



OPEN ACCESS

## ORIGINAL ARTICLE

# A cardiovascular disease policy model that predicts life expectancy taking into account socioeconomic deprivation

J D Lewsey,<sup>1</sup> K D Lawson,<sup>1</sup> I Ford,<sup>2</sup> K A A Fox,<sup>3</sup> L D Ritchie,<sup>4</sup> H Tunstall-Pedoe,<sup>5</sup> G C M Watt,<sup>6</sup> M Woodward,<sup>7</sup> S Kent,<sup>1</sup> M Neilson,<sup>1</sup> A H Briggs<sup>1</sup>

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/heartjnl-2014-305637>).

For numbered affiliations see end of article.

## Correspondence to

Dr Jim Lewsey, Health Economics and Health Technology Assessment (HEHTA), Institute of Health & Wellbeing, 1 Lilybank Gardens, University of Glasgow, Glasgow G12 8RZ, UK; [jim.lewsey@glasgow.ac.uk](mailto:jim.lewsey@glasgow.ac.uk)

Received 12 February 2014  
Revised 16 September 2014  
Accepted 18 September 2014  
Published Online First  
16 October 2014



Open Access  
Scan to access more  
free content



CrossMark

To cite: Lewsey JD, Lawson KD, Ford I, et al. *Heart* 2015;101:201–208.

## ABSTRACT

**Objectives** A policy model is a model that can evaluate the effectiveness and cost-effectiveness of interventions and inform policy decisions. In this study, we introduce a cardiovascular disease (CVD) policy model which can be used to model remaining life expectancy including a measure of socioeconomic deprivation as an independent risk factor for CVD.

**Design** A state transition model was developed using the Scottish Heart Health Extended Cohort (SHHEC) linked to Scottish morbidity and death records. Individuals start in a CVD-free state and can transit to three CVD event states plus a non-CVD death state. Individuals who have a non-fatal first event are then followed up until death. Taking a competing risk approach, the cause-specific hazards of a first event are modelled using parametric survival analysis. Survival following a first non-fatal event is also modelled parametrically. We assessed discrimination, validation and calibration of our model.

**Results** Our model achieved a good level of discrimination in each component (c-statistics for men (women)—non-fatal coronary heart disease (CHD): 0.70 (0.74), non-fatal cerebrovascular disease (CBVD): 0.73 (0.76), fatal CVD: 0.77 (0.80), fatal non-CVD: 0.74 (0.72), survival after non-fatal CHD: 0.68 (0.67) and survival after non-fatal CBVD: 0.65 (0.66)). In general, our model predictions were comparable with observed event rates for a Scottish randomised statin trial population which has an overlapping follow-up period with SHHEC. After applying a calibration factor, our predictions of life expectancy closely match those published in recent national life tables.

**Conclusions** Our model can be used to estimate the impact of primary prevention interventions on life expectancy and can assess the impact of interventions on inequalities.

## INTRODUCTION

The Global Burden of Disease Study<sup>1</sup> estimated that in 2010 cardiovascular disease (CVD), including rheumatic heart diseases, hypertensive diseases, ischaemic heart diseases, pulmonary heart disease, other forms of heart disease, cerebrovascular diseases (CBVDs), diseases of arteries and diseases of veins, was the cause of death in approximately 30% of all global deaths. In Scotland, although mortality rates have declined steadily for decades (eg, coronary heart disease (CHD) mortality rates for men were 72% lower in 2009 than in 1950), in 2009,

Scottish CHD mortality rates for men and women were 39% and 64% higher, respectively, than the average for Western Europe.<sup>2</sup> Furthermore, despite improvements, inequalities persist in Scotland. For example, in 2011, the European age-standardised CHD mortality rates for the most deprived fifth of the Scottish Index of Multiple Deprivation (SIMD) scores<sup>3</sup> were 62% higher than the corresponding rates for the least deprived fifth of SIMD scores.<sup>4</sup>

There are many types of CVD interventions (eg, lifestyle, pharmaceuticals, legislation, etc.) which aim to reduce the disease burden, ranging from those that target the individual to those with population coverage. Reimbursement agencies, such as the National Institute for Health and Care Excellence<sup>5</sup> in England and Wales and the Scottish Medicines Consortium<sup>6</sup> in Scotland, require evidence that interventions are cost-effective prior to adoption. A challenge in generating this evidence is that randomised trials are short term in nature and so often modelling is necessary to predict longer term cost-effectiveness.

A definition of a policy model is a model that can evaluate the effectiveness and cost-effectiveness of interventions and inform policy decisions. There are a wide variety of CVD policy models in existence.<sup>7</sup> A recent example,<sup>8</sup> set in England and Wales, uses Framingham risk equations to build a model which can estimate the impact of potential interventions in terms of CVD events prevented, life years and quality-adjusted life years gained and costs to the National Health Service. A limitation of this model, as the authors acknowledge, is that it uses a limited time frame (10 years) rather than a lifetime perspective.

In developing a model to be used by policy makers, it is important that the approach is consistent with prediction models that are used in clinical practice. The Scottish Intercollegiate Guidelines Network<sup>9</sup> has recommended the use of the ASSIGN score<sup>10</sup> as the clinical prediction tool for prioritising individuals for primary prevention in Scotland. A key feature of this score is the inclusion of an area-based measure of socioeconomic deprivation, SIMD,<sup>3</sup> as an independent risk factor. This has the potential to reduce inequalities because, holding the other risk factors constant, people residing in areas with higher levels of socioeconomic deprivation will be given higher ASSIGN scores. Furthermore, if the ASSIGN score is used in modelling exercises to estimate the impact of new

interventions, it also provides an assessment of how the new intervention will affect the level of inequality.

The aim of our study is to develop a CVD policy model for use in Scotland using the same risk factors as ASSIGN but taking a lifetime perspective. The key outputs from this model will be life expectancy, quality-adjusted life expectancy and lifetime healthcare costs. These outputs can be used in decision analysis to assess the cost-effectiveness of interventions and their impact on health inequalities. We will report our model in a comprehensive and transparent manner, following best practice guidelines.<sup>11</sup>

## METHODS

We describe the methods below with additional technical details available in the online supplementary appendix.

### Model structure

As for ASSIGN, the endpoints of our model are non-fatal CHD hospitalisation, non-fatal CBVD hospitalisation and deaths from CVD. However, with the focus on life expectancy we also needed to consider deaths from non-CVD causes and the additional life expectancy experienced after a non-fatal CHD or CBVD event. Figure 1 illustrates the structure of the state transition model. People enter the model in the CVD event-free state and then transit into one of four events ‘competing’ to be first. If a hospitalised patient died within 28 days of their admission the first event was reclassified as fatal. If the first event experienced is non-fatal, then there is a final transition to death. Men and women were modelled separately.

### Data source

The Scottish Heart Health Extended Cohort (SHHEC) is made up of individuals from the Scottish Heart Health Study<sup>12</sup> which recruited random samples of the Scottish population between 1984 and 1987, and individuals from the Scottish MONICA Project<sup>13</sup> which recruited in Edinburgh in 1986 and North Glasgow in 1986, 1989, 1992 and 1995. The SHHEC participants, aged between 25 and 74 years, attended a survey clinic where cardiovascular risk factors were measured.

The data were linked to hospital admissions using the Scottish Morbidity Record Scheme and deaths using the General Register Office (GRO) for Scotland. Risk factors used for modelling the first event were age at survey (years), systolic blood pressure (SBP; mm Hg), total cholesterol (TC; mmol/L), high-density lipoprotein (HDL) cholesterol (mmol/L), cigarettes per day (CPD), self-reported diabetes, self-reported family history of heart disease and SIMD score (2004 version). Risk factors used for modelling death after a non-fatal first event were age at first event, self-reported family history of heart disease and SIMD. Any missing data in the risk factors were taken into account using the multiple imputation of chained equations technique.<sup>14</sup>

It should be noted that the modifiable risk factors of SBP, TC, HDL cholesterol and CPD can only directly influence the risk of having a first event as these variables were only measured at baseline. Therefore, the focus of our policy model is to evaluate primary prevention interventions.

