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School for Public Health Research (SPHR) Diabetes Prevention Model: Detailed Description of Model Background, Methods, Assumptions and Parameters

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School for Public Health Research (SPHR) Diabetes Prevention Model: Detailed Description of Model Background, Methods, Assumptions and Parameters

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ABSTRACT: Type-2 diabetes is a complex disease with multiple risk factors and health consequences whose prevention is a major public health priority. We have developed a microsimulation model written in the R programming language that can evaluate the effectiveness and cost-effectiveness of a comprehensive range of different diabetes prevention interventions, either in the general population or in subgroups at high risk of diabetes. Within the model individual patients with different risk factors for diabetes follow metabolic trajectories (for body mass index, cholesterol, systolic blood pressure and glycaemia), develop diabetes, complications of diabetes and related disorders including cardiovascular disease and cancer, and eventually die. Lifetime costs and quality-adjusted life-years are collected for each patient. The model allows assessment of the wider social impact on employment and the equity impact of different interventions. Interventions may be population-based, community-based or individually targeted, and administered singly or layered together. The model is fully enabled for probabilistic sensitivity analysis (PSA) to provide an estimate of decision uncertainty. This discussion paper provides a detailed description of the model background, methods and assumptions, together with details of all parameters used in the model, their sources and distributions for PSA.

1 CONTENTS

2 BACKGROUND

This project aims to provide a coherent framework for the evaluation of strategies for the prevention of type 2 diabetes. Specifically, the focus is to enable the design of preventive strategies that are effective and cost-effective in combination, and support decision making around these. This is to enable a rational allocation of resources between population/community level interventions, which aim to alter the distribution of risk factors for diabetes, and targeted identification/screening interventions such as the NHS health checks programme, which aim to identify and provide management for individuals at increased risk.

There are a number of necessary steps involved in translating knowledge from epidemiological studies in diabetes into preventive action: Identification of individuals or groups who are at increased risk; description of the important risk factors that can be altered; identification of key influences on risk factors (e.g. attitudes or environmental aspects); development of interventions to act on risk factors (e.g. promoting walking); development of methods to identify people likely to benefit from an intervention; evaluation of the success of an intervention and estimation of its potential impact on public health.

Modelling can play a key role in developing our understanding of this complex system. Firstly it can estimate the potential impact of different risk identification and management strategies on public health outcomes and help in pinpointing the most cost-effective strategies for intervention. Furthermore, it can play a key role in facilitating the iterative research cycle by helping us identify and analyse key current uncertainties, focus further research and input into the design of the next generation of interventions.

As part of this project we conducted a review of previous decision analytic models used to evaluation diabetes prevention interventions (1). This review confirmed that no other diabetes models were sufficient to meet the objectives of this project and identified some areas of development from previous models to consider in the model design.

3 DEVELOPING THE CONCEPTUAL MODEL

A conceptual model of the problem and a model-based conceptual model were developed according to a new conceptual modelling framework for complex public health models (2). In line with this framework the conceptual models were developed in collaboration with a project stakeholder group comprising health economists, public health specialists, research collaborators from other SPHR groups, diabetologists, local commissioners and lay members. The conceptual model of the problem mapped out all relevant factors associated with diabetes based upon iterative literature searches. Key initial sources were reports of two existing diabetes prevention models used for National Institute for Health and Care Excellence public health guidance (3;4). This conceptual model of the problem was presented at a Stakeholder Workshop. Discussion at the workshop led to modifications of the model, identifying additional outcomes such as depression and helping to identify a suitable conceptual model boundary for the cost-effectiveness model structure. Table 1 describes which factors included within the conceptual model of the problem were chosen to be included and excluded from the health economic model as agreed by stakeholders following the workshop. This final model boundary based upon Table 1 provided the final scope for the simulation model developed. A review of previous economic evaluations of diabetes prevention was also instrumental in deciding on the final boundary of the economic model (1).

Table 1: Diabetes model boundary selection

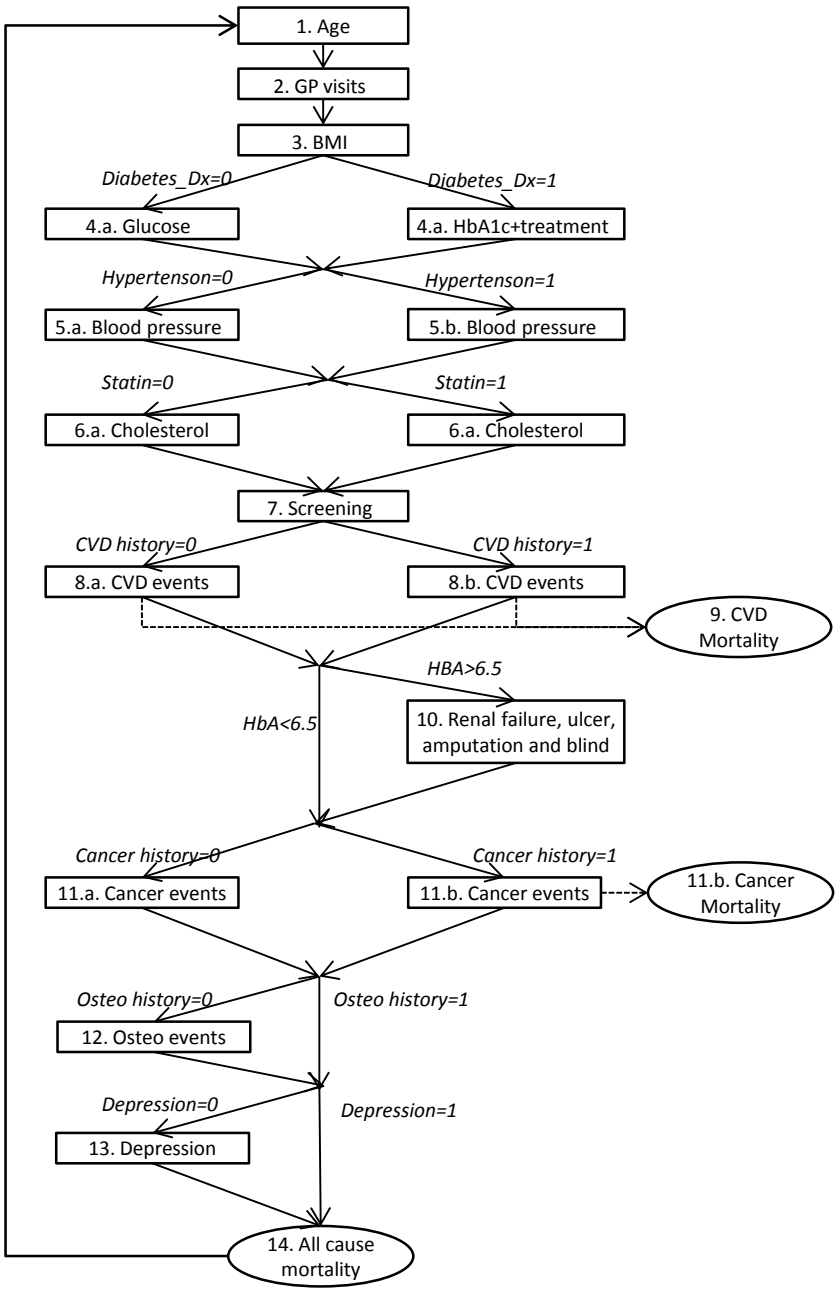
Factor	Include/Exclude	Reason for inclusion/exclusion
Risk factors	Include	Key component of causal diagram
Gestational diabetes/ pregnancy complications	Exclude	This is a small subgroup and is not considered to be a focus of this project.
Osteoarthritis	Include	Diabetes has been found to be an independent risk factor for osteoarthritis independent of the effect of BMI (5). In addition, the report by Gillett et al. suggests that the cost of osteoarthritis is comparable to the cost of diabetes (6).
Risk factors of next generation	Exclude	Within the high risk group, only a minority of people will parent a young child due to the age of the people affected, thus there would be limited impact upon the next generation. Within the general population, Whitaker et al. suggest that parental obesity more than doubles the risk of adult obesity among their children. This could bear substantial future costs and effects; however because these costs and outcomes would occur so far in the future, by applying a discount rate to both costs and effects, there would be minimal impact upon the model results. Time would be better spent elsewhere.
Blood glucose levels/ Non-diabetic hyperglycaemia/ Diabetes	Include	Key component of causal diagram.
Hypoglycaemia & weight gain associated with pharmacological interventions	Include (but not as a separate factor)	The quality of life implications of hypoglycaemia and weight gain are likely to be captured within the quality of life of people with diabetes. There are likely to be minimal additional costs associated with hypoglycaemia and weight gain above those associated with treating the disease.
Non-alcoholic fatty liver	Include (but not as a separate factor)	This is likely to be included within the costs and quality of life estimates associated with diabetes and obesity.
Fatigue	Include (but not as a separate factor)	The quality of life implications of fatigue are likely to be captured within the quality of life of people with disease. There are likely to be minimal additional costs associated with fatigue above those associated with treating disease.
Neuropathy	Include	Key outcome associated with diabetes.
Erectile dysfunction	Include (but not as a separate factor)	This is likely to be included within the costs and quality of life impacts of neuropathy.
Nephropathy	Include	Key outcome associated with diabetes.
Retinopathy	Include	Key outcome associated with diabetes
Cancers (post-menopausal breast cancer, colorectal cancer)	Include	The report by the World Cancer Research Fund (WCRF) Panel on Food, Nutrition, Physical Activity and the Prevention of Cancer suggests that BMI has a significant impact upon the incidence and mortality of post-menopausal breast cancer, colorectal cancer, oesophagus cancer, kidney cancer, endometrial cancer, gall bladder cancer and pancreatic cancer (7). It also suggests that physical activity is associated with colorectal cancer, postmenopausal breast cancer and endometrial cancer.
CVD including hypertension, coronary heart disease (leading to heart attacks & angina), congestive heart failure, and cerebrovascular disease (incl. stroke & dementia)	Include	Has a substantial impact upon both costs and effects.
Mental illness (incl. dementia)	Partially include (but not as a separate factor for all illnesses)	Depression was included as a separate factor. However, the relationship between mental illness and diabetes is complex and currently not completely understood. Part of the relationship is associated with the incidence of cerebrovascular disease and the impact of mental illness will be captured within these costs and outcomes. The remaining associations, such as the direct increase in mental illness as a result of being diagnosed and living with diabetes, are difficult to untangle and are expected to have a small impact upon the model outcomes relative to other model factors.
Obstructive sleep apnoea	Include (but not as a separate factor)	The relationship between risk factors and CVD is expected to capture those events resulting from obstructive sleep apnoea. The quality of life associated with people who are overweight is likely to include poorer quality of life resulting from obstructive sleep apnoea. In the instances where sleep apnoea is treated, the cost is minimal.
Infectious diseases	Exclude	Relative to other model factors, this is likely to have a smaller impact upon the model outcomes.
Environmental outcomes (congestion, CO2, pollutants)	Not currently clear	This depends upon the choice of interventions within the model (see Section 1).

4 MODEL STRUCTURE

We developed an individual patient simulation that estimates individuals' health in yearly cycles until death. The simulation draws baseline demographic and clinical status for individuals sampled from the Health Survey for England (HSE) 2011 (8). The simulation estimates yearly changes in metabolic risk factors based upon the individuals' baseline characteristics. Within each annual cycle the individuals may be screened for hypertension, dyslipidaemia or diabetes during a visit to the GP. The opportunistic screening is used to determine diabetes diagnosis or the initiation of anti-hypertensive treatment or statins. Baseline characteristics and metabolic risk factors determine the individuals' probability of cardiovascular events, diabetes microvascular complications, cancer, osteoarthritis and depression. Individuals within the model may die in any cycle as a result of cardiovascular disease, cancer or from other causes.

Figure 1 illustrates the sequence of updating clinical characteristics and clinical events that are estimated within a cycle of the model. This sequence is repeated for every annual cycle of the model. The first stage of the sequence updates the age of the individual. The second stage estimates how many times the individual attends the GP. The third stage estimates the change in BMI of the individual from the previous period. In the fourth stage, if the individual has not been diagnosed as diabetic (Diabetes_Dx=0) their change in glycaemia is estimated using the Whitehall II model. If they are diabetic (Diabetes_Dx=1), it is estimated using the UKPDS model. In stages five and six the individual's blood pressure and cholesterol are updated using the Whitehall II model if the individual is not identified as hypertensive or receiving statins. In stage seven, the individual may undergo assessment for diabetes, hypertension and dyslipidaemia during a GP consultation. From stage eight onwards the individual may experience cardiovascular outcomes, diabetes related complications, cancer, osteoarthritis or depression. If the individual has a history of cardiovascular disease (CVD history=1), they follow a different pathway in stage eight to those without a history of cardiovascular disease (CVD history=0). Individuals with HbA1c greater than 6.5 are assumed to be at risk of diabetes related complications. Individuals who do not have a history of cancer (Cancer history=0) are at risk of cancer diagnosis, whereas those with a diagnosis of cancer (Cancer history=1) are at risk of mortality due to cancer. Individuals without a history of osteoarthritis or depression may develop these conditions in stages 12 and 13. Finally, all individuals are at risk of dying due to causes other than cardiovascular or cancer mortality. Death from renal disease is included in the estimate of other-cause mortality.

Figure 1: Model Schematic



5 DATA SELECTION

Having developed and agreed the model structure and boundary with the stakeholder group the project team sought suitable sources of data for the baseline population, GP attendance, metabolic risk trajectories, treatment algorithms, and risk models for long term health outcomes, health care and health related. Given the complexity of the model it was not possible to use systematic review methods to identify all sources of data for these model inputs. As a consequence we used a series of methods to identify the most appropriate sources of data within the time constraints of the project.

Firstly, we discussed data sources with the stakeholder groups and identified key studies in the UK that have been used to investigate diabetes and its complications and comorbidities. The stakeholder group included experts in the epidemiology of non-communicable disease who provided useful insight into the strengths and limitations of prominent cohort studies and trials that have studies the risks of long term health outcomes included in the model. The stakeholder group included diabetes prevention cost-effectiveness modellers, whose understanding of studies that could be used to inform risk parameters, costs and health related quality of life estimates. Secondly, we used a review of economic evaluations of diabetes prevention and weight management cost-effectiveness studies to identify sources of data used in similar economic evaluations (1). Thirdly, we conducted targeted literature searches where data could not be identified from large scale studies of a UK population, or could be arguably described as representative of a UK population through processes described above. Justification for data inputs for all model parameters are described below.

6 BASELINE POPULATION CHARACTERISTICS

6.1 CHOICE OF HEALTH SURVEY FOR ENGLAND 2011 DATASET

The model required demographic, anthropometric and metabolic characteristics that would be representative of the UK general population. The Heath Survey for England (HSE) was suggested by the stakeholder group because it collects up-to-date cross-sectional data on the characteristics of all ages of the English population. It also benefits from being a reasonably good representation of the socioeconomic profile of England. A major advantage of this dataset is that includes important clinical risk factors such as HbA1c, SBP, and cholesterol. The characteristics of individuals included in the cost-effectiveness model were based sampled from the HSE 2011 dataset (8). The HSE 2011 focused on CVD and associated risk factors. The whole dataset was obtained from the UK Data Service.

6.2 EXCLUSION CRITERIA

The total sample size of the HSE 2011 was 10,617. Individuals from the HSE dataset who met the following criteria were excluded from the sample. The list of exclusion criteria and the number of individuals that met these criteria are listed below.

1. Individuals younger than 16 years (N=2007)
2. Individuals with a previous diagnosis of diabetes (N=572)

This left a final sample size of 8038 individuals.

6.3 DATA EXTRACTION

Only a subset of variables reported in the HSE 2011 cohort was needed to inform the baseline characteristics in the economic model. A list of model baseline characteristics and the corresponding variable name and description from the HSE 2011 are listed below in Table 2. Two questions for smoking were combined to describe smoking status according to the QRISK2 algorithm in which former smokers and the intensity of smoking are recorded within one measure. The number of missing data for each observation in the HSE data is detailed in Table 2 and summary statistics for the data extracted from the HSE2011 dataset are reported in Table 3.

Table 2: HSE variable names and missing data summary

Model requirements	HSE 2011	HSE 2011 variable description	No. Missing

	variable name		data entries (N=8038)
Age	Age	Age last birthday	0
Sex	Sex	Sex	0
Ethnicity	Origin	Ethnic origin of individual	36
Deprivation (Townsend)	qimd	Quintile of IMD SCORE	0
Weight	wtval	Valid weight (Kg) inc. estimated>130kg	1284
Height	htval	Valid height (cm)	1207
BMI	bmival	Valid BMI	1431
Waist circumference	wstval	Valid Mean Waist (cm)	2871
Waist-Hip ratio	whval	Valid Mean Waist/Hip ratio	2882
Total Cholesterol	cholval	Valid Total Cholesterol Result	4760
HDL cholesterol	hdlval	Valid HDL Cholesterol Result	4760
HbA1c	glyhbval	Valid Glycated HB Result	4360
FPG			N/A
2-hr glucose			N/A
Systolic Blood pressure	omsysval	Omron Valid Mean Systolic BP	3593
Hypertension treatment	medcinbp	Currently taking any medicines, tablets or pills for high BP	6050
Gestational diabetes	pregdi	Whether pregnant when told had diabetes	8008
Anxiety/depression	Anxiety	Anxiety/Depression	930
Smoking	cigsta3	Cigarette Smoking Status: Current/Ex-Reg/Never-Reg	75
	cigst2	Cigarette Smoking Status - Banded current smokers	74
Statins	lipid	Lipid lowering (Cholesterol/Fibrinogen) - prescribed	5804
Rheumatoid Arthritis	compm12	XIII Musculoskeletal system	5
Atrial Fibrillation	murmur1	Doctor diagnosed heart murmur (excluding pregnant)	2008
Family history diabetes			N/A
History of Cardiovascular disease	cvdis2	Had CVD (Angina, Heart Attack or Stroke)	3
Economic Activity	econact	Economic status	37

Table 3: Characteristics of final sample from HSE 2011 (N=8038)

	Number	Percentage	
Male	3506	43.6	
White	7212	89.7	
IMD 1 (least deprived)	1700	21.1	
IMD 2	1699	21.1	
IMD 3	1696	21.1	
IMD 4	1479	18.4	
IMD 5 (most deprived)	1464	18.2	
Non-smoker	6415	79.8	
Anti-hypertensive treatment	2092	26.0	
Statins	665	8.3	

Employed	4525	56.3	
Unemployed	385	4.8	
Retired	1945	24.2	
Economically Inactive	1183	14.7	
	Mean	**Standard deviation**	**Median**
Age	48.59	18.49	47.00
BMI	27.13	5.18	26.40
Total Cholesterol	5.42	1.07	5.40
HDL Cholesterol	1.53	0.44	1.50
HbA1c	5.61	0.47	5.60
Systolic Blood Pressure	125.90	16.92	123.50
EQ-5D (TTO)	0.836	0.232	0.883
BMI Body Mass Index; IMD Index of Multiple Deprivation; EQ-5D 5 dimensions Euroqol (health related quality of life index)			

A complete dataset was required for all individuals at baseline. However, no measurements for Fasting Plasma Glucose (FPG) or 2 hour glucose were obtained for the HSE 2011 cohort. In addition, the questionnaire did not collect information about individual family history of diabetes or family history of Cardiovascular Disease (CVD). These variables were imputed from other datasets.

Many individuals were lacking responses to some questions but had data for others. One way of dealing with this is to exclude all individuals with incomplete data from the sample. However, this would have reduced the sample size dramatically, which would have been detrimental to the analysis. It was decided that it would be better to make use of all the data available to represent a broad range of individuals within the UK population. With this in mind, we decided to use assumptions and imputation models to estimate missing data.

6.4 MISSING DATA IMPUTATION

6.4.1 Ethnicity

Only a small number of individuals had missing data for ethnicity. In the QRISK2 algorithm the indicator for white includes individuals for whom ethnicity is not recorded. In order to be consistent with the QRISK2 algorithm we assumed that individuals with missing ethnicity data were white.

6.4.2 Anthropometric data

A large proportion of anthropometric data was missing in the cohort. Table 4 reports the number of individuals with two or more anthropometric records missing. This illustrates that only 758 individuals had no anthropometric data at all. Imputation models for anthropometric data were developed utilising observations from other measures to help improve their accuracy.

Table 4: Multi-way assessment of missing data

Conditions	Number of individuals
No weight and no height	1060
No weight and no waist circumference	907
No weight and no hip circumference	906
No height and no waist circumference	818
No height and no hip circumference	817
No hip and no waist	2865
No anthropometric data	758

Two imputation models were generated for each of the following anthropometric measures: weight, height, waist circumference and hip circumference. The first imputation method included an alternative anthropometric measure to improve precision. The second included only age and/or sex, to be used if the alternative measure was also missing. Simple ordinary least squares (OLS) regression models were used to predict missing data. Summary data for each measure confirmed that the data were approximately normally distributed. Covariate selection was made by selecting the anthropometric measure that maximised the Adjusted R-squared statistic, and age and sex were included if the coefficients were statistically significant ($P<0.1$).

The imputation models for weight are reported in Table 5. Individuals' sex and age were included in both models. A quadratic relationship between age and weight was identified. Waist circumference had a positive and significant relationship with weight. The R^2 for model 1 suggested that 80% of the variation in weight is described by the model. The R^2 for model 2 was much lower as only 18% of the variation in weight was described by age and sex. The residual standard error is reported for both models.

Table 5: Imputation model for weight

Coefficient	**Model 1**	**Model 2**
Intercept	-17.76	50.249
Sex	2.614	13.036
Age	0.064	0.903
Age*Age	-0.0027	-0.0086
Waist circumference	1.060	
R-squared	0.7981	0.1831
Residual standard error	7.483	15.31

The imputation models for height are reported in Table 6. Individuals' sex and age were included in both models. A quadratic relationship between age and height was identified. Waist circumference had a positive and significant relationship with height. The R^2 for model 1 suggested that 53% of the variation in height is described by the model suggesting a fairly good fit. The R^2 for model 2 was

slightly lower in which 52% of the variation in height was described by age and sex. The residual standard error is reported for both models.

Table 6: Imputation model for height

Coefficient	Model 1	Model 2
Intercept	157.4	162.1
Sex	12.82	13.43
Age	0.081	0.1291
Age*Age	-0.0021	-0.0025
Waist circumference	0.071	
R-squared	0.532	0.5244
Residual standard error	6.617	6.682

The imputation models for waist circumference are reported in Table 7. Individuals' sex and age were included in both models. A quadratic relationship between age and waist circumference fit to the data better than a linear relationship. Weight had a positive and significant relationship with waist circumference. The R^2 for model 1 suggested that 81% of the variation in waist circumference is described by the model suggesting a very good fit. The R^2 for model 2 was much lower in which only 22% of the variation in waist circumference was described by age and sex which is a moderately poor fit. The residual standard error is reported for both models.

Table 7: Imputation model for waist

Coefficient	Model 1	Model 2
Intercept	28.73	65.327
Sex	0.5754	9.569
Age	0.1404	0.7617
Age*Age	0.0007	-0.0053
Weight	0.7098	
R-squared	0.8096	0.2196
Residual standard error	6.122	12.44

The imputation models for hip circumference are reported in Table 8. Individuals' sex and age were included in both models. A quadratic relationship between age and hip circumference fit to the data better than a linear relationship. Weight had a positive and significant relationship with hip circumference. The R^2 for model 1 suggested that 80% of the variation in hip circumference is described by the model suggesting a very good fit. The R^2 for model 2 was much lower in which only 2% of the variation in hip circumference was described by age and sex which is a very poor fit. The residual standard error is reported for both models.

Table 8: Imputation model for hip

Coefficient	Model 1	Model 2
Intercept	66.9145	96.891
Sex	-8.3709	-0.9783
Age	-0.1714	0.3528
Age*Age	0.0021	-0.0029
Weight	0.5866	
R-squared	0.7949	0.023
Residual standard error	4.539	10.1

6.4.3 Metabolic data

A large proportion of metabolic data was missing in the cohort, ranging from 2997-4309 observations for each metabolic measurement. Table 9 reports the number of individuals with two or more metabolic records missing. This illustrates that 2987 individuals have no metabolic data. Imputation models for metabolic data were developed utilising observations from other measures to help improve their accuracy.

Table 9: Multi-way assessment of missing data

Conditions	Number of individuals
No HbA1c and no cholesterol	4309
No HbA1c and no blood pressure	2997
No cholesterol and no blood pressure	3050
No metabolic data	2987

Two imputation models were generated for each of the following metabolic measures: total cholesterol, high density lipoprotein (HDL) cholesterol, HbA1c and systolic blood pressure (SBP) and. The first imputation method included an alternative metabolic measure to improve precision. The second included only age and/or sex, to be used if the alternative measure was also missing. Simple ordinary least squares (OLS) regression models were used to predict missing data. Summary data for each measure confirmed that the data were approximately normally distributed. Covariate selection was made by selecting the metabolic measure that maximised the adjusted R-squared statistic, and age and sex were included if the coefficients were statistically significant ($P<0.1$).

These imputation models were developed to estimate metabolic data from information collected in the HSE. An alternative approach would have been to use estimates of these measures from the natural history statistical models. At the time of the analysis it was uncertain what form and design the natural history models would take, therefore the HSE imputation models were developed for use until a better alternative was found.

The imputation models for total cholesterol are reported in Table 10. Individuals' age was included in both models. A quadratic relationship between age and weight was identified. Diastolic blood pressure had a positive and significant relationship with total cholesterol. The R^2 for model 1 suggested that 20% of the variation in total cholesterol is described by the model. The R^2 for model 2 was lower in which only 18% of the variation in total cholesterol was described by age. The residual standard error is reported for both models.

Table 10: Imputation model for total cholesterol

Coefficient	Model 1	Model 2
Intercept	1.973	2.821
Age	0.0774	0.0904
Age*Age	-0.0006	-0.0007
Diastolic blood pressure	0.0159	
R-squared	0.2035	0.1792
Residual standard error	0.9526	0.9741

The imputation models for HDL cholesterol are reported in Table 11. Individuals' sex and age were included in both models. A quadratic relationship between age and height was identified. Diastolic blood pressure had a negative and significant relationship with HDL cholesterol. The R^2 for model 1 suggested that only 13% of the variation in HDL cholesterol is described by the model suggesting a relatively poor fit. The R^2 for model 2 suggested that 12% of the variation in HDL cholesterol was described by age and sex. The residual standard error is reported for both models.

Table 11: Imputation model for HDL Cholesterol

Coefficient	Model 1	Model 2
Intercept	1.501	1.383
Sex	-0.279	-0.274
Age	0.0086	0.0075
Age*Age	-0.0001	-0.00004
Diastolic blood pressure	-0.0018	
R-squared	0.1198	0.1157
Residual standard error	0.4122	0.417

The imputation models for HbA1c are reported in Table 12. Individuals' age was included in both models. A quadratic relationship between age and HbA1c fit to the data better than a linear relationship. SBP had a positive and significant relationship with HbA1c. The R^2 for model 1 suggested that only 19% of the variation in HbA1c is described by the model, suggesting a modest fit. The R^2 for model 2 described 18% of the variation in HbA1c by age alone. The residual standard error is reported for both models.

Table 12: Imputation model for HbA1c

Coefficient	Model 1	Model 2
Intercept	4.732	4.962
Age	0.0141	1.422
Age*Age	-0.00003	-0.00003
Systolic blood pressure	0.002	
R-squared	0.1941	0.1835
Residual standard error	0.4243	0.4228

The imputation models for SBP are reported in Table 13. Individuals' sex and age were included in both models. A linear relationship between age and SBP fit to the data better than a quadratic relationship. Total cholesterol and HbA1c had a positive and significant relationship with SBP, whereas HDL cholesterol had a negative significant relationship with SBP. The R^2 for model 1 suggested that 22% of the variation in SBP is described by the model suggesting a modest fit. The R^2 for model 2 was similar in which only 20% of the variation in SBP was described by age and sex. The residual standard error is reported for both models.

Table 13: Imputation model for Systolic Blood Pressure

Coefficient	Model 1	Model 2
Intercept	84.983	104.132
Sex	6.982	6.396
Age	0.330	0.380
Total cholesterol	2.093	
HDL cholesterol	-0.746	
HbA1c	1.986	
R-squared	0.2235	0.2047
Residual standard error	14.59	15.1

6.4.4 Treatment for Hypertension and Statins

A large proportion of individuals had missing data for questions relating to whether they received treatment for hypertension or high cholesterol. The majority of non-responses to these questions were coded to suggest that the question was not applicable to the individual. As a consequence it was assumed that individuals with missing treatment data were not taking these medications.

6.4.5 Gestational Diabetes

Only 30 respondents without current diabetes reported that they had been diagnosed with diabetes during a pregnancy in the past. Most individuals had missing data for this question due to it not being applicable. The missing data was assumed to indicate that individuals had not had gestational diabetes.

6.4.6 Anxiety/Depression

Most individuals who had missing data for anxiety and depression did so because the question was not applicable. A small sample N=69 refused to answer the question. We assumed that individuals with missing data for anxiety and depression did not have severe anxiety/depression.

6.4.7 Smoking

Individuals with missing data for smoking status were assumed to be non-smokers, without a history of smoking.

6.4.8 Rheumatoid Arthritis and Atrial Fibrillation

A very small sample of individuals had missing data for musculoskeletal illness (N=5) and atrial fibrillation (N=1). These individuals were assumed to not suffer from these illnesses.

6.4.9 Family history of diabetes

No questions in the HSE referred to the individual having a family history of diabetes, so this data had to be imputed. It was important that data was correlated with other risk factors for diabetes, such as HbA1c and ethnicity. We analysed a cross-section of the Whitehall II dataset to generate a logistic regression to describe the probability that an individual has a history of diabetes conditional on their HbA1c and ethnic origin. The model is described in Table 14.

Table 14: Imputation model for history of diabetes

	Coefficient
Intercept	-3.29077 (0.4430)
HbA1c	0.28960 (0.0840)
HDL Cholesterol	0.81940 (0.13878)

6.4.10 Economic Activity

Individuals without information about their employment status were assumed to be retired if aged 65 or over and in employment if under 65.

7 GP ATTENDANCE IN THE GENERAL POPULATION

GP visit frequency was simulated in the dataset for two reasons; firstly, to estimate the healthcare utilisation for the general population without diabetes and cardiovascular disease and secondly, to predict the likelihood that individuals participate in opportunistic screening for diabetes and vascular risks. Analysis of wave 1 of the Yorkshire Health Study (Table 15: Model 1) investigated whether disease comorbidity, BMI, IMD deprivation score, ethnicity and EQ-5D contributed to the rate of GP attendance. The analysis used a negative binomial regression model to estimate self-reported rate of GP attendance per 3 months. The results show that non-white individuals and those from poorer backgrounds visit the GP more frequently. This suggested that GP attendance would be a poor proxy for uptake of screening and prevention services, which are known to be lower in deprived groups. It is possible that higher GP attendance in deprived and ethnic groups reflect poorer health amongst these communities. Model 2 was used in the final model to describe GP attendance conditional on age, sex, BMI, ethnicity, and health outcomes. We did not relate GP attendance to IMD, because we did not have accurate IMD data in the HSE 2011, and EQ-5D was removed to avoid double counting with disease outcomes. The estimated number of GP visits was multiplied by 4 to reflect the annual number of visits per year.

Table 15: GP attendance reported in the Yorkshire Health Study (N= 18,437)

	Model 1		**Model 2**	
	Mean	Standard error	Mean	Standard error
Age	0.0057	0.0005	0.0076	0.0005
Male	-0.1502	0.0155	-0.1495	0.0159
BMI	0.0020	0.0015	0.0110	0.0015
IMD score 2010	0.0043	0.0005		
Ethnicity (Non-white)	0.1814	0.0370	0.2620	0.0375
Heart Disease	0.1588	0.0281	0.2533	0.0289
Depression	0.2390	0.0240	0.6127	0.0224
Osteoarthritis	0.0313	0.0240	0.2641	0.0238
Diabetes	0.2023	0.0270	0.2702	0.0278
Stroke	0.0069	0.0460	0.1659	0.0474
Cancer	0.1908	0.0400	0.2672	0.0414
Intercept	0.6275	0.0590	-0.5014	0.0468
Alpha	0.3328	0.0097	0.3423	0.0108

The coefficients of the Negative Binomial model described in Table 15, were used to estimate the first parameter of the Negative Binomial distribution μ_i.

$$\mu_i = \exp(x_i\beta)$$

The dispersion parameter of the Negative Binomial distribution v_i was sampled from a gamma distribution with mean 1 and variance α based on estimates reported in. The dose was estimated from the Poisson function.

$$p(Y = y|y > 0, x) = \frac{(v_i\mu_i)^y e^{-(v_i\mu_i)}}{y!}$$

In the probabilistic sensitivity analysis the parameters of the Yorkshire Health Study negative binomial model are sampled from a multivariate normal distribution, using the mean estimates described in Table 15 and covariance matrix in Table 16.

Table 16: Variance-covariance matrix for GP attendance regression

	Age	Male	BMI	Ethnicity (Non-white)	Heart Disease	Depression	Osteoarthritis	Diabetes	Stroke	Cancer	Intercept	Alpha
Age	0.0000											
Male	0.0000	0.0003										
BMI	0.0000	0.0000	0.0000									
Ethnicity (Non-white)	0.0000	0.0000	0.0000	0.0014								
Heart Disease	0.0000	0.0000	0.0000	0.0000	0.0008							
Depression	0.0000	0.0000	0.0000	0.0000	0.0000	0.0005						
Osteoarthritis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0006					
Diabetes	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0000	0.0000	0.0008				
Stroke	0.0000	0.0000	0.0000	0.0000	-0.0002	-0.0001	0.0000	-0.0001	0.0022			
Cancer	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0017		
Intercept	0.0000	0.0000	-0.0001	-0.0002	0.0002	0.0000	0.0002	0.0003	0.0000	0.0001	0.0022	
Alpha	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0010

8 LONGITUDINAL TRAJECTORIES OF METABOLIC RISK FACTORS

A search of epidemiology studies of metabolic risk factor trajectories identified a number of studies estimating changes in HbA1c, SBP, total cholesterol, and HDL cholesterol over time from longitudinal studies. However, no analysis had looked at the correlations and associations between these risk factors. Including the correlation between risk factor trajectories was would affect the long term risk profile for cardiovascular disease and other complications, therefore a statistical analysis of the Whitehall II cohort study (9) was developed to describe correlated longitudinal changes in metabolic risk factors. The analysis was developed in collaboration with epidemiologists at University College London, and in consultation with the stakeholder group.

