ONLINE ONLY SUPPLEMENTAL MATERIAL

Full Title: Assessing the Potential Return on Investment of the Proposed NHS Diabetes Prevention Programme in Different Population Subgroups: An Economic Evaluation

Running Title: Return on Investment of the NHS DPP

Chloe Thomas, Susi Sadler, Penny Breeze, Hazel Squires, Michael Gillett, Alan Brennan

A) SUPPLEMENTARY TABLES & FIGURES

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A) SUPPLEMENTARY TABLES & FIGURES

CHARACTERISTIC	NUMBER	PERCENTAGE	
Male	644	43.2%	
Female	848	56.8%	
White	1332	89.3%	
BME	160	10.7%	
Indian	46	3.1%	
Pakistani	23	1.5%	
Bangladeshi	5	0.3%	
Other Asian	19	1.3%	
Caribbean	16	1.1%	
African	28	1.9%	
Chinese	4	0.3%	
Other	19	1.3%	
Age1 < 40	279	18.7%	
Age2 40-59	482	32.3%	
Age3 60-74	453	30.4%	
Age4 75+	278	18.6%	
IMD 1 (least deprived)	339	22.7%	
IMD 2	436	29.2%	
IMD 3	177	11.9%	
IMD 4	297	19.9%	
IMD 5 (most deprived)	243	16.3%	
Working	679	45.5%	
Retired	584	39.1%	
Other	229	15.3%	
BMI1 < 25 kg/m^2	409	27.4%	
BMI2 25-29 kg/m^2	586	39.3%	
BMI3 30-34 kg/m^2	324	21.7%	
BMI4 ≥ 35 kg/m^2	173	11.6%	
HbA1c 6-6.1 % (42-44 mmol/mol)	763	51.1%	
HbA1c 6.2-6.4 % (45-47 mmol/mol)	729	48.9%	
	MEAN	STANDARD DEVIATION	MEDIAN
Age (years)	57.1	17.8	58.0
BMI (kg/m^2)	28.4	5.7	27.8
Total Cholesterol (mmol/l)	5.7	1.0	5.7
HDL Cholesterol (mmol/l)	1.5	0.4	1.5
HbA1c (%)	6.19	0.14	6.19
Systolic Blood Pressure (mm Hg)	129.7	17.2	128.5
EQ-5D (TTO)	0.739	0.307	0.796
BME Black and Minority Ethnic; BMI Body Mass Index; IMD Index of Multiple Deprivation; CVD Cardiovascular Disease; IGR Impaired Glucose Regulation; HDL High Density Lipoprotein; EQ-5D 5 dimensions Euroqol (health related quality of life index); TTO Time Trade-Off			

Table S1: Baseline characteristics of the IGR individuals from HSE 2011, following imputation of missing metabolic data (N=1,492).

SPECIFICATION	BASE-CASE	SA 1	SA 2	SA 3	SA 4
Intervention Uptake*	32%	32%	32%	32%	32%
Intervention Effectiveness [6;15]:					
Mean weight change (kg)	-3.24	-3.24	**-2.43**	-3.24	-3.24
Mean BMI change (kg/m^2)	-1.47	-1.47	**-1.10**	-1.47	-1.47
Mean SBP change (mmHg)	-6.57	-6.57	**-0.15**	-6.57	-6.57
Mean cholesterol change (mmol/1)	-0.28	-0.28	**-4.93**	-0.28	-0.28
Mean HbA1c change (%)	-0.20	-0.20	**-0.21**	-0.20	-0.20
Stratification of Intervention Effectiveness (kg) [6] **	-0.23	**None**	-0.23	-0.23	-0.23
Intervention Cost*	£270	£270	£270	£270	**£350**
Time to Weight Regain*	5 years	5 years	5 years	**3 years**	5 years

* PHE estimates of expected values

** extra weight loss per unit increase in baseline BMI above 31.5 kg/m^2, or weight gain per unit decrease in baseline BMI below 31.5 kg/m^2

Table S2: Key intervention specification parameters in the basecase and one-way sensitivity analysis (SA) scenarios. Values in bold indicate differences from basecase.

	TOTAL COST	QALYS	NET MONETARY BENEFIT*	PROBABILITY COST-EFFECTIVE**	PROBABILITY COST-SAVING
Total Population	-£131	0.038	-£3,376	97%	70%
IMD Q1: low deprivation	-£110	0.041	-£2,638	83%	57%
IMD Q2	-£121	0.039	-£3,034	87%	60%
IMD Q3	-£141	0.039	-£3,608	71%	53%
IMD Q4	-£138	0.039	-£3,543	83%	58%
IMD Q5: high deprivation	-£159	0.033	-£4,760	78%	60%
Age <40	-£35	0.019	-£1,811	64%	46%
Age 40-59	-£215	0.036	-£5,909	89%	72%
Age 60-74	-£194	0.054	-£3,591	91%	66%
Age 75+	£24	0.043	£563	81%	40%
Male	-£105	0.041	-£2,529	91%	59%
Female	-£156	0.036	-£4,303	94%	68%
BMI <25	£123	0.016	£7,396	51%	26%
BMI 25-29	-£83	0.039	-£2,130	89%	55%
BMI 30-34	-£277	0.051	-£5,360	92%	74%
BMI 35+	-£627	0.067	-£9,286	93%	83%
White	-£132	0.039	-£3,311	97%	70%
BME	-£121	0.030	-£4,045	61%	51%
HbA1c 6-6.1	-£39	0.029	-£1,305	87%	49%
HbA1c 6.2-6.4	-£226	0.048	-£4,706	96%	76%
Working	-£150	0.036	-£4,090	91%	68%
Retired	-£102	0.048	-£2,088	93%	58%
Other	-£101	0.025	-£3,915	68%	52%

*Value of a QALY assumed to be £60,000 for net monetary benefit analysis [17]
**At a willingness to pay threshold of £20,000 per QALY

Table S3: Summary table showing incremental PSA results for each subgroup compared with no DPP intervention. All results are reported per person given the intervention at 20 years following intervention implementation. Costs are discounted at 3.5% and QALYs at 1.5%. Higher cost savings, QALY gains and net monetary benefit are shown in deeper shades of red, whereas lowest cost savings, QALY gains and net monetary benefit are shown in blue.

	BASECASE*		SA1		SA2		SA3		SA4	
	Year CS	Year CE	Year CS	Year CE	Year CS	Year CE	Year CS	Year CE	Year CS	Year CE
Total Population	12	6	10	5	20	7	NCS	8	NCS	7
IMD Q1	13	6	10	5	NCS	7	NCS	8	NCS	7
IMD Q2	12	5	10	5	NCS	6	NCS	7	NCS	6
IMD Q3	13	6	10	5	NCS	7	NCS	8	NCS	7
IMD Q4	11	6	10	5	16	6	NCS	8	17	7
IMD Q5	11	6	9	5	16	7	NCS	9	17	7
Age <40	19	9	11	8	NCS	11	NCS	17	NCS	11
Age 40-59	11	6	9	6	14	7	NCS	9	14	7
Age 60-74	9	5	8	4	12	6	NCS	6	13	6
Age 75+	NCS	4	NCS	4	NCS	5	NCS	5	NCS	5
Male	13	6	10	5	NCS	6	NCS	8	NCS	7
Female	11	6	10	5	16	7	NCS	8	18	7
BMI <25	NCS	10	11	6	NCS	13	NCS	NCE	NCS	13
BMI 25-29	16	6	10	5	NCS	7	NCS	8	NCS	7
BMI 30-34	9	5	9	5	11	6	NCS	6	11	6
BMI 35+	5	3	7	4	6	4	8	4	7	4
White	11	6	10	5	19	6	NCS	7	NCS	6
BME	14	7	10	6	NCS	9	NCS	11	NCS	9
HbA1c 6-6.1	NCS	7	14	6	NCS	8	NCS	10	NCS	9
HbA1c 6.2-6.4	9	5	8	4	12	6	NCS	6	12	6
Working	12	7	10	6	17	8	NCS	9	19	8
Retired	11	5	9	4	NCS	5	NCS	6	NCS	5
Other	14	7	10	6	NCS	8	NCS	11	NCS	9

CS Cost-Saving; CE Cost-Effective; NCS Not Cost-Saving within 20 years; NCE Not Cost-Effective within 20 years
*Stratified intervention effect by BMI, 5 year duration of intervention effect, intervention cost £270.