### Modelling stage 1: estimating risk of having first event

Survival analysis was used to model the cause-specific hazards of the competing first events (equation 1 in figure 1). By the end of follow-up not all SHHEC participants had experienced a first event, so a parametric approach (Gompertz regression) was required to extrapolate the modelling so total remaining life expectancy could be estimated. Predicted cumulative incidence

of events was calculated from the cause-specific hazards and the probability of surviving from any of the competing events at a given time.

### Modelling stage 2: estimating life expectancy following non-fatal CHD and CBVD events

Gompertz regression was also used to model the hazard of death following a first event (equation 2 in figure 1). Due to censoring it was necessary to extrapolate the survival analysis to a time point when for a given covariate profile the probability of surviving beyond that time point was zero. The area under the survival curve was obtained by applying the trapezoidal rule<sup>15</sup> with half cycle correction and this provided an estimate of remaining life expectancy.

### Modelling stage 3: estimating overall life expectancy

The state transition model uses a cycle period of 1 year. At the end of a model cycle an individual can either remain in the CVD-free state or move to one of the four competing events. To calculate remaining life expectancy, the model sums the time before an event and survival time after non-fatal event (area under the survival curve). The model cycles annually for 100 years and within each cycle the model estimates the consequences if each of the competing first events occurred. For example, if a person has a non-fatal CHD event after 3 years the additional life expectancy is those 3 years added to the life expectancy following the non-fatal event predicted from the survival analysis (modelling stage 2). Whereas, if a person dies of CVD causes after 3 years the additional life expectancy is just those 3 years. All these first event possibilities are weighted by the probability of that event occurring at that particular time which comes from the predicted cumulative incidence estimates (modelling stage 1).

For measuring inequalities in life expectancy, we calculated the Slope Index of Inequality (SII)<sup>16</sup> which takes into account the whole distribution of life expectancy across the range of SIMD.

### Discrimination, validation and calibration of the model

The discrimination of the statistical models was assessed using Harrell’s concordance statistic (c-statistic).<sup>17</sup> It is important to note this will only assess discrimination where we have observed events to compare with the model predictions. As a validation exercise, we used the West of Scotland Coronary Prevention Study (WOSCOPS)<sup>18</sup> to test the extent to which our model can predict events in a Scottish population that did not inform the development of the model. WOSCOPS was a randomised trial investigating the effectiveness of pravastatin in preventing CHD in asymptomatic men aged between 45 and 64 years. Further details of the validation exercise are shown in the online supplementary appendix.

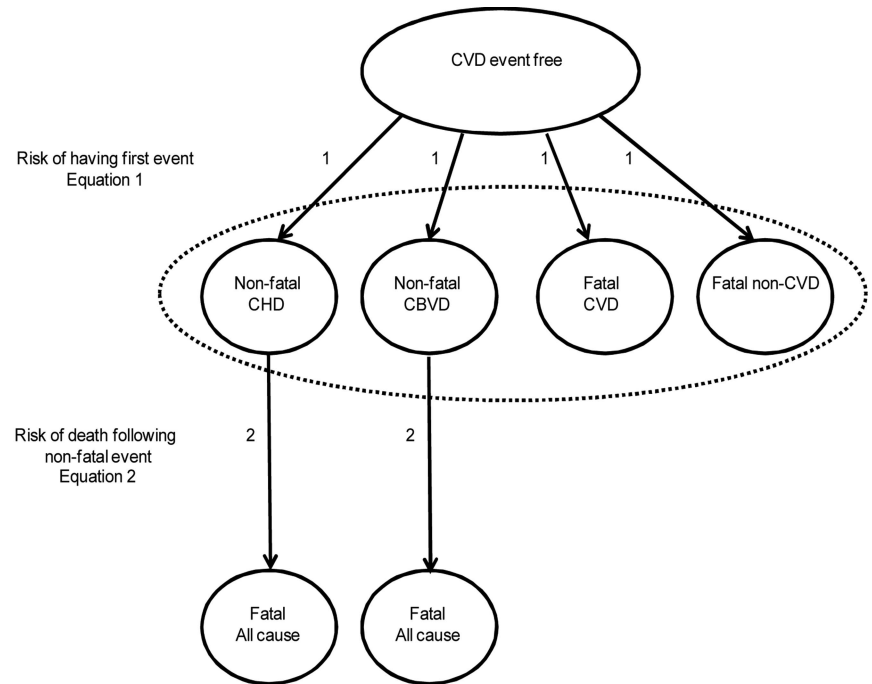
Predicted life expectancies were obtained from a model where the risk factor values are provided by average values from the Scottish Health Survey 2009.<sup>19</sup> These predicted life expectancies were compared with life expectancies published in GRO life tables.<sup>20</sup> A calibration factor was used to adjust the linear predictor of the Gompertz regressions for first events to minimise the root mean square error between the predicted and observed life expectancy values for individuals aged 40, 60 and 80 years.

## RESULTS

### Description of demographics and event outcomes

A total of 16 560 SHHEC participants were free of CVD at baseline, 8611 (52%) were women. The distribution of risk

**Figure 1** Structure of the state transition model. CBVD, cerebrovascular disease; CHD, coronary heart disease; CPD, cigarettes per day; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol (mmol/L); SIMD, Scottish Index of Multiple Deprivation; SBP, systolic blood pressure (mm Hg); TC, total cholesterol (mmol/L).



Equation 1: Function (age at survey, SBP, TC, HDL, CPD, family history, SIMD)

Equation 2: Function (age at first event, family history, SIMD)

factors is shown in table 1. The median survival time to first event was 20.8 years (IQR 14.5, 23.6 years). A total of 6175 people (37.3%) had a first event observed during the follow-up period.

### Illustration of the three modelling stages

We illustrate how the model moves from risk of events to remaining life expectancy using the following individual profile: 60-year-old man, no family history of CVD, non-diabetic,

SIMD score of 60.8, SBP of 160 mm Hg, TC of 7 mmol/L, HDL of 1 mmol/L and 20 CPD. The predicted cumulative incidence of the four first events and survival probabilities after a first non-fatal event (as well as the survival model estimates that produce the predictions) are detailed in the online supplementary appendix.

Table 2 shows how life expectancy is estimated. The top panel of table 2 shows remaining life expectancy estimated at the end of every cycle and for each of the four first events. For example, at the end of cycle 24 the estimated life expectancy for a man experiencing a non-fatal CHD event at that time is the 24 years alive and event free plus 3.3 years, which is the estimated life expectancy following the event. The probabilities of having a first event for each cycle are shown in the middle panel of table 2. These are obtained from the cumulative incidence curves by subtracting the cumulative probability from the previous year from the current year. The bottom panel of table 2 shows the weighted life expectancies which are obtained by multiplying together the values in the corresponding cells in the previous two panels. The sum of all the cells in the bottom panel of table 2 is the remaining expected life expectancy, which for this illustration equals 14.07 years (so life expectancy is 60+14.07=74.07 years).

### Discrimination, validation and calibration of model

The discrimination of all statistical models was good with c-statistics in the range 0.65–0.80 (see online supplementary appendix). Discrimination was better for the first event models than the models following a first non-fatal event, better for the fatal CVD outcome compared with the other competing first events, and generally better for models for women than for men.

Figure 2 shows the comparison between observed cumulative incidence of first events from WOSCOPS with predictions made

**Table 1** Demographics of SHHEC participants free of cardiovascular disease at baseline

	Men	Women
Cohort size	7949	8611
Age (years)	48.6 (9.3)	48.6 (9.3)
SIMD groups (fifths), n (%):		
1 (least deprived)	1390 (17.5)	1467 (17.0)
2	1197 (15.1)	1214 (14.1)
3	1264 (15.9)	1364 (15.8)
4	1479 (18.6)	1675 (19.5)
5 (most deprived)	2619 (32.9)	2891 (33.6)
Diabetes, n (%)	125 (1.6)	117 (1.4)
Family history, n (%)	2061 (25.9)	2788 (32.4)
Cigarette smokers, n (%)	3083 (39.2)	3317 (38.9)
CPD	20.4 (10.2)	16.8 (7.9)
SBP (mm Hg)	133.6 (19.3)	129.7 (21.0)
TC (mmol/L)	6.2 (1.2)	6.4 (1.3)
HDL (mmol/L)	1.3 (0.5)	1.6 (0.4)

Statistics are mean (SD) unless otherwise stated; cigarettes per day (CPD) statistics are reported for smokers only.

