Appendix B1. Diabetes Model Technical Document

Introduction

Currently over 3.2 million people in the UK have been diagnosed with diabetes mellitus type 2 (T2DM). Moreover, 90% of these cases represent T2DM. T2DM is a growing problem in the UK, with a dramatic increase recorded each year. Based on current trends it is estimated that there will be 5 million people in the UK with diabetes by 2025 (1).

T2DM can increase the risk of stroke, kidney failure, retinopathy, cardiac failure, angina and amputations resulting in increased costs to the NHS. Obesity is one of the major risk factors for DMT2. Other risk factors include age, hypertension, tobacco consumption, pre-diabetes, parental history of diabetes, statins and ethnicity (2,3). Both pre-diabetes and diabetes may be diagnosed by an impaired fasting glucose (IFG) and an impaired glucose tolerance (IGT) test along with symptoms such as polyuria. The glucose concentrations by diabetes state and glucose measure are detailed in Table 1 (4).

Table 1 Glucose measures and the outcomes for determining both pre-diabetes and diabetes.

	Glucose measure	
Diabetes state	Impaired fasting glucose (IFG)	Impaired glucose tolerance (IGT)
Pre-diabetes	≥6.1 mmol/L and <7 mmol/L	≥7.8 mmol/L and <11.1 mmol/L
T2DM	≥7 mmol/L	≥11.1 mmol/L

Research suggests that a combination of measures may be more effective than a single measurement in diagnosing type 2 diabetes (5–8). Hu (6) and Inoue (8) found a combination of FPG and HbA1c was more sensitive than using either measurement alone for type 2 diabetes and IGT diagnosis. In morbidly obese patients, using fPG with the WHO recommended cut-off of 6.1 mmol/l identified 95% of subjects with unknown diabetes, whilst additional OGTT tests identified the remaining subjects (9). Sullivan (10) found stratification of high risk patients identified by IFG had improved identification of risk level when used in combination with the PreDx Diabetes Risk Score, with an incremental cost-effectiveness ratio of $17,100/QALY at 5 and cost saving in 10 years. Pajunen (11) found that based on the OGTT tests, 60% of subjects would have been undiagnosed if based on HbA1c >6.5%.

Seif-Rabiei (12) found IFG had an 80.25% sensitivity whilst Cambuli (13) found IFG did not detect IGT in children, with a predictive value of 73% and sensitivity 17.6%.

Other tests for predicting diabetes included the 'muffin test' and Oral disposition index (DI(O)). The 'muffin test' had 100% sensitivity compared to OGTT when diagnosing IGT (14). DI(0) was effective in predicting the development of diabetes (15).

Previously, a wide range of mathematical methods have been used to model diabetes progression. An ordinary differential equation model of diabetes categorised people with diabetes into two stages either with or without complications. The simulations gave information about the evolution of people between these two stages. Different scenarios which aimed at altering the rate of this progression where evaluated in terms of their cost-effectiveness and output (16). Some models have focused on diabetes as a single

discrete state (17) whereas other models have simulated the glucose levels of individuals with time. Individuals in these models get diabetes when their glucose levels are within the predefined range (18).

This EConDA diabetes model included two discrete states: pre-diabetes and diabetes. A microsimulation model will be used to study the impact of obesity on the prevalence of different stages of diabetes. Previous models have focused on diabetes as a single state disease.

Model structure

The microsimulation model has been extended to include the ability to model diabetes by state. The structure of the model is shown in Figure 1.