8.1 WHITEHALL II DATA ANALYSIS

Changes in BMI, latent blood glucose, total cholesterol, HDL cholesterol and systolic blood pressure were estimated from statistical analysis of the Whitehall II cohort. The growth factors for all 5 risk factors were estimated using parallel latent growth modelling. This enabled the growth factors for BMI to be implemented as covariates for the growth processes of glycaemia, systolic blood pressure, and total cholesterol [1]. The structural assumptions of the analysis are described in more detail below.

In the Whitehall II data analysis we assume that individuals have an underlying level of glycaemia, which cannot be observed but can be measured by HbA1c, fasting plasma glucose (FPG) and 2-hour glucose. We describe this underlying propensity for diabetes as latent glycaemia. The statistical model estimated the unobservable latent glycaemia and from this identified associations with test results for HbA1c, FPG, and 2-hour glucose. The longitudinal changes in BMI, glycaemia, systolic blood pressure, total and HDL cholesterol could then be estimated through statistical analysis.

These growth factors are conditional on several individual characteristics including age, sex, ethnicity, smoking, family history of CVD, and family history of type 2 diabetes. Deprivation was excluded from the final analysis because it was not associated with the growth models, and it estimated counter-intuitive coefficients. Last known employment grade was considered to be an alternative specification of socioeconomic status. However, this was excluded from the final analysis because it was not a statistically significant predictor of glycaemia. We related the effect of changes in BMI to changes in glycaemia, systolic blood pressure and total cholesterol. Unobservable

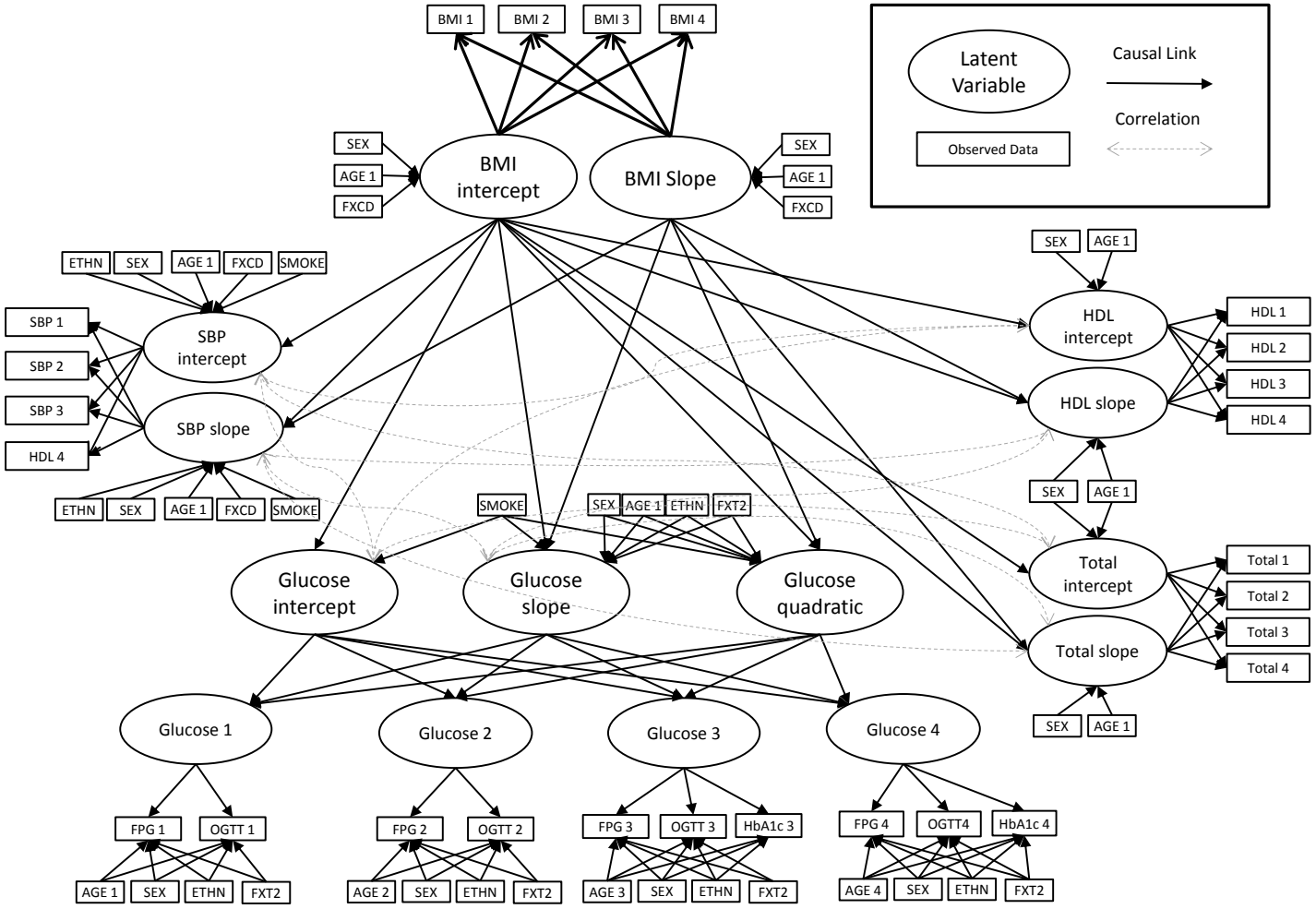
[1] The model did not converge when BMI slope was included as a predictor for HDL growth.

heterogeneity between individual growth factors not explained by patient characteristics was incorporated into the growth models as random error terms. Correlation between the random error terms for glycaemia, total cholesterol, HDL cholesterol and systolic blood pressure was estimated from the Whitehall II cohort. This means that in the simulation, an individual with a higher growth rate for glycaemia is more likely to have a higher growth rate of total cholesterol and systolic blood pressure.

An advantage of our parallel growth analysis is that we were able to estimate the effect of growth in BMI on the other metabolic risk factors. We were also able to estimate correlation between changes in glycaemia, systolic blood pressure, total cholesterol and HDL cholesterol. As a consequence, the growth factor random error terms were not assumed to be independent and were sampled from a multivariate normal distribution $\boldsymbol{v} \sim N(0, \Omega)$. Estimates for the covariance matrix are derived from the covariance estimates reported in the statistical analysis.

The baseline observations for BMI, HbA1c, systolic blood pressure, cholesterol and HDL cholesterol were extracted from the Health Survey for England 2011 in order to simulate a representative sample. The predicted intercept for these metabolic risk factors was estimated using the Whitehall II analysis to give population estimates of the individuals' starting values, conditional on their characteristics. The difference between the simulated and observed baseline risk factors was taken to estimate the individuals' random deviation from the population expectation. The individual random error in the slope trajectory was sampled from a conditional multivariate normal distribution to allow correlation between the intercept and slope random errors.

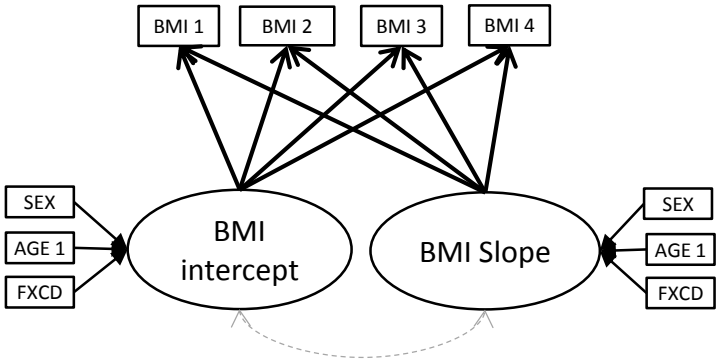
Figure 2: Path analysis of final statistical analysis of the Whitehall II cohort



8.2 BMI TRAJECTORY

The Whitehall II analysis estimates longitudinal trajectories for BMI. The path diagram for BMI is illustrated in Figure 3.

Figure 3: The path diagram for BMI growth



We simulated annual changes in BMI for all individuals within the simulation. At baseline, BMI estimates from the HSE determine an individual's BMI. BMI at any time period in the model is estimated using the following quadratic equation.

$$BMI_t = \beta_{10} + \beta_{11}t + \beta_{12}t^2 + \varepsilon_1$$

$$\beta_{10} = \alpha_{10} + \boldsymbol{\gamma_{10}X} + \upsilon_{10}$$

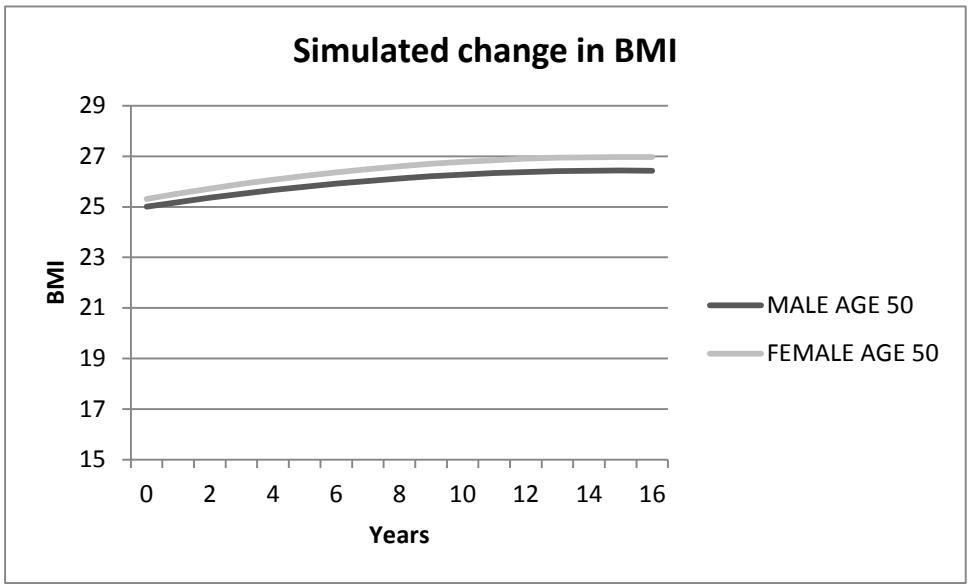
$$\beta_{11} = \alpha_{11} + \boldsymbol{\gamma_{11}X} + \upsilon_{11}$$

$$\beta_{12} = \alpha_{12} + \boldsymbol{\gamma_{12}X}$$

The intercept of the BMI calculation is described by β_{10}, the linear slope β_{11} , quadratic term β_{12} and a measurement error term ε_1. The intercept β_{10} is conditional on the population mean intercept α_{10}, coefficients, $\boldsymbol{\gamma_{10}}$ for patient characteristics $\boldsymbol{X}$, and an individual level random error term υ_{10}. Annual change in BMI is determined by β_{11} and β_{12}, which are also conditional on population intercepts and covariate adjustments. The linear slope includes an individual patient random error term υ_{11}, whereas the quadratic slope term does not contain an error term. The conceptual model for BMI assumes that age at baseline, sex and family history of cardiovascular disease predict the intercept,

slope and quadratic term in the BMI model. Figure 4 illustrates simulated changes in BMI over time for a man and women aged 50 at baseline.

Figure 4: Simulated data using the Whitehall II Statistical analysis to illustrate BMI over time

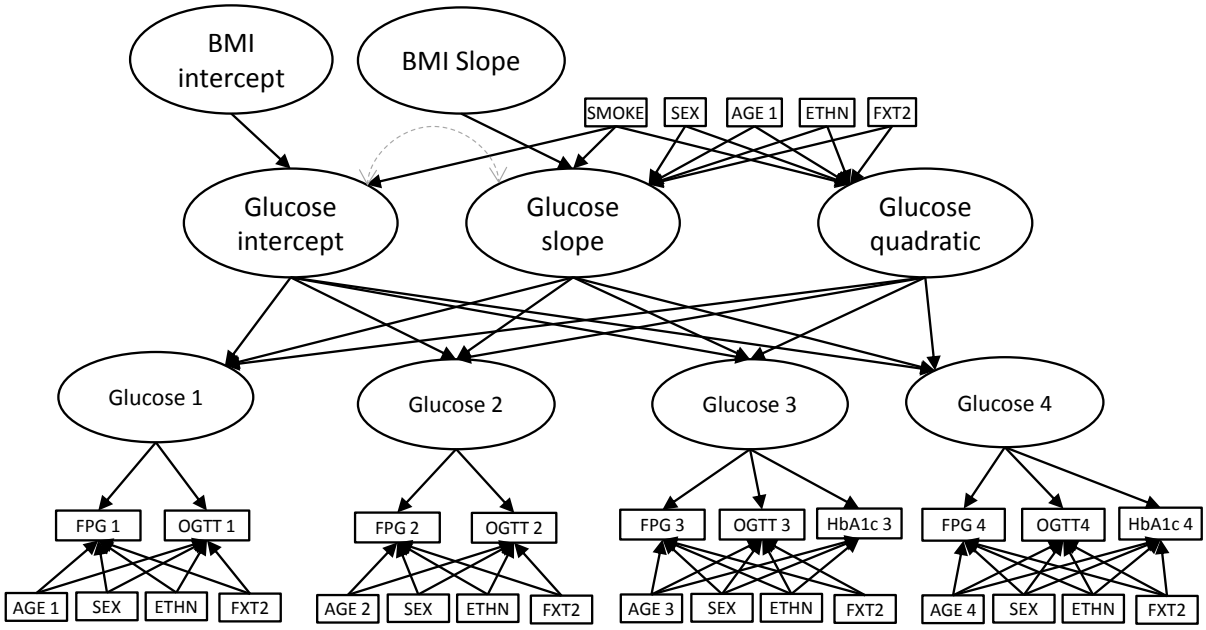


The growth factors are estimated in the model to be conditional on baseline BMI, age at baseline, sex, Townsend deprivation index, family history of cardiovascular disease and an error parameter to reflect unobservable variability in growth trajectories between individuals. This allows us to relate the rate of BMI growth to individual characteristics. For example, in our statistical analysis we found that the rate of BMI growth was lower in men and older adults.

8.3 GLYCAEMIC TRAJECTORY IN NON-DIABETICS/UNDIAGNOSED DIABETES

We simulated annual changes in HbA1c, FPG, and 2-hr glucose within the simulation. We conceptualised a latent glycaemic variable to describe an individual's underlying level of hyper-glycaemia. Latent glycaemia can be tested using 2-hr glucose, FPG or HbA1c tests, but each test is an imperfect measure of the individual's true glycaemic status. The path diagram to describe changes in glycaemia, 2-hr glucose, FPG and HbA1c from the Whitehall II cohort is illustrated in Figure 5.

Figure 5: The path diagram for glycaemic growth



We assume that changes in latent glycaemia have a quadratic relationship with time. Latent glycaemia (glyc) at any time period in the model is estimated using the following quadratic equation.

$$glyc_t = \beta_{20} + \beta_{21}t + \beta_{22}t^2 + \varepsilon_2$$

$$\beta_{20} = \alpha_{20} + \boldsymbol{\gamma_{20}X} + \tau_{20}\beta_{10} + \upsilon_{20}$$

$$\beta_{21} = \alpha_{21} + \boldsymbol{\gamma_{21}X} + \tau_{21}\beta_{10} + \tau_{22}\beta_{11} + \upsilon_{21}$$

$$\beta_{22} = \alpha_{22} + \boldsymbol{\gamma_{22}X} + \upsilon_{22}$$

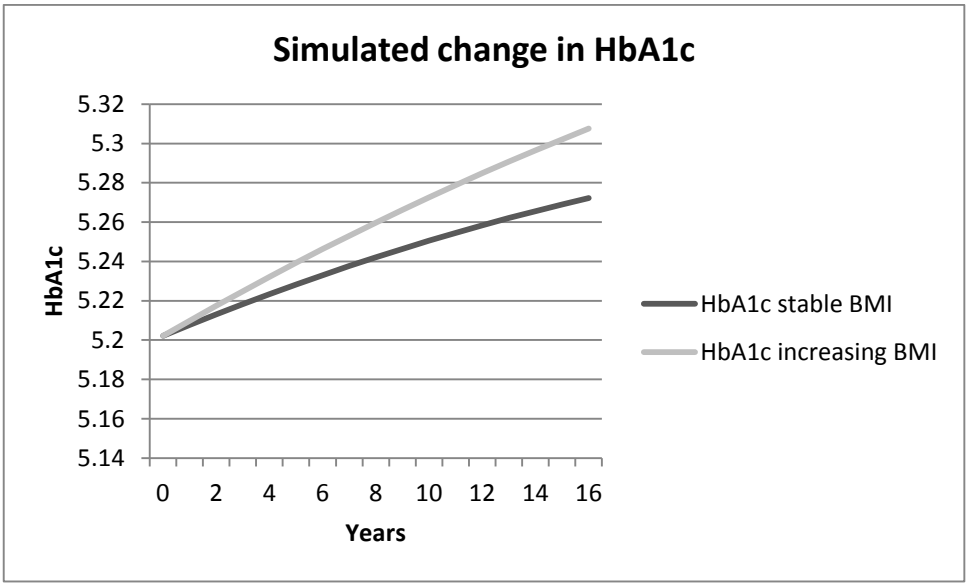
The intercept of the latent glycaemia is described by β_{20}, the linear slope β_{21} , quadratic term β_{22} and a measurement error term ε_2. The intercept β_{20} is conditional on the population mean intercept α_{20}, coefficients $\boldsymbol{\gamma_{20}}$ for patient characteristics $\boldsymbol{X}$, the growth intercept for BMI β_{10}, and an individual level random error term υ_{20}. Annual change in latent glycaemia is determined by β_{21} and β_{22}, which are also conditional on population intercepts, covariate adjustments and individual level random error terms. The growth factors β_{20} and β_{21} are also conditional on the growth factors for BMI.

The glycaemic test results (FPG, 2-hr glucose, HbA1c) were assumed to be conditional on latent glycaemia, *glyc*. The model estimates test results for each period of observation (*t*=1,2,3,4…*t*). The factor glycaemia is measured by three non-overlapping observations of 2-hr glucose, FPG and HbA1c. The scale of the factor is fixed by setting one factor loading (2-hr glucose) to 1.

$$\begin{bmatrix} FPG_t \\ 2HR_t \\ A1C_t \end{bmatrix} = \begin{bmatrix} \mu_0 \\ \mu_1 \\ \mu_2 \end{bmatrix} + \begin{bmatrix} \theta_{01} \\ \theta_{11} \\ \theta_{21} \end{bmatrix} [glyc_t] + \begin{bmatrix} \theta_{02} \\ \theta_{12} \\ \theta_{22} \end{bmatrix} [AGE_t] + \begin{bmatrix} \theta_{03} \\ \theta_{13} \\ \theta_{23} \end{bmatrix} [SEX] + \begin{bmatrix} \theta_{04} \\ \theta_{14} \\ \theta_{24} \end{bmatrix} [ETHN] + \begin{bmatrix} \theta_{05} \\ \theta_{15} \\ \theta_{25} \end{bmatrix} [FXT2] + \begin{bmatrix} \varepsilon_{20} \\ \varepsilon_{21} \\ \varepsilon_{22} \end{bmatrix}$$

We assumed that the models to predict blood glucose were constant with time. The parameters that determine an individual's latent glycaemic growth trajectory are a function of sex, ethnicity, age at baseline, non-white ethnicity, smoking and family history of type 2 diabetes. Furthermore, the statistical analysis found that an increase in BMI will accelerate the rate of growth in latent glycaemia. The effect of BMI on simulated HbA1c for an example individual is illustrated in Figure 6. The trajectory for an individual with increasing BMI (0.21kg/m^2 per year) is steeper than that with zero change in BMI.

Figure 6: Simulated data using the Whitehall II Statistical analysis to illustrate the effect of BMI on HbA1c trajectories



At baseline, HbA1c estimates from the HSE determine HbA1c in year 1. We used this measure of HbA1c to estimate corresponding FPG and 2-hr glucose test results. We chose to simulate all three tests to allow comparisons of screening methods within the model. We have designed the model so that the three tests are correlated, but imperfectly so. This means that it is possible that an individual will be classified as diabetic using an HbA1c test, but would be below the threshold for diabetes using the FPG test.

8.4 HBA1C TRAJECTORY IN TYPE 2 DIAGNOSED DIABETICS

Following a diagnosis of diabetes in the simulation all individuals experience an initial fall in HbA1c due to changes in diet and lifestyle as observed in the UKPDS trial (10). We have estimated the expected change in HbA1c conditional on HbA1c at diagnosis by fitting a simple linear regression to

three aggregate outcomes reported in the study. These showed that the change in HbA1c increases for higher HbA1c scores at diagnosis. The regression parameters to estimate change in HbA1c are reported in Table 17.

Table 17: Estimated change in HbA1c following diabetes diagnosis

	Mean	Standard error
Change in HbA1c Intercept	-2.9465	0.0444513
HbA1c at baseline	0.5184	0.4521958

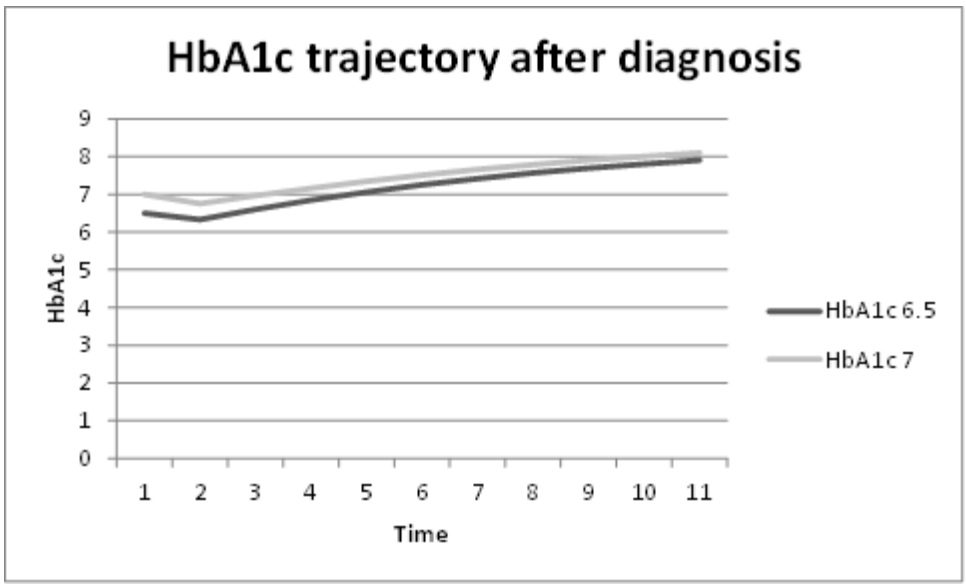
After this initial reduction in HbA1c the longitudinal trajectory of HbA1c is estimated using the UKPDS outcomes model (11) rather than the Whitehall II statistical analysis. The UKPDs dataset is made up of a newly diagnosed diabetic population. As part of the UKPDS Outcomes model, longitudinal trial data were analysed using a random effects model (Appendix B), which means that unobservable differences between individuals are accounted for in the analysis. The coefficients of the model are reported in Table 18.

Table 18: Coefficient estimates for HbA1c estimated from UKPDS data

	Mean Coefficient	Coefficient standard error
Intercept	-0.024	0.017
Log transformation of year since diagnosis	0.144	0.009
Binary variable for year after diagnosis	-0.333	0.05
HbA1c score in last period	0.759	0.004
HbA1c score at diagnosis	0.085	0.004

The model can be used to predict HbA1c over time from the point of diagnosis. The model suggests that HbA1c increases with time. A graph illustrating change in HbA1c over time from two different HbA1c levels at diagnosis is illustrated in Figure 7.

Figure 7: Trajectory of HbA1c estimated from UKPDS longitudinal model

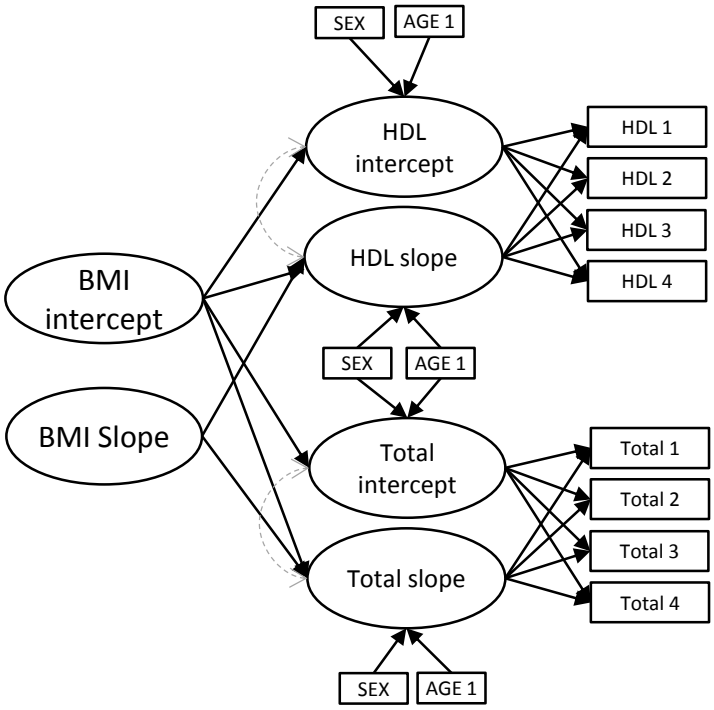


It was important to maintain heterogeneity in the individual glycaemic trajectories before and after diagnosis. Therefore, the random error terms used to determine individual trajectories in glycaemia before diagnosis were used to induce random noise in the trajectory after diagnosis. We sampled the expected random error term for each individual after diagnosis conditional on pre-diagnosis slope, assuming a 0.8 correlation between these values.

8.5 TOTAL CHOLESTEROL AND HDL CHOLESTEROL TRAJECTORIES IN INDIVIDUALS NOT RECEIVING STATINS

In the simulation, individuals had annual changes in total and HDL cholesterol according to the estimates from the statistical analysis of the Whitehall II cohort. The path diagram for total and HDL cholesterol is illustrated in Figure 8.

Figure 8: The path diagram for total and HDL cholesterol growth



Total cholesterol (TC) at any time period in the model is estimated using the following linear equation.

$$TC_t = \beta_{40} + \beta_{41}t + \varepsilon_4$$

$$\beta_{40} = \alpha_{40} + \boldsymbol{\gamma_{40}X} + \tau_{40}\beta_{10} + \upsilon_{40}$$

$$\beta_{41} = \alpha_{41} + \boldsymbol{\gamma_{41}X} + \tau_{41}\beta_{10} + \tau_{41}\beta_{11} + \upsilon_{41}$$

The intercept of the systolic blood pressure growth model is described by β_{40}, the linear slope β_{41} and a measurement error term ε_4. The intercept β_{40} is conditional on the population mean intercept α_{40}, coefficients $\boldsymbol{\gamma_{40}}$ for patient characteristics $\boldsymbol{X}$, a factor τ_{40}, describing the association with the growth intercept for BMI β_{10}, and an individual level random error term υ_{40}. Annual change in TC is determined by β_{41}, which is also conditional on population intercepts, covariate adjustments and an individual level random error term. Growth in total cholesterol is conditional on baseline BMI and the growth rate of BMI.

HDL cholesterol (HDL) at any time period in the model is estimated using the following linear equation.

$$HDL_t = \beta_{50} + \beta_{51}t + \varepsilon_5$$

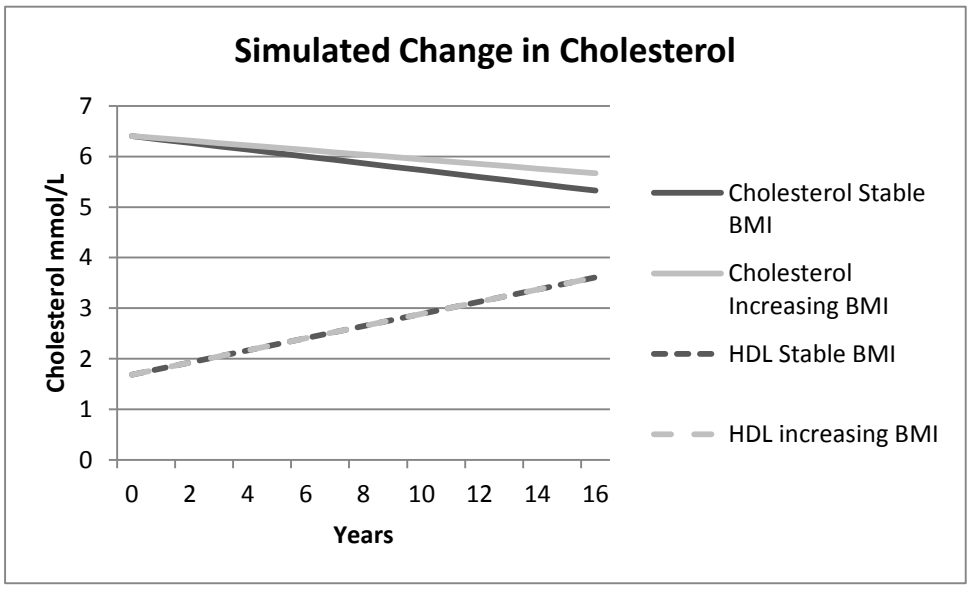
$$\beta_{50} = \alpha_{50} + \boldsymbol{\gamma_{50}X} + \tau_{51}\beta_{10} + \upsilon_{50}$$

$$\beta_{51} = \alpha_{51} + \boldsymbol{\gamma_{51}X} + \tau_{51}\beta_{10} + \upsilon_{51}$$

The intercept of the systolic blood pressure growth model is described by β_{50}, the linear slope β_{51} and a measurement error term ε_5. The intercept β_{50} is conditional on the population mean intercept α_{50}, coefficients $\boldsymbol{\gamma_{50}}$ for patient characteristics $\boldsymbol{X}$, a factor τ_{50}, describing the association with the growth intercept for BMI β_{10}, and an individual level random error term υ_{50}. Annual change in HDL cholesterol is determined by β_{51}, which is also conditional on population intercepts, covariate adjustments and an individual level random error term. Growth in HDL is conditional on baseline BMI only.

At baseline, an individual's total and HDL cholesterol is determined from the HSE 2011 data. The slope of total and HDL cholesterol are assumed to be linear with time. These growth factors are estimated in the model to be conditional on cholesterol at baseline, age at baseline, sex, and an error parameter to reflect unobservable variability in growth trajectories between individuals. As with latent glycaemia, changes in total cholesterol are also influenced by the trajectory of BMI. Figure 9 illustrates the trajectories for total and HDL cholesterol according to changes in BMI. We did not identify if changes in BMI impact upon changes in HDL cholesterol.

Figure 9: Simulated data using the Whitehall II Statistical analysis to illustrate the effect of BMI on cholesterol



8.6 TOTAL CHOLESTEROL AND HDL CHOLESTEROL TRAJECTORIES IN INDIVIDUALS RECEIVING STATINS

During the simulation process, individuals are prescribed statins to reduce their risk of cardiovascular disease. It is assumed within the model that the statins are effective in reducing an individual's total cholesterol, and an average effect is applied to all patients receiving statins. A recent HTA reviewed the literature on the effectiveness and cost-effectiveness of statins in individuals with acute coronary syndrome (12). This report estimated the change in LDL cholesterol for four statin treatments and doses compared with placebo from a Bayesian meta-analysis. The analysis estimated a reduction in LDL cholesterol of -1.45 for simvastatin. This estimate was used to describe the effect of statins in reducing total cholesterol. It was assumed that the effect was instantaneous upon receiving statins and maintained as long as the individual receives statins. It was also assumed that individuals receiving statins no longer experienced annual changes in cholesterol. HDL cholesterol was assumed constant over time if patients receive statins.

Non-adherence to statin treatment is a common problem. Two recent HTAs reviewed the literature on continuation and compliance with statin treatment. They both concluded that there was a lack of adequate reporting, but that the proportion of patients fully compliant with treatment appears to decrease with time, particularly in the first 12 months after initiating treatment, and can fall below 60% after five years (12;13). Although a certain amount of non-compliance is included within trial data, clinical trials are not considered to be representative of continuation and compliance in general practice. A yearly reduction in statin compliance used in the HTA analysis is reported in Table 19. It is based on the published estimate of compliance for the first five years of statin treatment for primary prevention in general clinical practice (13). Compliance declines to a minimum of 65% after five years of treatment. It is assumed that there is no further drop after five years.

Table 19: Proportion of patients assumed to be compliant with statin treatment, derived from Table 62 in (12)

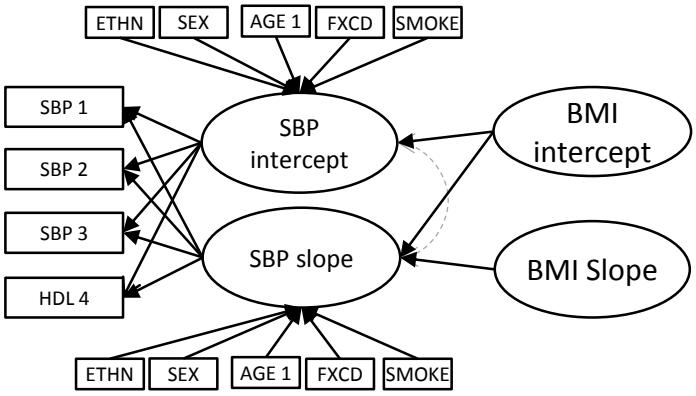
Year after statin initiation	1	2	3	4	5
Proportion compliant	0.8	0.7	0.68	0.65	0.65

In the simulation, we assume in the base case that only 65% of individuals initiate statins when they are deemed eligible. However those that initiate statins remain on statins for their lifetime. Those who refuse statins may be prescribed them again at a later date.