HDL, high-density lipoprotein; SBP, systolic blood pressure; SHHEC, Scottish Heart Health Extended Cohort; SIMD, Scottish Index of Multiple Deprivation; TC, total cholesterol.

**Table 2** Process of estimating life expectancy

Conditional life years remaining (event type and timing)

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	Fatal CVD	Fatal non-CVD
1	15.6	14.2	1.0	1.0
2	15.8	14.5	2.0	2.0
3	16.1	14.8	3.0	3.0
.				
22	25.8	25.9	22.0	22.0
23	26.5	26.7	23.0	23.0
24	27.3	27.4	24.0	24.0
.				
100	100.5	100.5	100.0	100.0

Probability of event occurring (event type and timing)

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	Fatal CVD	Fatal non-CVD
1	0.023	0.008	0.016	0.013
2	0.023	0.008	0.016	0.013
3	0.023	0.008	0.016	0.013
.				
22	0.003	0.002	0.004	0.003
23	0.002	0.002	0.003	0.002
24	0.002	0.001	0.002	0.002
.				
100	0.000	0.000	0.000	0.000

Weighted remaining life years (estimates from top panel multiplied by estimates from middle panel)

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	Fatal CVD	Fatal non-CVD	Sum
1	0.361	0.108	0.016	0.013	0.498
2	0.365	0.113	0.032	0.026	0.537
3	0.368	0.119	0.049	0.040	0.576
.					
22	0.084	0.057	0.079	0.067	0.286
23	0.066	0.046	0.064	0.054	0.230
24	0.050	0.036	0.050	0.043	0.179
.					
100	0.000	0.000	0.000	0.000	0.000

Total life years remaining (cumulative sum over each model cycle)=

14.07

Overall life expectancy (age upon entering model plus life years remaining)=

74.07

CBVD, cerebrovascular disease; CHD, coronary heart disease; CVD, Cardiovascular Disease.

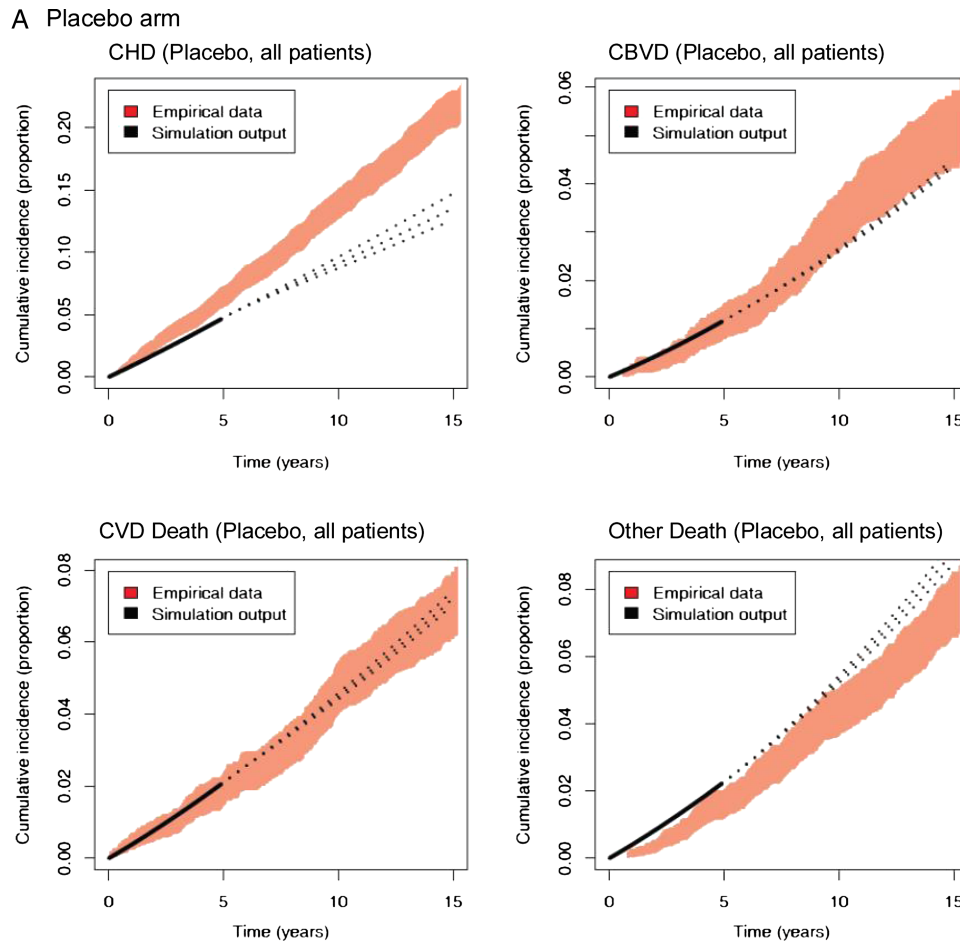
with our model. For the placebo arm, the predicted line falls well within the CI limits for non-fatal CBVD and fatal CVD events. However, the model underpredicts for non-fatal CHD and overpredicts for fatal non-CVD. The latter may be explained by the fact that WOSCOPS is a clinical trial where stringent exclusion criteria can result in lower mortality than observed in the general population. For the treatment arm, the agreement is good for all cardiovascular endpoints (given the exclusion of cancers from the trial), illustrating that the model has the potential to predict the impact of CVD interventions.

Without applying a calibration factor, the original model over-predicted life expectancy. After applying a calibration factor (see online supplementary appendix for details), all model estimates were within half a year of life table estimates with the exception of 80-year-old women.

### Illustration of life expectancies

The online supplementary table shows predicted life expectancies for men and women across a wide range of individual profiles. The table shows how age, SBP, cholesterol, smoking (where 'smoker' is defined as somebody smoking 20 CPD) and SIMD influence life expectancy while holding diabetes and family history of heart disease constant at their average values. It can be seen that even after adjusting for traditional CVD risk factors, socioeconomic deprivation has a large impact on life expectancy. To illustrate the socioeconomic deprivation gradient, figure 3 shows the predicted life expectancies for 60-year olds across ranked fifths of SIMD scores (within each ranked group average values risk factor values were obtained from the Scottish Health Survey 2009). The difference in predicted life expectancy using the SII to compare the least and





**Figure 2** A and B, Validation of model predictions using West of Scotland Coronary Prevention Study trial population. CBVD, cerebrovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease.

most deprived groups is 6.8 and 5.7 years for men and women, respectively.

## DISCUSSION

### Summary

This paper introduces an alternative CVD Policy Model, which includes a measure of socioeconomic deprivation as an independent risk factor. The inputs to the statistical models are the ASSIGN risk factors and the output is predicted life expectancy. By including a measure of socioeconomic deprivation as one of the risk factors, the model can account for disparity in life expectancy according to the deprivation.

### Comparison with other studies

There are many CVD/CHD policy models in the existing literature and they vary considerably in their methodology. In this section, we consider models that have used life expectancy as the outcome for evaluating the effectiveness of interventions.

The CHD policy model<sup>21</sup> is a state transition model developed in the USA. It has been used to evaluate the cost-effectiveness of both primary and secondary prevention strategies.<sup>22</sup> In a later application,<sup>23</sup> the model was used to evaluate the impact of risk factor modification on life expectancy. Like our model, it used a nationally representative survey to obtain baseline distributions of risk factors but unlike our model it used relative risks from Framingham risk equations in conjunction with national mortality rates to estimate annual incidence rates of CHD and non-CHD events, rather than following up the survey

participants as a cohort study. Unlike our model, it did not include a measure of socioeconomic deprivation.

