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Development of Diabetes Complication Progression Model

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Introduction

The accumulation of epidemiological research findings on diabetes in the literature over the last decade has significantly increased our understanding of the natural history of the disease and its progression to complications. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) ⁽¹⁻⁴⁾, The Population-Based Perspective Study in Rochester, Minnesota ⁽⁵⁻⁶⁾, Diabetes Control and Complication Trial (DCCT) ⁽⁷⁻⁹⁾ and The UK Prospective Diabetes Study (UKPDS) ⁽¹⁰⁻¹⁵⁾ are among the most famous population studies which described the overall complication process in the general population and how risk factors such as HbA_{1c} and blood pressure could impact complication progression. Information gained from those studies can be used to build a mathematic model to represent the disease process.

Such a model could have at least following three applications: (a) A tool to educate individual patients about future risk of complications and, more importantly, how better control of HbA_{1c}, blood pressure and lipids could impact the future risk of serious complications such as blindness, amputation, heart attack, stroke, end stage renal disease. An interactive computer program with such a model embedded could motivate individual diabetic patients to be more proactive in changing lifestyles and more compliant to treatment. (b) A disease management tool to evaluate patient's complication risk. Patients could be stratified according to their risk and enrolled into different programs and receive different disease management interventions. When tying the risks to cost estimates, such a tool also could be used to predict the healthcare savings due to a patient's improved outcome, either through program interventions, improved performance of provider or better patient's compliance. (c) A research tool to evaluate the cost-effectiveness of intervention strategies. For example, how many blindness cases can be prevented by increasing the screening for diabetic retinopathy? What is the overall cost-effectiveness of improving intensive glycemic control and blood pressure control?

In this paper such a mathematic model is presented together with a description of how it was developed, what the assumptions were and how it performed.

Methods

Model construction

Probabilistic (Monte Carlo) techniques were used to development the model. The model includes 18 disease stages. Progressions to different stages were assumed to be irreversible and were based on the transitional probabilities. Each transitional probability was a conditional probability depending on current disease stages and covariates such as age, sex, ethnicity, smoking, HbA_{1c}, blood pressure etc. To calculate the probability of a subject progressing to certain disease stages within a certain time period, 100 hypothetical patients with the same covariates were simulated and progressed according to the transitional probability at two-month intervals. The number of hypothetical patients who ended up in each health stage at the end of the time period indicated the probability of the subject progressing to that stage.

A schematic drawing of the model's stages of progression of retinopathy, nephropathy neuropathy and cardiovascular diseases (CVDs) are shown in Figure1. There are 18 disease stages overall and 17 transitional pathways. The transitional probabilities were derived from a review of the literature. If more than one variables was believed to affect the transitional probability then a formula in the form of a multivariate regression equation was developed to best reflect the association between the variables and the transitional probability.

Model validation

To test the validity of the model, the predictions from the model were compared with observed/reported results from UKPDS and DCCT. UKPDS was a 9-year clinical trial among type 2 diabetic patients. DCCT was an average 6 years intervention study among type 1 diabetic patients. The UKPDS are essentially two separate clinical trials. One was for glycemic control ⁽¹⁰⁻¹¹⁾ and the other was for blood pressure control ⁽¹²⁻¹⁵⁾. DCCT was a glycemic control clinical trial which also consists of two cohorts, one is a "primary prevention cohort" with subjects has no retinopathy at the baseline. The other is "secondary intervention cohort" with mild retinopathy at the baseline ⁽⁷⁾. Since the complication rates were very low in the primary prevention cohort, only the data from the secondary intervention cohort were used in the presented study.