8.7 SYSTOLIC BLOOD PRESSURE TRAJECTORIES IN INDIVIDUALS NOT RECEIVING ANTI-HYPERTENSIVE TREATMENT

In the simulation, individuals' systolic blood pressure changes every year according to the estimates from the statistical analysis of the Whitehall II cohort. The Path diagram for systolic blood pressure is illustrated in Figure 10.

Figure 10: Systolic blood pressure path diagram for Whitehall II Statistical analysis



Systolic blood pressure at any time period in the model is estimated using the following linear equation.

$$SBP_t = \beta_{30} + \beta_{31}t + \varepsilon_3$$

$$\beta_{30} = \alpha_{30} + \boldsymbol{\gamma_{30}X} + \tau_{30}\beta_{10} + \upsilon_{30}$$

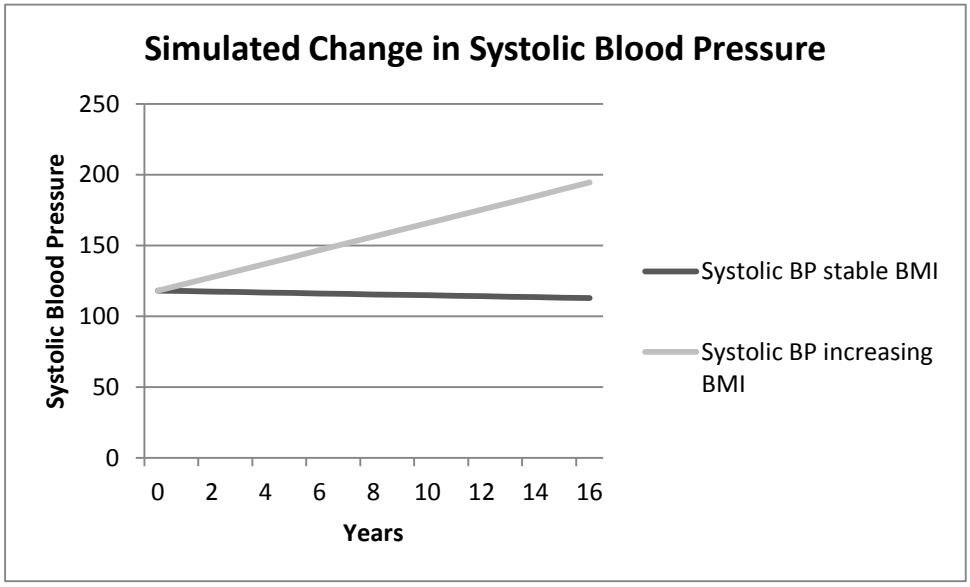
$$\beta_{31} = \alpha_{31} + \boldsymbol{\gamma_{31}X} + \tau_{31}\beta_{10} + \tau_{32}\beta_{11} + \upsilon_{31}$$

The intercept of the systolic blood pressure growth model is described by β_{30}, the linear slope β_{31} and a measurement error term ε_3. The intercept β_{30} is conditional on the population mean intercept α_{30}, coefficients $\boldsymbol{\gamma_{30}}$ for patient characteristics $\boldsymbol{X}$, the growth intercept for BMI, and an individual level random error term υ_{30}. Annual change in SBP is determined by β_{31}, which is also conditional on population intercepts, covariate adjustments and an individual level random error term. Growth in SBP is also conditional on baseline BMI and the growth rate of BMI.

The annual change in systolic blood pressure is assumed to be linear with time. At baseline an individual's systolic blood pressure is determined from the HSE 2011 data. The growth factors are estimated in the model to be conditional on systolic blood pressure at baseline, age at baseline, sex, ethnicity, family history of cardiovascular disease, smoking and an error parameter to reflect

unobservable variability in growth trajectories between individuals. Changes in systolic blood pressure are also influenced by the trajectory of BMI as illustrated in Figure 11.

Figure 11: Simulated data using the Whitehall II Statistical analysis to illustrate the effect of BMI on blood pressure



8.8 SYSTOLIC BLOOD PRESSURE TRAJECTORIES IN INDIVIDUALS RECEIVING ANTI-HYPERTENSIVE TREATMENT

During the simulation process, if individuals are identified as having systolic blood pressure higher than 160mm Hg, or higher than 140mm Hg with comorbid diabetes, cardiovascular disease, or 10 year risk of cardiovascular disease greater than 20%, they will be prescribed anti-hypertensive treatment (14). The change in systolic blood pressure following initiation of calcium channel blockers was estimated in a meta-analysis of anti-hypertensive treatments (15). This study identified an average change in systolic blood pressure of -8.4 for monotherapy with calcium channel blockers. It is assumed that this reduction in systolic blood pressure is maintained for as long as the individual receives anti-hypertensive treatment. For simplicity we do not assume that the individual switches between anti-hypertensive treatments over time. Once an individual is receiving anti-hypertensive treatment it is assumed that their systolic blood pressure is stable and does not change over time.

8.9 METABOLIC RISK FACTOR SCREENING

We assume that individuals eligible for anti-hypertensive treatment or statins will be identified through opportunistic screening if they meet certain criteria and attend the GP for at least one visit in the simulation period.

1. Individuals with a history of cardiovascular disease;
2. Individuals with a major microvascular event (foot ulcer, blindness, renal failure or amputation);
3. Individuals with diagnosed diabetes;
4. Individuals identified with Impaired Glucose Regulation;
5. Individuals with systolic blood pressure greater than 160mmHg.

Individuals may also be detected for diabetes through opportunistic screening if the following criteria are met.

1. Individuals with a history of cardiovascular disease;
2. Individuals with a major microvascular event (foot ulcer, blindness, renal failure or amputation);
3. Individuals identified with impaired glucose regulation;
4. At baseline individuals are assigned an HbA1c threshold above which diabetes is detected opportunistically, individuals with an HbA1c above their individual threshold will attend the GP to be diagnosed with diabetes. The threshold is sampled from the distribution of HbA1c tests in a cohort of recently diagnosed patients in clinical practice (16).

The base case has been designed to represent a health system with moderate levels of screening for hypertension, diabetes, and dyslipidaemia. Alternative assumptions for more or less intensive opportunistic screening can be assumed.

8.10 DIAGNOSIS AND TREATMENT INITIATION

It is assumed that there are three, non-mutually exclusive outcomes from the vascular checks or opportunistic screening. Firstly, that the patient receives statins to reduce cardiovascular risk. Secondly, that the patient has high blood pressure and should be treated with anti-hypertensive medication. Thirdly, the model evaluates whether the blood glucose test indicates a diagnosis with type 2 diabetes. The following threshold estimates were used to determine these outcomes.

1. Statins are initiated if the individual has greater than or equal to 20% 10 year CVD risk estimated from the QRISK2 2012 algorithm (17).
2. Anti-hypertensive treatment is initiated if systolic blood pressure is greater than 160. If the individual has a history of CVD, diabetes or a CVD risk >20%, the threshold for systolic blood pressure is 140 (14).

3. Type 2 diabetes is diagnosed if the individual has an HbA1c test greater than 6.5. In the base case it is assumed that FPG and 2-hr glucose are not used for diabetes diagnosis. However, future adaptations of the model could use these tests for diagnosis.

Recent guidelines for hypertension have recommended that hypertension be confirmed with ambulatory blood pressure monitoring (ABPM) (14). The cost of ABPM assessment is included in the cost of diagnosis (£53.40) (18), however, we assume that the test does not alter the initial diagnosis.

9 COMORBID OUTCOMES AND MORTALITY

In every model cycle individuals within the model are evaluated to determine whether they have a clinical event, including mortality, within the cycle period. In each case the simulation estimates the probability that an individual has the event and uses a random number draw to determine whether the event occurred.

9.1 CARDIOVASCULAR DISEASE

9.1.1 First Cardiovascular event

Several statistical models for cardiovascular events were identified in a review of economic evaluations for diabetes prevention (1). The UKPDS outcomes model (19), Framingham risk equation (20) and QRISK2 (21) have all been used in previous models to estimate cardiovascular events. The Framingham risk equation was not adopted because, unlike the QRISK2 model, it is not estimated from a UK population. The UKPDS outcomes model would be ideally suited to estimate the risk of cardiovascular disease in a population diagnosed with type 2 diabetes. Whilst this is an important outcome of the cost-effectiveness model, there was concern that it would not be representative of individuals with normal glucose tolerance or impaired glucose regulation. It was important that reductions in cardiovascular disease risk in these populations were represented to capture the population-wide benefits of public health interventions. The QRISK2 model was selected for use in the cost-effectiveness model because it is a validated model of cardiovascular risk in a UK population that could be used to generate probabilities for diabetic and non-diabetic populations. We considered using the UKPDS outcomes model specifically to estimate cardiovascular risk in patients with type 2 diabetes. However, it would not be possible to control for shifts in absolute risk generated by the different risk scores due to different baselines and covariates. This would lead to some individuals experiencing counterintuitive and favourable shifts in risk after onset of type 2 diabetes. Therefore, we decided to use diabetes as a covariate adjustment to the QRISK2 model to ensure that the change in individual status was consistent across individuals.

We accessed the 2012 version of the QRISK from the website (22). The QRISK2 equation estimates the probability of a cardiovascular event in the next year conditional on ethnicity, smoking status, age, BMI, ratio of total/HDL cholesterol, Townsend score, atrial fibrillation, rheumatoid arthritis, renal disease, hypertension, diabetes, and family history of cardiovascular disease. Data on all these variables was available from the HSE 2011. Table 20 reports the coefficient estimates for the QRISK2 algorithm. The standard errors were not reported within the open source code. Where possible,

standard errors were imputed from a previous publication of the risk equation (23). Coefficients that were not reported in this publication were assumed to have standard errors of 20%.

Table 20: Coefficients from the 2012 QRISK2 risk equation and estimate standard errors

	Estimated coefficients adjusting for individual characteristics								
	Women		Men			Women		Men	
Covariates	Mean	Standard error	Mean	Mean	Interaction terms	Mean	Standard error	Mean	Standard error
White	0.0000	0.0000	0.0000	0.0000	Age1*former smoker	0.1774	0.035	-3.881	0.776
Indian	0.2163	0.0537	0.3163	0.0425	Age1*light smoker	-0.3277	0.066	-16.703	3.341
Pakistani	0.6905	0.0698	0.6092	0.0547	Age1*moderate smoker	-1.1533	0.231	-15.374	3.075
Bangladeshi	0.3423	0.1073	0.5958	0.0727	Age1*Heavy smoker	-1.5397	0.308	-17.645	3.529
Other Asian	0.0731	0.1071	0.1142	0.0845	Age1*AF	-4.6084	0.922	-7.028	1.406
Caribbean	-0.0989	0.0619	-0.3489	0.0641	Age1*renal disease	-2.6401	0.528	-17.015	3.403
Black African	-0.2352	0.1275	-0.3604	0.1094	Age1*hypertension	-2.2480	0.450	33.963	6.793
Chinese	-0.2956	0.1721	-0.2666	0.1538	Age1*Diabetes	-1.8452	0.369	12.789	2.558
Other	-0.1010	0.0793	-0.1208	0.0734	Age1*BMI	-3.0851	0.617	3.268	0.654
Non-smoker	0.0000	0.0000	0.0000	0.0000	Age1*family history CVD	-0.2481	0.050	-17.922	3.584
Former smoker	0.2033	0.0152	0.2684	0.0108	Age1*SBP	-0.0132	0.003	-0.151	0.030
Light smoker	0.4820	0.0220	0.5005	0.0166	Age1*Townsend	-0.0369	0.007	-2.550	0.510
Moderate smoker	0.6126	0.0178	0.6375	0.0148	Age2*former smoker	-0.0051	0.001	7.971	1.594
Heavy smoker	0.7481	0.0194	0.7424	0.0143	Age2*light smoker	-0.0005	0.000	23.686	4.737
Age 1*	5.0327		47.3164		Age2*moderate smoker	0.0105	0.002	23.137	4.627
Age 2*	-0.0108		-101.2362		Age2*Heavy smoker	0.0155	0.003	26.867	5.373
BMI*	-0.4724	0.0423	0.5425	0.0299	Age2*AF	0.0507	0.010	14.452	2.890
Ratio Total / HDL chol	0.1326	0.0044	0.1443	0.0022	Age2*renal disease	0.0343	0.007	28.270	5.654
SBP	0.0106	0.0045	0.0081	0.0046	Age2*hypertension	0.0258	0.005	-18.817	3.763
Townsend	0.0597	0.0068	0.0365	0.0048	Age2*Diabetes	0.0180	0.004	0.963	0.193
AF	1.3261	0.0310	0.7547	0.1018	Age2*BMI	0.0345	0.007	10.551	2.110
Rheumatoid arthritis	0.3626	0.0319	0.3089	0.0445	Age2*family history CVD	-0.0062	0.001	26.605	5.321
Renal disease	0.7636	0.0639	0.7441	0.0702	Age2*SBP	0.0000	0.000	0.291	0.058
Hypertension	0.5421	0.0115	0.4978	0.0112	Age2*Townsend	-0.0011	0.000	3.007	0.601
Diabetes	0.8940	0.0199	0.7776	0.0175					
Family history of CVD	0.5997	0.0122	0.6965	0.0111					
AF Atrial Fibrillation CVD Cardiovascular disease SBP systolic blood pressure * covariates transformed with fractional polynomials									

The QRISK2 risk equation can be used to calculate the probability of a cardiovascular event including coronary heart disease (angina or myocardial infarction), stroke, transient ischaemic attacks and fatality due to cardiovascular disease. The equation estimates the probability of a cardiovascular event in the next period conditional on the coefficients listed in Table 20. The equation for the probability of an event in the next period is calculated as

$$p(Y = 1) = 1 - S(1)^{\theta}$$

$$\theta = \sum \beta X$$

The probability of an event is calculated from the survival function at 1 year raised to the power of θ, where θ is the sum product of the coefficients reported in Table 20 multiplied by the individual's characteristics. Underlying survival curves for men and women were extracted from the QRISK2 open source file. Mean estimates for the continuous variables were also reported in the open source files.

We modified the QRISK assumptions regarding the relationship between IGR, diabetes and cardiovascular disease. Firstly, we assumed that individuals with HbA1c>6.5 have an increased risk of cardiovascular disease even if they have not received a formal diagnosis. Secondly, risk of cardiovascular disease was assumed to increase with HbA1c for test results greater than 6.5 to reflect observations from the UKPDS that HbA1c increases the risk of MI and Stroke(19) . Thirdly, prior to type 2 diabetes (HbA1c>6.5) HbA1c is linearly associated with cardiovascular disease. A study from the EPIC Cohort (Khaw 2004) has found that a unit increase in HbA1c increases the risk of coronary heart disease by a hazard ratio of 1.25, after adjustment for other risk factors. Individuals with an HbA1c greater than the mean HBA1c observed in the HSE 2011 cohort were at greater risk of CVD than those with an HbA1c lower than the HSE mean.

The QRISK algorithm identifies which individuals experience a cardiovascular event but does not specify the nature of the event. The nature of the cardiovascular event was determined independently. A targeted search of recent Health Technology appraisals of cardiovascular disease was performed to identify a model for the progression of cardiovascular disease following a first event. All QRISK events are assigned to a specific diagnosis according to age and sex specific distributions of cardiovascular events used in a previous Health Technology Assessment (HTA) (13). Table 21 reports the probability of cardiovascular outcomes by age and gender. Stakeholders suggested that there may be different relationships between the risk factors and the different types of CVD (eg. hypertension is more of a risk factor for stroke). However, we decided not to incorporate these factors in evaluating the risk of cardiovascular event types due to a lack of evidence.

Table 21: The probability distribution of cardiovascular events by age and gender

	Age	Stable angina	Unstable angina	MI rate	Fatal CHD	TIA	Stroke	Fatal CVD
Men	45-54	0.307	0.107	0.295	0.071	0.060	0.129	0.030
	55-64	0.328	0.071	0.172	0.086	0.089	0.206	0.048
	65-74	0.214	0.083	0.173	0.097	0.100	0.270	0.063
	75-84	0.191	0.081	0.161	0.063	0.080	0.343	0.080
	85+	0.214	0.096	0.186	0.055	0.016	0.351	0.082
Women	45-54	0.325	0.117	0.080	0.037	0.160	0.229	0.054
	55-64	0.346	0.073	0.092	0.039	0.095	0.288	0.067
	65-74	0.202	0.052	0.121	0.081	0.073	0.382	0.090
	75-84	0.149	0.034	0.102	0.043	0.098	0.464	0.109
	85+	0.136	0.029	0.100	0.030	0.087	0.501	0.117

9.1.2 Subsequent Cardiovascular events

After an individual has experienced a cardiovascular event, it is not possible to predict the transition to subsequent cardiovascular events using QRISK2. Instead, as with assigning first CVD events, the probability of subsequent events was estimated from the HTA evaluating statins (13). This study reported the probability of future events, conditional on the nature of the previous event. Table 22 to Table 26 report the probabilities within a year of transitioning from stable angina, unstable angina, myocardial infarction (MI), transient ischemic attack (TIA) or stroke for individuals in different age groups. The tables suggests that, for example 99.46% of individuals with stable angina will remain in the stable angina state, but 0.13%, 0.32% and 0.01% will progress to unstable angina, MI or death from coronary heart disease (CHD) respectively.

Table 22: Probability of cardiovascular event conditional on age and status of previous event (age 45-54)

Age 45-54		To									
		Stable angina	Unstable angina 1	Unstable angina 2	MI 1	MI 2	TIA	Stroke 1	Stroke 2	CHD death	CVD death
From	Stable angina	0.9946	0.0013	0	0.0032	0	0	0	0	0.0009	0
	Unstable angina (1st yr)	0	0	0.9127	0.0495	0	0	0	0	0.0362	0.0016
	Unstable angina (subsequent)	0	0	0.9729	0.0186	0	0	0	0	0.0081	0.0004
	MI (1st yr)	0	0	0	0.128	0.8531	0	0.0015	0	0.0167	0.0007
	MI (subsequent)	0	0	0	0.0162	0.978	0	0.0004	0	0.0052	0.0002
	TIA	0	0	0	0.0016	0	0.9912	0.0035	0	0.0024	0.0013
	Stroke (1st yr)	0	0	0	0.0016	0	0	0.0431	0.9461	0.0046	0.0046
	Stroke (subsequent)	0	0	0	0.0016	0	0	0.0144	0.9798	0.0021	0.0021
MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease											

Table 23: Probability of cardiovascular event conditional on age and status of previous event (age 55-64)

Age 55-64		To									
		Stable angina	Unstable angina 1	Unstable angina 2	MI 1	MI 2	TIA	Stroke 1	Stroke 2	CHD death	CVD death
From	Stable angina	0.9880	0.0033	0	0.0057	0	0	0	0	0.0030	0
	Unstable angina (1st yr)	0	0	0.8670	0.0494	0	0	0	0	0.0800	0.0036
	Unstable angina (subsequent)	0	0	0.9415	0.0471	0	0	0	0	0.0109	0.0005
	MI (1st yr)	0	0	0	0.1087	0.8409	0	0.0047	0	0.0439	0.0019
	MI (subsequent)	0	0	0	0.0183	0.9678	0	0.0015	0	0.0119	0.0005
	TIA	0	0	0	0.0029	0	0.9666	0.0159	0	0.0079	0.0068
	Stroke (1st yr)	0	0	0	0.0029	0	0	0.0471	0.9159	0.0171	0.0171
	Stroke (subsequent)	0	0	0	0.0029	0	0	0.0205	0.9622	0.0072	0.0072
MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease											

Table 24: Probability of cardiovascular event conditional on age and status of previous event (age 65-74)

Age 65-74		To									
		Stable angina	Unstable angina 1	Unstable angina 2	MI 1	MI 2	TIA	Stroke 1	Stroke 2	CHD death	CVD death
From	Stable angina	0.9760	0.0060	0	0.0110	0	0	0	0	0.0070	0
	Unstable angina (1st yr)	0	0	0.8144	0.0479	0	0	0	0	0.1319	0.0059
	Unstable angina (subsequent)	0	0	0.9021	0.0844	0	0	0	0	0.0129	0.0006
	MI (1st yr)	0	0	0	0.0948	0.8106	0	0.0098	0	0.0811	0.0036
	MI (subsequent)	0	0	0	0.0183	0.9585	0	0.0032	0	0.0191	0.0008
	TIA	0	0	0	0.0055	0	0.9174	0.0423	0	0.0185	0.0163
	Stroke (1st yr)	0	0	0	0.0055	0	0	0.0485	0.8673	0.0393	0.0393
	Stroke (subsequent)	0	0	0	0.0055	0	0	0.0237	0.9412	0.0148	0.0148
MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease											

Table 25: Probability of cardiovascular event conditional on age and status of previous event (age 75-84)

Age 75-84		To									
		Stable angina	Unstable angina 1	Unstable angina 2	MI 1	MI 2	TIA	Stroke 1	Stroke 2	CHD death	CVD death
From	Stable angina	0.9680	0.0087	0	0.0163	0	0	0	0	0.0070	0
	Unstable angina (1st yr)	0	0	0.7366	0.0448	0	0	0	0	0.2093	0.0093
	Unstable angina (subsequent)	0	0	0.8360	0.1484	0	0	0	0	0.0149	0.0007
	MI (1st yr)	0	0	0	0.0794	0.7502	0	0.0200	0	0.1440	0.0064
	MI (subsequent)	0	0	0	0.0171	0.9466	0	0.0066	0	0.0286	0.0013
	TIA	0	0	0	0.0082	0	0.8514	0.0878	0	0.0185	0.0342
	Stroke (1st yr)	0	0	0	0.0082	0	0	0.0471	0.7736	0.0856	0.0856
	Stroke (subsequent)	0	0	0	0.0082	0	0	0.0251	0.9107	0.0280	0.0280
MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease											

Table 26: Probability of cardiovascular event conditional on age and status of previous event (age 85-94)

Age 85-94		To									
		Stable angina	Unstable angina 1	Unstable angina 2	MI 1	MI 2	TIA	Stroke 1	Stroke 2	CHD death	CVD death
From	Stable angina	0.9600	0.0114	0	0.0216	0	0	0	0	0.0070	0
	Unstable angina (1st yr)	0	0	0.6315	0.0396	0	0	0	0	0.3149	0.0140
	Unstable angina (subsequent)	0	0	0.7255	0.2568	0	0	0	0	0.0170	0.0008
	MI (1st yr)	0	0	0	0.0623	0.6498	0	0.0380	0	0.2393	0.0106
	MI (subsequent)	0	0	0	0.0148	0.9311	0	0.0124	0	0.0399	0.0018
	TIA	0	0	0	0.0108	0	0.7967	0.1286	0	0.0185	0.0453
	Stroke (1st yr)	0	0	0	0.0108	0	0	0.0409	0.6153	0.1665	0.1665
	Stroke (subsequent)	0	0	0	0.0108	0	0	0.0248	0.8655	0.0494	0.0494
MI Myocardial Infarction; TIA Transient Ischemic Attack; CHD Coronary Heart Disease; CVD Cerebrovascular disease											

9.1.3 Congestive Heart Failure

The review of previous economic evaluations of diabetes prevention cost-effectiveness studies found that only a small number of models had included congestive heart failure as a separate outcome. Discussion with the stakeholder group identified that the UKPDS Outcomes model would be an appropriate risk model for congestive heart failure in type 2 diabetes patients. However, it was suggested that this would not be an appropriate risk equation for individuals with normal glucose tolerance or impaired glucose tolerance. The Framingham risk equation was suggested as an alternative. The main limitation of this equation is that it is quite old and is based on a non-UK population. However, a citation search of this article did not identify a more recent or UK based alternative.

Congestive heart failure was included as a separate cardiovascular event because it was not included as an outcome of the QRISK2. The Framingham Heart Study has reported logistic regressions to estimate the 4 year probability of congestive heart failure for men and women (24). The equations included age, diabetes diagnosis (either formal diagnosis or a HbA1c>6.5), BMI and systolic blood pressure to adjust risk based on individual characteristics. We used this risk equation to estimate the probability of congestive heart failure in the SPHR diabetes prevention model. Table 27 describes the covariates for the logit models to estimate the probability of congestive heart failure in men and women.

Table 27: Logistic regression coefficients to estimate the 4-year probability of congestive heart failure from the Framingham study

Variables	Units	Regression Coefficient	OR (95% CI)	P
Men				
Intercept		-9.2087		
Age	10 y	0.0412	1.51 (1.31-1.74)	<.001
Left ventricular hypertrophy	Yes/no	0.9026	2.47 (1.31-3.77)	<.001
Heart rate	10 bpm	0.0166	1.18 (1.08-1.29)	<.001
Systolic blood pressure	20 mm Hg	0.00804	1.17 (1.04-1.32)	0.007
Congenital heart disease	Yes/no	1.6079	4.99 (3.80-6.55)	<.001
Valve disease	Yes/no	0.9714	2.64 (1.89-3.69)	<.001
Diabetes	Yes/no	0.2244	1.25 (0.89-1.76)	0.2
Women				
Intercept		-10.7988		
Age	10 y	0.0503	1.65 (1.42-1.93)	<.001
left ventricular hypertrophy	Yes/no	1.3402	3.82 (2.50-5.83)	<.001
Heart rate	100 cL	0.0105	1.11 (1.01-1.23)	0.03
Systolic blood pressure	10 bpm	0.00337	1.07 (0.96-1.20)	0.24
congenital heart disease	20 mm Hg	1.5549	4.74 (3.49-6.42)	<.001
Valve disease	Yes/no	1.3929	4.03 (2.86-5.67)	<.001
Diabetes	Yes/no	1.3857	4.00 (2.78-5.74)	<.001
BMI	kg/m2	0.0578	1.06 (1.03-1.09)	<.001
Valve disease and diabetes	Yes/no	-0.986	0.37 (0.18-0.78)	0.009
*OR indicates odds ratio; CI, confidence interval; LVH, left ventricular hypertrophy; CHD, congenital heart disease; and BMI, body mass index. Predicted probability of heart failure can be calculated as: p = 1/(1+exp(-xbeta)), where xbeta = Intercept + Sum (of regression coefficient*value of risk factor)				

Many of the risk factors included in this risk equation were not simulated in the diabetes model, therefore they could not be included in the model to predict CHD. We adjusted the baseline odds of CHD to reflect the expected prevalence of these symptoms in a UK population.

The proportion of the UK population with left ventricular hypertrophy was assumed to be 5% in line with previous analyses of the Whitehall II cohort (25). The heart rate for men was assumed to be 63.0bpm and for women 65.6bpm based on data from previous Whitehall II cohort analyses (26). The prevalence of congenital heart disease was estimated from an epidemiology study in the North of England. The study reports the prevalence of congenital heart disease among live births which was used to estimate the adult prevalence (27). This may over-estimate the prevalence, because the life expectancy of births with congenital heart disease is reduced compared with the general population. However, given the low prevalence it is unlikely to impact on the results. The prevalence of valve disease was estimated from the Echocardiographic Heart of England Screening study (28).

Using the estimated population values we adjusted the intercept values to account for the population risk in men and women. This resulted in a risk equation with age, systolic blood pressure, diabetes, and BMI in women to describe the risk of congestive heart failure for the policy analysis model.

9.2 MICROVASCULAR COMPLICATIONS

The review of previous economic evaluations identified that the UKPDS data was commonly used to estimate the incidence of microvascular complications (1). This data has the advantage of being estimated from a UK diabetic population. Given that the events described in the UKPDS outcomes model are indicative of late stage microvascular complications, we did not believe it was necessary to seek an alternative model that would be representative of an impaired glucose tolerance population.

We adopted a simple approach to modelling microvascular complications. We used both versions of the UKPDS Outcomes model to estimate the occurrence of major events relating to these complications, including renal failure, amputation, foot ulcer, and blindness (11;19). These have the greatest cost and utility impact compared with earlier stages of microvascular complications, so are more likely to have an impact on the SPHR diabetes prevention outcomes. As a consequence, we assumed that microvascular complications only occur in individuals with HbA1c>6.5. Whilst some individuals with hyperglycaemia (HbA1c>6.0) may be at risk of developing microvascular complications, it is unlikely that they will progress to renal failure, amputation or blindness before a diagnosis of diabetes. Importantly, we did not assume that only individuals who have a formal diagnosis of diabetes are at risk of these complications. This allows us to incorporate the costs of undetected diabetes into the simulation.

The UKPDS includes four statistical models to predict foot ulcers, amputation with no prior ulcer, amputation with prior ulcer and a second amputation (19). In order to simplify the simulation of neuropathy outcomes we consolidated the models for first amputation with and without prior ulcer into a single equation. The parametric survival models were used to generate estimates of the cumulative hazard in the current and previous period. From which the probability of organ damage being diagnosed was estimated.

$$p(Death) = 1 - \exp(H(t) - H(t-1)) \quad (1.1)$$

The functional form for the microvascular models included exponential and Weibull. The logistic model was also used to estimate the probability of an event over the annual time interval.

9.2.1 Retinopathy

We used the UKPDS outcomes model v2 to estimate the incidence of blindness in individuals with HbA1c>6.5. The exponential model assumes a baseline hazard λ, which can be calculated from the model coefficients reported in Table 28 and the individual characteristics for $\boldsymbol{X}$.

$$\lambda = exp(\beta_0 + \boldsymbol{X}\boldsymbol{\beta_k})$$

Table 28: Parameters of the UKPDS2 Exponential Blindness survival model

	Mean coefficient	**Standard error**	**Modified mean coefficient**
Lambda	-11.607	0.759	-10.967
Age at diagnosis	0.047	0.009	0.047
HbA1c	0.171	0.032	0.171
Heart rate	0.080	0.039	
SBP	0.068	0.032	0.068
White Blood Count	0.052	0.019	
CHF History	0.841	0.287	0.841
IHD History	0.0610	0.208	0.061

The age at diagnosis coefficient was multiplied by age in the current year if the individual had not been diagnosed with diabetes or by the age at diagnosis if the individual had received a diagnosis. The expected values for the risk factors not included in the SPHR model (heart rate and white blood count) were taken from Figure 3 of the UKPDS publication in which these are described (19). Assuming these mean values, it was possible to modify the baseline risk without simulating heart rate and white blood cell count.

9.2.2 Neuropathy

We used the UKPDS outcomes model v2 to estimate the incidence of ulcer and amputation in individuals with HbA1c>6.5. The parameters of the ulcer and first amputation models are reported in Table 29.

Table 29: Parameters of the UKPDS2 Exponential model for Ulcer, Weibull model for first amputation with no prior ulcer and exponential model for 1st amputation with prior ulcer

	Ulcer		1st Amputation no prior ulcer		1st Amputation prior ulcer		2nd Amputation	
	Logistic		Weibull		Exponential		Exponential	
	Mean	Standard error	Mean	Standard error	Mean	Standard error	Mean	Standard error
lambda	-11.295	1.130	-14.844	1.205	-0.881	1.39	-3.455	0.565
Rho			2.067	0.193				
Age at diagnosis	0.043	0.014	0.023	0.011	-0.065	0.027		
Female	-0.962	0.255	-0.0445	0.189				
Atrial fibrillation			1.088	0.398				
BMI	0.053	0.019						
HbA1c	0.160	0.056	0.248	0.042			0.127	0.06
HDL			-0.059	0.032				
Heart rate			0.098	0.050				
MMALB			0.602	0.180				
PVD	0.968	0.258	1.010	0.189	1.769	0.449		
SBP			0.086	0.043				
WBC			0.040	0.017				
Stroke History			1.299	0.245				

The exponential model assumes a baseline hazard λ, which can be calculated from the model coefficients reported in Table 29 and the individual characteristics for $\boldsymbol{X}$.

$$\lambda = exp\left(\beta_0 + \boldsymbol{X\beta}\right)$$

The Weibull model for amputation assumes a baseline hazard:

$$h(t) = \rho t^{\rho-1}\exp(\lambda)$$

where λ is also conditional on the coefficients and individual characteristics at time t. The logistic model for ulcer is described below.

$$\Pr(\mathrm{y} = 1|\mathbf{X}) = \frac{\exp(\mathbf{X\beta})}{1 + \exp(\mathbf{X\beta}))}$$

The ulcer and amputation models include a number of covariates that were not included in the simulation. As such it was necessary to adjust the statistical models to account for these measures. We estimated a value for the missing covariates and added the value multiplied by the coefficient to the baseline hazard.

The expected values for the risk factors not included in the SPHR model (heart rate, white blood count, micro-/macroalbuminurea, peripheral vascular disease and atrial fibrillation) were taken from Figure 3 of the UKPDS publication in which these are described (19). In the ulcer model we assumed that 2% of the population had peripheral vascular disease.

The amputation risk model with a history of ulcer was not included in the simulation, but was used to estimate an additional log hazard ratio to append onto the amputation model without a history of ulcer. The log hazard was estimated for each model assuming the same values for other covariates. The difference in the log hazard between the two models was used to approximate the log hazard ratio for a history of ulcer in the amputation model (10.241). The final model specifications are reported in Table 30.

Table 30: Coefficients estimates for Ulcer and 1st Amputation

	Ulcer		**1st Amputation**		**2nd Amputation**	
	Logistic		Weibull		Exponential	
	Mean	Standard error	Mean	Standard error	Mean	Standard error
Lambda	-11.276	1.13	-13.954	1.205	-3.455	0.565
Rho			2.067	0.193		
Age at Diagnosis	0.043	0.014	0.023	0.011		
Female	-0.962	0.255	-0.445	0.189		
BMI	0.053	0.019				
HbA1c	0.160	0056	0.248	0.042	0.127	0.06
HDL			-0.059	0.032		
Stroke			1.299	0.245		
Foot Ulcer			10.241			

9.2.3 Nephropathy

We used the UKPDS outcomes model v1 to estimate the incidence of renal failure in individuals with HbA1c>6.5. Early validation analyses identified that the UKPDS v2 model implements in the SPHR model substantially overestimated the incidence of renal failure. The Weibull model for renal failure assumes a baseline hazard:

$$h(t) = \rho t^{\rho-1}\exp(\lambda)$$

where λ is also conditional on the coefficients and individual characteristics at time t. The parameters of the renal failure risk model are reported in Table 31.