The IMPACT CHD mortality model<sup>24</sup> was developed to estimate the fall in CHD mortality in Scotland attributable to treatment and risk factor change in Scotland between 1975 and 1994. It was later used<sup>25</sup> to estimate the attributable gains in terms of life years by multiplying the number of deaths prevented/postponed by estimates of median survival taken from Scottish cohort studies linked to national morbidity and mortality records. In the original paper, the reduction in CHD deaths caused by changes in socioeconomic deprivation over time was calculated. The components of this model were obtained from various sources to obtain, for example, percentage reduction in mortality to be expected from one percentage change in risk factors.

The heart protection study was originally a randomised controlled study that demonstrated both the effectiveness and the cost-effectiveness of simvastatin.<sup>26</sup> In a later application the cost-effectiveness of simvastatin was evaluated for remaining life expectancy of the trial population for a range of different risks of vascular disease and age groups.<sup>27</sup> This evaluation was performed using a Markov state transition model and internally validated by comparing observed with predicted number of events. Unlike our cohort, the trial participants had a history of CVD or were being treated for hypertension. Alongside the treatment effect, many risk factors, including creatinine which was not part of our models (but no measure of socioeconomic deprivation), were used in parametric survival risk equations for vascular endpoints.

## B Treatment arm

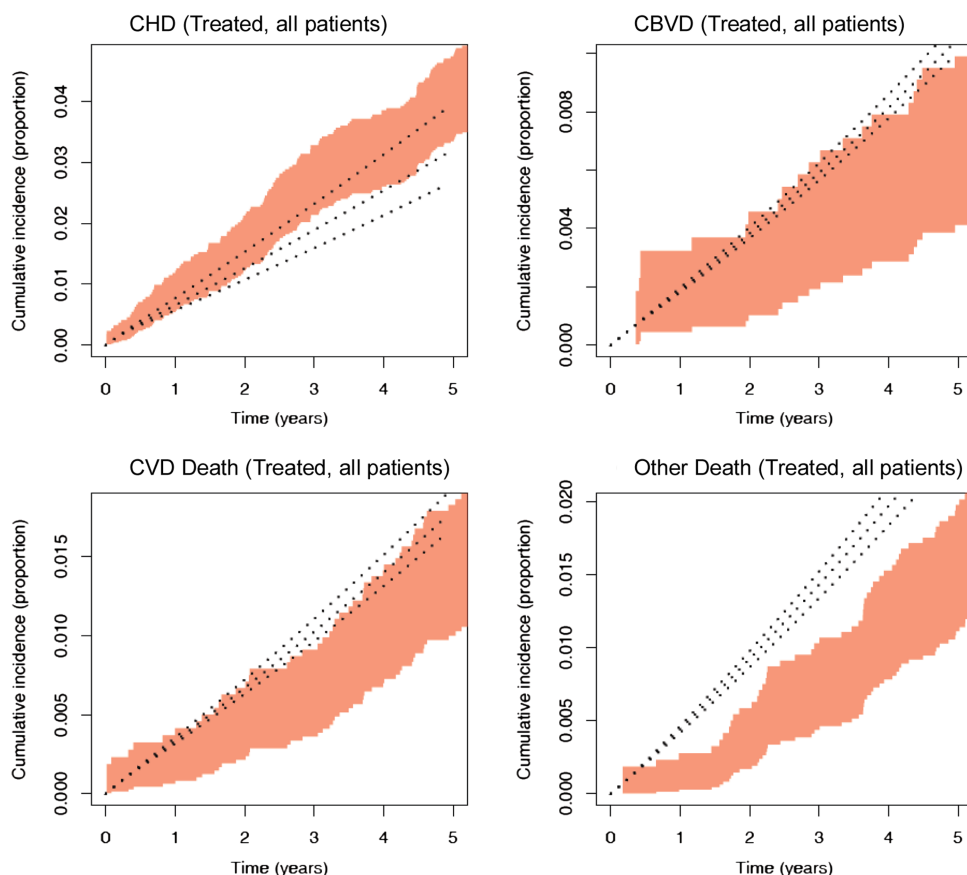


Figure 2 Continued

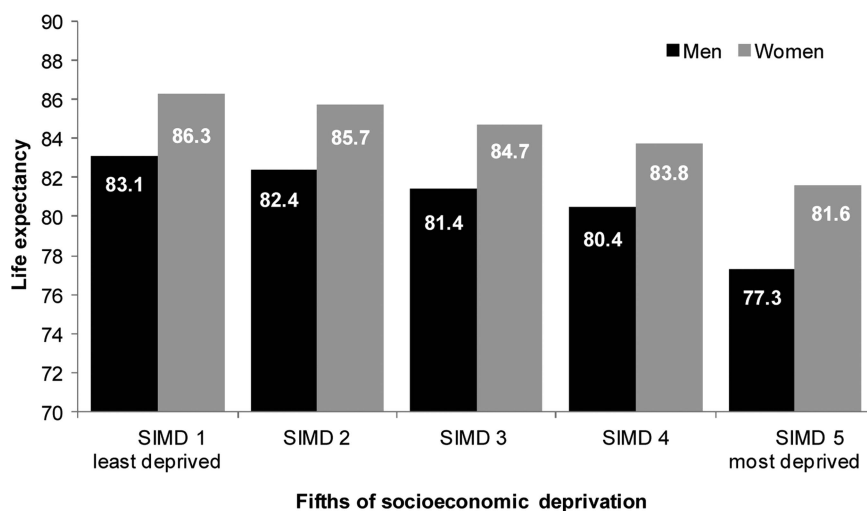
The Rotterdam Ischaemic heart disease & Stroke Computer (RISC) model<sup>28</sup> is a state transition model which has been externally validated.<sup>29</sup> The states of the model are similar to ours but also includes a state for CHD and stroke. Although many risk factors are considered, socioeconomic deprivation was not included. Like our model, the baseline distribution of risk factors and the risk equations for predicting model transition probabilities come from a cohort that has been followed up. The main difference in modelling strategy is that RISC uses a Monte Carlo–Markov framework for obtaining transition probabilities,

whereas our approach uses competing risk parametric survival models.

## Strengths

A major strength of this model is the data source. The SHHEC survey linked to national hospital discharge and death records allows individuals to be followed up for a long time (median survival time to first event was almost 21 years). The linked data set allowed us to undertake a competing risk analysis to estimate the association between risk factors and CVD (and non-CVD)

**Figure 3** Predicted life expectancy for ranked fifths of socioeconomic deprivation (SIMD) scores.



outcomes using a single cohort of individuals. This is a more sophisticated approach than CVD risk scores based on a single composite endpoint where the estimate of CVD risk does not take into account competing causes. Furthermore, the inclusion of a measure of socioeconomic deprivation as an independent risk factor is congruent with an inequalities policy agenda, which is a particular priority in Scotland. In addition, the risk factors measured in SHHEC were carefully standardised and the data were very complete. Further strengths are that we have reported the performance of the model to discriminate over the observed follow-up period, shown how our model predictions compare with observed data from an external source, and taken into account and reported on how well our model is calibrated.

### Limitations

Although there was long follow-up, over 60% of individuals were still to experience a first event at the end of the observation period. Therefore, it was necessary to extrapolate survival curves and we had to use a calibration factor to ensure that the average differences between model predictions and life table estimates of life expectancy were within 1 year. A second limitation is that modifiable risk factors were only measured at baseline with no follow-up measurement occasions. As we intend this model to be used to assess primary prevention interventions we do not view this as a major drawback. However, for targeted interventions any attributed gains in life expectancy could be exaggerated if beneficial changes to other modifiable risk factors not influenced by the intervention under study occur. Third, the first events we modelled were hospitalisations and so less serious CHD and CBVD events that could be treated in a primary care setting are not explicitly modelled as a health state but any future hospitalisation(s) for such patients would be captured. Fourth, as well as capturing the true effect of socioeconomic deprivation, SIMD will be acting as a proxy for unmeasured risk factors and complex causal pathways involving SIMD, unmeasured variables and the interaction between them. As such, it is likely that any predicted gradient in socioeconomic deprivation using SIMD will be an overestimation of the true inequality in life expectancies. Finally, in our validation exercise, our model predictions were different to WOSCOPS for non-fatal CHD and fatal non-CVD endpoints. Although this could be partly due to differences between trial populations and general populations, we acknowledge that our external validation results were suboptimal and in future research we would like to repeat this exercise with another external data source (which includes women).

