, by study year			
1	1853	Lognormal (1853, 1582)	Herman (2005)[7]; a $50 annual cost of metformin was assumed
2	925	Lognormal (975, 793)	
≥3	955	Lognormal (955, 769)	
Intensive glycemic control when HbA1c ≥7%, by study year			
1	2015	Lognormal (2015, 1890)	CDC/RTI International DM Cost-Effectiveness Study Group(2002)[11]
2	1889	Lognormal (1889, 1778)	
3	1960	Lognormal (1960, 1810)	
4	2025	Lognormal (2025, 2200)	
5	2083	Lognormal (2083, 2223)	
6	2127	Lognormal (2127, 2301)	
7	2186	Lognormal (2186, 2325)	
8	2212	Lognormal (2212, 2404)	
9	2242	Lognormal (2242, 2485)	
10	2266	Lognormal (2266, 2305)	
11	2297	Lognormal (2297, 2350)	
12	2314	Lognormal (2314, 2512)	
13	2348	Lognormal (2348, 2589)	

14	2357	Lognormal (2357, 2632)
15	2366	Lognormal (2366, 2697)
≥16	2385	Lognormal (2385, 2746)

[a] Normal (*a,b*)=normal distribution with *a* as the lower bound and *b* as the upper bound of the 95% Confidence Interval; triangle (*a,b,c*)=triangle distribution with minimum *a*, mode *b*, and maximum *c*; Lognormal (*a,b*)=lognormal distribution with mean *a*, and with *b* as the lower bound of the 95% CI.

[b] The health utility score is the baseline health utility score minus the penalty scores for the combination of characteristics, treatments, and complications. For each variable, only the penalty score associated with the most-severe level should be used. The baseline health utility represents the mean health utility score for a diet-controlled white man with type 2 diabetes, BMI of 30, and without microvascular, neuropathic, or cardiovascular risk factors or complications. Adapted from Coffey and colleagues.[10]

DM, diabetes mellitus; ESRD, end-stage renal disease

V. Calculation of Incremental Cost-Effectiveness Ratios

For each FPG cutoff, a calculation was made of the incremental cost per QALY gained, relative to the next-higher IFG cutoff. For instance, the incremental cost per QALY gained at a cutoff of 115mg/dl was calculated relative to the cutoff of 120mg/dl. The formula for the incremental cost-effectiveness ratio (ICER) is as follows:

$$ICER_i = \frac{C_i - C_{i+5}}{E_i - E_{i+5}}$$

where C denotes the medical cost; i denotes FPG cutoff point of i, and E denotes effectiveness, measured as QALY in our study.

We calculated the ICER in this stepwise fashion, instead of comparing with one fixed cutoff, as it is usually impossible to detect the presence of either strict or extended dominance using only one comparison group[12] (see Garber and Solomon, for example[13]). Consider the following example. Suppose that the ICER of FPG level of 115mg/dl compared to an FPG level of 120mg/dl is $40,000/QALY, and the CE ratio of an FPG level of 110mg/dl compared to 115mg/dl is $30,000/QALY. If a decision maker were to choose an FPG level of 115mg/dl versus 120mg/dl as the cutoff, it suggests that a gain of a QALY is worth at least $40,000. If that were the case, then it would be true that it is worth an additional $30,000 to gain another QALY, so that an FPG of 110mg/dl would be chosen over 115mg/dl.

Therefore, the cutoff of 115mg/dl is "extended dominated" by 110mg/dl. However, this conclusion cannot be reached by comparing both 115md/dl and 110mg/dl to 120mg/dl. If the CE ratio of an FPG level of 110md/dl compared to 120mg/dl is lower than $40,000/QALY, it is hard to tell whether 115mg/dl is dominated by 110mg/dl. This is because, given the same CE ratio, the incremental cost and QALY of 110mg/dl compared with 120mg/dl could be higher or lower than those for 115mg/dl. For example, the incremental cost and QALY of 115mg/dl relative to 120mg/dl are $10,000 and 0.25, respectively (so ICER = $10,000/0.25 = $40,000/QALY). If we know that the ICER of 110mg/dl relative to 120mg/dl is $20,000/QALY, then the incremental cost and QALY of 110mg/d relative to 120mg/dl could be either $4,000 and 0.2, respectively, or $15,000 and 0.75, respectively. In the first case, since the incremental QALY of 115mg/dl is higher than the 110mg/dl QALY, the FPG level of 115mg/dl might be preferred since it results in a higher QALY gained and the CE ratio is still lower than the $50,000/QALY.