Table 31: Parameters of the UKPDS2 Weibull renal failure survival model

	Mean	Standard error
Lambda	-10.016	0.939
Shape parameter	1.865	0.387
SBP	0.404	0.106
BLIND History	2.082	0.551

9.3 CANCER

The conceptual model identified breast cancer and colorectal cancer risk as being related to BMI. However, these outcomes were not frequently included in previous cost-effectiveness models for diabetes prevention. Discussion with stakeholders identified the EPIC Norfolk epidemiology cohort study as a key source of information about cancer risk in a UK population. Therefore, we searched publications from this cohort to identify studies reporting the incidence of these risks. In order to obtain the best quality evidence for the relationship between BMI and cancer risk we searched for a recent systematic review and meta-analysis using key terms 'Body Mass Index' and 'Cancer', filtering for meta-analysis studies.

9.3.1 Breast cancer

Incidence rates for breast cancer in the UK were estimated from the European Prospective Investigation of Cancer (EPIC) cohort. This is a large multi-centre cohort study looking at diet and cancer. In 2004 the UK incidence of breast cancer by menopausal status was reported in a paper from this study investigating the relationship between body size and breast cancer (29). The estimates of the breast cancer incidence in the UK are reported in Table 32.

Table 32: UK breast cancer incidence

	Number of Cases	Person Years	Mean BMI	Incidence Rate of per person-year	Reference
UK pre-menopause	102	103114.6	24	0.00099	(29)
UK post-menopause	238	84214.6	24	0.00283	(29)

A large meta-analysis that included 221 prospective observational studies has reported relative risks of cancers per unit increase in BMI, including breast cancer by menopausal status (30). We included a risk adjustment in the model so that individuals with higher BMI have a higher probability of pre-and post-menopausal breast cancer (30). In the simulation we adjusted the incidence of breast cancer by multiplying the linear relative risk by the difference in the individual's BMI and the average BMI

reported in the EPIC cohort. The relative risk and confidence intervals per 5mg/m^2 increase in BMI are reported in Table 33.

Table 33: Relative risk of Breast cancer by BMI

	Mean Relative risk	2.5th Confidence Interval	97.5th Confidence Interval	Reference
UK pre-menopause	0.89	0.84	0.94	(30)
UK post-menopause	1.09	1.04	1.14	(30)

9.3.2 Colorectal cancer

Incidence rates for colorectal cancer in the UK were reported from the European Prospective Investigation of Cancer (EPIC) cohort. The UK incidence of colorectal cancer is reported by gender in a paper from this study investigating the relationship between body size and colon and rectal cancer (29). The estimates of the colorectal cancer incidence are reported in Table 34.

Table 34: UK colorectal cancer incidence

	Number of Cases	Person Years	Mean Age	Mean BMI	Incidence Rate of per person-year	Reference
Male	125	118468	53.1	25.4	0.00106	(31)
Female	145	277133	47.7	24.5	0.00052	(31)

The risk of colorectal cancer has been linked to obesity. We included a risk adjustment in the model to reflect observations that the incidence of breast cancer is increased in individuals with higher BMI. A large meta-analysis that included 221 prospective observational studies has reported relative risks of BMI and cancers, including colon cancer by gender (30). We selected linear relative risk estimates estimated from pooled European and Australian populations. In the simulation we adjusted the incidence of colorectal cancer by multiplying the relative risk by the difference in the individual's BMI and the average BMI reported in the EPIC cohort. The relative risk and confidence intervals per 5mg/m^2 increase in BMI are reported in Table 35.

Table 35: Relative risk of colon cancer by BMI

	Mean Relative risk	2.5th Confidence Interval	97.5th Confidence Interval	Reference
UK pre-menopause	1.21	1.18	1.24	(30)
UK post-menopause	1.04	1	1.07	(30)

9.4 OSTEOARTHRITIS

The stakeholder group requested that BMI and diabetes be included as independent risk factors for osteoarthritis based on recent evidence (5). Osteoarthritis had not been included as a health state in previous cost-effectiveness models. A search for studies using key words 'Diabetes', 'Osteoarthritis' and 'Cohort Studies' did not identify a UK based study with diabetes and BMI included as independent covariates in the risk model. The Bruneck cohort, a longitudinal study of inhabitants of a town in Italy reported diabetes and BMI as independent risk factors for osteoarthritis (5). The cohort may not be representative of the UK. However, the individuals are from a European country, the study has a large sample size and has estimated the independent effects of BMI and diabetes on the risk of osteoarthritis. No UK based studies identified in our searches met these requirements. The data used to estimate the incidence of osteoarthritis is reported in Table 36.

Table 36: Incidence of osteoarthritis and estimated risk factors

	No cases	Person years	Mean BMI	Incidence rate	Reference
No diabetes	73	13835	24.8	0.0053	(5)
	Hazard ratio	2.5th	97.5th		Reference
HR Diabetes	2.06	1.11	3.84		(5)
HR BMI	1.076	1.023	1.133		(5) Personal communication

9.5 DEPRESSION

Depression was not included as a health state in previous cost-effectiveness models for diabetes prevention. However, a member of the stakeholder group identified that a relationship between diabetes and depression was included in the CORE diabetes treatment model (32). With this in mind, we decided to include depression as a health state in the model, but not to model its severity.

Some individuals enter the simulation with depression at baseline according to individual responses in the Health Survey for England 2011 questionnaire. Depression is described as a chronic state from which individuals do not completely remit. We did not estimate the effect of depression on the longitudinal changes for BMI, glycaemia, systolic blood pressure and cholesterol. As a consequence it was not possible to relate the impact of depression to the incidence of diabetes and cardiovascular risk.

In the simulation, individuals can develop depression in any cycle of the model. The baseline incidence of depression among all individuals without a history of depression was estimated from a study examining the bidirectional association between depressive symptoms and type 2 diabetes (33). Although the study was not from a UK population, the US cohort included ethnically diverse men and women aged 45 to 84 years. We assumed that diagnosis of diabetes and/or cardiovascular

disease increases the incidence of depression in individuals who do not have depression at baseline. We identified a method for inflating risk of depression for individuals with diabetes from the US cohort study described above (33). The risk of depression in individuals who have had a stroke was also inflated according to a US cohort study (34). Odds of depression and odds ratios for inflated risk of depression due to diabetes or stroke are presented in Table 37.

Table 37: Baseline incidence of depression

Baseline Risk of depression			
	Mean	2.5th CI	97.5th
Depression cases in NGT	336		
Person years	9139		
Odds of depression	0.0382		
Log odds of depression	-3.266		
Inflated risk for Diabetes			
Odds ratio of diabetes	1.52	1.09	2.12
Log odds ratio of diabetes	0.419		
Inflate risk of stroke			
Odds ratio of stroke	6.3	1.7	23.2
Log odds ratio stroke	1.8406		
NGT Normal Glucose Tolerance			

9.6 MORTALITY

9.6.1 Cardiovascular Mortality

Cardiovascular mortality is included as an event within the QRISK2 and the probability of subsequent cardiovascular events obtained from an HTA assessing statins (13) as described in the cardiovascular disease section above.

9.6.2 Cancer Mortality

Cancer mortality rates were obtained from the Office of National statistics (35). The ONS report one and five year net survival rates for various cancer types, by age group and gender. Net survival was an estimate of the probability of survival from the cancer alone. It can be interpreted as the survival of cancer patients after taking into account the background mortality that the patients would have experienced if they had not had cancer.

The age-adjusted 5-year survival rate for breast cancer and colorectal cancer were used to estimate an annual risk of mortality assuming a constant rate of mortality. We assume that the mortality rate does not increase due to cancer beyond 5 years after cancer diagnosis. The five year survival rate for breast cancer is 84.3%, which translated into a 3.37% annual probability of death from breast cancer.

The five year survival rate for persons with colorectal cancer is 55.3%, which translated into an 11.16% annual probability of death from colorectal cancer.

9.6.2.1 Other cause Mortality (including diabetes risk)

Other cause mortality describes the risk of death from any cause except cardiovascular disease and cancer. All-cause mortality rates by age and sex were extracted from the Office of National Statistics (36). The mortality statistics report the number of deaths by ICD codes for 5-year age groups. We subtracted the number of cardiovascular disease, breast and colorectal cancer related deaths from the all-cause mortality total to estimate other cause mortality rates by age and sex (Table 35).

Table 38: All cause and derived other cause mortality from the Office of National statistics

	All cause	All cause	Other cause	Other cause		All cause	All cause	Other cause	Other cause
	Men	Women	Men	Women		Men	Women	Men	Women
1	0.0004	0.0003	0.0003	0.0003	51	0.0034	0.0024	0.0025	0.0017
2	0.0002	0.0002	0.0002	0.0002	52	0.0039	0.0026	0.0029	0.0019
3	0.0001	0.0001	0.0001	0.0001	53	0.0044	0.0028	0.0032	0.0020
4	0.0001	0.0001	0.0001	0.0001	54	0.0045	0.0032	0.0034	0.0022
5	0.0001	0.0001	0.0001	0.0001	55	0.0051	0.0033	0.0037	0.0024
6	0.0001	0.0001	0.0001	0.0001	56	0.0057	0.0037	0.0041	0.0027
7	0.0001	0.0001	0.0001	0.0000	57	0.0061	0.0041	0.0044	0.0030
8	0.0001	0.0001	0.0001	0.0000	58	0.0069	0.0041	0.0050	0.0030
9	0.0001	0.0001	0.0001	0.0001	59	0.0071	0.0050	0.0052	0.0036
10	0.0001	0.0000	0.0001	0.0000	60	0.0081	0.0054	0.0059	0.0040
11	0.0001	0.0001	0.0001	0.0001	61	0.0086	0.0057	0.0063	0.0042
12	0.0001	0.0001	0.0001	0.0001	62	0.0096	0.0062	0.0070	0.0046
13	0.0001	0.0001	0.0001	0.0001	63	0.0104	0.0067	0.0076	0.0050
14	0.0001	0.0001	0.0001	0.0001	64	0.0108	0.0072	0.0079	0.0053
15	0.0002	0.0001	0.0002	0.0001	65	0.0125	0.0082	0.0091	0.0061
16	0.0002	0.0001	0.0002	0.0001	66	0.0141	0.0090	0.0103	0.0067
17	0.0003	0.0002	0.0003	0.0002	67	0.0148	0.0097	0.0108	0.0072
18	0.0004	0.0002	0.0004	0.0002	68	0.0162	0.0107	0.0118	0.0079
19	0.0004	0.0002	0.0004	0.0002	69	0.0181	0.0118	0.0132	0.0087
20	0.0005	0.0002	0.0005	0.0002	70	0.0218	0.0138	0.0157	0.0101
21	0.0005	0.0002	0.0005	0.0002	71	0.0234	0.0145	0.0168	0.0106
22	0.0005	0.0002	0.0005	0.0002	72	0.0252	0.0167	0.0182	0.0122
23	0.0005	0.0002	0.0005	0.0002	73	0.0269	0.0173	0.0193	0.0127
24	0.0005	0.0002	0.0005	0.0002	74	0.0310	0.0200	0.0223	0.0147
25	0.0006	0.0003	0.0006	0.0002	75	0.0327	0.0222	0.0233	0.0157
26	0.0006	0.0003	0.0005	0.0002	76	0.0375	0.0249	0.0267	0.0176
27	0.0006	0.0004	0.0005	0.0003	77	0.0411	0.0284	0.0293	0.0202
28	0.0007	0.0003	0.0006	0.0003	78	0.0458	0.0321	0.0326	0.0228
29	0.0007	0.0003	0.0006	0.0003	79	0.0523	0.0358	0.0372	0.0254
30	0.0007	0.0004	0.0006	0.0003	80	0.0585	0.0411	0.0418	0.0289
31	0.0008	0.0004	0.0007	0.0004	81	0.0652	0.0456	0.0465	0.0321
32	0.0007	0.0005	0.0007	0.0004	82	0.0745	0.0530	0.0531	0.0372
33	0.0008	0.0005	0.0007	0.0004	83	0.0833	0.0606	0.0594	0.0426
34	0.0009	0.0005	0.0008	0.0004	84	0.0931	0.0678	0.0664	0.0476
35	0.0010	0.0006	0.0008	0.0005	85	0.1040	0.0760	0.0738	0.0537
36	0.0011	0.0006	0.0010	0.0005	86	0.1147	0.0872	0.0814	0.0617
37	0.0013	0.0006	0.0011	0.0005	87	0.1300	0.0977	0.0923	0.0692
38	0.0013	0.0007	0.0011	0.0006	88	0.1468	0.1106	0.1042	0.0782
39	0.0013	0.0007	0.0011	0.0006	89	0.1643	0.1242	0.1166	0.0879
40	0.0015	0.0009	0.0012	0.0006	90	0.2285	0.1982	0.1660	0.1425
41	0.0016	0.0010	0.0013	0.0007	91	0.2285	0.1982	0.1660	0.1425
42	0.0018	0.0010	0.0015	0.0008	92	0.2285	0.1982	0.1660	0.1425
43	0.0018	0.0012	0.0015	0.0009	93	0.2285	0.1982	0.1660	0.1425
44	0.0020	0.0012	0.0017	0.0009	94	0.2285	0.1982	0.1660	0.1425
45	0.0022	0.0014	0.0017	0.0010	95	0.2285	0.1982	0.1751	0.1509
46	0.0023	0.0016	0.0018	0.0011	96	0.2285	0.1982	0.1751	0.1509
47	0.0023	0.0015	0.0018	0.0011	97	0.2285	0.1982	0.1751	0.1509
48	0.0027	0.0017	0.0021	0.0012	98	0.2285	0.1982	0.1751	0.1509
49	0.0028	0.0019	0.0022	0.0014	99	0.2285	0.1982	0.1751	0.1509
50	0.0030	0.0021	0.0023	0.0015	100	0.2285	0.1982	0.1751	0.1509

The rate of other cause mortality by age and sex was treated as the baseline hazard. Following input from stakeholders, an increased risk of mortality was assigned to individuals with diabetes using data

from a published meta-analysis (37). This study used data from 820,900 people from 97 prospective studies to calculate hazard ratios for cause-specific death, according to baseline diabetes status (37). Cause of death was separated into vascular disease, cancer and other cause mortality. From this study we estimated that individuals with a diagnosis of diabetes have a fixed increased risk of other cause mortality (Hazard ratio 1.8 (95% CI 1.71-1.9)). The estimates reported in the meta-analysis include increased risk of death from renal disease, therefore mortality from renal disease was not simulated separately to avoid double counting of benefits.

10 DIRECT HEALTH CARE COSTS

At any given time period of the model individuals can have multiple health complications that incur direct healthcare costs. Some of the health states are mutually exclusive; however an individual can accrue multiple complications within the model. Each health state is associated with an average cost, which is accrued by all individuals for every time period for which the state is indicated. Resource use for each comorbidity is added together and no savings are assumed to be made from the use of the same resources for two or more comorbidities for an individual. An exception to this is an assumed adjustment to the utilisation of GP services for individuals with chronic diseases.

In some instances we have adopted costs and prices from old studies. We have inflated all prices and costs to 2013 prices using inflation indices reported in the Personal Social Services Research Unit (PSSRU) (38). This documents health related inflation up to 2011/12 prices. Price inflation was assumed at 2% per year to inflate costs to 2012/2013 prices.

Primary care and community care costs were sought from the Personal Social Services Research Unit (PSSRU) (38), and secondary care costs from UK reference costs (39). Drug costs were obtained from the British National Formulary (40). In most instances costs for long term health outcomes were sought from recent Health Technology Appraisals as this was thought to be the best source of evidence for costs and resource use by disease area in the UK. If an HTA appraisal were not identified, searches for good quality cost-effectiveness analyses for the relevant disease area were conducted to identify the appropriate UK costs.

10.1 GP ATTENDANCE

The costs of each visit to a General Practitioner were estimated at £43 from the Personal Social Services Research Unit (PSSRU) (38).

10.2 DIABETES

We were advised by stakeholders to model a simplified diabetes treatment pathway. It was recommended that a single annual cost of prescriptions be applied to all patients diagnosed with diabetes. Initially we explored this as an option but concluded that the timing of more costly treatments for type 2 diabetes is important because treatment costs will be discounted. The model assesses interventions that lower HbA1c and so have the potential to impact on the level of treatment required.

We decided to implement a three stage treatment regimen as a trade-off between model simplicity and capturing key cost differences between the interventions. At diagnosis all patients are prescribed low cost treatments, such as Metformin and Sulfonylurea. We chose Metformin, 500mg/day to describe the average cost of these medications. If HbA1c increases above a threshold the individual is prescribed a more expensive Gliptins in addition to Metformin. The individual continues to receive Metformin plus Gliptins for a period of time until they require insulin.

10.2.1 Metformin Monotherapy

Cost estimates from the British National Formulary indicate that the cost of Metformin is approximately £11 per tablet. The use of blood glucose self-monitoring strips was described in a recent UK based study in which 36% of patients used monitoring strips at a mean weekly consumption of 3.1 (41) for individuals prescribed Metformin only, at a cost of 31p per strip as reported in the BNF. Other resource use costs and utilisation assumptions for diabetics receiving Metformin monotherapy are detailed in Table 39.

Table 39: Drug costs and resource utilisation costs for low cost diabetes monotherapy

Resource	Assumption for costs	Unit cost	Source	Inflation	Annual utilisation	Source	Cost per year
Metformin	500mg 56 tab pack	£0.11	BNF 65	1	730	Assumption	£80.04
Nurse at GP	Nurse advanced per surgery consultation with qualifications	£25	(38)	1	1	Stakeholder workshop	£25.00
Health care assistant	Clinical support worker patient work 10 mins	£4.17	(38)	1	1	Stakeholder workshop	£4.17
Urine sample	Biochemistry	£1		1	3	Stakeholder workshop	£1
Eye screening	Optometrist test 2006 price	£18.39	(42)	1.235	1	Stakeholder workshop	£22.71
HbA1c	Haematology	£3		1	1	Stakeholder workshop	£3.00
Lipids	Chemistry	£1		1	1	Stakeholder workshop	£1.00
Liver function	Chemistry	£1		1	1	Stakeholder workshop	£1.00
B12	Chemistry	£1		1	1	Stakeholder workshop	£1.00
Smoking cessation	Nicotine replacement therapy	£102	(38)	1	0.3*	Stakeholder workshop	£30.6
							£169.51
* Assumed 20% smoking prevalence and 50% uptake of smoking cessation services							

The cost of diabetes in the year after diagnosis is assumed to be greater than subsequent years because the individual will receive more contact time whilst their diabetes is being controlled. The additional costs of diabetes in the year after diagnosis are reported in Table 40.

Table 40: Drug costs and resource utilisation costs for the first year of low cost diabetes treatment

Resource	Assumption for costs	Unit cost	Source	Inflation	Annual utilisation	Source	Cost per year
Nurse at GP	Nurse advanced per surgery consultation with qualifications	£25	(38)	1	1	Stakeholder workshop	£50.00
Health care assistant	Clinical support worker patient work 10 mins	£4.17	(38)	1	1	Stakeholder workshop	£8.33
Urine sample	Biochemistry	£1		1	3	Stakeholder workshop	£2
HbA1c	Haematology	£3		1	1	Stakeholder workshop	£6.00
Lipids	Chemistry	£1		1	1	Stakeholder workshop	£2.00
Liver function	Chemistry	£1		1	1	Stakeholder workshop	£2.00
B12	Chemistry	£1		1	1	Stakeholder workshop	£2.00
							£72.33

10.2.2 Metformin plus Gliptins

Simulated individuals experience an annual increase in HbA1c. Gillett et al. (2012) assume that individuals switch to dual treatment if HbA1c increases above 7.4% (6). Within the model, the individual is switched to a dual treatment in the first annual cycle in which HbA1c exceeds 7.4%. For costing purposes the second drug to be added to Metformin was Sitagliptin, which is reported in the British National Formulary to cost £1.41 per day. Belsey et al. (2009) report that 48% of patients used monitoring strips at a mean weekly consumption of 3.3 (reference needed). Table 41 reports the other resource use costs and utilisation assumptions for diabetics receiving Metformin plus Gliptins.

Table 41: Drug costs and resource utilisation costs for Metformin and Gliptins

Resource	Assumption for costs	Unit cost	Source	Inflation	Annual utilisation	Source	Cost per year
Sitagliptin	100mg per day 28 tab pack	£1.19	BNF 65	1	730	Assumption	£867.14
Metformin	5mg per day, 28 tab pack	£0.11	BNF 65	1	730	Assumption	£80.04
Self-monitoring strips	50 strip pack Active®	£0.314	BNF 65	1	82.20	(41)	£25.81
Nurse at GP	Nurse advanced per surgery consultation with qualifications	£25	(38)	1	1	Stakeholder workshop	£25.00
Health care assistant	Clinical support worker patient work 10 mins	£4.17	(38)	1	3	Stakeholder workshop	£4.17
Urine sample	Biochemistry	£1		1	1	Stakeholder workshop	£1
Eye screening	Optometrist test 2006 price	£18.39	(42)	1.235	1	Stakeholder workshop	£22.71
HbA1c	Haematology	£3		1	3	Stakeholder workshop	£3.00
Lipids	Chemistry	£1		1	3	Stakeholder workshop	£1.00
Liver function	Chemistry	£1		1	3	Stakeholder workshop	£1.00
B12	Chemistry	£1		1	3	Stakeholder workshop	£1.00
Smoking cessation	Nicotine replacement therapy	£102	(38)	1	0.3*	Stakeholder workshop	£30.60
							£1062.46
* Assumed 20% smoking prevalence and 50% uptake of smoking cessation services							

10.2.3 Insulin plus Oral Anti-diabetics

The second major treatment change is assumed to be initiation of insulin. Gillett et al. (2012) assumed that individuals switch to insulin if HbA1c increases above 8.5% (6). Within the model the individual is switched to insulin in the first annual cycle at which HbA1c exceeds 8.5%. The insulin Glargine was chosen to represent insulin treatment in the UK and is consistent with Gillett et al. (2012) (6). Furthermore, recent cost studies from the UK have promoted the use of Glargine to reduce costs (43). The total resource use and costs of this health state are reported in Table 42 and Table 43.

Table 42: Costs of insulin treatment

	Price	Source
Glargine	£628.44	(43) (2006 prices)
Oral anti-diabetics	£43.68	(43) (2006 prices)
Reagent test strips	£221.43	(43) (2006 prices)
Hypoglycaemic rescue	£23.43	(43) (2006 prices)
Pen delivery devices	£54.79	(43) (2006 prices)
Sharps	£68.82	(43) (2006 prices)
Total cost per year	£1,013.51	

Table 43: Drug costs and resource utilisation costs for insulin and oral anti-diabetics

Resource	Assumption for costs	Unit cost	Source	Inflation (2013)	Annual utilisation	Source	Cost per year
Insulin treatment costs	Total annual cost	£1,013.51	(43)	1.235	NA	N/A	£1251.53
Nurse at GP	Nurse advanced per surgery consultation with qualifications	£25	(38)	1	3	Stakeholder workshop	£75.00
Health care assistant	Clinical support worker patient work 10 mins	£4.17	(38)	1	3	Stakeholder workshop	£12.50
Urine sample	Biochemistry	£1		1	3	Stakeholder workshop	£3.00
Eye screening	Optometrist test 2006 price	£18.39	(42)	1.235	1	Stakeholder workshop	£22.71
HbA1c	Haematology	£3		1	3	Stakeholder workshop	£9.00
Lipids	Chemistry	£1		1	3	Stakeholder workshop	£3.00
Liver function	Chemistry	£1		1	3	Stakeholder workshop	£3.00
B12	Chemistry	£1		1	3	Stakeholder workshop	£3.00
Smoking cessation	Nicotine replacement therapy	£102	(38)	1	0.3*	Stakeholder workshop	£30.60
							£1413.34
* Assumed 20% smoking prevalence and 50% uptake of smoking cessation services							

10.3 STATINS

We assumed that individuals who are prescribed statins receive a daily dose of 40mg of generic Simvastatin. The British National Formulary reports a cost of approximately 3p per day. The individual remains on statins for the rest of their life. Table 44 reports the derived annual costs for statins.

Table 44: Annual treatment costs of statins

	Assumption for costs	Unit cost	Source	Inflation	Annual utilisation	Cost per year
Statins	Simvastatin 20mg	£0.0325	BNF 65	1	730	£23.72

10.4 ANTI-HYPERTENSIVES

A search of the literature did not identify any recent publications of anti-hypertensive prescriptions in the UK. As a consequence the best estimates of cost of anti-hypertensive treatment dated from 2004. These were inflated to current prices (44). Due to the number of different anti-hypertensive treatments available and possibilities for combination therapies, using the cost from this study of prescriptions was preferred to using costs directly from the BNF.

Table 45: Annual cost of anti-hypertensive prescription expenditure per patient

	Price	Inflation	Cost per year	Source
Anti-hypertensive prescriptions	£144	1.2709	£183.01	(44)

10.5 CARDIOVASCULAR EVENTS

Costs for cardiovascular disease were obtained from a 2009 HTA for high dose lipid-lowering therapy (12). Table 46 describes the costs and resource use assumptions that were used for this study. It also reports the health states to which we have applied each cost in the model. The costs of congestive heart failure were estimated from the UKPDS costing study for complications related to diabetes (45). The unit costs for cardiovascular events are detailed in Table 47.

Table 46: Resources use assumptions and costs for cardiovascular outcomes

	Resource assumptions	Cost (2009)	Cost (2012/13)	Health States applied
Unstable Angina year 1	Secondary care costs: 100% hospitalisation, 50% revascularisation procedure, three outpatient appointments). Primary care costs (three GP visits) and medications	£3880	£4365.52	UANG1
MI year 1	Secondary care costs: 100% hospitalisation, 50% revascularisation procedure, three outpatient appointments) Primary care costs (three GP visits) and medications.	£3996	£4482.81	MI1
Subsequent ACS care costs	Secondary care costs (one outpatient appointment). Primary care costs (three GP visits) and medications.	£340	£382.53	SANG, UANG, MI, TIA
Stroke year 1	Costs of acute events reported in Youman et al. (46) weighted by the distribution of severity of stroke (13).	£8066	£9075.02	STRO1
Stroke subsequent costs	The costs of ongoing care at home or in an institution weighted by the distribution of severity of stroke and discharge locations.	£2266	£2549.59	STRO2
Fatal CHD	Palmer et al. (47). Assumed that 50% of fatalities incurred cost.	£592	£665.50	
Fatal non cardiac vascular event	Youman et al. (46). Assumed 50% fatalities incurred cost	£3688	£4149.52	
	Source	Cost (2004)	Cost (2012/13)	
Congestive heart failure	UKPDS (45)	£2221	£2887.20	

Table 47: Unit costs for Cardiovascular cost estimates taken from HTA report (12)

Unit Cost	Mean	Inflation	Mean (2012/13)	Standard error	Distribution
Unstable Angina hospital: EB05SZ	£1059	1.13829	£1205.45	120.5447	GAMMA
Revasc. Hospital mixture of HRG codes	£5011.81	1.13829	£5704.88	570.4883	GAMMA

MI Hospital: EB107	£1290.88	1.13829	£1469.39	146.9393	GAMMA
First Outpatient	£137.28	1.13829	£156.26	15.62642	GAMMA
Subsequent appointment	£91.37	1.13829	£104.01	10.40054	GAMMA
GP visit year1	£102	1.13829	£116.11		CONSTANT
GP visit year 2	£91.37	1.13829	£104.01		CONSTANT
Fatal CHD (Palmer (47) Inflated)	£591.52	1.13829	£673.32	67.332	GAMMA
Fatal stroke (Youman (46) inflated)	£3688.23	1.13829	£4198.27	419.8267	GAMMA
First year stroke	£8066.18	1.13829	£9181.63	918.1635	GAMMA
Subsequent year stroke	£2266.16	1.13829	£2579.54	257.9542	GAMMA
Glytrin Spray	£10.47	1.13829	£11.92		CONSTANT
Isosorbide mononitrate	£11.24	1.13829	£12.79		CONSTANT
Verapamil	£41.98	1.13829	£47.79		CONSTANT
Atenolol	£30.24	1.13829	£34.42		CONSTANT
Aspirin	£6.65	1.13829	£7.57		CONSTANT
Ramipril	£75.09	1.13829	£85.47		CONSTANT
ARB	£210.27	1.13829	£239.35		CONSTANT
Clopidogrel	£460.27	1.13829	£523.92		CONSTANT

10.6 MICROVASCULAR EVENTS

10.6.1 Renal Failure

The cost of renal failure was estimated for the UK using relevant published studies. A recent costing study reported the costs of dialysis types (48). The prevalence of dialysis and transplants were taken from a second study reporting the prevalence of renal failure in the UK in 2008 (49). The cost of renal transplantation was taken from a costing study investigating the cost-effectiveness of renal transplantation (50). The overall cost was estimated as a weighted average of the treatment outcomes. All costs were inflated to 2012/13 prices.

Table 48: Unit costs for renal failure

	Cost (£)	Source	Inflation	Cost (2012/13)	Proportion
Haemodialysis with overheads	34,236	(48)	1.14719	39,275	0.469
Automated peritoneal dialysis (APD)	22,160	(48)	1.14719	25422	0.045*
Continuous ambulatory peritoneal dialysis (CAPD)	16,074	(48)	1.14719	18440	0.045*
Transplant	17,000	(50)	1.29995	22099	0.442
Immunosuppressant	5000	(50)	1.29995	6499	
* Assumed 50% split of peritoneal dialysis types					

10.6.2 Foot Ulcers

The cost of foot ulcers was estimated from a US Cost of Illness study (51). The costs were converted from dollars to pounds using Purchasing Power Parities reported by the OECD (52). The costs were also inflated to UK 2012/13 prices.

Table 49: Estimated cost of foot ulcers

Resource component	Not Infected	With Cellulitis	With Osteomyelitis
Prevalence	0.874	0.09	0.036
Mean cost per patient	$178.97	$472.73	$876.52
Mean cost per patient (2012/13 £)	£158.53	£418.73	£776.40
Standard error	15.85	41.87	77.64
Total Cost PPP (2012/13 £)			£204.19

10.6.3 Amputation

The cost of amputation in the first year of surgery and subsequent years has been reported In a UKPDS costing study (45). The costs were extracted and inflated to 2012/13 prices. The cost of amputation in the first year was £11,125 (standard error £2,123) and in subsequent years was £395 (standard error £98).

10.6.4 Blindness

The cost of blindness in the first year of surgery and subsequent years has been reported In a UKPDS costing study (45). The costs were extracted and inflated to 2012/13 prices. The cost of blindness in the first year was £1,147 (standard error £232) and in subsequent years was £370 (standard error £62).

10.7 CANCER

A recent appraisal for cancer screening estimated the overall cost of breast cancer as a weighted average depending on the prognosis at diagnosis to be £10,452 in 2006/7 prices and £13,058 when inflated to 2012/13 prices (53).

The cost of colorectal cancer was taken from a screening appraisal which reported the lifetime costs of colorectal cancer according to the Dukes stage of the tumour (54). The appraisal also reported the proportion of cancers identified at each stage, which allowed us to estimate the weighted average

cost of colorectal cancer. Table 50 reports the overall cost of colorectal cancer by stage of disease at diagnosis.

Table 50: Estimated cost of colorectal cancer

Resource component	Dukes' Stage A	Dukes' Stage B	Dukes' Stage C	Stage D
Number of patients	3241.92	9,431.04	7,662.72	8,841.60
Prevalence	0.111	0.323	0.263	0.303
Mean cost per patient	£7,250.84	£12,441.41	£19,076.90	£11,945.78
Price Inflation				1.296
Mean cost per patient (2012/13)	£9,536	£16,363	£25,090	£15,711
Standard error (2012/13)	£953.64	£1,636.32	£2,509.03	£1,571.13
Total Cost (2012/13)				£17,699.07

10.8 OSTEOARTHRITIS

The annual cost of osteoarthritis were estimated in a report in 2010 (55). In this report the authors estimated the expected cost of osteoarthritis from three previous costing studies. The costs include GP attendance, nurse consultations, replacement surgery, help at home and prescription medications. The estimated annual cost of osteoarthritis was £783 in £2008. This was inflated to 2012/13 prices at £908 (standard error £90.88).

10.9 DEPRESSION

A recent trial to prevent secondary depressive episodes collected comprehensive cost data from a sample of individuals with depression (56). The resource uses identified in the control arm were extracted to estimate the costs of depression. The costs from this data (inflated to 2013 prices) were not implemented directly into the SPHR diabetes prevention model as this would have over-estimated the number of GP visits. The model already accounts for GP attendance due to depression as described in Section 10.1. Therefore, a revised estimate of the cost of depression, excluding GP consultation was estimated using updated unit costs. The resource use estimates and revised unit cost estimates used to generate a cost of depression excluding GP utilisation are reported in Table 51.