Tables 1 and 2 show the baseline information of the two clinical trials of UKPDS ^(10,12) and the second cohort of DCCT ⁽⁷⁾. To validate the model performance, a hypothetic dataset was first simulated based on the baseline characteristic from each clinical trial data. All continuous variables were assumed to have a normal distribution and all categorical variables were assumed to be randomly distributed, based on the prevalence. Then the model was applied to the data to compute the predicted complication rates. To predict the effectiveness of intervention, the HbA_{1c} levels in the UKPDS glucose control trials were set at 7.0 % (treatment) and 7.9 % (control), and for the DCCT cohort at 7.0% (treatment) and 9.0% (control). The systolic blood pressures in the blood pressure control trial of UKPDS were set at 144 mmHg (treatment) and 154 mmHg (control).

The predicted vs. observed/reported comparisons include the comparisons of complication incidence rates and the effectiveness of the intervention.

Results

The model predicted vs. observed/reported cumulative incidence of major complications and the effects of intensive glycemic control and blood pressure control in the UKPDS are shown in Table 3 and 4.

The selected end outcomes are the most clinical meaningful end stage microvascular outcomes including blind (retinopathy), amputation (neuropathy), end stage renal disease (nephropathy) and macrovascular (cardiovascular) outcomes including heart attack (myocardial infraction (MI) and angina) and stroke.

As shown in Table 3 and Table 4, the predicted incidences of the listed complications were all similar to what were observed in both trials. The predicted

risk reductions were also very close to what were observed. The predicted relative risks for treatment all fall in the observed 95% confidence interval.

For each individual complication, the 95% confidence intervals of the observed relative risk (RR) in the trials were all relative wide. Except for the incidence of microalbuminuria in the glucose control trial and the incidence of stroke in the blood pressure control trial, they all included 1, meaning the differences between the treatment and control were not statistically different. The lack of statistically significance differences may be due to the relatively small sample size and the low incidences of those severe end stage complications. The overall findings of the UKPDS were: (1) Intensive glucose control significantly reduced microvascular complications (retinopathy, neuropathy and nephropathy) as whole. The reduction in risk was of borderline significant for myocardial infraction (MI) and there was no risk reduction for stroke ⁽¹⁰⁾. (2) Tight blood pressure control significantly reduced microvascular complications (retinopathy, neuropathy and nephropathy) as whole. It also significantly reduced the risk macrovascular complications (CHD and stroke), especially for stroke ⁽¹²⁾.

The predictions of the model were very consistent with the overall UKPDS findings, with one exception that the model did not predict any risk reduction of coronary heart disease (MI and angina) by glucose control, even though the trial showed a borderline significant risk reduction on MI (Table 3).

The comparisons of model prediction with the observed outcome in DCCT are shown in table 5. Due to the small sample size in DCCT, the incidences of severe microvascular complication such as blindness, end-stage renal disease and amputation were too low to make meaning comparisons. Therefore the selected outcomes to be compared were those intermediate stages reported in the DCCT literature such as macular edema, proliferative retinopathy (PDR), microalbuminuria (MA), gross proteinuria (GPA) and clinical neuropathy ⁽⁷⁾. DCCT reported macrovascular complications as the sum of all macrovascular events, which included not only CHD and stroke but also peripheral vascular disease. Since the present model only predicted CHD and stroke, the observed incidence would tend to be higher than predicted. The results was indeed so. DCCT reported the incidence of complication as rate/100 person year. To be compatible, average yearly incidence of the first ten years was used as the predicted rate. The predicted rate in either the treatment or control groups were all very similar to what were reported except for the all macrovascular events. The predicted risk reductions were all within the 95% confidence intervals of the reported treatment effect of intensive glycemic control.