Table S4: Comparison of the year that the intervention becomes cost-saving and cost-effective (using a threshold of £20,000 per QALY) between different population subgroups for each deterministic sensitivity analysis. Depth of shading represents how early cost-savings/cost-effectiveness occur, with darker grey representing earlier years.

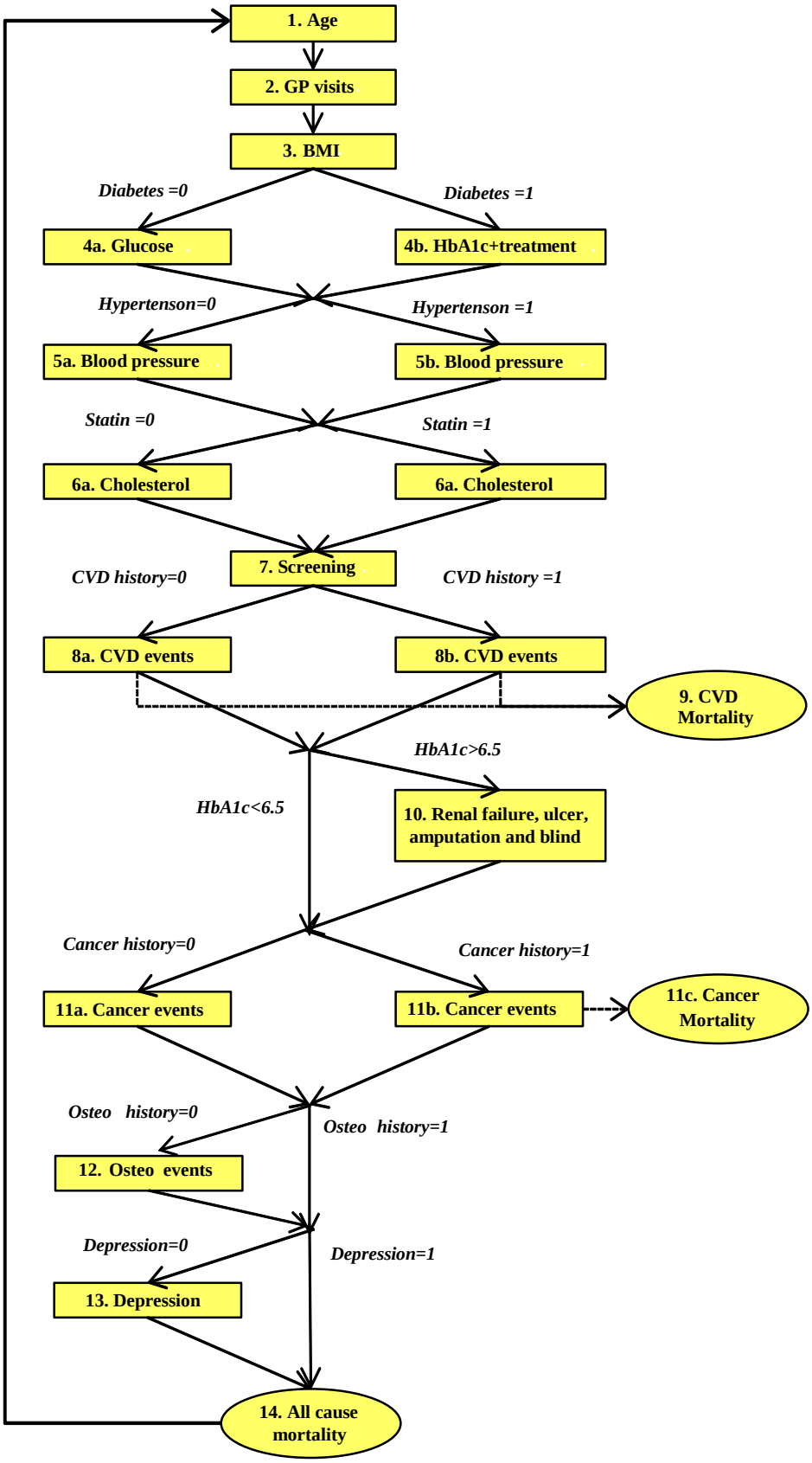


Figure S1: Model schematic showing what happens in each yearly cycle.

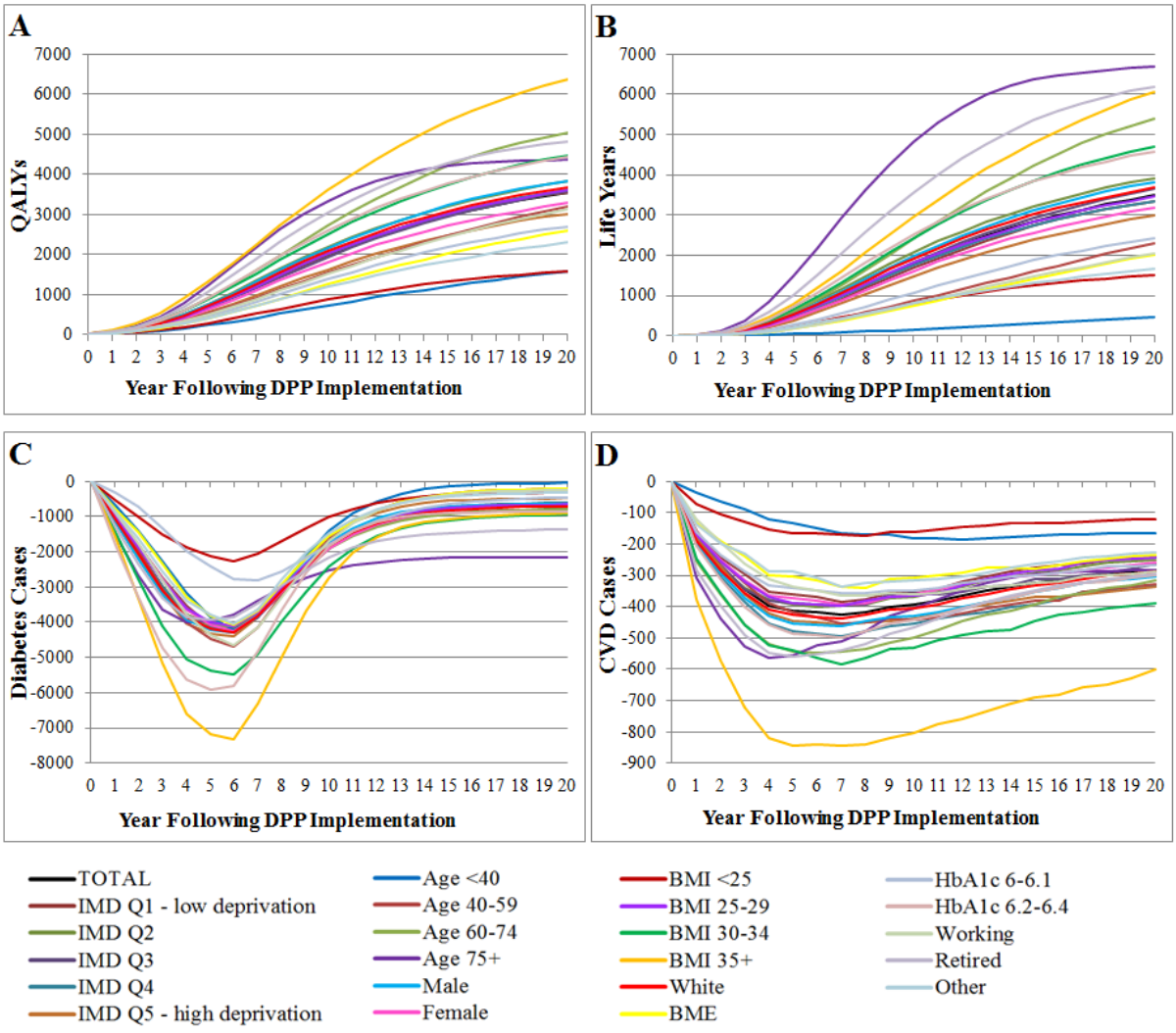


Figure S2: Graphs showing cumulative gain of A) QALYs and B) life years; and reduction in C) incremental diabetes cases and D) incremental CVD cases, per 100,000 individuals across all subgroups over 20 years.