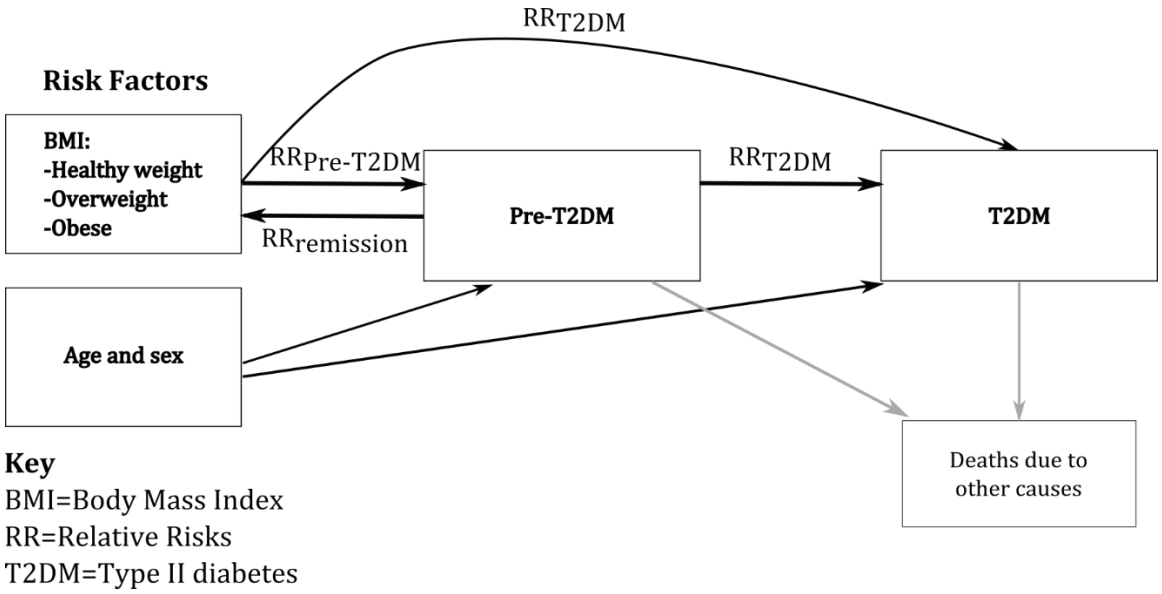

Figure 1 Schematic of diabetes multistate model structure. Risk factors BMI, age and sex are used to determine the incidence risk of transitioning between the two stages of diabetes. These stages include pre-T2DM and T2DM. Remission is only possible for individuals in the pre-T2DM state of the disease.

The modelling process used in this study is a dual modelling process. Firstly, BMI projections to 2035 have been created by fitting cross-sectional data to multivariate categorical regression models. The cross-sectional data used in this study has varied dependent on the country studied. For example in the UK, Health Survey for England annual datasets from 2000 until 2012 have been used. These BMI projections are used as input data for the microsimulation model. The microsimulation model originally developed for the Foresight: Tackling Obesities project (19) was adapted and further developed as part of the European Commission funded project EConDA (econdaproject.eu) to model multiple stages of T2DM. The BMI trends are used in the model to define an individuals' BMI based on their age and sex and control how their BMI will change with time as they age. An individual's BMI, age and sex will dictate the probability of an individual contracting a disease or state of a disease such as diabetes. In this model diabetes is not modelled as a terminal disease, so a simulated individual may die from other causes or terminal diseases in the model.

For single state diseases the incidence risk is calibrated based on the different BMI RR's because we do not have accurate incidence risk data by BMI category (e.g. healthy weight). For multistate diseases the calibration is applied to each state transition for both incidence and remission risk data. Further details of this method are described in the technical appendix B4.

Disease statistics

Many different disease statistics are required to model a multistage disease. These include relative risks, incidence and prevalence data. Diabetes is modelled as a non-terminal disease so survival data is not required in this instance.

Prevalence

Prevalence data for both stages of diabetes were obtained from the International Diabetes Federation. The prevalence data for pre-diabetes was represented by individuals with IGT.

Incidence

Incidence data collected for diabetes was separated into the incidence of diabetes from stage 0 (normoglycaemia) and the incidence of diabetes from stage 1 (pre-diabetes). The method used in the process is discussed in more detail in the technical appendix B4.