Discussion

Several mathematic models for diabetes complications have been reported in the literature ⁽¹⁶⁻²¹⁾. There are several differences between those models and the present one. First, those published models were either for only certain complications (retinopathy only) or only apply to one type of diabetes. The present model considered all complications for both type 1 and type 2. And the present model incorporated more recently published results into the model. For

example, the present model is the first to model the effect of blood pressure on the risk of complications based on the recently published results from UKPDS. Secondly all published models were developed as research tools to estimate the cost effectiveness of certain intervention strategy. The present model was developed primarily as an education tool for patient consulting and a disease management tool for population stratification or health risk assessment. These differences were reflected in the way the model was constructed. For example the present model did not take mortality into consideration as most of other models did. For a given population, the model not considering mortality will give higher prediction rates of complication incidences than the model considering mortality, because people may die of other reasons before they have a chance to develop complications. However, in the patient education and disease management context, all the predictions are conditional on the fact that the patients are still live. Therefore, the conditional probability (if the patient is still live) is what we are interested in for this objective.

The performance of the model was validated by applying the model to hypothetical simulated DCCT and UKPDS populations then comparing the predicted with observed complications incidence. Overall, the predicted outcomes were very close to what were observed in both DCCT and UKPDS. Although there was no statistical test to test how close is close enough, the predicted values from the model and observed outcomes from the studies were clearly in the same direction and with similar magnitude. The predicted effects of controlling HbA_{1c} and blood pressure on the complication incidence all fell in the 95% confidence interval of the observed effects.

The model prediction and DCCT and UKPDS studies show that reduction of HbA_{1c} and blood pressure decrease the risk of microvascular complications including retinopathy, nephropathy and neuropathy. For the risk of macrovascular complications, blood pressure control reduced the risk of CVD, especially stroke. Intensive glycemic control was not predicted to reduced the risk of either CHD or stroke risk even though in the UKPDS study the difference of CHD risk was marginally significant between glucose control and conventional group. Up to now, there is no convincing evidence indicating that glycemic control could reduce the macrovascular complications. The model was therefore constructed so.

The validation should be regarded mainly as internal validation, because most of the input information used to construct the model also comes from DCCT and UKPDS, even though information from other studies were used as well. The external validity of the model would then depends on the external validity of DCCT and UKPDS. Since DCCT and UKPDS have been regarded as gold standard studies in the field of diabetes complication research, then being consistent with the findings of DCCT and UKPDS means the model is at least consistent with our current understanding of diabetes complication progression. In fact this is exact the purpose of making such models.

The utility and the significance of using mathematic prediction models as a patient consulting tool has not been explored in literature ⁽²²⁾. It has been shown that education and motivation of the diabetes patient for the better control is critical in preventing complications. The main difference in using a mathematic

model like what we presented and the traditional education approach is that the model makes the education completely individualized. Embedding the model in computer software, the model can become an interactive graphic presentation, which would be more interesting to read and more motivational. It can also be more accessible because of the internet. A formal study to evaluate the effectiveness of such a model in term of increase knowledge and compliance of treatment is still needed.

Table 1. Baseline characteristic of the two clinical trials in UKPDS ^(10,12)

	Glucose control trial		Blood pressure control trial	
	Treatment	Control	Treatment	Control
Number of subjects	2729	1138	758	390
Mean age (SD)	53.2 (8.6)	53.4(8.6)	56.4(8.1)	56.5(8.1)
Male (%)	59	62	54	58
White Race (%)	81	81	86	88
Use of aspirin (%)	1.7	1.5	1.6	1.6
Exercise (%)				
Low	21	20	20	20
Moderate	34	37	35	35
High	45	43	45	45
Current smoker (%)	30	31	23	22
Total cholesterol (SD) (mmol/L)	5.4 (1.1)	5.4(1.0)	5.5(1.1)	5.6(1.1)
HDL (SD) (mmol/L)	1.07 (0.25)	1.08(0.24)	1.10(0.27)	1.10(0.28)
HbA1c (SD) (%)	7.05(1.42)	7.09(1.54)	6.9(1.7)	6.8(1.5)
Systolic blood pressure (SD) (mmHg)	135(19)	135(20)	159 (20)	160(18)
Micoalbuminuria (%)	11.3	12.8	18	16
Proteinuria (%)	1.7	2.1	3	4
Background retinopathy (%)	36	36	23	29