Use of the CE ratio compared with no prevention to rank the alternatives is also misleading because the objective is to compare the cutoff selection strategies with its alternatives, not to evaluate the cost effectiveness of a certain prevention strategy. Compared to no intervention or "doing nothing," the incremental cost includes both the fixed cost of setting up a new intervention program and a variable cost of intervention. The fixed cost is a constant cost regardless of the population involved. For instance, the costs of building the intervention infrastructure, and developing the intervention guideline and course, are not dependent on the size of the targeted population. However, the variable cost, such as the total personnel cost, the time cost, and the intervention instrument costs vary by the scope of the intervention. When determining whether a new medical intervention is cost effective, both fixed cost and variable cost should be included in the incremental cost calculation because they are both "new" additional cost. However, when determining what FPG cutoff to use so that different populations can be selected for intervention, only the variable cost has to be considered as additional cost in the incremental cost calculation. By calculating the CE ratio relative to the alternative cutoff, it is possible to separate out the fixed cost and consider only the variable cost.

VI. Effect of Compliance Rate and FPG distribution

The compliance rate to the lifestyle interventions and the FPG distribution were not expected to influence the cost-effectiveness ratio and thus were not included in the sensitivity analyses. These two parameters affect only the number of people receiving the intervention and are factored into both the total cost and total effectiveness. As a result, varying these parameters led to a proportional change in the numerator (cost) and denominator (effectiveness), and thus they cancel out. This point can be demonstrated by the following derivation for the ICER at the FPG cutoff of 105mg/dl:

$$ICER_{105} = [(p_{105-126}\, C'_{105-126} + p_{<105} C_{<105}) - (p_{110-126}\, C'_{110-126} + p_{<110} C_{<110})] \\ /[\, (p_{105-126}\, E'_{105-126} + p_{<105} E_{<105}) - (p_{110-126}\, E'_{110-126} + p_{<110} E_{<110})],$$

where p denotes the number of people; C' and E' denote the average cost and average effectiveness of the intervention, respectively; and C and E denote the average cost and average effectiveness without the intervention, respectively. The subscripts denote the values of HbA1c. The numerator in the formula above can be rewritten as follows:

$$(p_{110-126}\,C'_{110-126}+p_{105-110}C'_{105-110}+p_{<105}C_{<105}) - (p_{110-126}\,C'_{110-126}+p_{105-110}C_{105-110}+p_{<105}C_{<105})$$
$$= p_{105-110}(C'105_{-110} - C_{105-110}).$$

Similarly, the denominator in the formula above can be rewritten as follows:

$$(p_{110-126}\,E'_{110-126}+p_{105-110}E'_{105-110}+p_{<105}E_{<105}) - (p_{110-126}\,E'_{110-126}+p_{105-110}E_{105-110}+p_{<105}E_{<105})$$
$$= p_{105-110}(E'105_{-110} - E_{105-110}).$$

As a result, the $ICER_{105}$ can be simplified as:

$$ICER_{105} = p_{105-110}(C'105_{-110} - C_{105-110}) / p_{105-110}(E'_{105-110} - E_{105-110})$$
$$= \Delta C_{105-110}/\Delta E_{105-110.}$$

This suggests that the ICER associated with the cutoff of 105mg/dl is equivalent to the incremental cost-effectiveness ratio of providing the intervention to people with FPG values of (105, 110) compared to no intervention, and it is independent of the number of people in that FPG range and of the number of people receiving interventions.

VII. Cost-effectiveness Acceptability Curves (CEAcc)

The CEAcc was plotted for each FPG threshold for two purposes: (1) to determine whether ICERs of the cutoffs were statistically different from those of their neighboring cutoffs; and (2) to assess the robustness of the relationship between the CE ratio and the FPG cutoff to random variation in the model parameters.

The acceptability probabilities were estimated using the results of the probabilistic sensitivity analysis. For each FPG cutoff, 500 ICERs were produced by iterating the simulation 500 times with a randomly drawn set of parameters. A calculation was then made of the proportion of the ICERs of one cutoff that were higher than a given value of willingness-to-pay.

The curves represent the likelihoods that one threshold is cost-effective at different level of monetary values or willingness-to-pay of QALY. Given an increasing level of the monetary value of QALY, the probability of each threshold being cost-effective is expected to increase. For example, in a setting that the monetary value is $50,000 per QALY, the probability of the threshold 105 mg/dl being cost-effective was 0.92. That means that, in the 500 simulations, about 460 times we observed that the ICER associated with the threshold is below $50,000 per QALY.

In addition to CEAcc, we used 2-sided t-test to test the difference of the ICERs using the random sample generated in the probabilistic sensitivity analysis. Specifically, we combined the samples of the ICER of all FPG thresholds produced in the 500 iterations, in total N = 7x500 = 3,500. Based on the sample, we estimated the 95% confidence intervals for the ICERs of all thresholds evaluated and compared the ICER of one threshold with that of its next higher threshold.

References for Appendix

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