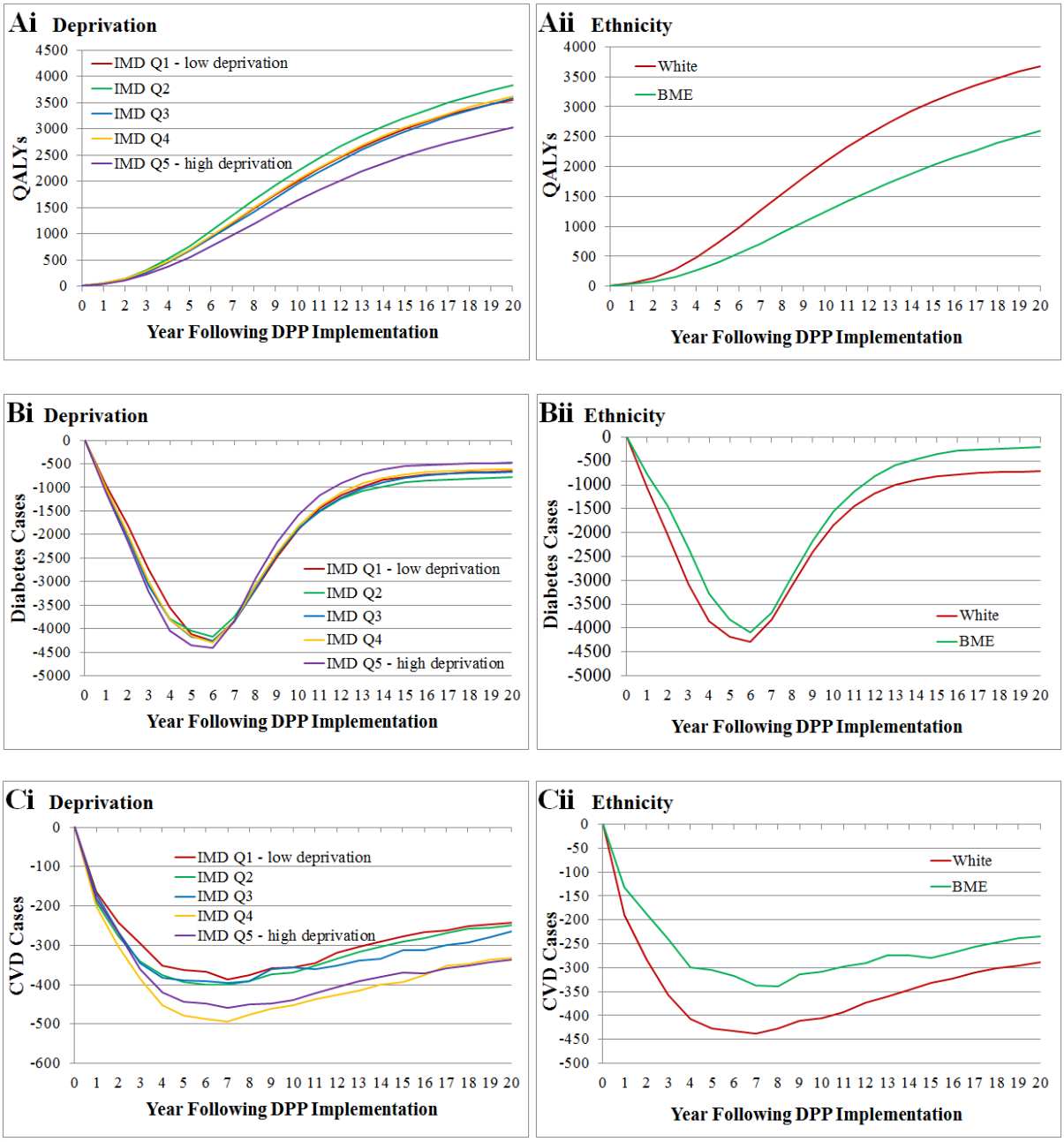


Figure S3: Graphs showing: A) cumulative incremental QALY gain; B) incremental reduction in diabetes cases and C) incremental reduction in CVD cases per 100,000 individuals in different deprivation quintiles (i) and ethnic groups (ii)

B) SUPPLEMENTARY METHODS

CONCEPTUAL MODELLING

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 (1). 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 (2;3). 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.

MODEL STRUCTURE

The model is based upon individual longitudinal trajectories of metabolic risk factors (BMI, systolic blood pressure [SBP], cholesterol and HbA1c [measure of blood glucose]). For each individual, yearly changes in these risk factors occur, dependent upon the individuals' baseline characteristics. Figure 1 in the main article 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.

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 also 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 (4). 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.

BASELINE POPULATION

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 (5). The HSE 2011 focused on CVD and associated risk factors. The whole dataset was obtained from the UK Data Service. The total sample size of the HSE 2011 is 10,617 but individuals aged under 16 were excluded resulting in 8,610 in total.

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 1. 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 1 and summary statistics for the data extracted from the HSE2011 dataset are reported in Table 2.

Table 1: HSE variable names and missing data summary

Model requirements	HSE 2011 variable name	HSE 2011 variable description	No. Missing data entries
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 2: Characteristics of final sample from HSE 2011 (N=8610)

Characteristic	**Number**	**Percentage**	
Male	3822	44.4%	
White	7719	89.7%	
Indian	206	2.4%	
Pakistani	141	1.6%	
Bangladeshi	46	0.5%	
Other Asian	97	1.1%	
Caribbean	78	0.9%	
African	120	1.4%	
Chinese	35	0.4%	
Other	168	2.0%	
IMD 1 (least deprived)	1774	20.6%	
IMD 2	1823	21.2%	
IMD 3	1830	21.3%	
IMD 4	1597	18.5%	
IMD 5 (most deprived)	1586	18.4%	
Non-smoker	4550	52.8%	
Past smoker	2353	27.3%	
Current smoker	1707	19.8%	
Anti-hypertensive treatment	1544	17.9%	
Statins	929	10.8%	
Pre-existing CVD	639	7.4%	
Diagnosed diabetes	572	6.6%	
Missing HbA1c data	4706	54.7%	
Undiagnosed diabetes (HbA1c ≥ 6.5) before imputation HbA1c	98	1.1% (2.5% those with HbA1c data)	
Undiagnosed diabetes (HbA1c ≥ 6.5) after imputation HbA1c	761	8.8%	
IGR (HbA1c 6-6.4%) before imputation HbA1c	529	6.1% (13.6% those with HbA1c data)	
IGR (HbA1c 6-6.4%) after imputation HbA1c	1492	17.3%	
	Mean	**Standard deviation**	**Median**
Age (years)	49.6	18.7	49.0
BMI (kg/m^2)	27.4	5.4	26.6
Total Cholesterol (mmol/l)	5.4	1.1	5.4
HDL Cholesterol (mmol/l)	1.5	0.4	1.5
HbA1c (%)	5.7	0.8	5.6
Systolic Blood Pressure (mm Hg)	126.3	17.0	124.5
EQ-5D (TTO)	0.825	0.244	0.848
BMI Body Mass Index; IMD Index of Multiple Deprivation; CVD Cardiovascular Disease; IGR Impaired Glucose Regulation; HDL High Density Lipoprotein; EQ-5D 5 dimensions EuroQol (health related quality of life index) ; TTO Time Trade-Off			

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.

MISSING DATA IMPUTATION

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.

Anthropometric data

A large proportion of anthropometric data was missing in the cohort. Table 3 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 3: 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 4. 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 4: 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 5. 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 5: 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 6. 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 6: 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 7. 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 7: 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

Metabolic data

A large proportion of metabolic data was missing in the cohort, ranging from 2997-4309 observations for each metabolic measurement. Table 8 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 8: 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 9. 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 9: 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 10. 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 10: 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 11. 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 11: 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 12. 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 12: 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

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.

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.

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.

Smoking

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

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.

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 13.

Table 13: Imputation model for history of diabetes

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

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.

POPULATION SELECTION

The DPP is only eligible to individuals with impaired glucose regulation (IGR), defined as HbA1c 6-6.4% in the model. The process of identifying eligible individuals or referring them to the DPP was not explicitly modelled. Instead, all individuals from the HSE 2011 with actual or imputed HbA1c levels between 6-6.4% are assumed to have been previously identified by a variety of means, and only these IGR individuals are included in the simulation. This means that the costs of identifying IGR individuals or referring them to the DPP intervention are not included.