Table 2 Baseline characteristic of the second cohort in DCCT ⁽⁷⁾

	Treatment group	Control group
Number of subjects	363	352
Age	27(7)	27(7)
Male (%)	53	54
White race (%)	97	97
Systolic blood pressure (SD) (mmHg)	114(12)	116(12)
Current smokers (%)	18	19
Total cholesterol (SD)(mmol/L)	4.6(0.8)	4.6(0.83)
HDL cholesterol (SD)(mmol/L)	1.27(0.31)	1.27(0.28)
NPDR		
Mild	18	23
Moderate	15	19
Urinary albumin excretion (SD) (mg/24 hr)	21(25)	19(24)

Table 3. Comparisons between the predicted and the observed outcomes in the glucose control trial of UKPDS ⁽¹⁰⁾

	Observed outcomes			Predicted outcomes		
	Treatment	Control	RR ^d	Treatment	Control	RR
Blind ^a	2.9	3.5	0.84 (0.51-1.40)	3.2	3.8	0.84
Amputation ^a	1.1	1.6	0.61 (0.28-1.33)	1.5	2.1	0.71
MA ^b	19.2	25.4	0.76 (0.62-0.91)	28.9	35.2	0.82
GPA ^c	4.4	6.5	0.67 (0.42-1.07)	3.8	5.5	0.69
Renal failure ^a	0.6	0.8	0.73 (0.25-2.14)	0.5	0.7	0.71
Heart attack	21.5	24.1	0.88 (0.71-1.00) ^e	20	20	1.00
Stroke	5.6	5.0	1.11 (0.81-1.51)	5.9	5.9	1.00

a: 10 years cumulative incidence (%)

b: MA microalbuminuria, the value is the 9-year cumulative incidence (%)

c: GPA Gross proteinuria, the value is the 9-year cumulative incidence (%)

d: RR is relative risk of treatment over control. The values in the parenthesis are the 95% confidence intervals.

e: The confidence interval of RR for overall heart attack (MI and angina) was not available. The listed values are for MI only, the majority of CHD.

Table 4. Comparisons between the predicted outcomes and the observed outcomes in the blood pressure control trial of UKPDS ⁽¹²⁾

	Observed outcomes			Predicted outcomes		
	Treatment	Control	RR ^d	Treatment	Control	RR
Blind ^a	3.1	4.4	0.71 (0.28-1.81)	2.9	3.1	0.93
Amputation ^a	1.4	2.7	0.51 (0.14-1.86)	1.8	2.0	0.90
MA ^b	28.8	33.1	0.87 (0.60-1.26)	32.4	36.6	0.88
GPA ^c	7.6	6.6	1.06 (0.42-2.67)	5.9	7.5	0.79
Renal failure ^a	1.4	2.3	0.58 (0.15-2.21)	0.9	1.1	0.82
Heart Attack	26.6	31.2	0.85 (0.59-1.07) ^e	23.8	25.7	0.93
Stroke	6.5	11.6	0.56 (0.35-0.89)	8.7	10.1	0.86

a: 10 years cumulative incidence (%)

b: MA is microalbuminuria, the value is the 9-year cumulative incidence (%)

c: GPA is gross proteinuria, the value is the 9-year cumulative incidence (%)

d: RR is relative risk of treatment over control. The values in the parenthesis are 95% confidence intervals.

e: The confidence interval of RR for overall heart attack (MI and angina) was not available. The listed values are for the MI, the majority of CHD.