These two sets of incidence statistics (stage 0 to stage 2 and stage 1 to stage 2) were used along with the prevalence data for pre-diabetes and diabetes and the pre-diabetes remission data to approximate the incidence of pre-diabetes. This method is detailed in the technical appendix B4.

Relative risks

Relative risk data for diabetes and pre-diabetes was approximated by BMI category (healthy weight, overweight and obese) from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) longitudinal study.

PREVEND database analysis

The PREVEND database contains a maximum of four follow ups (FU) for each individual in the study. Impaired fasting plasma glucose levels were analysed at each FU, if an individual fasted prior to the glucose measurement. The following definitions were used to classify individuals as either normoglycaemic, pre-diabetic and T2DM.

1. Normoglycaemia = IFG levels <6.1 mmol/L and not taking any antidiabetic treatment.
2. Pre-diabetes = IFG levels ≥6.1 mmol/L and <7 mmol/L and not taking any antidiabetic treatment.
3. Diabetes = Either IFG levels ≥7 mmol/L and not taking any antidiabetic treatment or any IFG level and taking antidiabetic treatment.

In this analysis it has been assumed that pre-diabetics are not prescribed antidiabetic treatment. Any subjects with incomplete data were removed from the analysis. Moreover, any subjects who were already categorised with diabetes mellitus and on insulin at baseline were excluded from the analysis. It was assumed that these individuals already had type I diabetes.

Incidence risk data

Incidence statistics were approximated for the following transitions:

1. Normal state (state 0) -> Pre-diabetes (state 1)
2. Normal state (state 0) -> Diabetes (state 2)
3. Pre-diabetes (state 1) -> Diabetes (state 2)
4. Pre-diabetes (state 1) -> Normal state (state 0)

Between each pair of follow ups the incidence of pre-diabetes and diabetes was recorded and stratified by BMI and time between follow up. The BMI category was determined based on the person's BMI at the end follow up for each follow up analysis. The following BMI categories were used in this analysis:

1. Healthy weight = BMI < 25 kg/m^2
2. Overweight = 25 ≤ BMI < 30 kg/m^2
3. Obese = BMI ≥ 30 kg/m^2

The time between two follow ups varied for each individual and was approximated to the nearest year. All of the data collected between different pairs of follow-ups was pooled and analysed by the number of years between two follow-ups. The observed transitions for a 2, 3 and 4 year follow up are stratified by BMI category and summarised in Table 2, Table 3 and Table 4.

Table 2 A summary of the diabetes state transitions of healthy weight (BMI < 25 kg/m^2) individuals by 2, 3 and 4 years between follow-ups. Where the possible diabetes states are normoglycaemia (0), pre-diabetes (1) and diabetes (2).

Initial State	Final state		
	0	1	2
2 year transitions			
0	1278	8	5
1	36	2	2
2	7	1	25
3 year transitions			
0	1686	48	7
1	10	4	4
2	3	2	42
4 year transitions			
0	1273	31	16
1	5	2	0
2	0	1	10

Table 3 A summary of the diabetes state transitions of pre-obese (25 ≤ BMI < 30 kg/m²) individuals by 2, 3 and 4 years between follow-ups. Where the possible diabetes states are normoglycaemia (0), pre-diabetes (1) and diabetes (2).

Initial State	Final state		
	0	1	2
2 year transitions			
0	1407	28	11
1	43	17	15
2	13	4	61
3 year transitions			
0	1522	71	17
1	21	18	19
2	5	4	81
4 year transitions			
0	1226	57	23
1	16	9	16
2	2	2	29

Table 4 A summary of the diabetes state transitions of obese (BMI ≥ 30 kg/m²) individuals by 2, 3 and 4 years between follow-ups. Where the possible diabetes states are normoglycaemia (0), pre-diabetes (1) and diabetes (2).