GP ATTENDENCE IN THE GENERAL POPULATION

Frequency of GP visits (separate from NHS health checks) was simulated in the dataset for two reasons; firstly, to estimate the healthcare utilisation for the ID population without diabetes and cardiovascular disease and secondly, to predict the likelihood that individuals participate in opportunistic screening for diabetes and vascular risks. It was assumed that GP attendance in the ID population occurs at the same frequency as in the general population. However, for cost purposes, consultations were assumed to take 40% longer than the general population average (see Costs section).

GP attendance conditional on age, sex, BMI, ethnicity, and health outcomes was derived from analysis of wave 1 of the Yorkshire Health Study (11). The analysis used a negative binomial regression model to estimate self-reported rate of GP attendance per 3 months (Table 14). The estimated number of GP visits was multiplied by 4 to reflect the annual number of visits per year.

Table 14: 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

LONGITUDINAL TRAJECTORIES OF METABOLIC RISK FACTORS

A detailed description of the statistical analysis behind the personalised metabolic risk factor trajectories that underlie disease risk in the SPHR Diabetes Prevention model has previously been published (12), so this report provides only a brief summary.

A statistical analysis of the Whitehall II cohort study (13) was developed to describe correlated longitudinal changes in metabolic risk factors including BMI, latent blood glucose (an underlying, unobservable propensity for diabetes), total cholesterol, HDL cholesterol and systolic blood pressure. Parallel latent growth modelling was used to estimate the unobservable latent glycaemia and from this identify associations with test results for HbA1c, FPG, and 2-hour glucose. The growth factors (longitudinal changes) for 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.

Unobservable 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.

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.

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 (14). The expected change in HbA1c conditional on HbA1c at diagnosis was estimated 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 15.

Table 15: 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 (15) 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, which means that unobservable differences between individuals are accounted for in the analysis. The model can be used to predict HbA1c over time from the point of diagnosis. The coefficients of the model are reported in Table 16.

Table 16: 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

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.

The epidemiological literature for many of the health outcomes included in the model treats diabetes diagnosis as a discrete health state, rather than a continuous risk function conditional on HbA1c. This poses two methodological challenges in type 2 diabetes modelling. Firstly, diabetes diagnosis is complex with several tests and a high proportion of undetected diagnoses. Therefore, it is not necessarily an appropriate indicator of risk in the model. Secondly, we would prefer to model the relationship on a continuous scale to avoid artificial steps in risk; however the evidence is not always available to describe risk on a continuous scale. We took two main steps to reduce the impact of this on our model. Firstly, we used the HbA1c threshold of 6.5% to indicate type-2 diabetes regardless of detection, and to ensure consistency in natural history across interventions and counterfactuals. Secondly, the QRISK2 model was adapted to incorporate continuous risk by HbA1c.

METABOLIC RISK FACTOR SCREENING, DIAGNOSIS AND TREATMENT

It is assumed 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 with systolic blood pressure greater than 160mmHg.

Individuals may also be detected with 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. 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.

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 (18).
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.

It is assumed within the model that if initiated, statins are effective in reducing an individual's total cholesterol, and so an average effect is applied to all patients being prescribed them. A recent HTA reviewed the literature on the effectiveness and cost-effectiveness of statins in individuals with acute coronary syndrome (20). 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 received 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 (20;21). 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 17. It is based on the published estimate of compliance for the first five years of statin treatment for primary

prevention in general clinical practice (21). 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 17: Proportion of patients assumed to be compliant with statin treatment, derived from Table 62 in (20)

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

In the simulation, it is assumed 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.

The change in systolic blood pressure following antihypertensive treatment was obtained from a meta-analysis of anti-hypertensive treatments (22). This study identified an average change in systolic blood pressure of -8.4 mmHg 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. Non-adherence and discontinuation are not modelled for anti-hypertensives.

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.

CARDIOVASCULAR DISEASE

First Cardiovascular event

Several statistical models for cardiovascular events were identified in a review of economic evaluations for diabetes prevention (4). The UKPDS outcomes model (23), Framingham risk equation (24) and QRISK2 (25) 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 (26). 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 18 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 (27). Coefficients that were not reported in this publication were assumed to have standard errors of 20%.

Table 18: 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 18. 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 18 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 (23). Thirdly, prior to type 2 diabetes (HbA1c>6.5) HbA1c is linearly associated with cardiovascular disease. A study from the EPIC Cohort 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 (28). 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) (21). Table 19 reports the probability of cardiovascular outcomes by age and gender.

Table 19: 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

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 (21). This study reported the probability of future events, conditional on the nature of the previous event. Table 20 to Table 24 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 20: 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 (1^{st} 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 (1^{st} 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 (1^{st} 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 21: 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 22: 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 23: 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 24: 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 (1^{st} 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 (1^{st} 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 (1^{st} 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											

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 (29). The equations included age, diabetes diagnosis (either formal diagnosis or 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 25 describes the covariates for the logit models to estimate the probability of congestive heart failure in men and women.

Table 25: 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. 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 (30). 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 (31). 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 (32). 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 (33).

Using the estimated population values, the intercept values were adjusted 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.

MICROVASCULAR COMPLICATIONS

The review of previous economic evaluations identified that the UKPDS data was commonly used to estimate the incidence of microvascular complications (4). 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 (15;23). 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 (23). 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.

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

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.

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 26 and the individual characteristics for $\boldsymbol{X}$.

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

Table 26: 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 (23). Assuming these mean values, it was possible to modify the baseline risk without simulating heart rate and white blood cell count.

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 27.

Table 27: 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 27 and the individual characteristics for $\boldsymbol{X}$.

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

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.

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

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 diabetes prevention 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 (23). 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 28.

Table 28: 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			

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 29.

Table 29: 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

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.

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 (34). The estimates of the breast cancer incidence in the UK are reported in Table 30.

Table 30: 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	(34)
UK post-menopause	238	84214.6	24	0.00283	(34)

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 (35). 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 (35). 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 31.

Table 31: Relative risk of Breast cancer by BMI

	Mean Relative risk	2.5^{th} Confidence Interval	97.5^{th} Confidence Interval	Reference
UK pre-menopause	0.89	0.84	0.94	(35)
UK post-menopause	1.09	1.04	1.14	(35)

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 (34). The estimates of the colorectal cancer incidence are reported in Table 32.

Table 32: 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	(36)
Female	145	277133	47.7	24.5	0.00052	(36)

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 (35). 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 33.

Table 33: 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	(35)
UK post-menopause	1.04	1	1.07	(35)

OSTEOARTHRITIS

The stakeholder group requested that BMI and diabetes be included as independent risk factors for osteoarthritis based on recent evidence (37). 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 (37). 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 34.

Table 34: Incidence of osteoarthritis and estimated risk factors

	No cases	Person years	Mean BMI	Incidence rate	Reference
No diabetes	73	13835	24.8	0.0053	(37)
	Hazard ratio	2.5th	97.5th		Reference
HR Diabetes	2.06	1.11	3.84		(37)
HR BMI	1.076	1.023	1.133		(37) Personal communication

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 (38). 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 CVD 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 (39). 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 (39). The risk of depression in individuals who have had a stroke was also inflated according to a US cohort study (40). Odds of depression and odds ratios for inflated risk of depression due to diabetes or stroke are presented in Table 35.

Table 35: 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			

MORTALITY

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 (21) as described in the cardiovascular disease section above.

Cancer Mortality

Cancer mortality rates were obtained from the Office of National statistics (41). 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.

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 (42). 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 33).

Table 36: 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 (43). 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 (43). 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.

UTILITIES

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 (44). 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 (21).

Utility Decrements

The utility decrements for long term chronic conditions were applied to the age and BMI adjusted EQ-5D score. It was 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 (45).

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 modelling 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 (46). 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.

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 (47). 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 (21) 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.

A systematic review of breast cancer utility studies was identified 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 (48), 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 (49).