Table 51: Depression utilisation of services and total estimated cost

	Assumption for costs	Unit cost	Source	Inflation	Annual utilisation	Source	Cost per year
Practice nurse at surgery	GP nurse face to face assume 10 mins	£8.83	(38)	1	2.28	(56)	£20.14
Practice nurse at home visit	GP nurse face to face assume 30 mins	£26.50	(38)	1	0.03	(56)	£0.80
Practice nurse telephone	GP nurse face to face assume 10 mins	£8.83	(38)	1	0.17	(56)	£1.46
Health visitor	Health visitor per hour visit 30 mins	£35.50	(38)	1	0.08	(56)	£2.66
District nurse	Community nurse 30 mins	£24.50	(38)	1	0.02	(56)	£0.37
Other nurse	GP nurse face to face assume 10 mins	£8.83	(38)	1	0.20	(56)	£1.72
HCA phelbotomist	Clinical support worker 10 mins	£4.17	(38)	1	0.47	(56)	£1.94
Other primary care	Advanced nurse with qualifications	£25.00	(38)	1	0.29	(56)	£7.13
Out of hours	Inflated of trial costs	£22.30	(56)	1.122	0.35	(56)	£8.63
NHS direct	Inflated of trial costs	£21.00	(56)	1.122	0.14	(56)	£3.18
Walk-in centre	Inflated of trial costs	£32.24	(56)	1.122	0.32	(56)	£11.39
Prescribed medications	Inflated of trial costs	£7.98	(56)	1.122	11.61	(56)	£103.96
Secondary care	Emergency Medicine, Any Investigation	£109.0	Reference costs	1	0.39	(56)	£42.51
							£205.88

11 EMPLOYER COSTS

In order to capture wider social benefits of interventions for diabetes prevention, the model was designed to estimate the number of sickness days taken conditional on health status. The model utilises data from a study that estimates productivity loss due to poor health, using days absent from paid employment and normal activities, EQ-5D score, International Classification of Disease (ICD) chapter and socio-demographic data (57). The results can be used to predict the level of productivity loss associated with EQ-5D values and specific disease diagnosis, measured by number of days absent from work. Data was used from a prospective survey of inpatients discharged from a hospital in Wales, United Kingdom from April 2002 to January 2009. The number of days absent from paid employment due to ill health (N=51,326) in the six weeks following discharge was estimated using a zero-inflated negative binomial regression model, which produced large spikes at 0 (zero days off paid employment/normal activities) and 42 days.

The following disease diagnoses were used in the model to estimate the impact of disease on work productivity.

1. Colorectal or breast cancer were associated with ICD group for neoplasms.
2. Diabetes diagnosis was associated with ICD group for Endocrine, nutritional and metabolic diseases.
3. Depression was associated with ICD group for Mental and behavioural disorders.
4. Cardiovascular disease was associated with ICD group for diseases of the circulatory system.

The statistical model estimated the number of days absent from work from an employed population. In the SPHR model the number of days absent from work was only applied to individuals in the HSE who reported being in employment and less than 65 years old. The simulated number of days of sick leave was multiplied by 8.67 to scale up the 6 week estimate to the annual cycle of the model.

The cost of sick days to the employer was calculated based on a method derived from a previous study of work absenteeism (58). In the SPHR model it is assumed that the employee's usual salary is not included in the employer cost because the productivity of the replacement worker would generate gains to the employer to compensate for the absent worker. Therefore the employer cost calculation includes excess costs incurred and/or loss of productivity during periods of worker absence. The cost to the employer of work absence due to ill health is based on the number of days of absence, losses due to work not completed, occupational sick pay and the cost of a replacement worker. Productivity losses were estimated based on the friction method, which assumes that there

are sufficient number of unemployed people within the UK in order to replace workers on sick leave after a given friction period. In this analysis we assumed a friction period of 10 weeks during which the employer incurs a cost due to productivity losses. After the friction period a replacement worker is assumed to be as productive as the employee on sick leave. During the sick leave period there are costs incurred because the employer is obliged to pay statutory sick pay for 28 weeks and many employers also provide occupational sick pay (OSP). In this analysis we assumed that the employee receives full pay for 15 weeks. Within the friction period this payment is subsumed into the employee's usual salary, which would have been paid by the employer in the absence of sick leave. However, after the friction period the OSP is included in our estimate of the employer's cost, because in this period the employer would be paying for the employee on sick leave in addition to a replacement worker. If the period of absence exceeds 15 weeks (75 days) the employer pays half the salary for a maximum of 16.4 weeks, and no further payments for the remaining period. Table 52 summarises the timing of costs incurred due to periods of absence from work.

The average salary per day is based on a UK national average salary plus national insurance contributions at this salary (59) . The cost of a replacement worker was calculated in a recent report which estimated the logistical costs of advertising spend for a new employee, the cost of using an agency to recruit for a new employee and the number of days taken for internal HR processes related to a new employee (60). We assume that there are no additional costs to training the replacement worker.

Table 52: Employer cost algorithm for days absent from work due to ill health

Days absence	Productivity lost over friction period	Occupational sick pay	Cost replacement worker
1-50	£103.4 per day		
51-75		Full pay £103.4 per day	Cost of advertising and recruitment temporary worker £5433.
76-157		Half pay £51.7 per day	
157-260		None	

If an individual of working age dies whilst in employment, the cost of recruiting a replacement worker is included in the calculation of employer costs.

12 UTILITIES

12.1 BASELINE UTILITY

Baseline utilities for all individuals in the cohort were extracted from the HSE 2011. The tariffs for the responses to the 3 level EQ-5D were derived from a UK population study (61). Baseline utility was assumed to decline due to ageing. In the simulation, utility declines by an absolute decrement of 0.004 per year. This estimate is based on previous HTA modelling in cardiovascular disease (13).

12.2 BMI AND UTILITY

We assumed that changes in BMI will impact on an individual's utility. In a previous HTA for diabetes screening, weight loss from education interventions was associated with an increase in utility of 0.0025 per kg change in weight. This estimate was derived from weight loss trial data in which all participants were overweight or obese. In the HSE population a large proportion of individuals are normal or underweight so it would not be appropriate to extrapolate the effects of weight loss on utility to these individuals. The change in utility due to changes in BMI was added to an individual's EQ-5D if they had a BMI greater than 25. As a consequence, individuals with an increasing BMI above 25 will experience a reduction in EQ-5D and obese individuals who lose weight will experience an increase in EQ-5D.

12.3 UTILITY DECREMENTS

The utility decrements for long term chronic conditions were applied to the age and BMI adjusted EQ-5D score. We assumed that a diagnosis of diabetes was not associated with a reduction in EQ-5D independent of the utility decrements associated with complications, comorbidities or depression. Cardiovascular disease, renal failure, amputation, foot ulcers, blindness, cancer, osteoarthritis and depression were all assumed to result in utility decrements. The utility decrements are measured as a factor which is applied to the individual's age and BMI adjusted baseline. If individuals have multiple chronic conditions the utility decrements are multiplied together to give the individual's overall utility decrement from comorbidities and complications, in line with current NICE guidelines for combining comorbidities (62).

Due to the number of health states it was not practical to conduct a systematic review to identify utility decrements for all health states. A pragmatic approach was taken to search for health states within existing health technology assessments for the relevant disease area or by considering studies

used in previous economic models for diabetes prevention. Discussions with experts in health economic modeling were also used to identify prominent sources of data for health state utilities.

Two sources of data were identified for diabetes related complications. A recent study from the UKPDS estimated the impact of changes in health states from a longitudinal cohort (63). They estimated the impact of myocardial infarction, ischaemic heart disease, stroke, heart failure, amputation and blindness on quality of life using seven rounds of EQ-5D questionnaires administered between 1997 and 2007. This data was used to estimate the utility decrement for amputation and congestive heart failure. The absolute decrement for amputation was converted into utility decrement factors that could be multiplied by the individuals' current EQ-5D to estimate the relative effect of the complication. Blindness was included in the statistical model used for this analysis however the UKPDS analysis reported an increase in health state utility following a diagnosis with blindness. Discussions with the authors highlighted that this was due to treatment following formal classification with blindness and it was decided that this increase in health state utility should not be included in the cost-effectiveness model.

Utility decrements for renal failure and foot ulcers were not available from the UKPDS study described above. A study by Coffey et al. (2000) was used to estimate utility decrements for renal failure and foot ulcers (64). In this study, 2,048 subjects with type 1 and type 2 diabetes were recruited from specialty clinics. The Self-Administered Quality of Well Being index (QWB-SA) was used to calculate a health utility score.

Utility decrements for cardiovascular events were taken from an HTA assessing statins to reflect the utility decrements in all patients (13) rather than using the UKPDS, which is only representative of a diabetic population. The study conducted a literature review to identify appropriate utility multipliers for stable angina, unstable angina, myocardial infarction and stoke. We used these estimates in the model and assume that transient ischaemic attack is not associated with a utility decrement in line with this HTA.

We identified a systematic review of breast cancer utility studies following consultation with colleagues with experience in this area. The review highlighted a single burden of illness study with a broad utility decrement for cancer (65), rather than utilities by cancer type or disease status. This study was most compatible with the structure of the cost-effectiveness structure. Within this study 1823 cancer survivors and 5469 age-, sex-, and educational attainment-matched control subjects completed EQ-5D questionnaires to estimate utility with and without cancer.

The utility decrement for osteoarthritis was taken from a Health Technology Assessment that assessed the clinical effectiveness and cost-effectiveness of glucosamine sulphate/hydrochloride and chondroitin sulphate in modifying the progression of osteoarthritis of the knee (66).

A review of cost-effectiveness studies highlights the scarcity of studies of health-related quality of life in depression (67). The utility studies identified in the review described depression states by severity and did not adjust for comorbid conditions. Furthermore, the valuations were variable between studies suggesting poor consistency in the estimations. Therefore, it was difficult to apply these in the model. We decided to use a study which had used the EQ-5D in an RCT, for consistency with our utility measure (68). They report an average post treatment utility of 0.67, from which we estimated the utility decrement compared with the average utility reported in the HSE dataset. The decrement was then converted into a relative utility reduction.

Table 53 reports the multiplicative utility factors that are used in the model to describe health utility decrements from comorbid complications. The mean absolute decrement estimated in each study is reported alongside the baseline utility for each study. The utility factor was estimated by dividing the implied health utility with the comorbidity by the baseline utility.

Table 53: Utility decrement factors

	Mean Absolute decrement	St. error absolute decrement	Baseline Utility	Multiplicative Utility Factor	Source
Foot ulcer	-0.099	0.013	0.689	0.856	Coffey (64)
Amputation	-0.172	0.045	0.807	0.787	UKPDS (69)
Blind	0.033	0.027	0.807	1.041	UKPDS (69)
Renal failure	-0.078	0.026	0.689	0.887	Coffey (64)
Stable Angina				0.801	Ward HTA (13)
Unstable Angina y1				0.770	Ward HTA (13)
Unstable Angina y2				0.770	Ward HTA (13)
Myocardial Infarction y1				0.760	Ward HTA (13)
Myocardial Infarction y2				0.760	Ward HTA (13)
Transient Ischaemic Attack				1.000	Ward HTA (13)
Stroke y1				0.629	Ward HTA (13)
Stroke y2				0.629	Ward HTA (13)
Breast Cancer	-0.060		0.800	0.913	Yabroff (65)
Colorectal Cancer	-0.060		0.800	0.913	Yabroff (65)
Osteoarthritis	-0.101				Black HTA (66)
Depression	-0.116		0.7905	0.875	Benedict (68)
Congestive Heart Failure	-0.101	0.032		0.875	UKPDS (69)
UKPDS baseline utility 0.807; HSE baseline 0.7905					

13 MODEL VALIDATION

The SPHR model has undergone a thorough process of error checking and internal and external validations. Model verification (comprising error checking and internal validation) included ensuring that mean PSA sampling values corresponded to mean parameter values, following individuals over time as they went through the model to ensure that trajectories were behaving as expected in response to treatments and interventions, and building the QRISK2 (21) separately in Excel to ensure that CVD predictions were accurate. We also tested the ability of the model to predict the results of the UKPDS outcomes model v2 (19), which acted as an internal validation for those outcomes encoded by UKPDS in the SPHR model, and an external validation for cardiovascular outcomes that were encoded in the SPHR model using QRISK2 (see below). As a consequence of this we realised that the SPHR model was vastly overestimating the incidence of renal failure, and resulted in our switching to UKPDS v1 for this outcome (11).

We developed four tests to compare model outcomes with reported data from external data sources. The first test assessed the incidence of type-2 diabetes in the population and sub-groups of the population and compared the results with incidence data from the EPIC study. This tested whether the Whitehall II glycaemia trajectories were performing adequately. The second validation study simulated data from the HSE 2003 cohort for eight years to observe predicted distributions of metabolic risk factors and the prevalence of health outcomes and compared them with the HSE 2011 cohort. The third validation exercise simulated the ADDITION diabetes trial and observed whether similar outcomes were observed compared with the data. Finally, a diabetic cohort was simulated in the model to compare outcomes with the UKPDS data.

13.1 PREDICTION OF DIABETES INCIDENCE

This validation assessed whether the Whitehall II model for glycaemia trajectories predicted incidence of diabetes diagnosed by the HbA1c test in sub-groups of patients from the HSE2003 cohort. Its objective was to assess the ability of the Whitehall II trajectories in the model to predict the recorded incidence of diabetes.

13.1.1 Methods

Data summarising the incidence of type 2 diabetes was obtained from the EPIC Norfolk cohort (70), which of similar studies was thought to be the most likely to represent the population distribution found in the HSE. EPIC Norfolk consists of 5735 individuals aged between 40 and 74, without

diabetes at baseline, who were followed for three years after an initial HbA1c test in the late 1990s. Diabetes incidence rates included both doctor diagnosed diabetes and diagnosis due to HbA1c≥6.5 in the follow-up period. Diabetes incidence was recorded for the total population and for sub-groups based upon their initial HbA1c status.

The model was run over a three year time course sampling only those individuals aged between 40 and 74 at the start of simulation. The starting population was generated from HSE 2003 rather than HSE 2011, as the dataset was more contemporaneous with the EPIC study and better reflected the population distribution within the IGR categories. Individuals with diabetes were excluded from the starting population. Diabetes incidence after three years of simulation was determined for subgroups of individuals who were initially measured with a high level of impaired glucose regulation (IGR) (HbA1c = 6.0-6.4%) or moderate IGR (HbA1c = 5.5-5.9%), and for the total population. Diabetes incidence in the model was represented by the total percentage of individuals in which HbA1c was measured as ≥6.5 in two consecutive health checks, rather than those with a diagnosis of diabetes, in order to reflect the EPIC data.

13.1.2 Results & Discussion

The incidence of diabetes in the simulation is summarised in Table 54. The diabetes model overestimates diabetes incidence in both the total population and in the high IGR population, but underestimates diabetes incidence in the moderate IGR population. The overestimation of total population incidence is likely to be a consequence of the overestimation of diabetes incidence in the high IGR group.

Baseline populations are relatively similar and cannot account for the large differences in diabetes incidence in the high and moderate IGR subgroups. We investigated whether the differences in incidence between high and moderate groups are due to differences between the Whitehall II cohort and the EPIC data. HbA1c values were collected in phases 7 and 9 of the Whitehall II cohort. The incidence of diabetes (defined by HbA1c greater than 6.5) after 5 years observation in the cohort was 2.5%. The incidence among high IGR was 44.2% and among moderate IGR was 5.12%. Therefore, the Whitehall II cohort does observe a much greater incidence of diabetes among those individuals with high IGR than the EPIC cohort. However, the low incidence of diabetes among those individuals with moderate IGR is not reflected in the Whitehall II cohort data.

Table 54: Comparison of simulated outcomes with the EPIC-Norfolk cohort

	Diabetes Prevention Model (N=50000)		**EPIC-Norfolk (N=5735)**		
Baseline characteristics					
	Mean	Standard deviation	Mean		Standard deviation
Age (years)	55.1	9.8	57.4		9.4
Male (%)	45.2	N/A	43.3		N/A
BMI (kg/m^2)	27.7	5.0	25.9		3.7
Diabetes incidence after 3 years					
Subset of individuals	Percentage of total individuals	Mean diabetes incidence (%)*	Percentage of total individuals	Mean diabetes incidence (%)**	95% CI
High IGR (HbA1c = 6.0-6.4)	5.9	11.2	6.5	7.0	4.8-10.1
Moderate IGR (HbA1c = 5.5-5.9)	27.9	0.2	24.4	1.5	1.0-2.3
Total Population	100	2.2	100	1.3	1.0-1.5
BMI Body Mass Index; CI Confidence Interval *HbA1c≥6.5 in two consecutive health checks; **HbA1c≥6.5 and/or doctor diagnosis of diabetes					

The low diabetes incidence among individuals with moderate IGR is likely to be a consequence of the way the trajectories for HbA1c work in the model. Most individuals have a gradually increasing HbA1c as they age, meaning that three years is insufficient in the vast majority of cases for a someone with moderate IGR to progress to diabetes. Equally, many more people with high IGR will progress to diabetes as they are already close to the threshold. We suggest that the model may be more accurate at predicting diabetes incidence over a longer time period due to the nature of the quadratic equations used to predict HbA1c.

Finally, it is possible that some individuals within the EPIC study who learnt they had high IGR at the beginning of the study would have changed their behaviour as a consequence of their high risk of diabetes or as a consequence of undergoing health screening (although this was not reported). Changes to diet and exercise would impact upon HbA1c and lead to underestimates of diabetes incidence. No such effect would occur in the model as individuals are unaware of their HbA1c status.

13.2 USING DATA FROM HSE 2003 TO PREDICT HSE 2011

This validation aimed to observe whether the Whitehall II statistical model predicted the future distribution of metabolic risk factors and prevalence of diabetes in age-selected sub-groups from the HSE 2003 data. We were aware that the Whitehall II cohort does not necessarily describe prospective changes in the population metabolic risk factors that were forecast. This analysis identified the potential error in the Whitehall II statistical models to describe temporal changes in

the risk profile of the population. The analysis also monitored whether the prevalence of diabetes and cardiovascular disease were correctly estimated for the age-groups. The objective was to evaluate the ability of the model to reproduce observed changes in population wide metabolic data between two time points.

13.2.1 Methods

Data from HSE 2003 was chosen as a starting point as values were obtainable for most of the parameters used in HSE 2011 (71). The total sample size of HSE 2003 is 18,553, which is considerably larger than the sample size of HSE 2011 (10,617).

Data was extracted from HSE 2003 using similar methods to those used for extraction of data from HSE 2011. A value for one of the parameters used in HSE 2011 was unavailable. This referred to diagnosis of "diabetes from blood sample or doctor diagnosis". However, the question on "doctor diagnosed diabetes" was thought to be adequate to assign individuals a diagnosis of diabetes. Individuals with a prior diagnosis of diabetes were included for the purposes of validation, but individuals under the age of 16 (n=3717) were removed from the dataset, resulting in a final sample size of 14,836. Missing data was estimated in the same way as described in section 6.4.

As for HSE 2011, QRISK scores and EQ-5D scores were calculated for all individuals. To align ethnicity in HSE 2003 to QRISK, all 'Asian' and 'British Asian' individuals were assumed to be 'Indian' (largest Asian subgroup and median risk ratio within all Asian subgroups in QRISK), all 'Black' and 'British Black' individuals were assumed to be 'Black Caribbean' (largest Black subgroup) and 'Mixed Race' individuals were assumed to be 'Other'. For those with a history of cardiovascular disease, the nature of the illness was randomly assigned according to age and sex-related probabilities of different types of cardiovascular event. The characteristics of HSE 2003 are described in Table 55.

Table 55: Characteristics of the final sample from HSE 2003 (N=14836), including individuals with diagnosed diabetes

	Number	Percentage	
Male	6602	44.50	
White	13661	92.08	
IMD1 (least deprived)	3334	22.47	
IMD2	2950	19.88	
IMD3	2929	19.74	
IMD4	3059	20.62	
IMD5 (most deprived)	2564	17.28	
Non-smoker	7445	50.18	
Anti-hypertensive treatment	2178	14.68	
Statins	791	5.33	
Diagnosed Diabetes	611	4.12	
Cardiovascular Disease (CVD)	1119	7.54	
SUBTYPES OF CVD	Number	Percentage of CVD	
Stable Angina	411	36.73	
Unstable Angina	122	10.90	
MI	246	21.98	
TIA	69	6.17	
Stroke	271	24.22	
	Mean	Standard Deviation	Median
Age (years)	48.21	18.49	47.00
BMI (kg/m^2)	26.96	5.01	26.35
Total Cholesterol (mmol/L)	5.70	1.18	5.60
HDL Cholesterol (mmol/L)	1.53	0.39	1.50
HbA1c (%)	5.34	0.73	5.20
Systolic Blood Pressure (mm Hg)	129.30	19.13	126.50
EQ-5D (TTO)	0.862	0.223	1.000

BMI Body Mass Index; IMD Index of Multiple Deprivation; EQ-5D 5 dimensions Euroqol (health related quality of life index); MI Myocardial Infarction; TIA Transient Ischaemic Attack

For the purposes of validation, it was also necessary to include the characteristics of patients with diagnosed diabetes in the HSE 2011 sample as a comparison with the projected HSE 2003 data. The characteristics of HSE 2011 including diagnosed diabetics are summarised in Table 56.

Table 56: Characteristics of the final sample from HSE 2011 (N=8610), including individuals with diagnosed diabetes

	Number	Percentage	
Male	3822	44.39	
White	7719	89.65	
IMD1 (least deprived)	1774	20.60	
IMD2	1823	21.17	
IMD3	1830	21.25	
IMD4	1597	18.55	
IMD5 (most deprived)	1586	18.42	
Non-smoker	4550	52.85	
Anti-hypertensive treatment	1544	17.93	
Statins	929	10.79	
Diagnosed Diabetes	572	6.64	
Cardiovascular Disease (CVD)	639	7.42	
SUBTYPES OF CVD	Number	Percentage of CVD	
Stable Angina	232	36.31	
Unstable Angina	83	12.99	
MI	137	21.44	
TIA	40	6.26	
Stroke	147	23.00	
	Mean	Standard Deviation	Median
Age (years)	49.64	18.70	49.00
BMI (kg/m^2)	27.39	5.36	26.64
Total Cholesterol (mmol/l)	5.42	1.07	5.40
HDL Cholesterol (mmol/l)	1.52	0.44	1.50
HbA1c (%)	5.73	0.78	5.60
Systolic Blood Pressure (mm Hg)	126.50	17.00	124.50
EQ-5D (TTO)	0.825	0.244	0.848
BMI Body Mass Index; IMD Index of Multiple Deprivation; EQ-5D 5 dimensions Euroqol (health related quality of life index); MI Myocardial Infarction; TIA Transient Ischaemic Attack			

Individuals from HSE 2003 were grouped into five different age bands (A=20-29, B=30-39, C=40-49, D=50-59, E=60-69), which were simulated separately. 50,000 individuals were generated for each age group then the model was run over a time course of 8 years to simulate the aging of individuals between 2003 and 2011. For each age group, separate sets of distribution statistics were obtained for HbA1c, BMI, systolic blood pressure, total and HDL cholesterol, diabetes prevalence and cardiovascular disease prevalence before and after simulation. This was compared with data extracted from equivalent age bands for HSE 2011 (A'=28-37, B'=38-47, C'=48-57, D'=58-67, E'=68-77).

13.2.2 Results & Discussion

Distribution statistics for each age group are presented in Table 57 -

Table 61. The differences between the HSE 2003 modelled projection and the HSE 2011 data are summarised as follows:

- There is a general tendency for the model to slightly under-predict mean HbA1c (Figure 12).
- There is a general over-prediction of systolic blood pressure in the model in all age groups (
- Figure 13).
- BMI is over-predicted in the model, particularly in younger age groups (
- Figure 14).
- The model slightly over-predicts cholesterol levels in the youngest age group, but under-predicts it for the older groups (Figure 15).
- EQ-5D is slightly over-predicted in the model (
- Figure 16).
- The model over-predicts diabetes diagnoses in all age groups apart from the middle one (age 48-47), where the HSE 2011 has an unexpected peak in diabetes diagnoses (Figure 17). The over-prediction is most evident in the youngest age groups.
- The model predicts cardiovascular disease quite accurately, although slightly over-predicts in the oldest age groups (
- Figure 18).

Table 57: Comparison of simulated outcomes from HSE 2003 with actual data from HSE 2011: Age group A - 20-29

A	**HSE 2003: Before simulation (n=1855) Age 20-29**			**HSE 2003: After simulation (n=49607) Age 28-37**			**HSE 2011: (n=1339) Age 28-37**		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Age (years)	24.8	2.9	25.0	32.8	2.8	33.0	32.5	2.9	33.0
HbA1c (%)	5.0	0.4	5.0	5.2	1.0	5.2	5.4	0.6	5.4
BMI kg/m^2	25.1	5.0	24.2	27.7	5.5	26.8	26.8	5.4	25.7
Systolic Blood Pressure (mm Hg)	119.0	11.9	119.0	125.2	15.6	125.3	118.2	12.6	117.5
Total Cholesterol (mmol/l)	4.9	1.0	4.8	5.3	0.9	5.3	5.0	1.0	4.9
HDL Cholesterol (mmol/l)	1.5	0.4	1.5	1.5	0.4	1.5	1.5	0.4	1.5
EQ-5D	0.929	0.153	1.000	0.901	0.212	1.000	0.894	0.186	1.000
	Number		Percentage	Number		Percentage	Number		Percentage
Diabetes	14		0.8	1448		2.9	16		1.2
Cardiovascular Disease	7		0.4	343		0.7	6		0.4
BMI Body Mass Index; SD Standard Deviation									

Table 58: Comparison of simulated outcomes from HSE 2003 with actual data from HSE 2011: Age group B - 30-39

B	HSE 2003: Before simulation (n=2788) Age 30-39			HSE 2003: After simulation (n=49382) Age 38-47			HSE 2011: (n=1595) Age 38-47		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Age (years)	34.7	2.9	35.0	42.7	2.9	43.0	42.5	2.9	42.0
HbA1c (%)	5.1	0.6	5.1	5.4	1.0	5.3	5.6	0.7	5.5
BMI kg/m^2	26.8	5.2	26.0	29.0	5.7	28.2	27.5	5.2	26.6
Systolic Blood Pressure (mm Hg)	120.0	12.6	119.0	127.4	15.1	126.9	121.0	13.9	120.0
Total Cholesterol (mmol/l)	5.4	1.1	5.3	5.4	0.9	5.4	5.4	0.9	5.3
HDL Cholesterol (mmol/l)	1.5	0.4	1.4	1.6	0.4	1.5	1.5	0.4	1.4
EQ-5D	0.911	0.178	1.000	0.887	0.223	1.000	0.849	0.226	1.000
	Number	Percentage		Number	Percentage		Number	Percentage	
Diabetes	37	1.3		2245	4.5		50	3.1	
Cardiovascular Disease	13	0.5		777	1.6		24	1.5	
BMI Body Mass Index; SD Standard Deviation									

Table 59: Comparison of simulated outcomes from HSE 2003 with actual data from HSE 2011: Age group C - 40-49

C	HSE 2003: Before simulation (n=2581) Age 40-49			HSE 2003: After simulation (n=48882) Age 48-57			HSE 2011: (n=1412) Age 48-57		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Age (years)	44.2	2.9	44.0	52.2	2.9	52.0	52.3	2.9	52.0
HbA1c (%)	5.3	0.8	5.2	5.6	1.1	5.4	5.8	0.9	5.6
BMI kg/m^2	27.4	5.2	26.7	29.1	5.7	28.4	28.4	5.5	27.5
Systolic Blood Pressure (mm Hg)	124.9	16.0	123.0	131.4	15.9	131.0	127.6	15.9	125.5
Total Cholesterol (mmol/l)	5.7	1.1	5.6	5.5	0.9	5.4	5.7	1.0	5.7
HDL Cholesterol (mmol/l)	1.5	0.4	1.5	1.6	0.4	1.6	1.6	0.5	1.5
EQ-5D	0.882	0.204	1.000	0.857	0.246	1.000	0.807	0.261	0.848
	Number	Percentage		Number	Percentage		Number	Percentage	
Diabetes	57	2.2		3286	6.7		108	7.6	
Cardiovascular Disease	46	1.8		2183	4.5		64	4.5	
BMI Body Mass Index; SD Standard Deviation									

Table 60: Comparison of simulated outcomes from HSE 2003 with actual data from HSE 2011: Age group D - 50-59

D	HSE 2003: Before simulation (n=2564) Age 50-59			HSE 2003: After simulation (n=47187) Age 58-67			HSE 2011: (n=1387) Age 58-67		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Age (years)	54.6	2.8	55.0	62.6	2.8	63.0	62.6	2.8	63.0
HbA1c (%)	5.4	0.7	5.3	5.7	1.1	5.6	5.9	0.8	5.8
BMI kg/m^2	27.9	4.9	27.2	29.1	5.4	28.4	28.3	5.2	27.6
Systolic Blood Pressure (mm Hg)	131.5	17.0	130.0	136.1	15.6	136.3	132.9	17.5	131.5
Total Cholesterol (mmol/l)	6.1	1.1	6.0	5.4	1.0	5.4	5.9	1.1	5.9
HDL Cholesterol (mmol/l)	1.6	0.4	1.5	1.7	0.4	1.6	1.6	0.5	1.5
EQ-5D	0.840	0.245	1.000	0.822	0.266	1.000	0.787	0.265	0.796
	Number	Percentage		Number	Percentage		Number	Percentage	
Diabetes	109	4.3		4814	10.2		121	8.7	
Cardiovascular Disease	157	6.1		5476	11.6		139	10.0	
BMI Body Mass Index; SD Standard Deviation									

Table 61: Comparison of simulated outcomes from HSE 2003 with actual data from HSE 2011: Age group E - 60-69

E	HSE 2003: Before simulation (n=1968) Age 60-69			HSE 2003: After simulation (n=43050) Age 68-77			HSE 2011: (n=989) Age 68-77		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Age (years)	64.2	2.9	64.0	72.1	2.9	72.0	72.2	2.8	72.0
HbA1c (%)	5.6	0.7	5.5	5.9	1.1	5.7	6.1	0.9	5.9
BMI kg/m^2	28.1	4.6	27.6	28.8	5.2	28.2	28.5	4.9	28.1
Systolic Blood Pressure (mm Hg)	137.8	18.9	136.0	139.7	16.3	139.5	134.5	17.0	133.0
Total Cholesterol (mmol/l)	6.2	1.0	6.2	5.2	1.1	5.2	5.8	1.1	5.8
HDL Cholesterol (mmol/l)	1.6	0.4	1.5	1.6	0.4	1.6	1.6	0.5	1.5
EQ-5D	0.813	0.250	0.848	0.790	0.272	0.802	0.744	0.278	0.796
	Number	Percentage		Number	Percentage		Number	Percentage	
Diabetes	165	8.4		6836	15.9		152	15.4	
Cardiovascular Disease	299	15.2		9741	22.6		199	20.1	
BMI Body Mass Index; SD Standard Deviation									

Figure 12: Comparison of actual mean HbA1c levels from different age groups within HSE 2011, with predicted mean HbA1c levels after 8 years simulation using HSE 2003 baseline data.

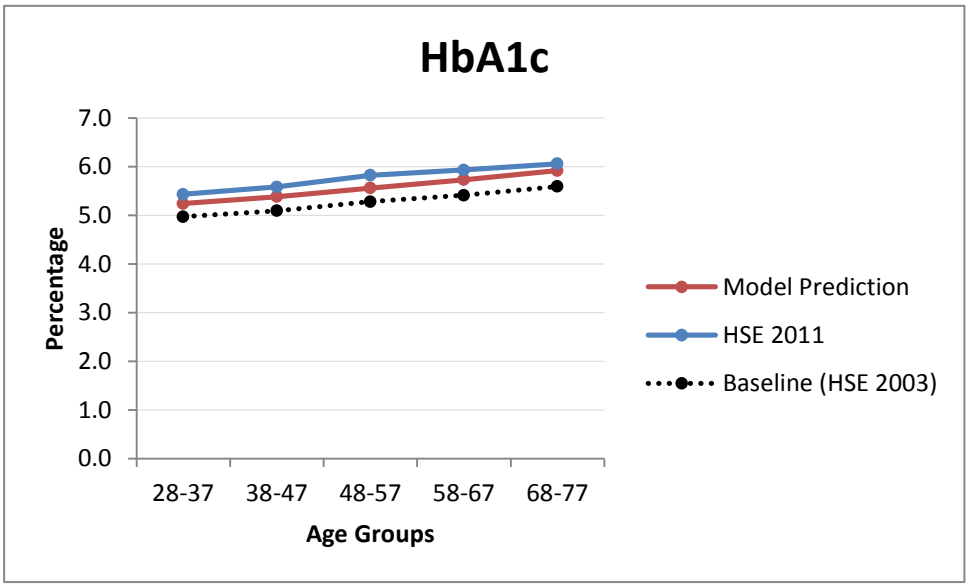


Figure 13: Comparison of actual mean systolic blood pressure from different age groups within HSE 2011, with predicted mean systolic blood pressure after 8 years simulation using HSE 2003 baseline data.

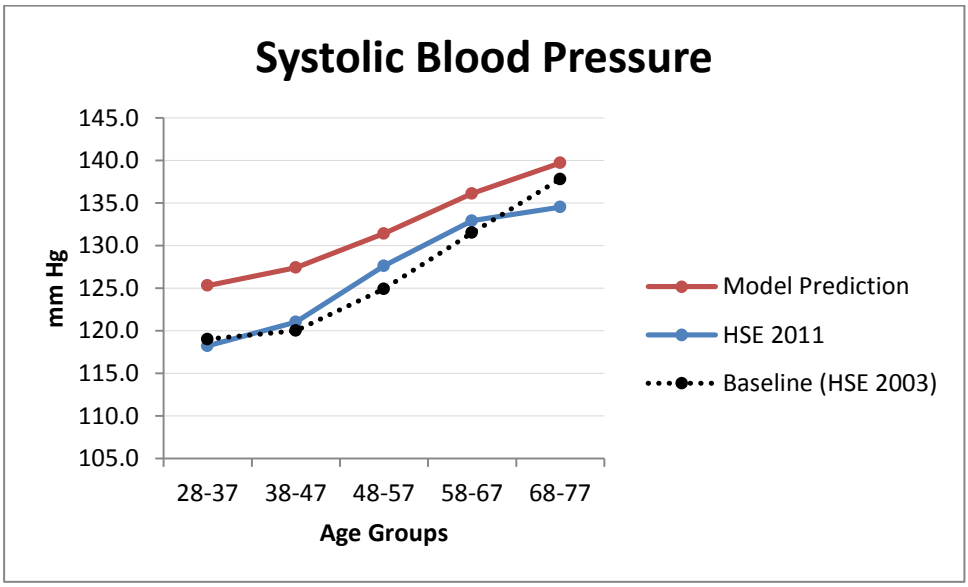


Figure 14: Comparison of actual mean BMI from different age groups within HSE 2011, with predicted mean BMI after 8 years simulation using HSE 2003 baseline data.