Initial State	Final state		
	0	1	2
2 year transitions			
0	522	33	14
1	35	9	13
2	8	6	67
3 year transitions			
0	454	62	30
1	16	11	13
2	3	4	101
4 year transitions			
0	434	34	33
1	8	8	15
2	4	2	20

Approximating one year transition matrices

The follow ups in the PREVEND study were not completed annually. In order to obtain annual relative risks so that they could be used directly in the model the incidence data obtained from 2, 3 and 4 year follow ups was used to approximate the 1 year incidence risk for PREVEND. A small number of people were followed up after 5 or 6 years, however, this dataset was too small to use for this analysis. The EM algorithm was used to compute an estimation for the 1 year transition matrix (20). The application of this method to the 2, 3 and 4 year follow up data (Table 2, Table 3 and Table 4) is described in the technical

appendix B4. An approximation for the one year transition probability by BMI category is shown in Table 5, Table 6, Table 7 and Table 8.

Table 5 The one year transition probability matrix for all BMI groups estimated from the PREVEND study

All BMI categories	*Final state*		
Initial State	0	1	2
0	0.978	0.019	0.003
1	0.290	0.591	0.119
2	0.000	0.000	1.000

Table 6 The one year transition probability matrix for health weight individuals estimated from the PREVEND study

Health Weight	*Final state*		
Initial State	0	1	2
0	0.986	0.012	0.002
1	0.496	0.460	0.043
2	0.000	0.000	1.000

Table 7 The one year transition probability matrix for overweight individuals estimated from the PREVEND study

Overweight	*Final state*		
Initial State	0	1	2
0	0.980	0.018	0.002
1	0.244	0.629	0.128
2	0.000	0.000	1.000

Table 8 The one year transition probability matrix for obese individuals estimated from the PREVEND study

Obese	*Final state*		
Initial State	0	1	2
0	0.944	0.044	0.011
1	0.278	0.579	0.142
2	0.000	0.000	1.000

The bootstrapping method as described in the technical appendix B4 was used to obtain a mean and 95% CI for the RR's. A summary of the results is shown in Table 9.

Table 9 Mean RR's approximated for pre-diabetes and diabetes by BMI category

Transitions	BMI				
	Normal Weight	Overweight (mean)	95% CI	Obese (mean)	95% CI
0->1	1	1.462754	0.017145	3.622611	0.038722
1->2	1	2.390031	0.1118772	2.725526	0.1216039
0->2	1	1.373392	0.04173235	7.595739	0.1804023
1->0	1	0.5459446	0.008719087	0.6242302	0.00708018

A previous study has reported a RR of 4.7 (2.71-6.7) for developing diabetes given impaired fasting glucose (pre-diabetes).

Dataset limitations

There were a number of limitations with using the PREVEND database:

1. The study did not represent the whole population and was limited to an age range of approximately 28 to 75 years in follow-up one and 37 to 85 years in follow-up four.
2. A closed cohort population was used for the study.
3. The study was relatively small and consisted of ~4200 participants.
4. Due to the relatively small sample size RR's were only stratified by BMI category and not by age and sex.
5. The duration between each follow-up varied for each individual.
6. A previous study observed that only 25% of individuals within a Caucasian population have both IFG and IGT when compared to individuals having just one of these measures (21). The RR's have been approximated from the PREVEND dataset which only provides an IFG measurement as opposed to IGT.

Model assumptions

There are a number of assumptions which have been made in the mathematical model:

1. When an individual enters into the final stage of the diabetes disease they are unable to transition back to pre-diabetes or normoglycaemia.
2. Pre-diabetes and diabetes are non-terminal diseases (22,23).
3. For the baseline model (without any interventions) pre-diabetes and diabetes screening is not being considered.
4. The time lag between diagnosis and contraction of both diabetes and pre-diabetes is not being considered.
5. BMI is assumed to be a risk factor for pre-diabetes and diabetes. The effects of diabetes on BMI has not been considered.

6. Pre-diabetes has been determined from measurements for impaired fasting glucose (IFG) measurements.

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