A review of cost-effectiveness studies highlights the scarcity of studies of health-related quality of life in depression (50). 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 (51). 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 37 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 37: 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 (47)
Amputation	-0.172	0.045	0.807	0.787	UKPDS (52)
Blind	0.033	0.027	0.807	1.041	UKPDS (52)
Renal failure	-0.078	0.026	0.689	0.887	Coffey (47)
Stable Angina				0.801	Ward HTA (21)
Unstable Angina y1				0.770	Ward HTA (21)
Unstable Angina y2				0.770	Ward HTA (21)
Myocardial Infarction y1				0.760	Ward HTA (21)
Myocardial Infarction y2				0.760	Ward HTA (21)
Transient Ischaemic Attack				1.000	Ward HTA (21)
Stroke y1				0.629	Ward HTA (21)
Stroke y2				0.629	Ward HTA (21)
Breast Cancer	-0.060		0.800	0.913	Yabroff (48)
Colorectal Cancer	-0.060		0.800	0.913	Yabroff (48)
Osteoarthritis	-0.101				Black HTA (49)
Depression	-0.116		0.7905	0.875	Benedict (51)
Congestive Heart Failure	-0.101	0.032		0.875	UKPDS (52)
UKPDS baseline utility 0.807; HSE baseline 0.7905					

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 the majority of cases it is assumed that the unit costs of healthcare for someone with ID would be the same as the unit costs for an individual in the general population. The exception was cost for a GP appointment, which was expected to be 40% higher than in the general population due to increased length of consultation. All costs were inflated to 2014/15 values using the retail price index where necessary, from the Personal Social Services Research Unit (PSSRU) sources of information (53). Table 38 shows a summary of all the unit costs used in the model and their sources.

Table 38: Summary of all drug, treatment, care and resource costs included in the model

	Drug, Treatment, Care and Resource Costs of	Cost per year/ incident in 2014/15 prices (* 2006 prices)	Source
Screening and Intervention costs			
	Intervention per person	£270	PHE
First line diabetes treatment - low cost diabetes monotherapy			
	Ongoing costs of diabetes monotherapy – made up of…	**£79.06**	
	Metformin 500 mg *bid* standard (85% of patients) or modified release (15%) tablets	£18.83	BNF (54)
	Nurse at GP (consultation)	£25.52	PSSRU (53)
	Health care assistant (10 mins)	£3.40	PSSRU (53)
	Urine sample	£1.00	(55)
	Eye screening	£24.31	(56)
	Lab tests – made up of…	£6.00	
	HbA1c test	£3.00	(55)
	Lipids test	£1.00	(55)
	Liver function test	£1.00	(55)
	B12 test	£1.00	(55)
	Additional first year costs of diabetes monotherapy – made up of…	**£103**	
	Nurse at GP (2 x consultations)	£51.03	PSSRU (53)
	Health care assistant (2 x 10 mins)	£6.80	PSSRU (53)
	Urine sample (x2)	£2.00	(55)
	Lab tests as above (x2)	£12.00	(55)
	Smoking cessation (central estimate of cost of nicotine replacement therapy) taken up by 50% of the assumed 20% of population who smoke	£30.90	PSSRU (53)
Second line diabetes treatment - Metformin and Gliptins– made up of…		**£529**	
	Sitagliptin 100 mg daily	£434	BNF (54)
	Metformin 500 mg *bid* standard (85% of patients) or modified release (15%) tablets	£85	BNF (54)
	Self-monitoring strips (82 per annum) (57)	£16.36	BNF (54)
	Nurse at GP (consultation)	£25.52	(53)
	Health care assistant (10 mins)	£3.40	(53)
	Urine sample	£1.00	(55)
	Eye screening	£24.31	(56)
	Lab tests as for first line treatment	£6.00	(55)
Third line diabetes treatment - Insulin and oral anti-diabetics – made up of…		**£1,503**	
	Nurse at GP (3 x consultations)	£76.55	PSSRU (53)
	Health care assistant (3 x 10 mins)	£10.21	PSSRU (53)
	Urine sample (x3)	£3.00	(55)
	Eye screening	£24.31	(56)
	Lab tests as for first line treatment (x3)	£18.00	(55)
	Insulin treatment costs – made up of…	£1,376	
	Glargine	*£830.83*	(58)
	Oral anti-diabetics	*£57.75*	(58)
	Reagent test strips	*£292.74*	(58)
	Hypoglycaemic rescue	*£30.98*	(58)
	Pen delivery devices	*£72.44*	(58)
	Sharps	*£90.98*	(58)

Other primary care costs				
	GP visit (17 minutes)		£46.95	PSSRU (53)
	Diagnosis of hypertension (including ambulatory blood pressure monitoring)		£56.51	(19)
	Annual treatment with statins (simvastatin 20 mg *bid*)		£26.59	BNF (54)
	Annual treatment with anti-hypertensives		£195.94	(59)
Cardiovascular disease costs				
	Unstable Angina year 1: *Secondary care costs: 100% hospitalisation, 50% revascularisation procedure, three outpatient appointments).* *Primary care costs (three GP visits) and medications*		£4,674	(20)
	Myocardial infarction year 1 *Secondary care costs: 100% hospitalisation,* *50% revascularisation procedure, three outpatient appointments)* *Primary care costs (three GP visits) and medications.*		£4,813	(20)
	Subsequent ACS care costs *Secondary care costs (one outpatient appointment).* *Primary care costs (three GP visits) and medications.*		£410	(20)
	Stroke year 1 (NHS costs) *Costs of acute events reported in Youman et al. (60) weighted by the distribution of severity of stroke (21).*		£9,716	(60)
	Social care costs of stroke in subsequent years *The costs of ongoing care at home or in an institution weighted by the distribution of severity of stroke and discharge locations.*		£2,730	(20)
	Fatal coronary heart disease *Assumed that 50% of fatalities incurred cost.*		£713	(61)
	Fatal non cardiac vascular event *Assumed that 50% of fatalities incurred cost.*		£4,443	(60)
	Congestive heart failure		£3,091	UKPDS (62)
Other complications of diabetes costs				
	Renal failure – weighted composite of…		£25,046	
		Haemodialysis with overheads	*£42,049*	(63)
		Automated peritoneal dialysis	*£27,217*	(63)
		Continuous ambulatory peritoneal dialysis	*£19,742*	(63)
		Transplant (year 1)	*£23,660*	(64)
		Immunosuppressant (10 years)	*£6,959*	(64)
	Foot ulcers		£216	(65)
	Amputation first year		£10,101	UKPDS (66)
	Amputation subsequent years		£1,896	UKPDS (66)
	Blindness first year		£1,434	UKPDS (66)
	Blindness subsequent years		£479	UKPDS (66)
	Breast cancer		£13,818	(67)
	Colorectal cancer		£18,729	(68)
	Osteoarthritis		£962	(69)
	Depression - made up of…		£137	(70)
		Practice nurse at surgery	*£13.70*	
		Practice nurse at home visit	*£0.54*	
		Practice nurse telephone	*£0.99*	
		Health visitor	*£1.94*	
		District nurse	*£0.38*	
		Other nurse	*£1.17*	
		HCA phlebotomist	*£1.05*	

		Other primary care	*£4.85*	
		Out of hours	*£6.18*	
		NHS direct	*£2.28*	
		Walk-in centre	*£8.15*	
		Prescribed medications	*£74*	
		Secondary care	*£21*	
Assumed 20% smoking prevalence and 50% uptake of smoking cessation services SANG Stable angina; UANG unstable angina; MI myocardial infarction; TIA transient ischemic attack; CHD congestive heart failure; ACS acute Coronary Syndrome; UKPDS United Kingdom prospective Diabetes Study. Assume				

Opportunistic screening

Recent guidelines for hypertension have recommended that hypertension be confirmed with ambulatory blood pressure monitoring (ABPM) (18). The cost of ABPM assessment is included in the cost of diagnosis (£53.40) (19), however, we assume that the test does not alter the initial diagnosis.

A cost of diabetes diagnosis is included in the model based on the cost of an HbA1c test.

The cost of screening for high cardiovascular risk was not included as a cost associated with initiation with statins because most GP practices in the UK routinely commission and use cardiovascular risk scores that are easy to access within a normal consultation.

Diabetes

A three stage diabetes treatment regimen is applied in the model as a trade-off between model simplicity and capturing key cost differences between the interventions. At diagnosis all patients are prescribed low cost treatments, represented by Metformin (weighted average of standard and modified release) to describe the average cost of these medications. If HbA1c increases above 7.4% the individual is prescribed the more expensive Gliptins in addition to Metformin, based on a recent HTA (71). For costing purposes the second drug to be added to Metformin was assumed to be Sitagliptin. The individual continues to receive Metformin plus Gliptins for a period of time until they require insulin. Within the model the individual is switched to insulin in the first annual cycle at which HbA1c exceeds 8.5% (71). The insulin Glargine was chosen to represent insulin treatment in the UK. The cost of diabetes in the year of diagnosis is assumed to be greater than subsequent years because the individual will receive more contact time whilst their diabetes is being controlled.