The model was developed using Scottish data sources (SHHEC and the ASSIGN risk variables), including a Scottish-specific measure of deprivation. It is intended for use in Scotland, in the first instance. Nonetheless, the model may have wider generalisability. It is common for models developed in one setting to be recalibrated for use elsewhere. For instance, the Framingham risk score has been recalibrated for use outside of the USA, such as in England.<sup>30</sup> A similar exercise could, in principle, be undertaken for the proposed policy model introduced in this paper.

### Public health and clinical implications

Our model can be used to estimate the impact of primary prevention interventions on life expectancy and can assess the impact of interventions on inequalities. Furthermore, our model can be used at the local level for predicting future burden of disease to aid planning and allocation of services. As well as being able to predict 5-year, 10-year and lifetime risk of CVD

outcomes given risk factor values for an individual, it can also predict life expectancy. This can help answer patient questions such as 'how much longer can I expect to live if I take part in this intervention?' and also be used as a tool to prioritise individuals for intervention.

### Key messages

#### What is already known on this subject?

Cardiovascular disease (CVD; rheumatic heart diseases, hypertensive diseases, ischaemic heart diseases, pulmonary heart disease, other forms of heart disease, cerebrovascular diseases, diseases of arteries and diseases of veins) is a leading cause of premature mortality, morbidity and health service costs. The incidence of CVD has also been shown to be socially patterned. The primary prevention of CVD is a policy priority, including the objective to reduce health inequalities. A policy model is a model capable of evaluating the effectiveness and cost-effectiveness of a wide range of interventions aimed at modifying known CVD risk factors.

#### What might this study add?

This policy model joins together risk estimation, individual patient decision making and societal policy making. By taking a competing risk approach the model estimates the impact of risk factor modification on CVD events and non-CVD mortality to predict life expectancy. By including a measure of socioeconomic deprivation as an independent risk factor the policy model can be used to assess the impact of interventions on health inequalities.

#### How might this impact on clinical practice?

This policy model uses the ASSIGN risk factors to estimate CVD risk and can project the full impact of risk factor modification on life expectancy. Consequently, the model can be used consistently as both a clinical and policy tool, to help prioritise individuals for intervention and to evaluate the effectiveness and cost-effectiveness of interventions.

### Author affiliations

<sup>1</sup>Health Economics and Health Technology Assessment, Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK

<sup>2</sup>Robertson Centre for Biostatistics, Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK

<sup>3</sup>BHF Centre for Research Excellence, University of Edinburgh, Edinburgh, UK

<sup>4</sup>Centre of Academic Primary Care, University of Aberdeen, University of Aberdeen, Aberdeen, UK

<sup>5</sup>Institute of Cardiovascular Research, University of Dundee, Ninewells Hospital, Dundee, UK

<sup>6</sup>General Practice & Primary Care, Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK

<sup>7</sup>The George Institute for Global Health, The University of Sydney, Sydney, New South Wales, Australia

**Contributors** JDL prepared the manuscript, with contribution from KDL and supervision from AHB. JDL and KDL undertook the analyses. All authors reviewed and contributed to the final manuscript.

**Funding** The development of the policy model was funded by the Chief Scientist Office for Scotland CZH/4/557.

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially,

and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

## REFERENCES

- Lozano R, Naghavi M, Foreman K, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2095–128.
- Glasgow Centre for Population Health. Still "The Sick Man of Europe"?—Scottish Mortality in a European Context, 1950–2010, an analysis of comparative mortality trends. [http://www.gcph.co.uk/publications/391\\_still\\_the\\_sick\\_man\\_of\\_europe](http://www.gcph.co.uk/publications/391_still_the_sick_man_of_europe) (accessed 15 Nov 2013).
- The Scottish Government. *Summary Technical Report—summary report detailing the domains, indicators and methodology of SIMD* 2004. <http://www.scotland.gov.uk/Publications/2004/06/19429/38161> (accessed 30 Oct 2012).
- Information Services Division Scotland. Heart Disease Statistics Update—Year ending 31st March 2012. <http://www.isdscotland.org/Health-Topics/Heart-Disease/Publications/2012-12-18/2012-12-18-Heart-Disease-Report.pdf?82319277525> (accessed 15 Nov 2013).
- NICE National Institute for Health and Care Excellence (<http://www.nice.org.uk/>).
- SMC Scottish Medicines Consortium (<http://www.scottishmedicines.org.uk/Home>).
- Unal B, Capewell S, Critchley J. Coronary heart disease policy models: a systematic review. *BMC Public Health* 2006;6:213.
- Barton P, Andronis L, Briggs A, *et al*. Effectiveness and cost effectiveness of cardiovascular disease prevention in whole populations: modeling study. *BMJ* 2011;343:d4044.
- SIGN Scottish Intercollegiate Guidelines Network (<http://www.sign.ac.uk/>).
- Woodward M, Brindle P, Tunstall-Pedoe H. for the SIGN group on risk estimation. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart* 2007;93:172–6.
- Caro J, Briggs A, Siebert U, *et al*. Modeling good research practices—overview: a report of the ISPOR-SMDM modeling good research practices task force-1. *Value Health* 2012;15:796–803.
- Tunstall-Pedoe H, Woodward M, Tavendale R, *et al*. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study. *BMJ* 1997;315:722–9.
- Tunstall-Pedoe H, ed.; for the WHO MONICA Project. *MONICA monograph and multimedia sourcebook*. Geneva: World Health Organization, 2003:124.
- van Buuren S, Boshuizen HC and Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Statistics in Medicine* 1999;18:681–94.
- Gray AM, Clarke PM, Wolstenholme JL, *et al*. *Applied methods of cost-effectiveness analysis in health care*. Oxford: Oxford University Press, 2012:72.
- Scot PHO. *Public Health Information for Scotland. Measuring Socio-Economic Inequalities in Health: A Practical Guide*, 2007. [http://www.scotpho.org.uk/downloads/scotphoreports/scotpho071009\\_measuringinequalities\\_rep.pdf](http://www.scotpho.org.uk/downloads/scotphoreports/scotpho071009_measuringinequalities_rep.pdf) (accessed 13 May 2014).
- Harrell FE, Lee KL and Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361–87.
- Shepherd J, Cobbe S, Ford I, *et al*. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301–8.
- The Scottish Government. Scottish Health Survey. <http://www.scotland.gov.uk/Topics/Statistics/Browse/Health/scottish-health-survey> (accessed 30 Oct 2012).
- General Register Office for Scotland. Life Expectancy at Scotland Level—Scottish Interim Life Tables. <http://www.gro-scotland.gov.uk/files2/stats/life-expectancy-at-scotland-level/table2-le-2009-2011.pdf> (accessed 30 Oct 2012).
- Weinstein MC, Coxson PG, Williams LW, *et al*. Forecasting coronary heart disease incidence, mortality, and cost: the coronary heart disease policy model. *Am J Public Health* 1987;77:1417–26.
- Goldman L, Weinstein MC, Goldman PA, *et al*. Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. *JAMA* 1991;265:1145–51.
- Tsevat J, Weinstein MC, Williams LW, *et al*. Expected gains in life expectancy from various coronary heart disease risk factor modifications. *Circulation* 1991;83:1194–201.
- Capewell S, Morrison CE, McMurray JJ. Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. *Heart* 1999;81:380–6.
- Critchley JA, Capewell S, Unal B. Life-years gained from coronary heart disease mortality reduction in Scotland—Prevention or treatment? *J Clin Epidemiol* 2003;56:583–90.
- Heart Protection Study Collaborative Group. Cost-effectiveness of simvastatin in people at different levels of vascular disease risk: economic analysis of a randomised trial in 20,536 people. *Lancet* 2005;365:1779–85.
- Heart Protection Study Collaborative Group. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. *BMJ* 2006;333:1145–8.
- Nijhuis RL, Stijnen T, Peeters A, *et al*. Apparent and internal validity of a Monte Carlo-Markov model for cardiovascular disease in a cohort follow-up study. *Med Decis Making* 2006;26:134–44.
- Van Kempen BIJ, Ferket BS, Hofman A, *et al*. Validation of a model to investigate the effects of modifying cardiovascular disease (CVD) risk factors on the burden of CVD: the rotterdam ischemic heart disease and stroke computer simulation (RISC) model. *BMC Med* 2012;10:158.
- British Cardiac Society, B.H.S., Diabetes UK, HEART UK, Primary Care Cardiovascular Society, The Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;91(Suppl 5):v1–v52.