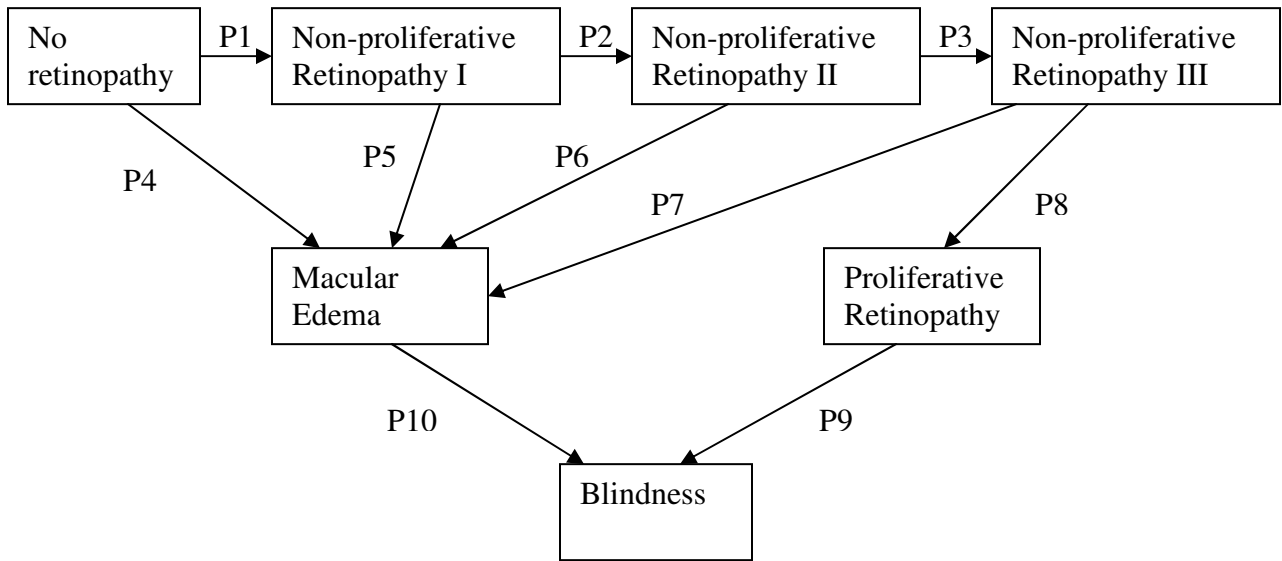
Table 5. Comparisons between the predicted annual incidence (%) and observed complication rates (rate/100 person year) in DCCT ⁽⁷⁾

	Observed outcomes			Predicted outcomes		
	Treatment	Control	% Risk reduction	Treatment	Control	% Risk reduction
ME	2.0	3.0	23 (-13-48)	1.7	2.1	19
PDR	1.1	2.4	47 (14-67)	1.4	2.3	39
MA	3.6	5.7	43 (21-58)	3.4	4.5	24
GPA	0.6	1.4	56 (18-76)	0.8	2.2	63
Clinical neuropathy	7.0	16.1	57 (29-73)	9.7	19.7	51
Macro-vascular	0.5	0.8	41 (-10-68)	0.2	0.2	0

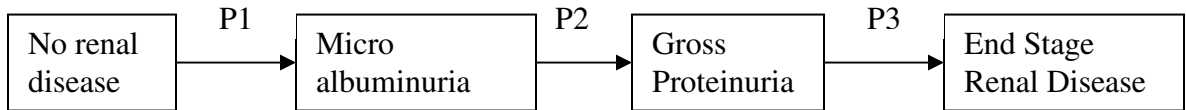
ME: macular edema; PDR: proliferative diabetic retinopathy; MA: microalbuminuria; GPA: gross proteinuria