Other Primary Care Costs

Individuals who are prescribed statins receive a daily dose of 40mg of generic Simvastatin. The individual remains on statins for the rest of their life. A unit cost of anti-hypertensives was obtained from a 2004 study (59) and inflated to 2014/15 prices. 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. The stakeholder group

advised that attendance at visits to monitor cardiovascular risk on statins and anti-hypertensives are not perfect. Therefore, the costs of GP attendance to monitor blood pressure and cardiovascular risk are assumed to be accounted for within the model for GP attendance.

Cardiovascular costs

Costs for cardiovascular disease were obtained from a 2009 HTA for high dose lipid-lowering therapy (20). Table 38 shows the details of included costs. The costs of fatal stroke and MI were obtained from two separate studies (60;61), and it was assumed that 50% of individuals would incur these costs. The costs of congestive heart failure were estimated from the UKPDS costing study for complications related to diabetes (62).

Microvascular costs

The cost of renal failure was estimated from three studies reporting the costs of dialysis type (63), the costs of transplantation (64) and the prevalence of dialysis and transplant (72). The overall cost was estimated as a weighted average of the treatment outcomes.

The cost of foot ulcers was estimated from a US Cost of Illness study (65). A search of the literature did not identify any UK based studies. The costs were converted from dollars to pounds using Purchasing Power Parities reported by the OECD (73).

The costs of amputation and blindness in the first year of surgery and in subsequent years were reported in a recent UKPDS costing study (66).

Costs of Other Comorbidities

Disease progression for breast cancer and colorectal cancer was not included in the model. Therefore, a lifetime cost of cancer care was imposed at diagnosis in the model. Costs for breast and colon cancer were taken from two screening appraisals (67;68). Breast cancer costs were estimated as a weighted average depending on the prognosis at diagnosis, whereas colon cancer costs were estimated as a weighted average depending on the Dukes tumour stage.

The annual cost of osteoarthritis was estimated in a costing study (69). 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.

A recent trial to prevent secondary depressive episodes collected comprehensive cost data from a sample of individuals with depression (70). The resource uses identified in the control arm were extracted to estimate the costs of depression. The costs from this data were not implemented directly into the model; this would have over-estimated the number of GP visits as the model already accounts for GP attendance due to depression. Therefore, a revised estimate of the cost of depression,

excluding GP consultation was estimated using updated unit costs. Given that this cost captures the costs of depression following the first acute episode we assumed that this cost adequately described the ongoing healthcare costs for individuals with a history of depression. It is possible that this will overestimate costs for patients who successfully remit and avoid future depression. However, there is evidence from the literature to suggest that individuals with a history of depression have a high utilisation of healthcare resources to support this assumption (74).

INTERVENTION

The subgroup analysis estimates the per person cost savings and health outcomes of delivering the DPP lifestyle intervention in the 22 chosen subgroups. Interventions will be commissioned from a handful of national providers and will include a mixture of dietary educational advice and physical activity, with the aim of reducing both weight and diabetes risk.

The SPHR Diabetes Prevention Model does not explicitly model changes in diet or physical activity. Instead interventions are assumed to impact directly upon individual risk factors such as BMI, blood pressure, cholesterol and HbA1c. In the model these changes then impact upon incidence rates of type 2 diabetes and related diseases. This section of the technical appendix describes the assumptions around the intervention that are used as default settings in the model.

Intervention Uptake

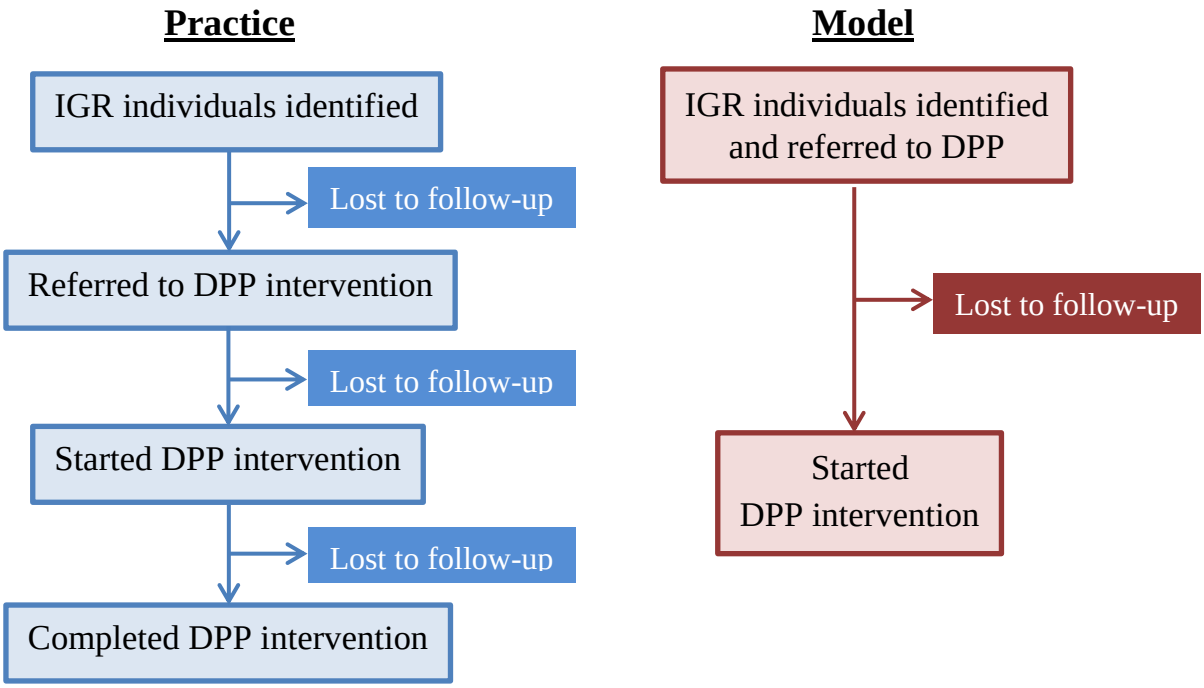
In practice, of the IGR individuals identified through HbA1c testing, only a proportion will receive the intervention. Some individuals may not be referred for intervention. Of those referred, some will choose not to take up the intervention, and of those that do attend the first intervention session, some will not complete the intervention (Figure 2).

Referral rates are not directly modelled, and instead it is assumed that all individuals are identified and referred for intervention prior to the model start. This is partly because of lack of data around referral rates and partly because referral rates are a function of the number of available intervention places.

Intervention uptake is defined as the proportion of those referred to the intervention who decide to take up the intervention. The original aim of the analysis was to include data around differential uptake of interventions in different population subgroups. However, good quality data could not be identified and instead a uniform uptake rate of 32% has been used. It is assumed that those who decided not to take up the intervention incur no costs and no benefits of intervention. No costs of identifying or referring individuals to intervention are modelled. In practice, some individuals who start the intervention will not complete it and therefore not gain full benefit. However, non-

completion is partially accounted for in the estimate of effectiveness used in the model (74), so has not been explicitly built in. This is discussed further below.

Figure 2: Schematic showing intervention uptake and completion in practice and in the model



Intervention Effectiveness

The effectiveness data used in the model comes from a PHE evidence review of pragmatic lifestyle interventions for prevention of type 2 diabetes (75). This updates a previous review by Dunkley and others (76). Both reviews incorporate meta-analyses of a wide range of different lifestyle interventions aimed at reducing type-2 diabetes, and report a variety of outcomes including type-2 diabetes incidence rate and weight loss. The PHE evidence review also includes some analysis of differential effectiveness in population subgroups and for different intervention characteristics.

PHE, NHS England and Diabetes UK have specified that they wish the commissioned DPP intervention to fulfil 9-12 NICE guidelines as recommended in PH38 (3). NICE guidelines include using particular strategies that are associated with increased effectiveness, specifying the minimum amount of contact time and follow-up sessions, and delivering the programme through qualified practitioners. Both the PHE evidence review and the Dunkley meta-analysis indicate that interventions have increased effectiveness if they fulfil a greater number of NICE guidelines (75;76). In line with this, the model uses the results from the subgroup analysis of interventions fulfilling 9-12 NICE guidelines as the mean effectiveness (weight loss of 3.24kg – Table 12 in the PHE Evidence Review (75)).