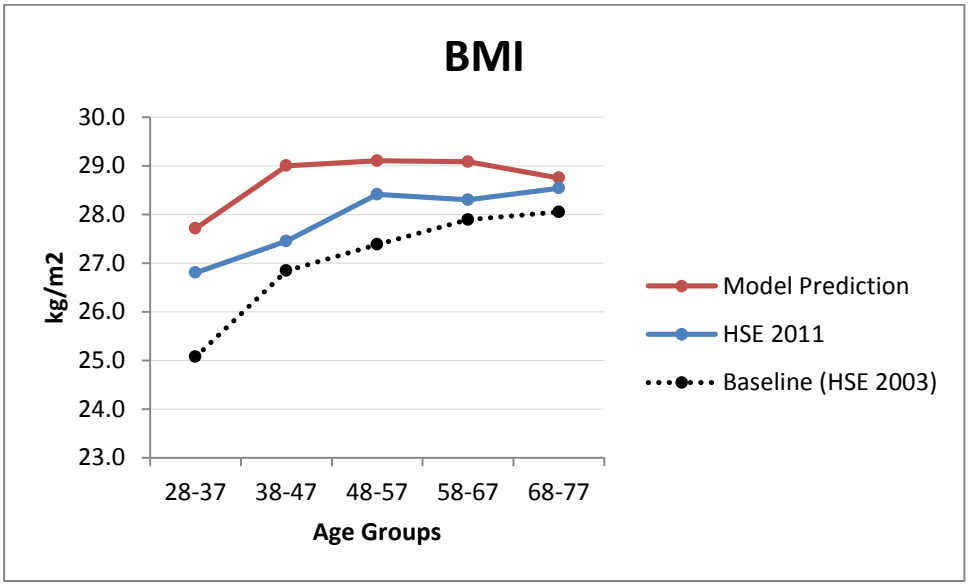


Figure 15: Comparison of actual mean total cholesterol from different age groups within HSE 2011, with predicted mean total cholesterol after 8 years simulation using HSE 2003 baseline data.

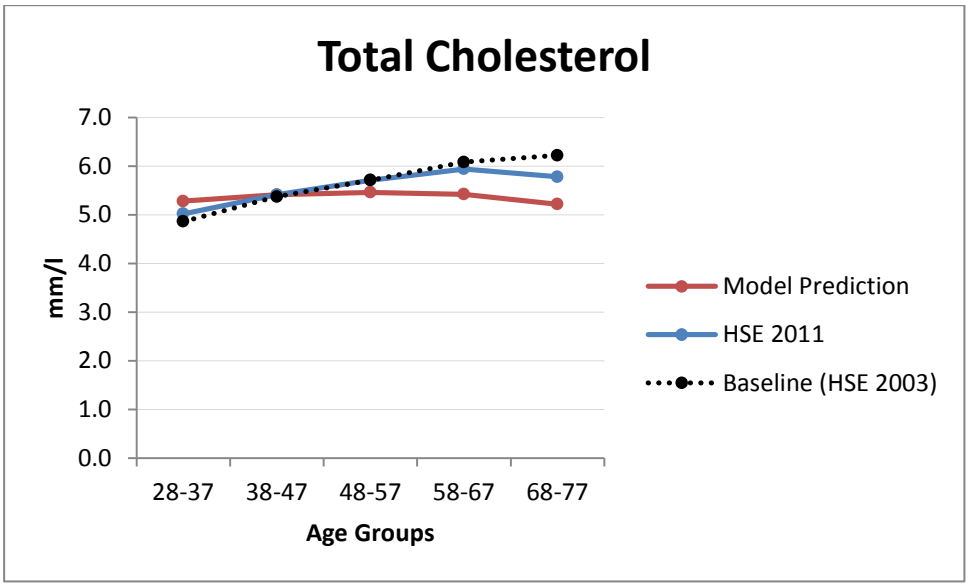


Figure 16: Comparison of actual mean EQ-5D values from different age groups within HSE 2011, with predicted mean EQ-5D values after 8 years simulation using HSE 2003 baseline data.

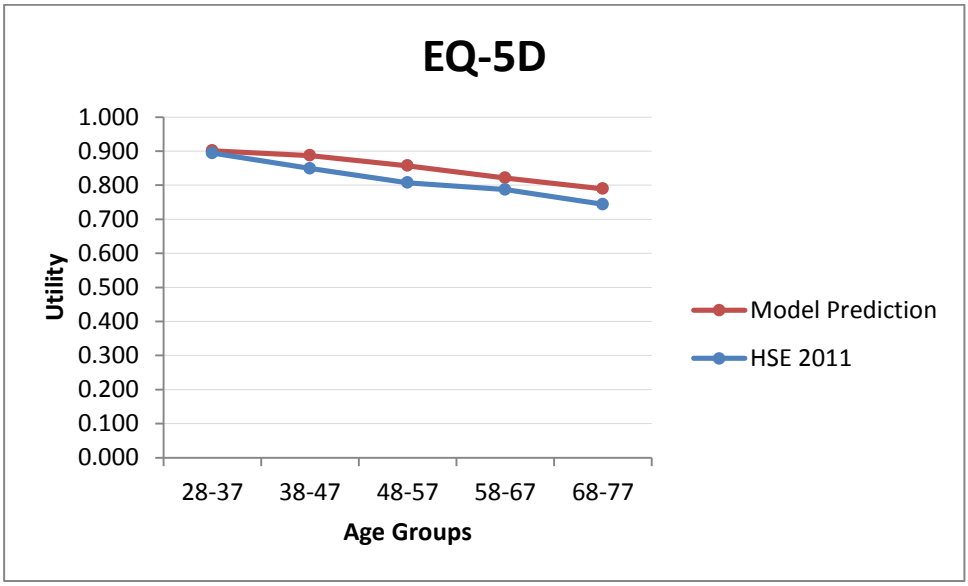


Figure 17: Comparison of actual diabetes prevalence from different age groups within HSE 2011, with predicted diabetes prevalence after 8 years simulation using HSE 2003 baseline data.

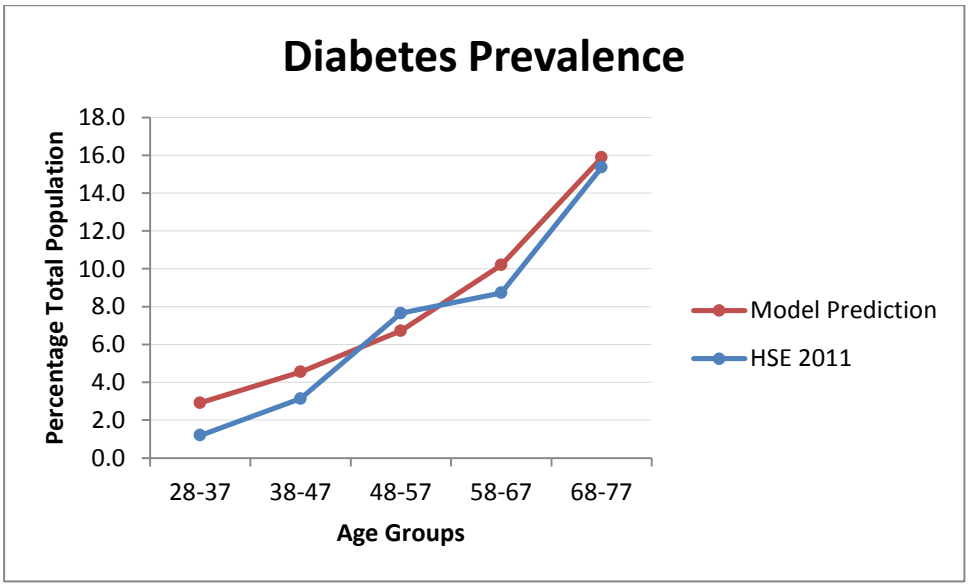
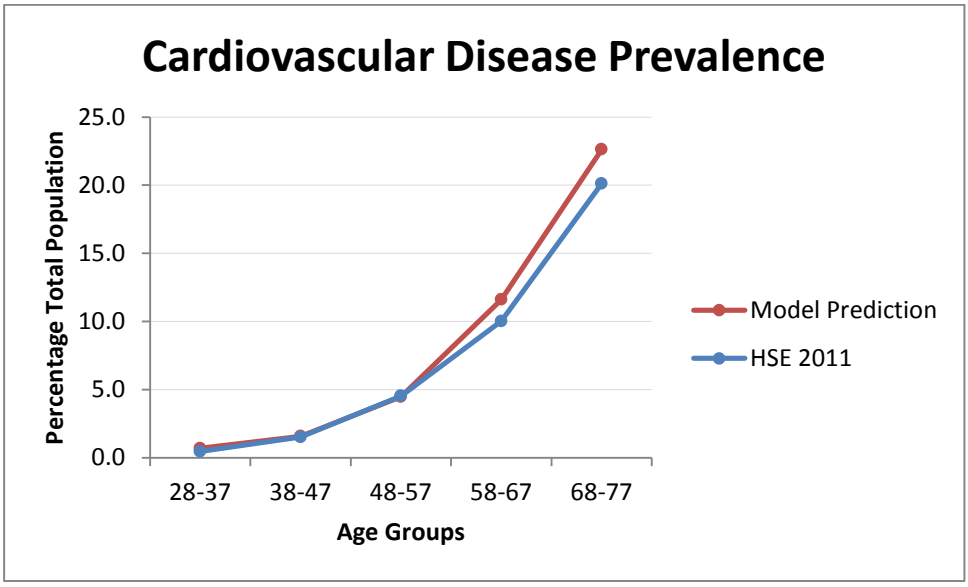


Figure 18: Comparison of actual cardiovascular disease prevalence from different age groups within HSE 2011, with predicted cardiovascular disease prevalence after 8 years simulation using HSE 2003 baseline data.



13.3 PREDICTING THE RESULTS OF THE ADDITION STUDY

The ADDITION trial monitored metabolic risk factors, cardiovascular disease and mortality of recruited patients. We compared the data reported in key publications from the ADDITION trial to observe whether similar outcomes were identified in the simulation. The objective was to evaluate the model's ability to simulate the results of a trial comparing an intensive intervention with usual care.

13.3.1 Methods

ADDITION is a cluster-randomised controlled trial of screening for type 2 diabetes that took place in the UK (Cambridge and Leicester), Denmark and the Netherlands (72). The trial aimed to evaluate the efficacy and cost-effectiveness of population based screening for type-2 diabetes, and the effect of an intensive intervention compared with usual care for people diagnosed with diabetes. The second aspect of the study was used for validation of the model. Evaluation of the intensive intervention was based on cardiovascular outcomes data from the entire ADDITION trial (73).

Baseline patient level data for the study was obtained from the ADDITION authors and used to populate the model. Evaluation of the model's ability to predict the effects of the intensive intervention was undertaken by comparing two versions of the model in which the individuals with

diabetes from the ADDITION-Europe study were subjected either to usual care or to an intensive intervention. In the ADDITION-Europe trial, intensive intervention included extra sessions with the GP and practice nurse, referral to a dietician, intensive optimisation of cholesterol levels, blood pressure and blood glucose over the course of the first year after diagnosis, use of a glucometer and a pack of educational materials for the patient. Many of these features could not be added directly to the model, so instead the difference in five year metabolic outcomes between the two trial arms was used. The only metabolic parameters that showed significant changes in the study after five years of intensive intervention when compared with usual care were SBP (-2.86 mm Hg), total cholesterol (-0.27 mmol/l) and HbA1c (-0.08%). For the purposes of simulation, these changes were applied for the first five years to all individuals in the intensive treatment arm of the model, and then cardiovascular outcomes were assessed.

13.3.2 Results & Discussion

In common with ADDITION-Cambridge, the SPHR Diabetes model does not predict a significant difference in mortality between screened and unscreened populations. Overall mortality rates are about one third higher in the Diabetes Prevention model than in the ADDITION-Cambridge study, indicating that the model is slightly over-predicting mortality.

The trajectories of all four metabolic parameters differ somewhat between the model and the ADDITION-Europe data (Table 62). In both arms of the ADDITION study, there is a reduction after diagnosis in the mean values of BMI, SBP, total cholesterol and HbA1c. However, in the SPHR Diabetes model there is an increase in HbA1c and BMI, whilst the reduction in SBP and total cholesterol is lower than that seen ADDITION-Europe. This indicates that the model may not be accurately reflecting improvements in health that occur as a consequence of normal care after diabetes diagnosis.

Table 62: Comparison of the Diabetes Prevention Model and the ADDITION-Europe study: metabolic data at baseline and after 5 years of follow-up/simulation

	SPHR Diabetes Model						**ADDITION-Europe Trial**							
	Before Simulation		**After Simulation**				**Before Treatment**				**After Treatment**			
	Both Arms (n=50,000)		Normal Care (n=50,000)		Intensive Intervention (n=50,000)		Normal Care (n=1,379)		Intensive Intervention (n=1,678)		Normal Care (n=1,285)		Intensive Intervention (n=1,574)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
BMI (kg/m^2)	31.6	5.5	32.3	5.8	32.3	5.8	31.6	5.6	31.6	5.6	31.0	5.6	31.1	5.7
SBP (mm Hg)	149.0	21.5	146.2	19.9	143.8	19.7	149.8	21.3	148.5	22.1	138.1	17.6	134.8	16.8

Total Cholesterol (mm/l)	5.5	1.1	4.8	1.2	4.5	1.2	5.6	1.2	5.5	1.1	4.4	0.9	4.2	0.9
HbA1c (%)	7.0	1.5	7.7	0.8	7.6	0.8	7.0	1.5	7.0	1.6	6.7	0.95	6.6	0.95
SPHR School for Public Health Research; ADDITION Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; BMI Body Mass Index; SBP Systolic Blood Pressure; HbA1c Glycated Haemoglobin; SD Standard Deviation														

In the ADDITION-Europe study, cardiovascular events, cardiovascular mortality and all-cause mortality were measured at the five year time point. Table 63 summarises these results and compares them with the simulated outcomes from the model. CVD and mortality are slightly over-predicted in both arms of the model compared with the trial, likely as a consequence of the higher metabolic values predicted by the model. However, the model predicts the slight but non-significant improvement in outcomes between the two arms of the trial fairly accurately.

Table 63: The ADDITION trial: comparison of simulated outcomes with the ADDITION-Europe study

	SPHR Diabetes Model				**ADDITION-Europe**			
	Normal Care	Intensive Intervention	Hazard Ratio		Normal Care	Intensive Intervention	Hazard Ratio	
	Percentage	Percentage	Mean	95% CI	Percentage	Percentage	Mean	95% CI
Cardiovascular events	9.9	9.5	0.96	0.93-1.00*	8.5	7.2	0.83	0.65-1.05
Cardiovascular mortality	2.8	2.7	0.95	0.88-1.02	1.6	1.5	0.88	0.51-1.51
All cause mortality	9.0	8.8	0.98	0.94-1.03	6.7	6.2	0.91	0.69-1.21
CI 95% Confidence Interval *The upper bound for the 95% CI is slightly below 1, meaning that the intervention is just significantly different at p=0.05								

13.4 UKPDS MAJOR EVENTS IN DIABETES

The UKPDS has recorded long-term outcomes for individuals with diabetes in the UK. It is currently used in many economic models of diabetes to predict the incidence of micro- and macro-vascular events as well as mortality in diabetes. In the SPHR diabetes model it is only used to estimate the incidence of renal failure, blindness, amputation and ulcers. This validation is hence an internal validation for the microvascular outcomes of the SPHR model, and an external validation for other outcomes. The aim was to evaluate if the incidence of microvascular, macrovascular and fatal complications of diabetes are similar to those estimated in the UKPDS outcomes model.

13.4.1 Methods

The UKPDS outcomes model 2 reports the simulated percentage of individuals with major events after 10 years from the UKPDS model (19). The SPHR diabetes model was tested by generating 50,000 individuals aged between 25 and 65 with diabetes from the HSE 2011. The model was run over a time course of 10 years to obtain figures for 10 year prevalence.

13.4.2 Results & Discussion

The incidences of major events in the UKPDS Outcomes model and the SPHR diabetes model are reported in Table 64.

Table 64: Major events in the UKPDS and SPHR simulation

10 year prevalence (%)	UKPDS Outcomes Model 2 (N=3984)	SPHR model (N=50000)
Renal Failure	0.5	0.4
Ulcer	1.8	1.8
Amputation	1.5	1.9
2nd Amputation	0.44	0.6
Blindness	2.9	3.0
MI	9.9	5.1
Stroke	6.2	6.1
Heart Failure	4	5.1
Death	22.5	13.9

The validation indicates that the SPHR Diabetes model predicts very similar 10 year prevalence values to the UKPDS outcomes model for those outcomes which are determined through the UKPDS itself. The exception to this is amputation, which is over-predicted in the SPHR model compared with the UKPDS model. In the UKPDS outcomes model, amputation is specified using a different algorithm for people with a pre-existing ulcer or for those without. To simplify things, the SPHR diabetes model uses a single algorithm to specify amputation, with the addition of an extra parameter for pre-existing ulcer estimated from the difference in the hazard ratio for amputation between individuals with or without pre-existing ulcer in the UKPDS. This is likely to be the source of the discrepancy in estimation of amputation prevalence, as alteration of this parameter has a large effect on prevalence of amputation (data not shown). However, overall this validation indicates that the UKPDS model has been correctly implemented in the SPHR Diabetes model.

The UKPDS model predicts a higher incidence of MI than is simulated in the SPHR model using the QRISK algorithm to predict first cardiovascular event. Other studies have found that the UKPDS Outcomes model v1 predicts higher risks for these events than are observed in other datasets (74), although the new UKPDS outcomes model v2 has been shown to predict lower incidence of these

outcomes than the UKPDS model v1. The lower still prediction of the SPHR model may reflect recent medical developments. Alternatively, given that the predictions for stroke are fairly accurate, the discrepancy may be in the way that CVD events are distributed rather than the number of CVD events per se.

The incidence of heart failure is higher in the SPHR simulation compared with the UKPDS. The incidence of congestive heart failure is simulated from the Framingham risk algorithm in men and women. It is possible that the higher incidence of heart failure is due to differences in the risk of heart failure in the UK and US. We have sought a UK algorithm for estimating the risk of congestive heart failure, however none were found. We considered whether it would be best to change the model to use the UKPDS equation only in diabetic patients. However, we dismissed this idea because this would assume that non-diabetics were not at risk of congestive heart failure. However, it is likely that the SPHR model currently over-estimates the incidence of congestive heart failure.

Finally, mortality is under-predicted in the SPHR model compared with the UKPDS outcomes model. One potential cause of this discrepancy is the incorporation in the SPHR model of improvements in diabetes care that may have been made since the UKPDS trial. Given that the SPHR model actually over-estimates mortality in some of the other validations (e.g. ADDITION) this is probably not a concern.

14 DIABETES PREVENTION INTERVENTIONS

14.1 IDENTIFYING INTERVENTIONS

We divided the potential interventions into the following population groups:

a) For the general population to reduce risk factors for diabetes;
b) For people with non-diabetic hyperglycaemia;
c) For people within the general population who are at high risk of developing non-diabetic hyperglycaemia and type 2 diabetes, including identification and risk assessment (eg. overweight or obese, low socioeconomic status, South Asian or those with CVD).

Systematic reviews produced for NICE projects already exist for points a and b (75;76). We have undertaken a literature review for population-level interventions (point c). This was limited to a review of systematic reviews due to the large number of studies in this area. We used interventions identified within a stakeholder workshop to help develop the searches. We did not identify any evidence for walking and cycling/ transport policy interventions within our review of systematic reviews. However, an existing NICE report describes a recent review of this area (77).

All of the above reviews are made up of heterogeneous studies in terms of population, intervention, comparator, outcomes and country. Meta-analysis was not appropriate for many of the studies, therefore the effectiveness and cost of each intervention assessed was generally based upon one specific study. Table 65 shows the interventions we have identified for possible comparison within the model. It also lists interventions which we have identified, but which were not considered to be relevant or have studies of sufficient quality, based upon the criteria below:

<u>Intervention grouping level</u>

1. Intervention is not generalisable to the UK in any of the studies due to substantial differences in current practice (e.g. transport infrastructure in the Netherlands), or populations (e.g. intervention provided to only a Hispanic population);
2. Intervention is not effective in any of the studies within the systematic reviews;
3. Intervention already exists as standard practice within the UK.

Individual study level

1. No outcomes reported related to diet, exercise or blood glucose levels (e.g. only impact upon traffic congestion reported for transport policy), or only subjective outcomes reported (e.g. only increased knowledge about diet, or intention to exercise reported);
2. Only poor evidence exists around intervention effectiveness due to:
    a. short term follow up;
    b. poor study design;
    c. poor reporting of the study (e.g. the intervention, comparator, population, outcomes or study design are unclear).

Table 65: Types of interventions considered for inclusion in the model

Intervention Coverage	Selected for Inclusion	Selected for Exclusion
General Population (Indiscriminate National Policy)	Taxation	Agricultural Policy
Communities	Workplace	Transport policy
	Retailer policy	
	Community education programme	
High-risk individuals	Non-diabetic hyperglycaemic (including exploring frequency of repeat tests)	Children/ early years / jobseekers/ gestational diabetes/ ethnicity

Table 66 shows key details of the studies which were considered for analysis within the model. No effectiveness evidence was identified within our search for systematic reviews around the following interventions:

1. Affordable access to healthier foods ;
2. Change in agricultural policy;
3. Work with supermarkets in promoting healthy food;
4. Increase green space;
5. Vegan lifestyle.

Table 66: Key Details of Studies

Author (year)	Intervention (incl. length of time provided & maintenance)	Population/ setting	Follow up period	Sample size	Study type	Outcomes	Effectiveness
Oaks (2005) in *Thow et al (2010)(78)*	State tax of 5.5% of soft drinks and snacks.	USA	15 years	Not stated in SR	Eco-logical	Obesity prevalence	No relationship.
Kim & Kawachi (2006) in *Thow et al (2010)(78)*	Change in state taxes on soft drinks or snack foods.	USA	Not stated in systematic review (SR)	Not stated in SR	Eco-logical	Obesity prevalence	No association with obesity point prevalence. With no tax more than 4 times as likely to experience a high relative increase in obesity prevalence; those that repealed a tax were more than 13 times as likely.
Fletcher et al. (2011)(79)	State soft drinks tax, average 3%.	USA	16 years	Not stated in SR	Eco-logical	BMI	1% tax decreased BMI by 0.003 points.
Jenum et al. (2003, 2006) in *Sheill et al (2008)(80)*	Community-based health education plus environmental change plus counselling. Intervention duration was 3 years.	Norway, community setting (2 multi-ethnic districts of Oslo)	Not stated in SR	Not stated in SR	Inter-vention	Physical activity (measured by self-report); BMI	Increase in PA in I (+9.5%, p<0.01) compared to minor changes in C (exact change not reported in original study). Smaller increase in BMI in I compared to C (exact difference not stated in SR).
Howard et al. (2006) in *Mernagh et al (2010)(81)*	Community based health promotion to promote a decrease in fat intake and increases in vegetable, fruit, and grain consumption. 18 group sessions in year 1, then 4 per year for the duration of the trial.	USA, community-based from 4 clinical centres, 50-79 years old	Mean follow-up 7.5 years, change at 1 year also reported in SR	48, 835 women	RCT	Change in body weight; BMI; waist circumference	Change at 1 year Weight I: -2.2kg (p<0.001) C: No change At the end of follow-up differences were observed between I & C in weight (0.5kg, p=0.01), BMI (0.3kg/m^2, p<0.001) and waist circumference (0.3cm, p=0.04).
Kuller et al. (2001) & Simkin-Silverman	Community based health promotion. Cognitive-behavioural programme with duration of 5 years.	USA, community-based, 44-50 years old	6, 18, 30, 42 and 54 months after randomis-ation	Up to 535 women	RCT	Weight; BMI; Body fat (%); waist circumference	Change at 54 months (from baseline) Weight I: 0.08 C: 2.36 (p<0.01) BMI I: 0.05±2.0 C: 0.96±1.8 (p<0.001) Body fat I: -0.5±4.1 C: 1.1±3.9

Author (year)	Intervention (incl. length of time provided & maintenance)	Population/ setting	Follow up period	Sample size	Study type	Outcomes	Effectiveness
et al. (2003) in *Mernagh et al (2010)*							(p<0.01) Waist circumference I: -2.90 C: -0.46 (p<0.01)
Hivert et al. (2007)(82)	Small-group interactive seminars to educate students and modify diet/ exercise behaviour. Fortnightly for the first 2 months of the semester, monthly for the rest of the 2 years (total = 23 seminars)	Canada, university students	1 year & 2 years	I: 58 C:57	RCT	Weight (kg); BMI	Change at 2 years Weight I: -0.6±0.5 C: +0.7±0.6 (p<0.05) BMI I: -0.3±0.2 C: +0.2±0.2 (p<0.05)
Holdsworth (2004)(83)	Environmental (low intensity) - changes to cafeteria menus. Duration of intervention was 6 months	UK, workplace-based, 4 intervention workplaces and 2 control	1 year	577 employees at 6 worksites I: 453 C: 124	Quasi-experi-mental study	Dietary habits measured using a food frequency questionnaire	Vegetable consumption I: 27% made +ve changes C: 19% made +ve changes Fruit consumption I: 37% made +ve changes C: 25% made +ve changes
Emmons (1999) in *Mhurchu et al (2010)(84)*	Workplace based environmental change – risk factor education programmes and changes to nutrition policy and practice.	USA, workplace-based intervention	130 weeks	397 employees at 22 worksites	Cluster RCT	Total fat, fibre and fruit and vegetable intake (FFQ)	Total fat I: -2.2% C: -1.8% Fruit & vegetable servings/day I: +0.2 C: -0.2
Sorensen (2003) in *Mhurchu et al (2010)(84)*	Workplace based environmental change – worker participation in programme planning, worksite environmental changes & individual behaviour change programmes	USA, workplace-based intervention	104 weeks	5156 employees at 15 manu-facturing worksites	Cluster RCT	Dietary intake (fruit and vegetable screening questionnaire)	Fruit and vegetable servings/day I: -0.1 (7 sites) C: +0.05 (8 sites)
Connell (1995) *(in Verweij et al. (2011)(85)*	Workplace based health checks – 3 intervention groups and control. Ia: Health promotion + Health risk appraisal (HRA) booklet, Ib: Health promotion, Ic: HRA booklet, C: HRA.	USA, workplace-based intervention with office workers, nurses & instructional staff	1 year	801 employees Ia: 142 Ib: 248 Ic: 253 C: 158	Cluster RCT	BMI	Significant decrease in Ia, Ib, Ic vs. C: ß: −0.05 (p < 0.01), ß: −0.05 (p < 0.01), ß: −0.04 (p < 0.05) vs. ß: 0
Hanlon et al. (1995, 1998) *(in Maes et*	Workplace based health checks. Health checks followed by a health education package that included an interview backed up by written	Scotland	5 months & 1 year	1,632	RCT	BMI; Diet; Physical activity	No significant effect on BMI or physical activity. Effect on diet.

Author (year)	Intervention (incl. length of time provided & maintenance)	Population/ setting	Follow up period	Sample size	Study type	Outcomes	Effectiveness
al. 2011(86))	information and feedback on risks. Intervention duration 12 months.						
Aldana (2005) *(in Anderson et al. 2009(87))*	Workplace based health education/promotion – lectures, pedometers, books, shop tours, cooking demonstrations, health knowledge test, compared to no contact. Intervention duration 1.5 months, maintenance not reported.	USA, workplace based intervention targeted to care provider employees.	6 months	145	RCT	Weight(kg)	Significant decrease in I compared with C. I: -4.4 C:-1.0 (p<0.0001)
Talvi (1999) *(in Maes et al. 2011(86))*	Workplace based health checks and education/promotion - employees were offered special counselling according to their individual needs in 9 target areas. Intervention duration different for each health promotion action.	Finland, oil refinery workers, one rig with intervention compared to one rig with minimal intervention	3 years	I: 412 C: 473	Non-RCT	BMI, Diet, Physical activity habits	No effect on BMI or diet. Effect in the targeted direction on physical activity.
Elberson (2001) *(in Anderson et al. 2009(87))*	Workplace based health checks and education/promotion – Ia (structured): planned exercise classes, Ib (unstructured): access to gym, no classes, Ic: all of the above. Intervention duration 12 months, maintenance not reported.	USA, workplace based intervention.	1 year	374	Retro-spective cohort	BMI	Structured: Baseline BMI 25.01, change at 12 months -0.57 (within group p=0.185) Unstructured: Baseline BMI 27.97, change at 12 months +0.30 (within group p=0.001)
Gomel (1993) *(in Anderson et al. 2009(87))*	Workplace-based health checks & education/promotion - risk assessment & feedback on risk factor profile; up to 6 life-style counselling sessions over a 10-week period; incentives incl. lottery tickets & money for achieving goals. Intervention 6 months.	Australia, workplace based intervention with ambulance employees	1 year	431	Cluster RCT	BMI	No difference between intervention groups and control.
Sloman et al 2010(88)	Sustainable travel towns which implemented intensive town wide Smarter Choice Programmes to encourage use of non-car options; bus use, cycling and walking, and less single occupancy cars	United Kingdom	30 Months	12,000	Eco-logical/ Cluster RCT	Cycle trips per head, walking trips per head	Cycle trips per head grew by 26-30%. Comparison towns cycle trips decreased. Walking trips per head grew substantially by 10-13% compared to a national decline in similar towns.

Author (year)	Intervention (incl. length of time provided & maintenance)	Population/ setting	Follow up period	Sample size	Study type	Outcomes	Effectiveness
Baker et al. (2008) (89)	Walking programme with goals set in steps using an open pedometer for feedback	United Kingdom	52 Weeks	63	RCT	Step counts	Intervention (77%) vs.Control (54%) achieved week 4 goals (X2= 4.752, p=0.03) Significant decrease in count week 16-52.
DPS, Finland *(in Jones et al.)*	Control group: lifestyle advice was given as 'standard care counselling' at baseline. Intensive intervention group: given individualised, detailed dietary counselling, with 7 sessions during the first year & every 3 months thereafter.	Finland, with IGT. All were middle-aged (40–64 years) & BMI>25 kg/m2 at baseline.	3 years	522 (172 men and 350 women)	RCT	Multiple outcomes including BMI, weight, waist circumference and incidence of diabetes.	During the first three years of the study, 22 subjects (9%) in the intervention group and 51 (20%) in the control group developed diabetes (p= 0.0001, 2 test).
Ashfield-Watt et al. (2007)(90)	Initiatives that involved building community networks to increase fruit and vegetable intakes in five deprived communities by improving awareness, attitudes & access to fresh fruits & vegetables. Intervention duration 12 months.	Residents in 5 UK deprived areas	1 year	1554	Non-RCT	Fruit & vegetable intake, measured using a short dietary/ attitude questionnaire	Median total fruit and vegetable intakes decreased significantly over one year in the control group (-0.4 portions per day, $p<0.01$), but there was no significant change in total fruit and vegetable intakes in the intervention group.
Bremner et al. (2006)(91)	'5-a-day' community intervention to increase fruit & vegetable intake, including home delivery & transport links, voucher schemes, media campaigns, growing & cookery skills & encouraging networking in groups involved in promoting healthy eating. Duration not specified but at least 1 year.	Residents in 66 (former) UK health authorities with the highest levels of deprivation and poorest health status.	Baseline (pre-test) was in 2003 and follow-up (post-test) was in 2005.	98,640	Non-RCT	Fruit & vegetable intake and knowledge	Fruit consumption (unadjusted): Experimental and control group respondents were more likely to consume fruit as a between meal snack at follow-up (significance not reported). Vegetable consumption (unadjusted): Experimental and control group respondents were more likely to consume vegetables as portions with main meals at follow-up (significance not reported).
Wrieden et al. (2007)(92)	Informal food skills and food education sessions, following a 'CookWell' manual. Intervention duration 7 months.	Adults in rural & urban communities in Scotland aged 30-55 in lower SES groups who do not exercise often.	2 & 6 months	93	Non-RCT	Fruit & vegetable intake; other eating habits (e.g. tuna and total fish intake)	At T2, a mean change equivalent to one portion a week was seen in the intervention group for fruit (P= 0.047), but no other significant changes were seen. This change was not sustained and there was no significant difference between the intervention and comparison groups (T1–T3).
McKellar et al. (2007)(93)	Mediterranean-type diet intervention involving a cookery course, weekly 2-hour sessions. Intervention duration 6 weeks.	Females with rheumatoid arthritis living in urban areas of deprivation in Glasgow.	3 & 6 month	130	Non-RCT	Fruit & vegetable intake; weight control; consumption of high fat foods; physiological measurements	Evaluation of cardiovascular risk factors showed a significant drop in systolic blood pressure by an average of 4 mm Hg in the intervention group (p=0.016), while the control group showed no change. Consumption of fruit, vegetables & legumes was below the recommended minimum of 5 portions a

Author (year)	Intervention (incl. length of time provided & maintenance)	Population/ setting	Follow up period	Sample size	Study type	Outcomes	Effectiveness
							day, in both groups at baseline. By 3 months this had improved significantly in the intervention group who were attending cooking classes. This group also had a significant improvement in ratio of monounsaturated :saturated fats consumed.
Cummins et al. (2008)(94)	Provision of a new food hypermarket within the intervention area (natural public health intervention). Intervention duration 1 year.	Residents of households in two deprived areas of Glasgow.	1 year	603	Pros-pective cohort study	Fruit and vegetable consumption, self reported & psychological health, & socio-demographic variables.	Weak evidence for an effect of the intervention on mean fruit consumption (-0.03, 95% CI -0.25 to 0.30), mean vegetable consumption (-0.11, 95% CI -0.44 to 0.22), and fruit and vegetables combined (-0.10, 95% CI -0.59 to 0.40). Odds ratios & 95% confidence intervals of reporting fair to poor self-reported health and poor psychological health for the intervention compared with comparison community.
Gray et al (2009)(95)	Camelon weight management group programme, tailored to men, incorporating advice on physical activity, diet and alcohol consumption. Intervention duration 12 weeks.	Male residents of a deprived community in Scotland.	Pre-programme, short-term (12-week, immediately post-programme, long-term (1 to 49 months after programme)	110	Case series	Weight loss, waist circumference reduction, BMI reduction.	Short-term (end of 12 weeks programme) weight loss for completers was a mean weight loss of 4.98 kg. 44.3% achieved a weight loss of 5% to 10%. Long-term weight loss maintained an average 3.7% weight loss (range = 32.6 weight loss to 25.6% weight gain) compared with their baseline weight (no further information on what this actually meant). Compared with pre-programme weight, 14 weighed less, 2 were stable (±0.5 kg) 4 weighed more; no further detail reported.
Schuit et al. (2006) (96)	Over 5 years 790 interventions were implemented in the local population and targeted groups.	Netherlands	5 years	3895	Cohort study	BMI, waist circumference, blood pressure, serum glucose & serum total & HDL cholesterol	Schuit et al. (2006) (96)

The interventions options were presented to a Stakeholder group in March 2013. Discussion within the workshop suggested that given the current rate of change in this area, it was important that the model was flexible and not fixed within a static environment to prevent it from becoming outdated very quickly. It was also suggested that the choice of interventions should not be limited by the evidence available. The NHS Health Checks should be incorporated into the model, but should be considered for possible disinvestment. The group suggested that we construct a set of interventions based on a stratification of intervention intensity and population risk. The spectrum of intervention types discussed were taxation, community education, agricultural policy, food retailer interventions, physical activity for transport, workplace interventions and risk assessment. Given the constraints of the project we needed to limit the interventions included within the final model, and based upon the discussion within the workshop we selected a subset of interventions for inclusion in the model.