Figure 1. Model schematic of progression of diabetic complications

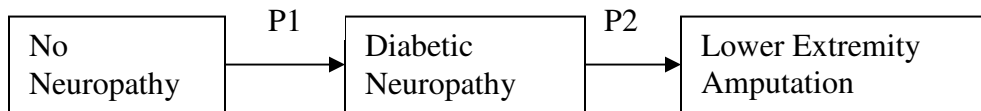
Retinopathy and macular edema



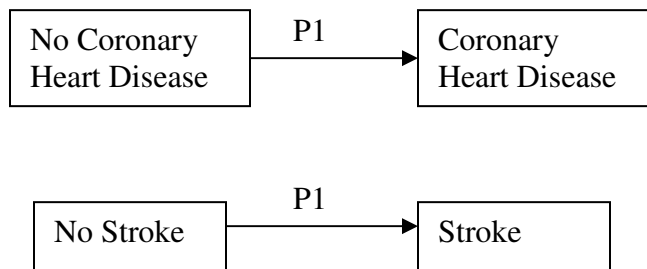
Nephropathy



Neuropathy



CVD



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Additional details on the methodology

The transitional probabilities or the formulas to calculate the transition probabilities are listed in Table 6 and appendix. Some of the probabilities are unconditional (always has the same value regardless other values) others are conditional on covariates. If there were more than one covariate then a regression equations (formula) were used. Most time such formulas were not available in the reference. The following procedures were used to develop the formulas.

First the relationship of a transitional probability (dependent variable) with the covariates (independent variable) was assumed to be in the logistic regression format, which is

$$\text{Log} (p/(1-p)) = a+b_1*X_1+b_2*X_2\dots+b_n*X_n \quad \text{It is equivalent to } P=1/(1+\text{Exp} (-a- b_1*X_1- b_2*X_2\dots-b_n*X_n))$$

P: transitional probability

b₁..b_n: regression coefficients

X₁..X_n: covariates or independent variables

a: intercept

Secondly, each b was derived from reference. By definition the Exp (b) is the odds ratio of P for every one-unit change of X. For example, according to the report of UKPDS ⁽¹²⁾, the annual incidences of retinopathy progress were 5.54% and 9.59% for intensive blood pressure control group (average systolic blood pressure (SBP) of 144 mmHg) and conventional group (mean of SBP=154

mmHg). The odds ratio= $(0.0959/(1-0.0959))/(0.0554/(1-0.0554))=1.84$. The regression coefficient $b=\log(1.84)/(154-144)=0.061$. $\text{Exp}(b)=1.063$, meaning for every increase one mmHg of systolic blood pressure the odds of retinopathy progress increase by 1.063 fold. The regression coefficients of other covariates were derived in a similar way, although they may be from different references. While the regression coefficient of HbA1c was determined, a log transformation of HbA1c was used. This is because that both DCCT and UKPDS study reported that the reduction of complications were linearly related with the percentage reduction of HbA1c value. The Log transformation could reflect that relation.

Finally, after all bs were known, the intercept a was calculated by applying the formula into a situation while the P and all X values were known. For example, the equation of retinopathy progression transition formula (formula 1 in the table 1 and appendix) was as following for type 2 diabetes: $P=1/(1+\text{Exp}(a-2.729*\text{Log}(\text{HbA}_{1c})-0.061*\text{SBP}-0.6931*\text{insulin}-0.747*\text{race1}-0.986*\text{race2}))$. According to UKPDS the annual incidence of retinopathy progression is 5.56% while $\text{HbA}_{1c}=7.9\%$, $\text{SBP}=135$ mmHg, 24% of the population using insulin, and race1 and race2 were set to 0. By applying those values into the formula the intercept a is calculated as 13.98

Formula 1 to 4 was all developed in the procedures as mentioned above. Formula 5 and 6, which are the probability of CHD and stroke, were from our previously developed prediction models, which were constructed by adding some additional risk factor into the Framingham CHD and stroke prediction model. For example, adding the physical exercise level, use of aspirin and race to the baseline Framingham CHD model.