## **Online appendix: A Cardiovascular Disease Policy Model that predicts life expectancy taking into account socio-economic deprivation**

This appendix provides an expanded methods section as well as additional model results and is intended to be read in conjunction with the main paper<sup>1</sup>.

### **Model structure**

The endpoints for our model are non-fatal CHD hospitalisation, non-fatal cerebrovascular disease (CBVD) hospitalisation and deaths from CVD. However, with the focus on life expectancy we also consider deaths from non-CVD causes and the additional life expectancy experienced after a non-fatal CHD or CBVD event. Figure A1 illustrates the structure of the state transition model. People enter the model in the CVD event free state and then transit into one of four events “competing” to be first. If a hospitalised patient died within 28 days of their admission the first event was re-classified as fatal. If the first event experienced is non-fatal, then there is a final transition to death. Men and women were modelled separately.

### **Data source**

The Scottish Heart Health Extended Cohort (SHHEC) is made up of individuals from the Scottish Heart Health Study<sup>2</sup> which recruited random samples of the Scottish population between 1984 and 1987, and individuals from the Scottish MONICA Project<sup>3</sup> which recruited in Edinburgh in 1986 and north Glasgow in 1986, 1989, 1992 and 1995. The SHHEC participants, aged between 25-74 years, attended a survey clinic where cardiovascular risk factors were measured.

Patients were defined as CVD event free if they did not self-report at recruitment having had angina, myocardial infarction, or a stroke in the past, no ECG appearance of previous myocardial infarction at survey clinic, and also did not have prior hospitalisations with discharge diagnoses of angina, CHD, stroke, acute coronary event, CBVD and transient ischaemic attacks. SHHEC participants gave permission to be followed up through routine records.

The data was linked to hospital admissions using the Scottish Morbidity Record Scheme (SMR) and deaths using the General Register Office (GRO) for Scotland. Follow-up extended from 1981 to the end of 2009. A CHD hospitalisation was identified by ICD9 codes 410-414 and ICD10 codes I20-I25, a CBVD hospitalisation by ICD9 430-438 (ICD10 G45, I60-I69), and a fatal CVD event by ICD9 390-459 (ICD10 I00-I99), with the codes appearing in any diagnostic

position in the SMR/GRO records. Fatal non-CVD events were defined as all deaths not having a CVD cause. Risk factors used for modelling the first event were age at survey (years), systolic blood pressure (SBP) (mm Hg), total cholesterol (TC) (mmol/l), HDL cholesterol (mmol/l), cigarettes per day (CPD), self-reported diabetes, self-reported family history of heart disease, and SIMD score (2004 version). These are the same risk factors that are in the ASSIGN cardiovascular risk score which was also developed using the linked SHHEC data set. Risk factors used for modelling death after a non-fatal first event were age at first event, self-reported family history of heart disease and SIMD. Any missing data in the risk factors was taken into account by using the multiple imputation of chained equations technique<sup>4</sup>.

It should be noted that the modifiable risk factors of systolic blood pressure, total cholesterol, HDL cholesterol and cigarettes per day can only directly influence the risk of having a first event as these variables were not measured at time of first event and therefore could not be used in the subsequent modelling of death after a non-fatal first event. Therefore, our policy model is intended to evaluate primary prevention interventions and not secondary prevention interventions.

### **Modelling stage 1 - estimating risk of having first event (equation 1 in Figure A1)**

Survival analysis was used to model the cause specific hazards of the competing first events. By the end of follow-up not all SHHEC participants had experienced a first event so a parametric approach was required to extrapolate the modelling so the total remaining life expectancy could be estimated. Similar to Cox regression, Gompertz regression is a proportional hazards type model but, in addition, an ancillary parameter is estimated from the data which describes how the hazard function is related to time<sup>5</sup>. The model results are shown in Table A1. The associated Choleskey decomposition matrices<sup>6</sup> are shown in Tables A3-A10.

The following was derived from section 3.2 in Putter *et al.* using parametric expressions for the cause specific hazards<sup>7</sup>. The predicted cumulative incidence estimates of first events can be obtained from the Gompertz regression as follows:

$$CI_k(t) = \sum p_k(t_j)$$

i.e., the cumulative incidence at time  $t$ ,  $CI_k(t)$ , is the cumulative sum of the unconditional probabilities of having event type  $k$  at time  $t_j$ ,  $\sum p_k(t_j)$ , up to and including time  $t$ . The unconditional probabilities are obtained by:

$$p_k(t_j) = h_k(t_j)S(t_{j-1})$$

Where  $h_k(t_j)$  is the cause specific hazard for event type  $k$  which for the Gompertz regression has the expression:

$$h_k(t_j) = \exp(xb)\exp(\gamma t)$$

Where  $xb$  is the linear predictor from the regression and  $\gamma$  is the ancillary shape parameter estimated from the data.  $S(t)$  is the probability of surviving from any of the four events at time  $t$  and is obtained by:

$$S(t) = \prod(1 - \sum h_k(t_j))$$

Where  $\sum h_k(t_j)$  is the sum of the four cause specific hazards at time  $t_j$ .

Figure A2a displays  $Cl_k(t)$  and  $S(t)$  for a particular covariate profile. The middle panel of Table 2 in the main paper shows the  $p_k(t_j)$  for the same covariate profile.

### **Modelling stage 2 - estimating life expectancy following non-fatal CHD and CBVD events (equation 2 in Figure A1)**

Gompertz regression was also used to model the hazard of death following a first event in hospital. Due to censoring it was necessary to extrapolate the survival analysis to a time point when for a given covariate profile the probability of surviving beyond that time point was zero. The model results are shown in Table A2. The associated Choleskey decomposition matrices are shown in Tables A11-A14. A predicted survival curve extrapolated until the probability of surviving beyond that time point was zero can be obtained for each covariate profile. Figures A2b-A2d show predicted survival curves for a particular covariate profile with different ages at first event. The area under the survival curve was obtained by applying the trapezoidal rule<sup>8</sup> with half cycle correction and this provided an estimate of remaining life expectancy.

### **Modelling stage 3 - estimating overall life expectancy**

The state transition model uses a cycle period of 1 year. At the end of a model cycle an individual can either remain in a CVD free state or move to one of the first four competing events. To calculate remaining life expectancy, the model sums the time before an event and

survival time post non-fatal event (area under the survival curve). The model cycles annually for 100 years and within each cycle the model estimates the consequences if each of the competing first events occurred. For example, if a person has a non-fatal CHD event after 3 years the additional life expectancy is those 3 years added to the life expectancy following the non-fatal event predicted from the survival analysis (modelling stage 2). Whereas, if a person dies of CVD causes after 3 years the additional life expectancy is just those 3 years. All these first event possibilities are weighted by the probability of that event occurring at that particular time which comes from the predicted cumulative incidence estimates (modelling stage 1). Finally, the estimated overall life expectancy is obtained by taking the sum of the expected additional life years and adding this to the age of the person at survey.

For measuring inequalities in life expectancy, it is possible to calculate the Slope Index of Inequality (SII) or Relative Index of Inequality (RII)<sup>9</sup> which takes into account the whole distribution of life expectancy across the range of the SIMD index, not just focusing on the top and bottom of the range.