At the national level we opted to use a taxation policy.

At the community level we included workplace interventions, retailer policy and community education programmes. Local transport policy was excluded because the final model did not include physical activity, therefore the modelling framework would not improve upon previous evaluations of physical activity interventions (97).

At the individual level we initially planned to consider three targeted groups: (1) those identified as high-risk through individual risk assessment; (2) women with gestational diabetes; (3) ethnic groups. In the final analysis this was restricted to those identified at high risk through an individual risk assessment. However, we also performed a subgroup analysis which included individuals from certain ethnic groups as one of the high risk subgroups. Of the other targeted groups identified in the stakeholder meeting we opted to exclude children (and other primordial prevention rather than primary prevention), due to the added complexity of modelling a life course, particularly as disease progression is based on the Whitehall cohort (adults only). This is an area for further research. Jobseekers and attendees at food banks were not included in the primary analysis since the workshop discussion suggested that, whilst these groups are important, the three groups above should be prioritised. However, the model is sufficiently flexible to enable these to be explored in the future without requiring many changes.

Within the intervention types listed in Table 65 there are a large number of interventions that could be implemented. For our taxation policy we focussed on the taxation of soft drinks. During the project a high quality modelling study of soft drinks taxation in the UK was published. This provided sufficient evidence about the effectiveness of this policy, to implement the analysis in the model

(98). For the workplace intervention, we decided to focus on environmental changes, rather than health checks or education programmes (99). This ensured that a broad range of intervention types were considered, rather than implementing similar interventions in different sub-groups of the population. For the retailer policy, we modelled the opening of a large supermarket in a deprived area to improve access to fruit and vegetables, rather than focusing on within store merchandising of healthy foods. We identified a large study of a new store opening in Leeds to derive this evidence (100). We also identified studies from three community education programmes, including promoting weight management in men from deprived areas, health promotion in ethnically diverse urban areas and increasing fruit and vegetable consumption in deprived areas (101-103).

The high risk identification strategy targeting non-diabetic hyperglycaemia is a translation programme which would be feasible in practice. A study collaborator provided us with results from a systematic review of translational diabetes prevention programmes in high risk individuals (104). Identification of individuals was based upon the NHS Health Checks. However, flexibility was built into the model to allow for variations upon this.

14.2 INTERVENTION A: SOFT-DRINKS TAX

14.2.1 Effectiveness

The effect of soft drinks taxation on BMI by age group and income has been estimated in a comprehensive modelling exercise (98). The effect on people aged 50 or above is not significant so was assumed to be zero in the base case, but allowed to vary in the probabilistic sensitivity analysis. These estimates were implemented straight into the Diabetes model without further assumptions.

Table 67: Change in BMI by age given a 20% tax on sugar sweetened soft drinks (98)

	16-29 year olds	30-49 year olds	>=50 year olds
Change in BMI	-0.23 (-0.28 to -0.20)	-0.05 (-0.07 to -0.03)	0.01 (-0.01 to 0.03)

14.2.2 Population

The soft drinks taxation policy was applied to the general population; however the effectiveness of the intervention was conditional on the age of the individual at the start of the model.

14.2.3 Cost

The soft drinks taxation was assumed to not incur any costs. In theory, taxation would probably generate additional income, but we decided that it was outside the scope of the model to estimate its value.

14.3 INTERVENTION B: FRUIT AND VEGETABLE RETAIL PROVISION

14.3.1 Effectiveness

The Wrigley Leeds Tesco store opening was studied to observe the impact on the local community's fruit and vegetable consumption. The results informed the formulation of a regression model to predict change in fruit and veg after the store opened (100). Using the data reported in this study it was estimated that the mean increase in fruit and vegetables consumed was 0.162 portions per day[2].

The evidence for relating a change in fruit and vegetable consumption to a change in BMI is contradictory. We instead decided to relate changes in fruit and vegetable consumption directly to changes in HbA1c and systolic blood pressure using data from two different studies.

A cross-sectional analysis from the European Prospective Investigation into Cancer and Nutrition in Norfolk (EPIC-Norfolk) investigated how plasma vitamin C levels relate to HbA1c (105). The study reported the results of a linear regression, which shows that a 20µmol/l increase in plasma vitamin C is associated with a reduction in HbA1c of 0.08% for men and 0.05% for women, when adjusted for possible confounders including age and BMI. According to the study, a 20µmol/l increase in plasma vitamin C is equivalent to eating an extra orange per day. Assuming that the vitamin C in one orange is equivalent to the vitamin C in one portion of fruit or veg, and taking the weighted mean for men and women, we estimated that the retail policy would reduce HbA1c by an average of 0.010% per person.

A randomised controlled clinical trial testing the efficacy of an intervention promoting consumption of fruit and vegetables, found that there was a mean increase of 1.4 portions of fruit or vegetables consumed per day in the intervention group compared with the control group (106). This was associated with a reduction in systolic blood pressure of 4.0 mm Hg. Implementing this value straight into the diabetes model suggested that the retail policy would reduce blood pressure by 0.46 mm Hg.

[2] 46% of individuals switch to the new store with an incremental change in fruit and veg of 0.252. 7.8% switch from a budget store with an additional incremental change of 0.595.

14.3.2 Population

We applied this intervention to individuals in the highest quintile of the Townsend deprivation score, as these people are more likely to have inadequate access to fruit and vegetable provision.

14.3.3 Costs

The costs of this intervention were assumed to be incurred by the private sector and were not included in the analysis. Therefore, the evaluation only considered the health gains of the policy.

14.4 INTERVENTION C: WORKSITE ENVIRONMENT

14.4.1 Effectiveness

The Heartbeat Award scheme implemented healthy food options in cafeterias in the workplace and observed the impact on workers dietary patterns before and after the menu changes (99). The results of the study reported the proportion of individuals who made a positive switch to healthier food options after the changes in the workplace café. The proportions were compared between participating and non-participating workplaces using odds ratios. The four food groups that demonstrated a significant improvement over the study were sweet puddings, fried food, fruit and milk. The magnitude of improvement or worsening was not reported in the statistical analysis. The benefits of the work place intervention were measured in terms of the increase in fruit consumption and the switching of milk from a higher to a lower fat choice. We decided not to account for the reduction in fried food and sweet puddings due to a lack of evidence about nutritional content and food substitution.

The study did not estimate the mean change in fruit and vegetable consumption for the 11.9% of individuals who made a positive change. Therefore, it was assumed that they increased their consumption of fruit by one portion per day. We used the same assumptions and evidence to translate change in fruit and vegetable consumption to HbA1c and systolic blood pressure that were described for the retail provision intervention (105;106); this translated to a mean reduction in HbA1c of 0.063%, and in systolic blood pressure of 2.86 mm Hg for the 11.9% who were reported as eating more fruit and vegetables.

8.9% of individuals were reported as switching their milk choice from a higher fat to a lower fat option. Milk choices were not documented, so it was assumed that individuals switched from full fat milk to lower fat milk choices based on population-wide consumption of milk types (Table 68).

Calorie and fat content in different milk types was obtained from the Dairy Council (107). The quantity of milk drunk by each individual was assumed to be the population mean of 1506ml per week; this value was obtained from the Defra Family Food Survey 2012 (108).

Table 68: Nutritional content and consumption of different milk types (107)

Type of Milk	Fat Content (g/100ml)	Saturated Fat (g/100ml)	Calories (per 100ml)	Consumption (% consumers)
Full fat	4.0	2.6	68	23
Semi-skimmed	1.8	1.1	47	63
Skimmed	0.3	0.1	35	6
1%	1.0	No data	No data	No data

It was assumed that fat consumption would reduce due to milk switching by the mean change in fat content of full fat milk, compared with the weighted mean of lower fat alternatives. The mean reduction in fat consumption was calculated as 2.33g per 100ml of milk, or 5.01g per day.

Evidence was available from a cross-sectional study from EPIC-Norfolk to relate HbA1c levels to dietary fat consumption as a percentage of daily calories (109). We estimated that mean daily fat intake would drop from 32% to 29.8% of total daily calories as a result of milk switching, which corresponds to a reduction in HbA1c of 0.0156%.

Table 69: Dietary fat consumption and changes in HbA1c (109)

Independent Variable	**Regression coefficients (per 1 SD change in fat)**	**P**	**Mean daily intake (weighted male and female)**	**Standard Deviation**
Total Fat	0.0420	<0.001	32%	5.9%
Saturated Fat	0.0476	<0.001	12.5%	3.4%
Ratio Polyunsaturated Fat to Saturated Fat	-0.0200	0.013	0.51	0.22

14.4.2 Population

We applied this intervention to randomly selected individuals in employment. We assumed that 20% of workplaces in the population have canteens which adopt the intervention. However, only 11.9% of individuals in the workplace were assumed to respond positively to the programme in terms of fruit consumption, and 8.9% of individuals were assumed to respond positively in terms of milk switching. Random selection of individuals was independent for the two responses.

14.4.3 Costs

The cost of the Heartbeat Award Scheme includes the cost of the environmental health officer to visit the premises and inspect menu changes for healthy eating options. The health authority also issue promotional material and certificates to the workplace and these printing costs were factored into the overall intervention cost (Table 70).

Table 70: Cost estimates for the Heartbeat Award Scheme

Cost type	Description	Unit cost
Personnel costs	Environment health officer to inspect establishments, and assess menus. A week of work per workplace valued at the UK average salary.	£474
Printing costs	Posters, leaflets, door stickers, flyers, certificates	£25
Total Cost per workplace		£499
Per capita cost (assuming 100 employees per workplace)		£4.99

14.5 INTERVENTION D: COMMUNITY EDUCATION PROGRAMMES

14.5.1 Effectiveness

We identified three community education programmes that could be included in the model to describe the effectiveness of targeted education interventions in "at risk" communities. Community nurses working in partnership with a community dietician in Camelon, a deprived area of Scotland, developed a group-based weight management intervention specifically for obese men (101). The second intervention was a Mediterranean diet class for socially deprived women with Rheumatoid Arthritis (102). The third intervention was a food skills intervention for individuals from urban deprived communities and was not included in the final analysis as it only reported changes in fruit and veg consumption and there were no significant differences in these outcomes at 6 months follow-up (103). As a consequence, we used the other two intervention programmes as an example of the effectiveness of community programmes in men and women respectively. A summary of how the interventions were added to the model is provided in Table 71. The increase in fruit and vegetable consumption was assumed to produce direct effects on HbA1c (-0.09%) and systolic blood pressure (-0.41 mm Hg) independently of the effects on BMI, in the same way as described in the fruit and vegetable retail provision intervention above (105;106).

Table 71: Estimates and assumptions applied in the model for community interventions

	Eligible	Uptake	Change in BMI	Change in fruit and veg	Assumptions
Mediterranean	Females in highest deprivation quintile	Assumed 11.4% to align with men	-1.04kg/m^2	0.143 extra portions per day	1. No compliance data reported. 2. Benefit at 6 months maintained to 12 months. 3. Applied to non-Rheumatoid arthritis population 4. Applied to highest quintile of Townsend score.
Men's diets	Men >30kg/m^2	11.4%	-1.29 kg/m^2	Assumed 0.143 extra portions per day to align with women.	1. Benefit at 6 months maintained to 12 months. 2. Applied to men with BMI>30 kg/m^2

14.5.2 Population

These interventions were combined such that within the same analysis, women with the highest deprivation quintile were offered a cooking class, whilst men with a BMI >30kg/m^2 were offered the multi-component small scale diet programme. The assumed uptake rates for these interventions are reported in Table 71.

14.5.3 Costs

The interventions described in Table 71 were previously evaluated as part of the NICE public health guidance (PH35). In this evaluation the estimated costs of the intervention were £82 for the Mediterranean cooking class and £179 for the men's diets per participant.

14.6 INTERVENTION E: TRANSLATIONAL DIABETES PREVENTION PROGRAMME

14.6.1 Effectiveness

A meta-analysis of translational diabetes prevention programmes was used to estimate the change in BMI, HbA1c, systolic blood pressure and cholesterol at 12 months (110). The review included studies that had run diet and or exercises classes for individuals with a high risk of diabetes. The definition of risk of diabetes varied between studies, but many included risk classification based on increased blood glucose. The review reported mean changes in metabolic measurements at 12 months (Table 72). In the model, the intervention was offered to individuals with impaired glucose regulation. The change in BMI was taken directly from the meta-analysis. The change in HbA1c, systolic blood pressure and total cholesterol were adjusted down to reflect the independent effect over and above the effect of changes in BMI estimated using the Whitehall statistical model. This avoided double counting of treatment benefits.

Table 72: Metabolic changes 12 months after diet and exercise interventions for individuals at high risk of diabetes

	BMI (kg/m^2)	HbA1c (%)	Systolic BP (mm Hg)	Total Cholesterol (mmol/l)
12 months after intervention	-0.94	-0.121	-0.1975	-0.098

14.6.2 Population

The process of identifying individuals at high risk of diabetes replicated the process previously evaluated as part of the NICE Public Health guidance (PH38).

14.6.3 Costs

The intervention costs were designed to replicate the costing methods used in the NICE Public Health guidance (PH38). Given the -2.12kg mean weight loss, this intervention most closely matched to the moderate intensity intervention described in the guideline which cost £100 per individual in the first year. We assumed that individuals received 6 monthly maintenance classes after the visits in years 2-4 at a cost of £60 per year.

14.7 MAINTENANCE OF INTERVENTION EFFECTS

Ideally, weight regain rates and the altered trajectories of HbA1c and systolic blood pressure would be modelled separately for each intervention based upon long term follow-up data. Unfortunately, this data was not available for most of the interventions considered. With this in mind, we decided to apply the full effectiveness of each intervention for the first year only, then in subsequent years, to assume that effectiveness would diminish linearly, reaching zero effect after 5 years.

14.8 LAYERING INTERVENTIONS

The model is sufficiently flexible to enable layering of interventions in order to determine which combinations are highly cost-effective and which combinations could be used to efficiently target certain subpopulations. Interventions can be layered in several different ways, to reflect what will occur when an individual is subject to more than one intervention. Layering can be considered to be either additive, synergistic (i.e. greater than additive), antagonistic (multiple interventions result in less effect than a single intervention) or it may have an effect that is somewhere between antagonistic and additive (one example being that the individual might only obtain an affect from one of the layered interventions).

14.9 TARGETING POPULATION SUBGROUPS AT HIGH RISK OF DIABETES

We selected six sets of criteria to identify and compare alternative sub-groups of individuals at high risk of diabetes within the UK general population who could be targeted with intensive interventions. The at-risk groups included individuals of South Asian ethnicity, individuals in the lowest quintile of deprivation (low SES), Individuals with HbA1c>6%, individuals with BMI>35kg/m^2, individuals aged 40-65, and individuals with a Finnish Diabetes Risk (FINDRISC) Score > 0.1 (111). Summary characteristics for the six groups and the general population are reported in Table 73. To enable fair comparison between the six scenarios we can assume that there is a budget constraint meaning that only 2% of the total adult population can be enrolled in the intervention.

Table 73: Summary of sub-population characteristics

	General UK Population	Age 40-65	Low Socioeconomic status	HbA1c >42 mmol/mol(6%)	Finnish Diabetes Risk Score (DRS) >0.1	BMI >=35k g/m^2	South Asian
Total population	100%	48%	18%	15%	12%	8%	4%
Male	44%	44%	44%	45%	40%	34%	42%
White	90%	92%	80%	92%	96%	91%	0%
Low SES	18%	15%	100%	16%	16%	24%	37%
Age	48.6 (18.4)	54.1 (8.4)	44.7 (8.2)	61.2 (16.0)	66.3 (14.0)	50.0 (16.0)	38.3 (13.6)
BMI, kg/m^2	27.2 (5.4)	27.9 (5.3)	27.4 (5.9)	28.7 (5.5)	34.21 (4.0)	39.0 (4.0)	26.6 (5.3)
HbA1c, %	5.6 (0.5)	5.7 (0.4)	5.6 (0.5)	6.2 (0.1)	5.9 (0.5)	5.7 (0.6)	5.1 (0.5)
HbA1c, mmol/mol	38	39	38	44	41	39	32
Systolic Blood pressure, mmHg	125 (17.1)	128 (16.5)	125 (17.0)	133 (17.3)	135 (17.0)	128 (16.9)	120 (15.5)
Total Cholesterol mmol/l	5.4 (1.1)	5.7 (1.0)	5.3 (1.1)	5.8 (1.0)	5.8 (1.0)	5.5 (1.0)	5.2 (1.1)
HDL Cholesterol, mmol/l	1.5 (0.4)	1.6 (0.5)	1.5 (0.4)	1.5 (0.5)	1.5 (0.4)	1.5 (0.4)	1.4 (0.4)
Standard deviation in brackets							

15 PROBABILISTIC SENSITIVITY ANALYSIS

Probabilistic sensitivity analysis (PSA) was enabled in the model to describe the uncertainty in parameter inputs of the model and how this translates into uncertainty in the outcomes of the model. A suitable distribution was selected for each parameter, based upon its mean and standard error. Random sampling simultaneously across all input parameter distributions allowed parameter uncertainty to be quantified. 1000 different random samples of parameter values were selected, and each was applied to a different random cohort of 20,000 individuals. For each PSA sample, the model was run and results compiled. Given the large number of parameters in the model and thus the capacity for error, a thorough process of checking that mean sampling values corresponded to mean parameter values was undertaken to ensure that the results were as accurate as possible. A list of model parameters, their distribution for PSA and their source is provided in the following tables.

15.1 GP ATTENDANCE IN THE GENERAL POPULATION

In the probabilistic sensitivity analysis the parameters of the Yorkshire Health Study negative binomial model are sampled from a multivariate normal distribution, using the mean estimates described in Table 15 and covariance matrix in Table 16.

Table 74: GP attendance reported in the Yorkshire Health Study (N= 18,437) (112)

	Mean	Standard error	Uncertainty Distribution
Age	0.0076	0.0005	MULTIVARIATE NORMAL
Male	-0.1495	0.0159	MULTIVARIATE NORMAL
BMI	0.0110	0.0015	MULTIVARIATE NORMAL
Ethnicity (Non-white)	0.2620	0.0375	MULTIVARIATE NORMAL
Heart Disease	0.2533	0.0289	MULTIVARIATE NORMAL
Depression	0.6127	0.0224	MULTIVARIATE NORMAL
Osteoarthritis	0.2641	0.0238	MULTIVARIATE NORMAL
Diabetes	0.2702	0.0278	MULTIVARIATE NORMAL
Stroke	0.1659	0.0474	MULTIVARIATE NORMAL
Cancer	0.2672	0.0414	MULTIVARIATE NORMAL
Intercept	-0.5014	0.0468	MULTIVARIATE NORMAL
Alpha	0.3423	0.0108	MULTIVARIATE NORMAL

Table 75: Variance-covariance matrix for GP attendance regression

	Age	Male	BMI	Ethnicity (Non-white)	Heart Disease	Depression	Osteo-arthritis	Diabetes	Stroke	Cancer	Intercept	Alpha
Age	0.0000											
Male	0.0000	0.0003										
BMI	0.0000	0.0000	0.0000									
Ethnicity (Non-white)	0.0000	0.0000	0.0000	0.0014								
Heart Disease	0.0000	0.0000	0.0000	0.0000	0.0008							

Depression	0.0000	0.0000	0.0000	0.0000	0.0000	0.0005						
Osteoarthritis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0006					
Diabetes	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0000	0.0000	0.0008				
Stroke	0.0000	0.0000	0.0000	0.0000	-0.0002	-0.0001	0.0000	-0.0001	0.0022			
Cancer	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0017		
Intercept	0.0000	0.0000	-0.0001	-0.0002	0.0002	0.0000	0.0002	0.0003	0.0000	0.0001	0.0022	
Alpha	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0010

15.2 WHITEHALL II STATISTICAL MODEL OF METABOLIC TRAJECTORIES

The parameters derived from the Whitehall II statistical model of metabolic trajectories are described in Table 76 and Table 78.

Table 76: Coefficient estimates for metabolic risk factor parallel growth models

	Parameter Description	**Estimated Mean**	**Standard error**	**p-value**
BMI Intercept				
α_{10}	Population mean BMI intercept	2.2521	0.045	<0.001
$\boldsymbol{\gamma_{10}}$	Age at baseline coefficient for BMI intercept	0.0056	0.001	<0.001
	Sex coefficient for BMI intercept	-0.0311	0.012	0.009
	Family history of CVD coefficient for BMI intercept	-0.0079	0.012	0.515
υ_{10}	Random error term for BMI intercept	0.1165	0.003	<0.001
BMI linear slope				
α_{11}	Population mean BMI linear slope	0.6409	0.042	<0.001
$\boldsymbol{\gamma_{11}}$	Age at baseline coefficient for BMI linear slope	-0.0084	0.001	<0.001
	Sex coefficient for BMI linear slope	-0.0285	0.011	0.009
	Family history of CVD coefficient for BMI linear slope	-0.0155	0.010	0.117
υ_{11}	Random error term for BMI linear slope	0.0222	<0.001	<0.001
BMI quadratic slope				
α_{12}	Population mean BMI quadratic slope	-0.2007	0.023	<0.001
$\boldsymbol{\gamma_{12}}$	Age at baseline coefficient for quadratic slope	0.0026	<0.001	<0.001
	Sex coefficient for quadratic slope	0.0089	0.006	0.147
	Family history of CVD coefficient for quadratic slope	0.0104	0.006	0.061
ε_1	Random error term for BMI	0.0104	<0.001	<0.001
Glyc Intercept				
α_{20}	Population mean glyc intercept	0	NA	NA
$\boldsymbol{\gamma_{20}}$	Smoker coefficient for glyc intercept	-0.1388	0.029	<0.001
τ_{20}	Association between BMI intercept and glyc intercept	0.2620	0.024	<0.001
υ_{20}	Random error term for glyc intercept	0.0851	0.008	<0.001
Glyc linear slope				
α_{21}	Population mean glyc linear slope	-0.4255	0.071	<0.001
$\boldsymbol{\gamma_{21}}$	Sex coefficient for glyc linear slope	0.1486	0.045	0.001
	Ethnicity coefficient for glyc linear slope	-0.0218	0.081	0.786
	Family history of T2DM coefficient for glyc linear slope	-0.0512	0.054	0.345
	Smoker coefficient for glyc linear slope	0.1796	0.066	0.007
τ_{21}	Association between BMI intercept and glyc linear slope	0.0821	0.024	0.001
τ_{22}	Association between BMI linear slope and glyc linear slope	0.1984	0.073	0.007
υ_{21}	Random error term for glyc linear slope	0.0222	0.011	0.053
Glyc quadratic slope				

α_{22}	Population mean glyc quadratic slope	0.1094	0.025	<0.001
$\boldsymbol{\gamma_{22}}$	Sex coefficient for glyc quadratic slope	-0.0855	0.027	0.002
	Ethnicity coefficient for glyc quadratic slope	0.0899	0.049	0.067
	Family history of T2DM coefficient for glyc quadratic slope	0.0633	0.033	0.052
	Smoker coefficient for glyc quadratic slope	-0.0390	0.040	0.330
υ_{22}	Random error term for glyc quadratic slope	0.0107	0.003	0.002
ε_2	Glyc measurement error	0.0707	0.005	<0.001
SBP Intercept				
α_{30}	Population mean SBP intercept	0.6934	0.021	<0.001
$\boldsymbol{\gamma_{30}}$	Age at baseline coefficient for SBP intercept	0.0043	<0.001	<0.001
	Sex coefficient for SBP intercept	0.0380	0.004	<0.001
	Smoking coefficient for SBP intercept	-0.0243	0.006	<0.001
	Ethnicity coefficient for SBP intercept	0.0078	0.007	0.300
	Family history of CVD coefficient for SBP intercept	0.0061	0.004	0.160
$\boldsymbol{\tau_{31}}$	Association between BMI intercept and SBP intercept	0.1080	0.006	<0.001
υ_{30}	Random error term for SBP intercept	0.0085	0.00	<0.001
SBP linear slope				
α_{31}	Population mean SBP linear slope	-0.0227	0.021	0.278
$\boldsymbol{\gamma_{31}}$	Age at baseline coefficient for SBP linear slope	0.0024	<0.001	<0.001
	Sex coefficient for SBP linear slope	-0.0004	0.004	0.927
	Smoking coefficient for SBP linear slope	0.0205	0.005	<0.001
	Ethnicity coefficient for SBP linear slope	0.0224	0.007	0.001
	Family history of CVD coefficient for SBP linear slope	-0.0013	0.004	0.748
$\boldsymbol{\tau_{31}}$	Association between BMI intercept and SBP linear slope	-0.0396	0.006	<0.001
	Association between BMI linear slope and SBP linear slope	0.2325	0.019	<0.001
υ_{31}	Random error term for SBP linear slope	0.0024	<0.001	<0.001
ε_3	SBP measurement error variance	0.0093	<0.001	<0.001
TC Intercept				
α_{40}	Population mean TC intercept	2.9956	0.176	<0.001
$\boldsymbol{\gamma_{40}}$	Age at baseline coefficient for TC intercept	0.0456	0.003	<0.001
	Sex coefficient for TC intercept	0.0660	0.036	0.070
τ_{40}	Association between BMI intercept and TC intercept	0.4459	0.049	<0.001
υ_{40}	Random error term for TC intercept	0.8960	0.025	<0.001
TC linear slope				
α_{41}	Population mean TC linear slope	2.1216	0.128	<0.001
$\boldsymbol{\gamma_{41}}$	Age at baseline coefficient for TC linear slope	-0.0316	0.002	<0.001
	Sex coefficient for TC linear slope	-0.2677	0.026	<0.001
τ_{41}	Association between BMI intercept and TC linear slope	-0.4808	0.035	<0.001
τ_{42}	Association between BMI linear slope and TC linear slope	0.9802	0.108	<0.001
υ_{41}	Random error term for TC linear slope	0.1583	0.011	<0.001
ε_4	TC measurement error variance	0.3426	0.006	<0.001
HDL Intercept				
α_{50}	Population mean HDL intercept	2.4124	0.054	<0.001
$\boldsymbol{\gamma_{50}}$	Age at baseline coefficient for HDL intercept	0.0032	0.011	<0.001
	Sex coefficient for HDL intercept	-0.3710	0.001	<0.001
τ_{51}	Association between BMI intercept and HDL intercept	-0.3514	0.015	<0.001
υ_{50}	Random error term for HDL intercept	0.0827	-0.040	<0.001
HDL linear slope				
α_{51}	Population mean HDL linear slope	0.1241	0.034	<0.001
$\boldsymbol{\gamma_{51}}$	Age at baseline coefficient for HDL linear slope	0.0020	0.001	<0.001
	Sex coefficient for HDL linear slope	0.0041	0.007	0.558
$\boldsymbol{\tau_{51}}$	Association between BMI intercept and HDL linear slope	-0.0400	0.010	<0.001
υ_{51}	Random error term for HDL linear slope	0.0090	0.001	<0.001
ε_5	HDL measurement error variance	0.0333	0.001	<0.001

Table 77: Coefficient estimates for latent glycaemic measurement model

	Parameter Description	Estimated Mean	Standard error	p-value
μ_0	FPG intercept	4.2903	0.089	<0.001
θ_{01}	Glycaemic factor to FPG	1	NA	NA
θ_{02}	Age to FPG	0.0031	0.001	0.022
θ_{03}	Sex to FPG	0.2129	0.021	<0.001
θ_{04}	Ethnicity to FPG	0.0100	0.037	0.786
θ_{05}	Family history of diabetes to FPG	0.1168	0.025	<0.001
ε_0	FPG measurement error variance	0.1649	0.007	<0.001
μ_1	2-hr Glucose intercept	0.5707	0.223	0.011
θ_{11}	Glycaemic factor to 2-hr glucose	2.4384	0.078	<0.001
θ_{12}	Age to 2-hr glucose	0.0716	0.003	<0.001
θ_{13}	Sex to 2-hr glucose	-0.1411	0.058	0.014
θ_{14}	Ethnicity to 2-hr glucose	0.3047	0.100	0.002
θ_{15}	Family history of diabetes to 2-hr glucose	0.3496	0.068	<0.001
ε_1	2-hr measurement error variance	2.3679	0.054	<0.001
μ_2	HbA1c intercept	4.4769	0.073	<0.001
θ_{21}	Glycaemic factor to HBA1c	0.5074	0.016	<0.001
θ_{22}	Age to HBA1c	0.0101	0.001	<0.001
θ_{23}	Sex to HBA1c	-0.0457	0.001	<0.001
θ_{24}	Ethnicity to HBA1c	0.1854	0.030	<0.001
θ_{25}	Family history of diabetes to HBA1c	0.0563	0.020	0.004
ε_2	HbA1c measurement error variance	0.1166	0.003	<0.001

Table 78: Covariance matrix Ω for individual random error

	υ_{10}	υ_{11}	υ_{20}	υ_{21}	υ_{22}	υ_{30}	υ_{31}	υ_{40}	υ_{41}	υ_{50}	υ_{51}
υ_{10}	0.1165										
υ_{11}	0.0095	0.0131									
υ_{20}	<0.0010	<0.0010	0.0851								
υ_{21}	<0.0010	<0.0010	0.0222	0.0209							
υ_{22}	<0.0010	<0.0010	<0.0010	<0.0010	0.0107						
υ_{30}	<0.0010	<0.0010	0.0080	<0.0010	<0.0010	0.0085					
υ_{31}	<0.0010	<0.0010	<0.0010	0.0018	<0.0010	<0.0017	0.0024				
υ_{40}	<0.0010	<0.0010	0.0324	<0.0010	<0.0010	0.0031	<0.0010	0.8960			
υ_{41}	<0.0010	<0.0010	<0.0010	-<0.0012	<0.0010	<0.0010	0.0066	-0.2229	0.1583		
υ_{50}	<0.0010	<0.0010	-0.0118	<0.0010	<0.0010	0.0010	<0.0010	0.0273	<0.0010	0.0827	
υ_{51}	<0.0010	<0.0010	<0.0010	-0.0059	<0.0010	<0.0010	0.0020	<0.0010	0.0159	0.0061	0.0090

15.2.1 HbA1c trajectory in individuals diagnosed with type 2 diabetes

The input parameters for the initial reduction in HbA1c and long term trend in HbA1c following diagnosis, derived from analysis of the UKPDS outcomes model (11), are reported in Table 79 and Table 80 respectively.

Table 79: Estimated change in HbA1c in first year following diabetes diagnosis

	Distribution	Parameter 1	Parameter 2	Central estimate
Change in HbA1c Intercept	NORMAL	-2.9465	0.0444513	-2.9465
HbA1c at baseline	NORMAL	0.5184	0.4521958	0.5184

Table 80: Estimated change in HbA1c following diabetes diagnosis over long term

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Longitudinal HbA1c for diabetes intercept	NORMAL	-0.024	0.017	-0.024
Longitudinal HbA1c for diabetes log(time since diagnosis)	NORMAL	0.144	0.009	0.144
Longitudinal HbA1c for diabetes Second year	NORMAL	-0.333	0.05	-0.333
Longitudinal HbA1c for diabetes lag HbA1c	NORMAL	0.759	0.004	0.759
Longitudinal HbA1c for diabetes HbA1c at diagnosis	NORMAL	0.085	0.004	0.0896

15.2.2 Systolic blood pressure and cholesterol trajectory following treatment

The changes in systolic blood pressure and total cholesterol following treatment with anti-hypertensives or statins and statin uptake are reported in Table 81.

Table 81: Treatment effects following treatment

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Simvastatin treatment effects	NORMAL	-1.45	0.11	-1.45	(12)
Anti-hypertensive treatment effect	NORMAL	-8.4	0.638	-8.4	(15)
Statin Uptake	UNIFORM	0.65	(0.4-0.9)	0.65	(13)

15.2.3 Metabolic Risk Factor screening

The distribution for the HbA1c threshold at which opportunistic screening for type 2 Diabetes is initiated even if the individual does not have a history of cardiovascular disease, microvascular disease or identified impaired glucose regulation is reported in Table 82.

Table 82: Threshold for HbA1c opportunistic diagnosis

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
HbA1c at diagnosis	NORMAL	8.1	0.073	8.1	(16)

15.3 COMORBID OUTCOMES AND MORTALITY

15.3.1 Cardiovascular disease

The parameter distributions for men and women based on the QRISK2 model (21) are reported in Table 83.