Table 6. Model Assumption on Transition Probabilities

Transition between stages	Annual probability	Reference
Retinopathy		
P1 No retinopathy to NPDR1	Formula1	
P2 NPDR1 to NPDR2	Formula 1	
P3 NPDR2 to NPDR3	Formula 1	
P4 No retinopathy to ME	0.1548%	4
P5 NPDR1 to ME	0.866%	4
P6 NPDR2 to ME	0.317%	4
P7 NPDR3 to ME	3.7%	4
P8 NPDR3 to PDR	8%	17
P9 PDR to Blindness		
With Photocoagulation	2%	20
Without photocoagulation	9%	20
P10 ME to Blindness		
With Photocoagulation	3%	20
Without photocoagulation	5%	20
Nephropathy		
P1 No renal disease to MA	Formula 2	
P2 MA to GPA	Formula 3	
P3 GPT to ESRD		
For type 1	1.9%	7
For type 2(depend on duration)		
1-11 years	0.42%	25
12-20 years	3.85%	25
>20 years	7.4%	25
Neuropathy		
P1: no neuropathy to neuropathy	Formula 4	
P2: neuropathy to LEA (depend on duration)		
1-8	2.8%	26
9-13 years	3.5%	26
14-19 years	4.7%	26
>19 years	14%	26
CVD		
P1: Non CHD to CHD	Formula 5	
P1: Non Stroke to Stroke	Formula 6	

a, detail of the formula of 1 to 6 are in Appendix

Appendix

The regression equation/formula to compute the transitional probabilities (Table 6).

Formula 1:

$$\text{type 1 } p = 1 / (1 + \text{Exp} (19.41 - 3.955 * \text{Log} (\text{HbA1c}) - 0.061 * \text{SBP} - 0.6931 * \text{insulin} - 0.747 * \text{race1} - 0.986 * \text{race2}))$$

Reference: HbA1c (7), SBP (12), insulin (3), race (23-24)

$$\text{type 2 } p = 1 / (1 + \text{Exp} (16.874 - 2.729 * \text{Log} (\text{HbA1c}) - 0.061 * \text{SBP} - 0.6931 * \text{insulin} - 0.747 * \text{race1} - 0.986 * \text{race2}))$$

Insulin yes=1 no=0; race1=1 if African-Americans and American Indians, otherwise race1=0; race2=1 if Hispanic American, otherwise race2=0

Reference; HbA1c (10), SBP (12), insulin (3), race(23-24)

Formula 2:

type 1 duration < 8 years

$$p = 1 / (1 + \text{Exp} (7.2605 - 1.78 * \text{Log} (\text{HbA1c}) - 0.0484 * (\text{SBP} - 115))$$

duration >= 8 years

$$p = 1 / (1 + \text{Exp} (7.1658 - 1.993 * \text{Log} (\text{HbA1c}) - 0.0484 * (\text{SBP} - 115)))$$

Reference HbA1c (7), SBP (12)

$$\text{type 2 } p = 1 / (1 + \text{Exp} (14.1488 - 5.044 * \text{Log} (\text{HbA1c}) - 0.0484 * (\text{SBP} - 135) - 0.693 * (\text{race} - 0.24)))$$

race=1 if African-Americans, American Indianans and Hispanic American

Reference: HbA1c (10), SBP (12), race (20)

Formula 3:

type 1 duration < 8 years

$$p = 0.038$$

Reference; (7)

duration >= 8 years

$$p = 1 / (1 + \text{Exp} (12.54 - 4.49 * \text{Log} (\text{HbA1c}) - 0.0219 * (\text{SBP} - 115)));$$

Reference: HbA1c (7), SBP (12)

$$\text{type 2 } p = 1 / (1 + \text{Exp} (12.6757 - 5.2177 * \text{Log} (\text{HbA1c}) - 0.0219 * (\text{SBP} - 135) - 0.693 * \text{race}(-0.24)));$$

race=1 if African-Americans, American Indianans and Hispanic American

Reference: HbA1c (10), SBP (12), race (20)

Formula 4:

$$\text{type 1 } p = 1 / (1 + \text{exp}(11.2281 - 3.602 * \text{log}(\text{hba1c}) - 0.0656 * (\text{sbp} - 115)));$$