### **Discrimination, validation and calibration of the model**

The discrimination of the statistical models was assessed using Harrell's concordance statistic (c-statistic)<sup>10</sup>. It is important to note this will only assess discrimination where we have observed events to compare to the model predictions. We will not know how well our model discriminates in the extrapolated period.

As a validation exercise, we used the West of Scotland Coronary Prevention Study (WOSCOPS)<sup>11</sup> to test the extent to which our model can predict events in a Scottish population that did not inform the development of the model. WOSCOPS was a randomised, double-blind, trial investigating the effectiveness of pravastatin in preventing coronary heart disease in asymptomatic males between 45-64 years old. Participants were recruited between 1989 and 1991, which is a slightly more recent cohort of patients than SHHEC (1984-1995). The trial period averaged 4.9 years and there was an additional 10 years of follow-up, where patients had returned to normal care. For the placebo group the validation was over the entire fifteen year period. Baseline risk factors were inputted into the model, and predictive accuracy was assessed by checking whether the predicted cumulative incidence curves fell within the 95% confidence interval limits of the observed cumulative incidence curves. For the intervention group, the validation proceeded indirectly through the effect of treatment on cholesterol in order to mimic the intended use of the model. This was only done for the 5 year trial period, as post-

trial only a proportion of patients continued to take statins (28.6% at 1 year, 33.6% at 3 years, 38.7% at 5 years).

Predicted life expectancies were obtained from a model where the risk factor values are provided by average values from the Scottish Health Survey 2009<sup>12</sup>, a sample which is broadly representative of the Scottish population. These predicted life expectancies were compared to life expectancies published in GRO life tables<sup>13</sup>. A calibration factor was used to adjust the linear predictor of the Gompertz regressions for first events to minimise the root mean square error (RMSE) between the predicted and observed life expectancy values for individuals aged 40, 60 and 80 years old. This was undertaken separately for men and women.

The Gompertz regressions were carried out using STATA v12 and the state transition model used to calculate life expectancy was implemented using Microsoft Excel.



Table A1: Gompertz regression modelling of cause specific hazards of first event

## a) Men

Covariate	non-fatal CHD		non-fatal CBVD		fatal CVD		fatal non-CVD	
	coeff. (95% CI)	p value	coeff. (95% CI)	p value	coeff. (95% CI)	p value	coeff. (95% CI)	p value
Age	0.045 (0.038, 0.052)	<0.001	0.066 (0.054, 0.078)	<0.001	0.093 (0.082, 0.103)	<0.001	0.094 (0.085, 0.102)	<0.001
SIMD sc.	0.004 (0.001, 0.007)	0.002	0.009 (0.005, 0.014)	<0.001	0.006 (0.003, 0.010)	<0.001	0.009 (0.007, 0.012)	<0.001
Diabetes	0.653 (0.292, 1.014)	<0.001	1.168 (0.664, 1.673)	<0.001	0.863 (0.389, 1.337)	<0.001	0.335 (-0.169, 0.839)	0.192
Fam. his.	0.408 (0.295, 0.522)	<0.001	-0.021 (-0.235, 0.193)	0.847	0.165 (-0.003, 0.332)	0.054	-0.015 (-0.162, 0.133)	0.845
CPD	0.018 (0.013, 0.022)	<0.001	0.024 (0.017, 0.031)	<0.001	0.031 (0.026, 0.037)	<0.001	0.031 (0.026, 0.035)	<0.001
SBP	0.008 (0.005, 0.011)	<0.001	0.012 (0.007, 0.016)	<0.001	0.015 (0.012, 0.019)	<0.001	-0.001 (-0.005, 0.002)	0.391
TC	0.255 (0.208, 0.302)	<0.001	0.083 (-0.002, 0.168)	0.056	0.120 (0.050, 0.189)	0.001	-0.051 (-0.111, 0.008)	0.092
HDL	-0.760 (-0.947, -0.574)	<0.001	-0.125 (-0.394, 0.144)	0.362	-0.143 (-0.370, 0.085)	0.218	0.384 (0.214, 0.554)	<0.001
Constant	-9.54 (-10.12, -8.96)	<0.001	-12.51 (-13.47, -11.54)	<0.001	-14.13 (-14.93, -13.33)	<0.001	-11.22 (-11.91, -10.53)	<0.001
Gamma	0.057 (0.049, 0.065)	<0.001	0.091 (0.076, 0.105)	<0.001	0.079 (0.068, 0.091)	<0.001	0.081 (0.071, 0.091)	<0.001

## b) Women

Covariate	non-fatal CHD		non-fatal CBVD		fatal CVD		fatal non-CVD	
	coeff. (95% CI)	p value	coeff. (95% CI)	p value	coeff. (95% CI)	p value	coeff. (95% CI)	p value
Age	0.058 (0.049, 0.067)	<0.001	0.080 (0.065, 0.095)	<0.001	0.102 (0.087, 0.116)	<0.001	0.091 (0.081, 0.101)	<0.001
SIMD sc.	0.009 (0.006, 0.012)	<0.001	0.013 (0.009, 0.018)	<0.001	0.004 (0.000, 0.009)	0.054	0.007 (0.004, 0.010)	<0.001
Diabetes	0.725 (0.343, 1.108)	<0.001	1.101 (0.595, 1.607)	<0.001	1.144 (0.680, 1.609)	<0.001	-0.037 (-0.668, 0.594)	0.908
Fam. his.	0.516 (0.389, 0.643)	<0.001	0.356 (0.150, 0.562)	0.001	0.239 (0.050, 0.428)	0.013	-0.018 (-0.165, 0.129)	0.814
CPD	0.021 (0.014, 0.027)	<0.001	0.027 (0.017, 0.037)	<0.001	0.048 (0.040, 0.056)	<0.001	0.038 (0.032, 0.044)	<0.001
SBP	0.006 (0.003, 0.009)	<0.001	0.014 (0.009, 0.018)	<0.001	0.018 (0.013, 0.022)	<0.001	0.003 (-0.001, 0.006)	0.112
TC	0.188 (0.136, 0.240)	<0.001	-0.051 (-0.150, 0.048)	0.308	0.057 (-0.022, 0.136)	0.159	-0.076 (-0.140, -0.013)	0.018
HDL	-0.746 (-0.937, -0.555)	<0.001	-0.346 (-0.636, -0.056)	0.020	-0.174 (-0.420, 0.073)	0.166	-0.045 (-0.229, 0.138)	0.626
Constant	-10.52 (-11.14, -9.89)	<0.001	-13.01 (-14.02, -12.00)	<0.001	-15.42 (-16.39, -14.46)	<0.001	-11.26 (-11.93, -10.58)	<0.001
Gamma	0.083 (0.073, 0.093)	<0.001	0.096 (0.080, 0.112)	<0.001	0.099 (0.084, 0.114)	<0.001	0.089 (0.078, 0.099)	<0.001

Note: 'Age' is age at survey

Table A2: Gompertz regression modelling of survival after non-fatal event

a) Men, after CHD event

Covariate	coeff. (95% CI)	p value
Age at event	0.077 (0.065, 0.090)	<0.001
SIMD score	0.013 (0.009, 0.017)	<0.001
Family history	-0.035 (-0.233, 0.162)	0.725
Constant	-8.597 (-9.479, -7.715)	<0.001
Gamma	0.038 (0.017, 0.059)	<0.001

b) Men, after CBVD event

Covariate	coeff. (95% CI)	p value
Age at event	0.067 (0.048, 0.087)	<0.001
SIMD score	0.009 (0.003, 0.015)	0.004
Family history	0.061 (-0.263, 0.385)	0.711
Constant	-7.447 (-8.852, -6.043)	<0.001
Gamma	0.024 (-0.015, 0.062)	0.226

c) Women, after CHD event

Covariate	coeff. (95% CI)	p value
Age at event	0.074 (0.059, 0.089)	<0.001
SIMD score	0.007 (0.003, 0.012)	0.003
Family history	-0.285 (-0.519, -0.051)	0.017
Constant	-8.360 (-9.488, -7.232)	<0.001
Gamma	0.041 (0.013, 0.068)	0.004

d) Women, after CBVD event

Covariate	coeff. (95% CI)	p value
Age at event	0.070 (0.050, 0.089)	<0.001
SIMD score	0.0002 (-0.007, 0.008)	0.961
Family history	0.181 (-0.152, 0.513)	0.287
Constant	-7.668 (-9.192, -6.144)	<0.001
Gamma	0.036 (-0.008, 0.080)	0.106