Unlike the Dunkley meta-analysis, the PHE evidence review does not report differences in HbA1c, systolic blood pressure (SBP) or cholesterol for this subgroup of interventions. However, it is clear from the Dunkley analysis that there will be concurrent reductions in these other metabolic factors, and that the effectiveness of the intervention would be underestimated in the model if they were not included. To incorporate these changes, the differences in HbA1c, SBP and cholesterol were extrapolated from the Dunkley analysis to reflect the updated weight loss used from the PHE evidence review. This assumes that relationships between changes in metabolic factors are linear. The intervention effectiveness for each metabolic factor used in the model is reported in Table 39.

Table 39: Mean intervention effectiveness used in the model

	Mean values from Dunkley et al supplementary Table 7 (76)	**Used in the DPP analysis**: **Default** Mean weight loss from Table 12 of PHE evidence review for 9-12 NICE guidelines (75)	**Used in the DPP analysis**: **Sensitivity analysis - 25% Lower**
Weight (kg)	-2.12	-3.24	-2.43
BMI (kg/m^2)	-0.96	-1.47	-1.10
HbA1c (%)	-0.13	-0.20	-0.15
Systolic Blood Pressure (mmHg)	-4.3	-6.57	-4.93
Total Cholesterol (mmol/l)	-0.18	-0.28	-0.21

There is good evidence from the PHE evidence review and other studies that intervention effectiveness is unlikely to be uniform across the population, and in particular varies according to the baseline BMI of individuals, those with higher baseline BMI reporting increased weight loss and diabetes risk reduction than those with lower baseline BMI (75;77-79). A differential intervention effect by baseline BMI was therefore implemented in the model. Again this was taken from the PHE evidence review as shown in Table 40 (75).

Table 40: Weight change results per unit baseline BMI from the PHE Evidence Review (75)

Subgroup	**Weight change**	**Unit**	**Study Median**
BMI	-0.23 kg (-0.53 to 0.07)	Per unit increase in mean study BMI	31.5 kg/m^2

Personalised intervention effects for each individual, dependent upon their baseline BMI were calculated using the following equation:

Personalised Intervention Effect = Mean Intervention Effect
+ BMI Effect * (Individual BMI – Median BMI)

Where: Mean Intervention Effect = -3.24 kg
BMI Effect = -0.23 kg
Individual BMI = the baseline BMI of each individual in the population
Median BMI = 31.5 kg/m^2 (the median of the mean BMI from each study included in the PHE meta-analysis)

For example, for an individual with baseline BMI of 30, the personalised intervention effect would correspond to a weight loss of 2.895kg (smaller than the mean intervention effect), whereas for an individual with baseline BMI of 35, the personalised intervention effect would correspond to a weight loss of 4.045kg (larger than the mean intervention effect). Note that in individuals with BMI < 17.5, the effect of the intervention would be to actually increase weight. However, there are very few such IGR individuals in the model and an intervention focussing on weight loss may not in any case be the best option for individuals who are already underweight.

From this personalised change in weight due to the intervention, individualised changes in BMI, HbA1c, SBP and cholesterol were derived. Individuals in the intervention arm of the model who take up the intervention were assumed to receive this reduction in their metabolic factors instantaneously at the start of the model.

In practice, some individuals who start the intervention will not complete it. The PHE evidence review contains a mixture of studies that have used either intention to treat or complete case analysis (75). Intention to treat analysis takes non-completion into account, whereas complete case analysis does not. However, it is unclear which studies have been used to derive the estimate of effectiveness for 9-12 NICE guidelines. It is likely therefore that the effectiveness estimate used in the model only partially accounts for non-completion and therefore may be higher than is realistic in practice.

The Whitehall II BMI trajectory model estimates an indirect relationship between BMI change and changes in metabolic risk factors. The changes to HbA1c, systolic blood pressure and cholesterol were adjusted to avoid double counting of the indirect effects through BMI and direct effects of the intervention.

Intervention Costs

The actual intervention cost of the DPP will be determined through the DPP procurement process in early 2016. As this was still undergoing at the time of this analysis, PHE suggested that the mid average cost from their impact assessment of £270 per participant should be used as the default cost. This incorporates expected retention rates of participants, but does not include any local costs of identifying or referring individuals for intervention.

Duration of Intervention Effect

There is very little published information about how long the effectiveness of intensive lifestyle interventions is likely to endure in participants before weight is regained. In the model, default intervention effectiveness is assumed to decline linearly from its peak at the start of the model until individuals reach the BMI/SBP/HbA1c/cholesterol level that they would have been without intervention. It has been assumed for the analysis that this process takes five years.

MODEL PARAMETERS

All parameters used in the model, their distributions for PSA and their sources are documented here.

GP Attendance in the General Population

GP attendance is estimated from statistical analysis of the Yorkshire Health Study (11). In the PSA, the parameters are sampled from a multivariate normal distribution, using the mean estimates described in Table 41 and covariance matrix in Table 42.

Table 41: GP attendance reported in the Yorkshire Health Study (N= 18,437) [(11)]

	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 42: 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

Whitehall II Statistical Model of Metabolic Trajectories

The metabolic trajectories used in the model are derived from statistical analysis of the longitudinal Whitehall II cohort (13). The parameters derived from this model are described in the following tables.

Table 43: 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 44: 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 45: 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

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 (15), are reported in Table 46 and Table 47 respectively.

Table 46: 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 47: 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

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 48.

Table 48: Treatment effects following treatment

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Simvastatin treatment effects	NORMAL	-1.45	0.11	-1.45	(20)
Anti-hypertensive treatment effect	NORMAL	-8.4	0.638	-8.4	(22)
Statin Uptake	UNIFORM	0.65	(0.4-0.9)	0.65	(21)

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 49.

Table 49: 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)

COMORBID OUTCOMES AND MORTALITY

Cardiovascular Disease

Cardiovascular risk is estimated using the QRISK2 model (25). Parameter distributions for men and women are reported in Table 50.

Table 50: 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 IGR and type 2 Diabetes (HbA1c>42 mmol/mol). The parameter distributions for these additional inputs are reported in Table 51.

Table 51: 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	[25]
Male RR of MI due to HbA1c in diabetics	LOGNORMAL	0.108	0.023	1.11	[25]
RR of stroke due to HbA1c in diabetics	LOGNORMAL	0.092	0.026	1.096	[25]
Log(RR) of cvd due to IGR	NORMAL	0.223	0.043	1.25	[28]

Congestive Heart Failure

The parameter distributions for congestive heart failure based on the Framingham Heart Study (29) are reported in Table 52.

Table 52: 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 & Diabetes	NORMAL	-0.986	1.4370	-0.986

Microvascular Complications

The parameter distributions for the risk models for foot ulcer, blindness, renal failure, first amputation and second amputation are reported in Table 53. Parameters for renal failure were based on the UKPDS Outcomes Model 1 (15), whereas parameters for other microvascular complications were based on the UKPDS Outcomes Model 2 (23).

Table 53: 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

Cancer

The parameter distributions for the incidence and hazard ratios for breast cancer and colorectal cancer are reported in Table 54.

Table 54: 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	(36)
Colorectal cancer women	NORMAL	0.0005	0.0000	0.0005	(36)
Breast cancer pre-menopause	NORMAL	0.0010	0.0001	0.0010	(34)
Breast cancer post-menopause	NORMAL	0.0028	0.0002	0.0028	(34)
Colorectal cancer BMI relative risk for men	LOGNORMAL	0.1906	0.0111	1.21	(35)
Colorectal cancer BMI relative risk for women	LOGNORMAL	0.0392	0.0151	1.04	(35)
Breast cancer BMI relative risk for pre-menopause	LOGNORMAL	-0.1165	0.0251	0.89	(35)
Breast cancer BMI relative risk for post-menopause	LOGNORMAL	0.0862	0.0205	1.09	(35)

The parameter distributions for breast and colorectal cancer mortality are reported in Table 55.