Reference: HbA1c (7), SBP(12)

$$\text{type 2 } p = 1 / (1 + \text{Exp} (4.226 - 2.758 * (\text{Log} (\text{HbA1c}) - \text{Log}(8)) - 0.0656 * (\text{sbp} - 135) - 1.098 * (\text{race} - 0.24)));$$

race=1 if African-Americans, American Indianans and Hispanic American
 Reference: HbA1c(10), SBP(12), race(20)

Formula 5: compute the 10-year risk of having CHD

If male Then $m = 11.1122 - 0.9119 * \text{Log}(\text{sbp}) - 0.2767 * \text{smoke} - 0.7181 * \text{Log}(\text{ratio}) - 1.4792 * \text{Log}(\text{age}) - 0.1759$
 If female Then $m = 11.1122 - 0.9119 * \text{Log}(\text{sbp}) - 0.2767 * \text{smoke} - 0.7181 * \text{Log}(\text{ratio}) - 5.8549 + 1.8515 * \text{Log}(\text{age} / 74) * \text{Log}(\text{age} / 74) - 0.3758$
 $u = (\text{Log}(10) - 4.4181 - m) / \text{Exp}(-0.3155 - 0.2784 * m)$
 $p1 = 1 - \text{Exp}(-\text{Exp}(u)); \text{logit1} = \text{Log}(p1 / (1 - p1))$

$P_chd = 1 / (1 + \text{Exp}(-\text{logit1} + 0.248 * (\text{aspirin} - 0.094) - 0.1764 * (\text{family} - 0.061) + 0.185 * (\text{act} - 2.107)))) / 10$

SBP: systolic blood pressure (mmHg)
 Smoke: 1 if current smoking 0 otherwise
 Ratio: total cholesterol/ HDL
 Aspirin: 1 if use aspirin
 Family: family history of premature CHD
 Act: physical activity (1 low, 2 moderate, 3 high)

Reference: (27)

Formula 6: compute the 10-year risk of having a stroke

If $\text{SBP} < 110$ Or $\text{SBP} > 200$ Then $\text{hrxsbp} = 0$
 Else $\text{hrxsbp} = \text{hprx} * (\text{SBP} - 110) * (200 - \text{SBP})$

If male Then $a = 0.0488 * \text{age} + 0.0152 * \text{SBP} + 0.00019 * \text{hrxsbp} + 0.546 * \text{CVD} + 0.5224 * \text{smoke} + 0.3429 - 5.677$
 If female Then $a = 0.0699 * \text{age} + 0.0161 * \text{SBP} + 0.00026 * \text{hrxsbp} + 0.4404 * \text{CVD} + 0.5419 * \text{smoke} + 0.5604 - 7.5766$

$p1 = 1 - 0.9353 ^ \text{Exp}(a); \text{logit1} = \text{Log}(p1 / (1 - p1))$
 $P_strok = 1 + \text{Exp}(-\text{logit1} + 0.1824 * (\text{act} - 2) - 0.59 * (\text{family} - 0.05))$

Hprx: 1 if using anti-hypertension medication, 0 otherwise
 Age: age in years
 Smoke: 1 is current smoking, 0 otherwise
 SBP: systolic blood pressure (mmHg)
 CVD; history of having any CVD
 Act: physical exercise level (1: low, 2 moderate, 3 high)
 Family: family history of having stroke

Reference: (27)

Use the following formula to convert the cumulative incidence to annual incidence.

$$P_1 = (\log(1/(1-P_t))) / T$$

P_1 : annual incidence

P_t : cumulative incidence at time T

For example, UKPDS reported the 7.5 year's cumulative incidence of retinopathy for the intensive blood pressure treatment group is 34% ⁽¹²⁾, Then the annual incidence = $(\log(1/(1-0.34))) / 7.5 = 0.0554$