Table 83: Input parameters of the QRISK2 risk model

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
QRISK female ethnicity 2	NORMAL	0.2163	0.0537	0.2163
QRISK female ethnicity 3	NORMAL	0.6905	0.069	0.6905
QRISK female ethnicity 4	NORMAL	0.3423	0.1073	0.3423
QRISK female ethnicity 5	NORMAL	0.0731	0.1071	0.0731
QRISK female ethnicity 6	NORMAL	-0.0989	0.0619	-0.0989
QRISK female ethnicity 7	NORMAL	-0.2352	0.1275	-0.2352
QRISK female ethnicity 8	NORMAL	-0.2956	0.1721	-0.2956
QRISK female ethnicity 9	NORMAL	-0.1010	0.0793	-0.1010
QRISK female smoke 2	NORMAL	0.2033	0.0152	0.2033
QRISK female smoke 3	NORMAL	0.48200	0.0220	0.4820
QRISK female smoke 4	NORMAL	0.6126	0.0178	0.6126
QRISK female smoke 5	NORMAL	0.7481	0.0194	0.7481
QRISK female age 1	NORMAL	5.0373	1.0065	5.0327
QRISK female age 2	NORMAL	-0.0108	0.0022	-0.0108
QRISK female bmi	NORMAL	0.4724	0.0423	0.4724
QRISK female cholesterol	NORMAL	0.6375	0.0143	0.6375
QRISK female sbp	NORMAL	0.0106	0.0045	0.0106
QRISK female townsend	NORMAL	0.060	0.0068	0.060
QRISK female fibrillation	NORMAL	1.3261	0.0310	1.3261
QRISK female RA	NORMAL	0.3626	0.0319	0.3626
QRISK female Renal	NORMAL	0.7636	0.0639	0.7636
QRISK female Hypertension	NORMAL	0.5421	0.0115	0.5421
QRISK female diabetes	NORMAL	0.8940	0.0199	0.8940
QRISK female family history cvd	NORMAL	0.5997	0.0122	0.5997
QRISK female age1 * smoke 1	NORMAL	0.1774	0.0355	0.1774
QRISK female age 1 * smoke 2	NORMAL	-0.3277	0.0655	-0.3277
QRISK age1 * smoke 3	NORMAL	-1.1533	0.2307	-1.1533
QRISK female age 1 * smoke 4	NORMAL	-1.5397	0.3079	-1.5397
QRISK female age 1 * atrial fibrillation	NORMAL	-4.6084	0.922	-4.6084
QRISK female age 1 * renal	NORMAL	-2.6401	0.5280	-2.6401
QRISK female age 1 * hypertension	NORMAL	-2.2480	0.4496	-2.2480
QRISK female age 1 * diabetes	NORMAL	-1.8452	0.3690	-1.8452
QRISK female age 1 * bmi	NORMAL	-3.0851	0.6170	-3.0851
QRISK female age 1 * family history cvd	NORMAL	-0.2481	0.0496	-0.2481
QRISK female age 1 * sbp	NORMAL	-0.0132	0.0026	-0.0132
QRISK female age 1 * town	NORMAL	-0.0369	0.0074	-0.0369
QRISK female age 2 * smoke 1	NORMAL	-0.0053	0..0001	-0.0053
QRISK female age 2 * smoke 2	NORMAL	-0.0005	0.0001	-0.0005
QRISK female age 2 * smoke 3	NORMAL	-0.0105	0.0021	-0.0105
QRISK female age 2 * smoke 4	NORMAL	-0.0155	0.0031	-0.0155
QRISK female age 2 * fibrillation	NORMAL	-0.0507	0.0101	-0.0507

QRISK female age 2 * renal	NORMAL	0.0343	0.0069	0.0343
QRISK female age 2 * hypertension	NORMAL	0.0258	0.0051	0.0258
QRISK female age 2 * diabetes	NORMAL	0.0180	0.0036	0.0180
QRISK female age 2 * bmi	NORMAL	0.0345	0.0069	0.0345
QRISK female age 2 * family history cardiovascular	NORMAL	-0.0062	0.0012	-0.0062
QRISK female age 2 * sbp	NORMAL	-0.000029	0.000006	-0.000029
QRISK female age 2 * townsend	NORMAL	-0.0011	0.0002	-0.0011
QRISK female 1 year survival	CONSTANT	0.9983	NA	NA
QRISK male ethnicity 2	NORMAL	0.3163	0.0425	0.3163
QRISK male ethnicity 3	NORMAL	0.6092	0.0547	0.6092
QRISK male ethnicity 4	NORMAL	0.5958	0.0727	0.5958
QRISK male ethnicity 5	NORMAL	0.1142	0.0845	0.1142
QRISK male ethnicity 6	NORMAL	-0.3489	0.0641	-0.3489
QRISK male ethnicity 7	NORMAL	-0.3604	0.1094	-0.3604
QRISK male ethnicity 8	NORMAL	-0.2666	0.1538	-0.2666
QRISK male ethnicity 9	NORMAL	-0.1208	0.0734	-0.1208
QRISK male SMOKE 2	NORMAL	0.2033	0.0152	0.2033
QRISK male SMOKE 3	NORMAL	0.4820	0.0220	0.4820
QRISK male SMOKE 4	NORMAL	0.6126	0.0178	0.6126
QRISK male SMOKE 5	NORMAL	0.7481	0.0194	0.7481
QRISK male age 1	NORMAL	47.316	9..4630	47.316
QRISK male age 2	NORMAL	-101.236	20.247	-101.236
QRISK male bmi	NORMAL	0.5425	0.0299	0.5425
QRISK male cholesterol	NORMAL	0.14425	0.0022	0.14425
QRISK male sbp	NORMAL	0.0081	0.0046	0.0081
QRISK male townsend	NORMAL	0.0365	0.0048	0.0365
QRISK male fibrillation	NORMAL	0.7547	0.1018	0.7547
QRISK male RA	NORMAL	0.3089	0.0445	0.3089
QRISK male renal	NORMAL	0.7441	0.0702	0.7441
QRISK male hypertension	NORMAL	0.6965	0.011	0.6965
QRISK male age 1 smoke 1	NORMAL	-3.8805	0.7761	-3.8805
QRISK male age 1 smoke 2	NORMAL	-16.703	3.3406	-16.703
QRISK male age 1 smoke 3	NORMAL	-15.3738	3.5291	-15.3738
QRISK male age 1 smoke 4	NORMAL	-17.6453	3.5291	-17.6453
QRISK male age 1 fibrillation	NORMAL	-7.0146	1.4056	-7.0282
QRISK male age 1 renal	NORMAL	-17.015	3.4029	-17.015
QRISK male age 1 hypertension	NORMAL	33.9625	6.7925	33.9625
QRISK male age 1 diabetes	NORMAL	12.7886	2.5577	12.7886
QRISK male age 1 bmi	NORMAL	3.2680	0.6536	3.2680
QRISK male age 1 fxcd	NORMAL	-17.9219	3.5844	-17.9219
QRISK male age 1 sbp	NORMAL	-0.1511	0.030	-0.1511
QRISK male age 1 town	NORMAL	-2.5502	0.5100	-2.5502
QRISK male age 2 SMOKE 1	NORMAL	7.9709	1.5942	7.9709
QRISK male age 2 SMOKE 2	NORMAL	23.6859	4.7372	23.6859
QRISK male age 2 SMOKE 3	NORMAL	23.1371	4.6274	23.1371
QRISK male age 2 SMOKE 4	NORMAL	26.8674	5.3735	26.8674
QRISK male age 2 Fibrillation	NORMAL	14.4518	2.8904	14.4518
QRISK male age 2 renal	NORMAL	28.2702	5.654	28.2702
QRISK male age 2 hypertension	NORMAL	-18.8167	3.7633	-18.8167
QRISK male age 2 diabetes	NORMAL	0.9630	0.1926	0.963
QRISK male age 2 bmi	NORMAL	10.5517	2.1103	10.5517
QRISK male age 2 FXCD	NORMAL	26.6047	5.3209	26.6047
QRISK male age 2 sbp	NORMAL	0.2911	0.0582	0.2911
QRISK male age 2 town	NORMAL	3.007	0.6014	3.007

QRISK2 male 1 year survival	CONSTANT	0.997	NA	NA

The QRISK2 model was modified to allow a linear relationship between HbA1c and the risk of cardiovascular disease for individuals with Impaired Glucose tolerance and type 2 Diabetes (HbA1c>42 mmol/mol). The parameter distributions for these additional inputs are reported in Table 84.

Table 84: Additional parameters for linear relationship between HbA1c and cardiovascular disease

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Female RR of MI due to HbA1c in diabetics	LOGNORMAL	0.078	0.030	1.08	(19)
Male RR of MI due to HbA1c in diabetics	LOGNORMAL	0.108	0.023	1.11	(19)
RR of stroke due to HbA1c in diabetics	LOGNORMAL	0.092	0.026	1.096	(19)
Log(RR) of cvd due to IGR	NORMAL	0.223	0.043	1.25	(113)

15.3.2 Congestive Heart Failure

The parameter distributions for congestive heart failure based on the Framingham Heart Study (24) are reported in Table 85.

Table 85: Input parameters for Congestive Heart Failure Risk model for men and women

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Male Heart failure baseline hazard	NORMAL	-9.2087	0.9209	-9.2087
Male Heart failure Age	NORMAL	0.0412	0.0278	0.0412
Male Heart failure LVH	NORMAL	0.9026	1.0359	0.9026
Male Heart failure Heart rate	NORMAL	0.0166	0.0174	0.0166
Male Heart failure Systolic blood pressure	NORMAL	0.00804	0.0117	0.00804
Male Heart failure CHD	NORMAL	1.6079	0.5336	1.6079
Male Heart failure Valve disease	NORMAL	0.9714	0.6557	0.9714
Male Heart failure Diabetes	NORMAL	0.2244	0.6682	0.2244
Female Heart failure baseline hazard	NORMAL	-10.7988	1.0799	-10.7988
Female Heart failure Age	NORMAL	0.0503	0.0301	0.0503
Female Heart failure LVH	NORMAL	1.3402	0.8298	1.3402
Female Heart failure Heart rate	NORMAL	0.0105	0.0193	0.0105
Female Heart failure Systolic blood pressure	NORMAL	0.00337	0.0109	0.00337
Female Heart failure CHD	NORMAL	1.5549	0.5973	1.5549
Female Heart failure Valve disease	NORMAL	1.3929	0.6707	1.3929
Female Heart failure Diabetes	NORMAL	1.3857	0.7105	1.3857
Female Heart failure BMI	NORMAL	0.0578	0.0555	0.0578
Female Heart failure Valve disease	NORMAL	-0.986	1.4370	-0.986

15.3.3 Microvascular Complications

The parameter distributions for the risk models for foot ulcer, blindness, renal failure, first amputation and second amputation are reported in Table 86. Parameters for renal failure were based on the UKPDS Outcomes Model 1 (11), whereas parameters for other microvascular complications were based on the UKPDS Outcomes Model 2 (19).

Table 86: Input parameters for microvascular complications

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Renal failure baseline hazard	NORMAL	-10.016	0.939	-10.016
Renal failure Weibull shape	NORMAL	1.865	1.4352	1.865
Renal failure systolic blood pressure	NORMAL	0.404	0.106	0.404
Renal failure blindness	NORMAL	2.082	0.551	2.082
Foot ulcer baseline hazard	NORMAL	-11.295	1.13	-11.295
Foot ulcer age at diagnosis	NORMAL	0.043	0.014	0.043
Foot ulcer female	NORMAL	-0.962	0.255	-0.962
Foot ulcer BMI	NORMAL	0.053	0.019	0.053
Foot ulcer HbA1c	NORMAL	0.16	0.056	0.16
Foot ulcer PVD	NORMAL	0.968	0.258	0.968
Amputation baseline hazard	NORMAL	-14.844	1.205	-14.844
Amputation age at diagnosis	NORMAL	0.023	0.011	0.023
Amputation female	NORMAL	-0.445	0.189	-0.445
Amputation atrial fibrillation	NORMAL	1.088	0.398	1.088
Amputation HbA1c	NORMAL	0.248	0.042	0.248
Amputation HDL	NORMAL	-0.059	0.032	-0.059
Amputation heart rate	NORMAL	0.098	0.05	0.098
Amputation MMALB	NORMAL	0.602	0.18	0.602
Amputation peripheral vascular disease	NORMAL	1.01	0.189	1.01
Amputation white blood count	NORMAL	0.04	0.017	0.04
Amputation Stroke	NORMAL	1.299	0.245	1.299
Amputation shape	NORMAL	2.067	0.193	2.067
Amputation with Ulcer lambda	NORMAL	-0.881	0139	-0.881
Amputation with Ulcer age at diagnosis	NORMAL	-0.065	0.027	-0.065
Amputation with Ulcer PVD	NORMAL	1.769	0.449	1.769
Second Amputation baseline hazard	NORMAL	-3.455	0.565	-3.455
Second Amputation HbA1c	NORMAL	0.127	0.06	0.127
Blindness baseline hazard	NORMAL	-10.6774	0.759	-10.6774
Blindness age at diagnosis	NORMAL	0.047	0.009	0.047
Blindness HbA1c	NORMAL	0.171	0.032	0.171
Blindness heart rate	NORMAL	0.08	0.039	0.08
Blindness systolic blood pressure	NORMAL	0.068	0.032	0.068
Blindness white blood cells	NORMAL	0.052	0.019	0.052
Blindness CHF	NORMAL	0.841	0.287	0.841
Blindness IHD	NORMAL	0.61	0.208	0.61

15.3.4 Cancer

The parameter distributions for the incidence and hazard ratios for breast cancer and colorectal cancer are reported in Table 87.

Table 87: Input parameters for breast cancer and colorectal cancer risk models

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Colorectal cancer men	NORMAL	0.0011	0.0001	0.0011	(31)
Colorectal cancer women	NORMAL	0.0005	0.0000	0.0005	(31)
Breast cancer pre-menopause	NORMAL	0.0010	0.0001	0.0010	(29)
Breast cancer post-menopause	NORMAL	0.0028	0.0002	0.0028	(29)
Colorectal cancer BMI relative risk for men	LOGNORMAL	0.1906	0.0111	1.21	(30)
Colorectal cancer BMI relative risk for women	LOGNORMAL	0.0392	0.0151	1.04	(30)
Breast cancer BMI relative risk for pre-menopause	LOGNORMAL	-0.1165	0.0251	0.89	(30)
Breast cancer BMI relative risk for post-menopause	LOGNORMAL	0.0862	0.0205	1.09	(30)

The parameter distributions for breast and colorectal cancer mortality are reported in Table 88.

Table 88: Input parameters for breast cancer and colorectal cancer mortality (35)

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Breast cancer 5 year survival	BETA	439.69	2354.44	0.157
Colorectal cancer 5 year survival	BETA	1457.56	1806.35	0.447

15.3.5 Osteoarthritis

The parameter distributions for the incidence and hazard ratios for osteoarthritis are reported below.

Table 89: Input parameters for the osteoarthritis risk model (5)

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Osteoarthritis incidence	NORMAL	0.0053	0.0000004	0.0053
Osteoarthritis RR of diabetes	LOGNORMAL	0.723	0.317	2.06
Osteoarthritis RR of BMI	LOGNORMAL	0.073	0.026	1.076

15.3.6 Depression

The parameter distributions for the incidence and hazard ratios for depression are reported below.

Table 90: Input parameters for the depression risk model

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Odds of depression	BETA	336	8803	0.0397	(33)
Odds ratio for diabetes	LOGNORMAL	0.4187	0.1483	1.52	(33)
Odds ratio for stroke	LOGNORMAL	1.8406	0.5826	6.3	(34)

15.3.7 Mortality

The other cause mortality rates by age were assumed constant in the probabilistic sensitivity analysis (36). The parameter distribution for the hazard ratio for other cause mortality with diabetes is reported below.

Table 91: Input parameters for mortality hazard ratio for diabetes (37)

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Mortality hazard ratio for diabetes	LOGNORMAL	0.588	0.186	1.80

15.4 UTILITIES

The parameter distributions used to estimate health state utilities in the model are reported below.

Table 92: Utility input parameters

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Renal/ulcer baseline utility	NORMAL	0.689	0.014	0.689	(64)
Renal dialysis	NORMAL	-0.078	0.026	-0.078	(64)
Foot ulcer	NORMAL	-0.099	0.013	-0.099	(64)
Amputation/heart failure baseline utility	NORMAL	0.807	0.005	0.807	(19)
Heart failure	NORMAL	-0.101	0.032	-0.101	(19)
Amputation	NORMAL	-0.172	0.045	-0.172	(19)
Stable angina multiplicative factor decrement	NORMAL	0.801	0.038	0.801	(13)
Unstable angina multiplicative factor decrement	NORMAL	0.77	0.038	0.77	(13)
MI multiplicative factor decrement	NORMAL	0.76	0.018	0.76	(13)
Stroke multiplicative factor decrement	NORMAL	0.629	0.04	0.629	(13)
Cancer baseline utility	NORMAL	0.8	0.0026	0.8	(65)
Cancer decrement	NORMAL	-0.06	0.008	-0.06	(65)
Osteoarthritis utility	NORMAL	0.69	0.069	0.69	(66)
Depression baseline utility	NORMAL	0.48	0.048	0.48	(68)
Depression remitters	NORMAL	0.31	0.031	0.31	(68)
Depression responders	NORMAL	0.20	0.020	0.20	(68)

Depression non-responders	NORMAL	0.070	0.007	0.070	(68)
Depression drop-outs	NORMAL	0.050	0.005	0.050	(68)
Weight loss utility decrement	NORMAL	-0.0025	0.001	-0.0025	(114;115)
Age utility decrement	NORMAL	-0.004	0.0001	-0.004	(13)

15.5 UNIT HEALTH CARE COSTS

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Cost of insulin	GAMMA	3.194	391.85	1251.5	(43)
Cost of anti-hypertensives	GAMMA	100	1.83	183.01	(44)
Cost of GP appointment	GAMMA	100	0.43	43	(38)
Nurse appointment (Advanced)	GAMMA	100	0.25	25	(38)
Health care assistant appointment	GAMMA	100	0.0417	4.17	(38)
Eye screening	GAMMA	15.366	1.478	22.709	(42)
HbA1c test	GAMMA	100	0.03	3	(39)
Lipids test	GAMMA	100	0.03	1	(39)
LfT test	GAMMA	100	0.03	1	(39)
B12 test	GAMMA	100	0.03	1	(39)
Urine test	GAMMA	100	0.03	1	(39)
Nicotine replacement therapy	GAMMA	100	1.02	102	(38)
HbA1c diagnosis screening	GAMMA	100	0.14	14	(39)
Unstable Angina hospital admission	GAMMA	311.79	3	1191.4	(12)
Revascularisation in hospital	GAMMA	300	17	5638.6	(12)
MI Hospital admission	GAMMA	248.48	5	1452.3	(12)
First Outpatient appointment	GAMMA	100	1	154.45	(12)
Subsequent outpatient appointments	GAMMA	75	1	102.8	(12)
Fatal CHD	GAMMA	300	2	665.5	(47)
Fatal Stroke	GAMMA	280	13	4149.5	(46)
First year stroke cost	GAMMA	350	23	9075	(46)
Subsequent year stroke cost	GAMMA	100	26	2579	(12)
Glytrin Spray	CONSTANT	11.92	NA	NA	(12)
Isosorbide mononitrate	CONSTANT	12.79	NA	NA	(12)
Verapamil	CONSTANT	47.79	NA	NA	(12)
Atenolol	CONSTANT	34.42	NA	NA	(12)
Aspirin	CONSTANT	7.57	NA	NA	(12)
Ramipril	CONSTANT	85.47	NA	NA	(12)
ARB	CONSTANT	239.35	NA	NA	(12)
Clopidogrel	CONSTANT	523.92	NA	NA	(12)
Congestive Heart Failure	GAMMA	67	43	2921	(45)
Blindness year 1	GAMMA	24	47	1147	(45)
Blindness subsequent years	GAMMA	36	10	370	(45)
Amputation year 1	GAMMA	27	405	11125	(45)
Amputation subsequent years	GAMMA	16	24	395	(45)
Renal Haemodialysis	GAMMA	100	397	39736	(48)
Renal Automated Peritoneal dialysis	GAMMA	100	257	25720	(48)
Renal Ambulatory peritoneal dialysis	GAMMA	100	187	18657	(48)
Renal transplant	GAMMA	100	224	22359	(50)
Immunosuppressants	GAMMA	100	66	6576	(50)
Foot ulcer not infected	GAMMA	100	1.59	158.53	(51)
Foot ulcer with cellulitis	GAMMA	100	4.19	419	(51)
Foot ulcer with osteomyelitis	GAMMA	100	7.76	776	(51)

Breast Cancer	GAMMA	100	130.58	13058	(53)
Colorectal cancer Dukes A	GAMMA	100	95.36	9536	(54)
Colorectal cancer Dukes B	GAMMA	100	163.63	163.63	(54)
Colorectal cancer Dukes C	GAMMA	100	250.90	25090	(54)
Colorectal cancer Dukes D	GAMMA	100	157.11	15711	(54)
Osteoarthritis	GAMMA	100	9.09	909	(55)
Depression – Practice nurse surgery	GAMMA	100	0.09	8.83	(56)
Depression – Practice nurse home	GAMMA	100	0.27	26.50	(56)
Depression – Practice nurse telephone	GAMMA	100	0.09	8.83	(56)
Depression – Health visitor	GAMMA	100	0.36	35.50	(56)
Depression – District nurse	GAMMA	100	0.25	24.50	(56)
Depression – Other nurse	GAMMA	100	0.09	8.83	(56)
Depression – HCA phlebotomist	GAMMA	100	0.04	4.17	(56)
Depression – Other primary care	GAMMA	100	0.25	25.00	(56)
Depression – Out of Hours	GAMMA	100	0.25	25.39	(56)
Depression – NHS Direct	GAMMA	100	0.24	23.90	(56)
Depression – Walk-in Centre	GAMMA	100	0.37	36.70	(56)
Depression – Prescribed medicines	GAMMA	100	0.09	9.09	(56)
Depression – Secondary Care	GAMMA	100	1.09	109.00	(56)

16 ONE-WAY SENSITIVITY ANALYSES

A series of one-way sensitivity analyses were carried out in order to test the strength of certain assumptions that we had made. These were of two types. Firstly, some of the assumptions based upon particularly weak data relating to the interventions were tested. In addition, we carried out sensitivity analyses related to some of the other parameters and assumptions used in the model.

16.1 SENSITIVITY ANALYSIS AROUND THE INTERVENTIONS

Much of the data for the five interventions is based upon assumptions and extrapolations from multiple data sources rather than from long term randomised controlled trials collecting data on multiple metabolic risk factor endpoints. We decided to test the sensitivity of the results to modifying those parameters that were based upon particularly weak data. They focus on three main areas of uncertainty; duration of intervention effect, intervention uptake and intervention efficacy. The one-way sensitivity analyses around the interventions are summarised in Table 93.

Table 93: One-way sensitivity analyses used to test the strength of parameters

Parameter Affected	Modification	Justification	Interventions Affected
Duration of Intervention Effect	Make effects last for duration of lifetime	Intervention is continuous due to policy change.	A B
	Increase duration of effects - diminish over ten years	Original five year duration based only on estimation	C D E
	Reduce duration of effects - diminish over two years	Original five year duration based only on estimation	C D E
Intervention Uptake	Switch uptake rates between Intervention D and Intervention E.	Would be useful to see how important uptake rates are on intervention success	D E
	Reduce number of people affected by intervention B to 50% of upper Townsend quintile.	Unlikely that everyone in deprived areas is lacking good retail provision.	B
Intervention Efficacy	Increase efficacy of intervention C by estimating extra effects on BMI and HbA1c due to reducing fried food/sweet puddings.	Increasing the competitiveness of the workplace intervention.	C
	Remove the effects of vitamin C and fat intake on HbA1c levels	Cross-sectional studies used to provide data. Only show correlation, not causation.	B C D

16.1.1 Duration of Intervention Effect

For the majority of interventions no data exists for the duration of intervention effect, and so for all interventions it was estimated to be maximal in year one, then diminish to zero (compared with basecase) over the following five years. A fixed duration of effect across all interventions was chosen to allow comparisons of the interventions independent upon the duration of response. This assumption is particularly unrealistic for interventions A and B, as both a soft drinks tax and a retail policy resulting in better access to fruit and vegetables would be likely to have a persistent effect in changing habits and behaviours. For interventions C, D and E, we decided to test the strength of the original assumption by either increasing the duration of effect to 10 years or reducing it to two years.

16.1.2 Intervention Uptake

The uptake of interventions is likely to have a large implication for their efficacy in reducing disease prevalence on a population-wide basis. Interventions D (community weight loss intervention) and E (screening and intensive intervention in high risk individuals) have very different uptake rates; only 11.4% of the eligible population choose to take up intervention D, whilst 42% choose to be screened and undergo intervention E. We decided to switch the uptake rates for interventions D and E to see how this affected their relative cost-effectiveness.

We also thought that there was some uncertainty around the question of how many people currently have poor access to fresh fruit and vegetables, and therefore would benefit from the retail intervention (B). There is very little data on how many people are actually living in 'food deserts', but it would be reasonable to assume that at least some of the most deprived people do currently have good local retail access and therefore that our initial assumptions would overestimate the numbers who would benefit. To test the sensitivity of the results to this assumption, we decided to randomly select 50% of the most deprived quintile of the population to receive the intervention.

16.1.3 Intervention Efficacy

Although efficacy is based on good quality data for many of the interventions, there are still a few areas for uncertainty. For the workplace intervention (C), the data was particularly poor as no information was given about the magnitude of changes in consumption of fruit, sweet puddings and fried food (99). The latter two are particularly difficult to estimate due to a lack of data about potential food substitution, or what in particular is represented by a sweet pudding or fried food, and therefore they were not included in the original analysis. We thought it would be interesting to try to maximise the potential health benefits of intervention C by estimating (in a fairly arbitrary way) the

effect of reductions in fried food and sweet puddings on BMI and HbA1c (via fat intake) as reported by 5.3% and 5.5% of individuals respectively. A reduction in fried food was considered to be a replacement of one Big Mac meal with a healthy home cooked meal each week, resulting in a reduction of 1000 calories and 70g of fat per week. A reduction in sweet puddings was considered to be a replacement of one sponge pudding with a low fat yoghurt each week, resulting in a reduction of 500 calories and 27g of fat per week.

Another area for uncertainty regarding intervention efficacy is surrounding two pieces of cross-sectional data that were used to derive reductions in HbA1c levels dependent upon vitamin C intake and fat intake (105;109). The data indicates that there is a correlation between HbA1c levels and vitamin C/fat intake, but this does not imply that there is a causative link. Given the lack of better quality data, values from these sources were used to inform the analysis. We decided that it was important to test how sensitive the cost-effectiveness of interventions B, C and D were to the removal of parameters based upon these correlations.

16.2 SENSITIVITY ANALYSIS AROUND OTHER PARAMETERS

The list of other one-way sensitivity analyses carried out is presented in

Table 94.

Table 94: List of sensitivity analyses

Description of Sensitivity Analysis
Discount rate 0%
Discount rate 3.5%
Non-intervention costs at 2.5th CI
Non-intervention costs at 97.5th CI
Cardiovascular costs at 2.5th CI
Cardiovascular costs at 97.5th CI
Diabetes costs at 2.5th CI
Diabetes costs at 97.5th CI
Microvascular costs at 2.5th CI
Microvascular costs at 97.5th CI
All utility decrements at 2.5th CI
All utility decrements 97.5th CI
Cardiovascular utility decrements at 2.5th CI
Cardiovascular utility decrements at 97.5th CI
Microvascular utility decrements at 2.5th CI
Microvascular utility decrements at 97.5th CI
BMI utility decrements at 2.5th CI
BMI utility decrements at 97.5th CI
Statin uptake 50%
Statin uptake 80%
QRISK IGR hazard ratio 2.5th CI
QRISK IGR hazard ratio 97.5th CI
No BMI effect on cancer incidence
No BMI or diabetes effect on osteoarthritis incidence
No diabetes or stroke effect on depression incidence
No diabetes effect on mortality

17 MODEL LIMITATIONS AND FURTHER RESEARCH

17.1 MODEL LIMITATIONS

Limited baseline sample data: The model is based on data from 8038 individuals from the HSE 2011. A large proportion of individuals were missing answers for at least one of the variables required for input into the model, so missing data had to be assumed or imputed. Imputation relied on an assumption that non-response was arbitrary for each variable, which may not be correct. For other variables, assumption of negative responses may underestimate the true numbers of individuals affected. Although the HSE should be broadly representative of the UK population, the relatively small numbers and the necessity to rely only on data from individuals who were willing to respond, means that data may be biased or skewed for some variables. The use of a UK adult population also means that the model may not be appropriate for modelling diabetes in other countries or in children.

Whitehall trajectories: Use of a quadratic form is beneficial because glycaemia increases at an increasing rate as observed in other studies (116). This provides a better description of the implications of not screening for diabetes, because unscreened individuals will not be detected until their HbA1c levels are much higher. A linear slope would describe a much more shallow progression of HbA1c before diabetes is detected. However, a disadvantage of this functional form is that all individuals are simulated with the same timescale, therefore progression is slow in the short term but increases for all individuals as time increases.

Poor quality intervention data: Many of the interventions are based upon poor quality data due to the lack of good information about the effect on metabolic factors, general lack of detail as to intervention efficacy and short follow-up times. In particular, the evidence relating fat intake or plasma vitamin C to HbA1c levels was based on two cross-sectional studies, which means the effect is only correlative and not necessarily causative. We have also had to make many assumptions in implementing interventions. The retail policy was assumed to affect all individuals living in deprived areas, but many of these people will now have good access to fruit and vegetable provision. The workplace intervention was assumed to affect 20% of the working population, although we have no data on how many individuals would really be affected. The workplace intervention data was also very vague in terms of quantifying diet changes and we were forced to assume its effects on fruit and vegetable consumption and milk switching. We also were unable to find studies relating intake of certain foods to effects on metabolic factors and as a consequence we have potentially

underestimated the efficacy of interventions. For example, we could not find any data linking sugar intake to HbA1c levels, or fruit and vegetable intake to cholesterol levels.

Model complexity: The complexity of the simulation is necessary to encompass the multiple factors impacting on type 2 diabetes and the multiple outcomes of hyper-glycaemia. However, this complexity also means that the model is difficult to understand and it is very difficult to ensure removal of all potential errors. This means that we cannot guarantee that the model is free of errors that could potentially have effects on costs, QALYs and resulting cost-effectiveness of interventions.

17.2 FURTHER RESEARCH

Improvements to the Whitehall model for metabolic risk trajectories: The Whitehall II analysis assumed that all participants were observed at equal time intervals between phases of the study. This was necessary to be able to implement the analysis in MPlus software, in which the data needed to be specified in wide format. Analyses by age group were investigated but could not be completed because of the low proportion of observations between age groups. The variation in time intervals between phases was not large and was not expected to impact substantially on the results of these analyses. Nonetheless we would recommend that further research explores an alternative specification of the model in which time is a continuous variable. This would also allow a more flexible specification of the trajectory of HbA1c and may avoid assuming a quadratic functional form.

The effect of changes in BMI on changes in glycaemia has been shown to be small in the Whitehall II analysis. It is likely that changes in physical activity and diet will have additional effects on changes in glycaemia, independent of their indirect effects on BMI. We have incorporated the effects of diet into the model using other data sources. However, further research should explore whether these factors could be incorporated into the Whitehall II analysis to allow them to be causally related to all metabolic risk factors in a longitudinal analysis.

Incorporate a behavioural intervention to increase physical activity: We identified a systematic review and meta-analysis of randomised controlled trials for behavioural interventions targeting physical activity and exercise in type 2 diabetics (117). The study found that a range of targeted behavioural interventions were successful in significantly increasing physical activity in diagnosed diabetics, leading to corresponding improvements in BMI and HbA1c. The mean reduction in BMI was 1.05 kg/m^2 and the mean reduction in HbA1c was 0.32% for follow-up times ranging from 1 month to 2 years.

These values could be implemented directly into the model in a similar way to those used for the translational diabetes prevention programme (Section 14.6). As for the other interventions, the effect could be assumed to be maximal in the first year and diminish linearly over the next 5 years, although sensitivity analysis should test the possibility of a sustained reduction over a longer period of time, as this was suggested from the small number of trials with 2 year follow-up. Intervention costs were not calculated in the study and would have to be estimated directly from clinical trial data or other sources. Cost and efficacy can vary widely depending upon the nature of the intervention and the training given to interventionists, so ideally sensitivity analysis would be used to determine cost-effectiveness given a range of intervention costs and associated improvements in BMI and HbA1c.

Incorporate fibre intake into dietary interventions: One of our stakeholders identified a meta-analysis linking intake of dietary fibre to HbA1c levels (118). This could be incorporated into the model as part of a dietary intervention in which participants are encouraged to eat more fibre. None of the studies used in the meta-analysis involved participants eating more fruit and vegetables; rather the focus was on eating high fibre bread and cereals, or on adding fibre such as Guar gum directly to the normal diet. In theory, the amount of fibre in an average portion of fruit and vegetables could be calculated and the resulting effect on HbA1c determined. However, given that the effect of fruit and vegetable intake on HbA1c is already incorporated within the model via plasma vitamin C levels, and it is unclear whether effects of fibre and vitamin C on HbA1c are independent, further research is required before this option is taken.

Investigate subgroup-specific differences in intervention uptake, efficacy or duration: Current analyses of high risk subgroups assume that interventions have the same uptake, the same efficacy in reducing metabolic trajectories and the same duration of action in different population subgroups. This is unlikely to be true as it is known for example, that individuals from deprived areas are less likely to take up screening opportunities. Further research is required to investigate the current evidence base on subgroup specific intervention effects and use the resulting data to tailor intervention effect accordingly.

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