Table 55: Input parameters for breast cancer and colorectal cancer mortality (41)

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

Osteoarthritis

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

Table 56: Input parameters for the osteoarthritis risk model (37)

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

Depression

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

Table 57: 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	[39]
Odds ratio for diabetes	LOGNORMAL	0.4187	0.1483	1.52	[39]
Odds ratio for stroke	LOGNORMAL	1.8406	0.5826	6.3	[40]

UTILITIES

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

Table 58: Utility input parameters

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Renal/ulcer baseline utility	NORMAL	0.689	0.014	0.689	[47]
Renal dialysis	NORMAL	-0.078	0.026	-0.078	[47]
Foot ulcer	NORMAL	-0.099	0.013	-0.099	[47]
Amputation/heart failure baseline utility	NORMAL	0.807	0.005	0.807	[23]
Heart failure	NORMAL	-0.101	0.032	-0.101	[23]
Amputation	NORMAL	-0.172	0.045	-0.172	[23]
Stable angina multiplicative factor decrement	NORMAL	0.801	0.038	0.801	[21]
Unstable angina multiplicative factor decrement	NORMAL	0.77	0.038	0.77	[21]
MI multiplicative factor decrement	NORMAL	0.76	0.018	0.76	[21]
Stroke multiplicative factor decrement	NORMAL	0.629	0.04	0.629	[21]
Cancer baseline utility	NORMAL	0.8	0.0026	0.8	[48]
Cancer decrement	NORMAL	-0.06	0.008	-0.06	[48]
Osteoarthritis utility	NORMAL	0.69	0.069	0.69	[49]
Depression baseline utility	NORMAL	0.48	0.048	0.48	[51]
Depression remitters	NORMAL	0.31	0.031	0.31	[51]
Depression responders	NORMAL	0.20	0.020	0.20	[51]
Depression non-responders	NORMAL	0.070	0.007	0.070	[51]
Depression drop-outs	NORMAL	0.050	0.005	0.050	[51]
Age utility decrement	NORMAL	-0.004	0.0001	-0.004	[21]

UNIT HEALTH CARE COSTS

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

Table 59: Cost input parameters

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
DPP Intervention	GAMMA			£270	PHE
DIABETES COSTS					
Insulin (annual cost)	GAMMA	3.367	408.6	£1375.72	[58]
Metformin (annual cost)	CONSTANT	NA	NA	£18.83	[54]
Sitagliptin (annual cost)	CONSTANT	NA	NA	£433.77	[54]

Nurse appointment (Advanced)	GAMMA	100	0.26	£25.52	[53]
Health care assistant appointment	GAMMA	100	0.03	£3.40	[53]
Eye screening	GAMMA	15.3664	1.58219	£24.31	[56]
HbA1c test	GAMMA	100	0.03	£3.00	[55]
Lipids test	GAMMA	100	0.01	£1.00	[55]
LfT test	GAMMA	100	0.01	£1.00	[55]
B12 test	GAMMA	100	0.01	£1.00	[55]
Urine test	GAMMA	100	0.01	£1.00	[55]
Nicotine replacement therapy	GAMMA	100	1.03	£103.00	[53]
CVD COSTS					
Unstable Angina hospital admission	GAMMA	100	12.75591	£1275.59	[20]
Revascularisation in hospital	GAMMA	100	60.36846	£6036.85	[20]
MI Hospital admission	GAMMA	100	15.54896	£1554.90	[20]
First Outpatient appointment	GAMMA	100	1.653571	£165.36	[20]
Subsequent outpatient appointments	GAMMA	100	1.100574	£110.06	[20]
Fatal CHD	GAMMA	100	7.125001	£712.50	[38]
Fatal Stroke	GAMMA	100	44.42562	£4442.56	[60]
First year stroke	GAMMA	100	97.15908	£9715.91	[60]
Subsequent year stroke	GAMMA	100	27.29644	£2729.64	[20]
Glytrin Spray	CONSTANT	NA	NA	£12.61	[20]
Isosorbide mononitrate	CONSTANT	NA	NA	£13.54	[20]
Verapamil	CONSTANT	NA	NA	£50.57	[20]
Atenolol	CONSTANT	NA	NA	£36.42	[20]
Aspirin	CONSTANT	NA	NA	£8.01	[20]
Ramipril	CONSTANT	NA	NA	£90.45	[20]
ARB	CONSTANT	NA	NA	£253.28	[20]
Clopidogrel	CONSTANT	NA	NA	£554.41	[20]
Congestive Heart Failure	GAMMA	67.20788	45.99274	£3091.07	[62]
MICROVASCULAR COSTS					
Blindness year 1	GAMMA	10.26317	139.7079	£1433.85	[66]
Blindness subsequent years	GAMMA	11.31099	42.37999	£479.36	[66]
Amputation year 1	GAMMA	19.37193	521.4492	£10101.48	[66]
Amputation subsequent years	GAMMA	4.597909	412.4212	£1896.28	[66]
Renal Haemodialysis	GAMMA	100	420.49	£42049.00	[63]
Renal Automated Peritoneal dialysis	GAMMA	100	272.1714	£27217.14	[63]
Renal Ambulatory peritoneal dialysis	GAMMA	100	197.4225	£19742.25	[63]
Renal transplant	GAMMA	100	236.5973	£23659.73	[64]
Immunosuppressants	GAMMA	100	69.58745	£6958.75	[64]
Foot ulcer not infected	GAMMA	100	1.677526	£167.75	[65]
Foot ulcer with cellulitis	GAMMA	100	4.431003	£443.10	[65]
Foot ulcer with osteomyelitis	GAMMA	100	8.215817	£821.58	[65]
OTHER DISEASE COSTS					
Breast Cancer	GAMMA	100	138.1811	£13818.11	[67]
Colorectal cancer Dukes A	GAMMA	100	100.9135	£10091.35	[68]
Colorectal cancer Dukes B	GAMMA	100	173.1532	£17315.32	[68]
Colorectal cancer Dukes C	GAMMA	100	265.5026	£26550.26	[68]
Colorectal cancer Dukes D	GAMMA	100	166.2553	£16625.53	[68]
Osteoarthritis	GAMMA	100	9.616886	£961.69	[69]
Depression – Practice nurse surgery	GAMMA	100	0.090154	£9.02	[70]
Depression – Practice nurse home	GAMMA	100	0.270463	27.05	[70]
Depression – Practice nurse telephone	GAMMA	100	0.090154	9.02	[70]
Depression – Health visitor	GAMMA	100	0.387834	38.78	[70]
Depression – District nurse	GAMMA	100	0.377628	37.76	[70]
Depression – Other nurse	GAMMA	100	0.090154	9.02	[70]
Depression – HCA phlebotomist	GAMMA	100	0.034021	3.40	[70]
Depression – Other primary care	GAMMA	100	0.255154	25.52	[70]
Depression – Out of Hours	GAMMA	100	0.268661	26.87	[70]
Depression – NHS Direct	GAMMA	100	0.25295	25.30	[70]
Depression – Walk-in Centre	GAMMA	100	0.388316	38.83	[70]
Depression – Prescribed medicines	GAMMA	100	0.096144	9.61	[70]

Depression – Secondary Care	GAMMA	100	0.81	81.00	[70]
DIAGNOSIS AND OTHER COSTS					
GP appointment	GAMMA	100	0.47	£46.95	[53]
Diabetes diagnosis	GAMMA	100	0.12	£14.81	[55]
Hypertension diagnosis	GAMMA	100	0.57	£56.51	[19]
Anti-hypertensives	GAMMA	100	1.96	£195.94	[59]
Simvastatin	CONSTANT	NA	NA	£26.59	[54]

QUALITY ASSURANCE

Within ScHARR, research is conducted within a framework of standards and systems that ensure high quality science and governance. This includes ensuring staff receive appropriate training and operate within a culture of high quality research, building sufficient time into each project for quality assurance (including error checking and validation), internal and external review of models and ideally external peer review through publication in academic journals.

The SPHR Diabetes Prevention Model has undergone an extensive process of quality assurance and error checking, both during its development and during the adaptations required for this analysis. Face validity around the model structure and assumptions was provided during model development by means of regular input from a group of stakeholders, including clinicians, diabetes researchers, patients and public health commissioners, and during model adaptation by a group of stakeholders representing the seven DPP demonstrator sites.

A guide to checking, avoiding and identifying errors in health economic models has recently been developed within ScHARR (81). Where possible, the suggested black box verification tests were carried out as part of model development. A more complex set of internal validations were also carried out to ensure that the model was behaving as planned (e.g. that metabolic trajectories and risk equations work in the intended way). The model has also undergone a series of validations against external data (82), and the structure and model assumptions have undergone formal peer review for a publications associated with the model (12). Finally, in addition to ScHARR's own process of model quality assurance and error checking, the model code was externally reviewed and refactored as part of the PHE project adaptation by Dr Mat Hall, a software engineer from the Department of Computer Science at the University of Sheffield.

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