Table A3: Cholesky decomposition matrix for model in Table A1a (non-fatal CHD)

	Age	SIMD sc.	Diabetes	Fam. his.	CPD	SBP	TC	HDL	Constant	Gamma
Age	1.26E-05									
SIMD sc.	-5.63E-08	1.67E-06								
Diabetes	-1.9E-05	-9.68E-06	0.03375							
Fam. his.	1.32E-05	-1.65E-06	0.000132	0.003352						
CPD	8.88E-07	-4.29E-07	2.49E-05	-7.14E-07	4.76E-06					
SBP	-1.36E-06	-8.92E-08	-9.51E-06	-2.38E-06	5.41E-08	1.97E-06				
TC	-1.82E-06	2.97E-06	-0.00025	-6.5E-05	-1.65E-06	-3.02E-06	0.000577			
HDL	-1.9E-05	4.02E-06	0.000214	8.21E-06	1.71E-05	-2.24E-06	-0.00022	0.008855		
Constant	-0.00045	-5.9E-05	0.002371	-0.00105	-0.0001	-0.00018	-0.00306	-0.0087	0.086123	
Gamma	1.54E-06	6.02E-07	4.04E-05	4.01E-06	5.24E-07	2.54E-07	2.35E-06	-2.1E-05	-0.00034	1.76E-05

Table A4: Cholesky decomposition matrix for model in Table A1a (non-fatal CBVD)

	Age	SIMD sc.	Diabetes	Fam. his.	CPD	SBP	TC	HDL	Constant	Gamma
Age	3.79E-05									
SIMD sc.	-1.01E-06	4.46E-06								
Diabetes	-5.6E-05	-3.3E-05	0.065828							
Fam. his.	3.75E-05	-4.72E-06	0.000427	0.011873						
CPD	3.28E-06	-1.23E-06	7.57E-05	-7.44E-06	1.32E-05					
SBP	-3.95E-06	-3.16E-07	-1E-05	-1.2E-05	5.24E-08	4.98E-06				
TC	-7.37E-06	9.44E-06	-0.00024	-0.00017	-1.20E-07	-7.77E-06	0.001865			
HDL	-3E-05	3.05E-06	0.002974	-0.00029	2.43E-05	-1.8E-05	-0.00071	0.018683		
Constant	-0.00143	-0.00011	-0.002	-0.00161	-0.00033	-0.00041	-0.00964	-0.01667	0.241253	
Gamma	5.86E-06	1.87E-06	0.000121	6.77E-06	1.76E-06	7.97E-07	3.09E-06	-3.7E-05	-0.00118	5.37E-05

Table A5: Cholesky decomposition matrix for model in Table A1a (fatal CVD)

	Age	SIMD sc.	Diabetes	Fam. his.	CPD	SBP	TC	HDL	Constant	Gamma
Age	2.84E-05									
SIMD sc.	-1.41E-06	3.04E-06								
Diabetes	-2.9E-05	-2.2E-05	0.057734							
Fam. his.	2.89E-05	-4.29E-06	0.000287	0.007269						
CPD	2.89E-06	-8.25E-07	3.37E-05	-7.79E-06	8.31E-06					
SBP	-2.68E-06	-2.19E-07	-3.69E-06	-1E-05	-1.17E-07	2.82E-06				
TC	3.20E-06	6.64E-06	-0.00037	-7.8E-05	4.02E-06	-3.16E-06	0.001252			
HDL	-3E-05	-1.52E-07	-0.00018	-0.00031	7.41E-06	-2.5E-05	-0.0006	0.013304		
Constant	-0.00119	-3.2E-05	0.001989	-0.00097	-0.00026	-0.0002	-0.00717	-0.00859	0.165284	
Gamma	4.71E-06	1.12E-06	0.0001	1.81E-06	1.27E-06	4.50E-07	4.01E-06	-4E-05	-0.00078	3.56E-05

Table A6: Cholesky decomposition matrix for model in Table A1a (fatal non-CVD)

	Age	SIMD sc.	Diabetes	Fam. his.	CPD	SBP	TC	HDL	Constant	Gamma
Age	1.83E-05									
SIMD sc.	-7.87E-07	2.10E-06								
Diabetes	-1.7E-05	-1.3E-05	0.06594							
Fam. his.	1.73E-05	-2.54E-06	0.000451	0.005661						
CPD	1.72E-06	-5.79E-07	3.27E-05	-3.54E-06	5.78E-06					
SBP	-1.63E-06	-1.57E-07	-4.59E-06	-5.03E-06	7.55E-08	2.71E-06				
TC	-2.47E-06	4.63E-06	-0.00014	-8E-05	1.39E-06	-4.19E-06	0.000922			
HDL	-1.6E-05	1.42E-06	0.001089	-1.2E-05	8.01E-06	-9.23E-06	-0.00024	0.007462		
Constant	-0.00076	-3.8E-05	-0.00081	-0.00098	-0.00018	-0.00024	-0.00479	-0.00697	0.123588	
Gamma	3.27E-06	8.97E-07	3.96E-05	1.28E-06	8.05E-07	3.28E-07	2.69E-07	-1.2E-05	-0.00056	2.51E-05

Table A7: Cholesky decomposition matrix for model in Table A1b (non-fatal CHD)

	Age	SIMD sc.	Diabetes	Fam. his.	CPD	SBP	TC	HDL	Constant	Gamma
Age	2.18E-05									
SIMD sc.	-7.96E-07	2.26E-06								
Diabetes	-2.9E-05	-9.53E-06	0.037997							
Fam. his.	0.000018	-2.08E-06	8.26E-05	0.004177						
CPD	2.66E-06	-8.93E-07	2.72E-05	-1.58E-06	9.93E-06					
SBP	-2.46E-06	-1.20E-07	-2.51E-06	-4.40E-06	2.39E-07	2.50E-06				
TC	-3.7E-05	5.10E-06	-0.00027	-0.00013	-1.2E-05	-3.42E-06	0.000695			
HDL	-3.7E-05	3E-05	0.00214	-4E-05	3.5E-05	3.95E-06	-0.00022	0.009329		
Constant	-0.00054	-9.9E-05	-0.00115	-0.00131	-0.00021	-0.00019	-0.00201	-0.01228	0.100345	
Gamma	2.87E-06	8.61E-07	3.61E-05	8.54E-06	7.60E-07	1.70E-07	-2.70E-06	-3.3E-05	-0.00048	2.55E-05

Table A8: Cholesky decomposition matrix for model in Table A1b (non-fatal CBVD)

	Age	SIMD sc.	Diabetes	Fam. his.	CPD	SBP	TC	HDL	Constant	Gamma
Age	5.7E-05									
SIMD sc.	-3.01E-06	5.43E-06								
Diabetes	-8.7E-05	-3E-05	0.066499							
Fam. his.	5.36E-05	-3.65E-06	0.000852	0.011053						
CPD	7.60E-06	-2.08E-06	5.76E-05	2.80E-06	2.46E-05					
SBP	-5.89E-06	-3.39E-07	-1.1E-05	-4.99E-06	4.55E-07	5.78E-06				
TC	-0.00012	1.56E-05	-0.00029	-0.00044	-2.7E-05	-1.4E-05	0.002499			
HDL	-9.3E-05	6.54E-05	0.003344	0.00022	8.84E-05	3.79E-06	-0.00045	0.021592		
Constant	-0.00143	-0.0002	-0.00087	-0.00427	-0.00059	-0.00041	-0.00758	-0.02873	0.264345	
Gamma	9.61E-06	2.25E-06	8.87E-05	2.39E-05	2.09E-06	4.86E-07	-1.4E-05	-7.9E-05	-0.0014	6.83E-05



Table A9: Cholesky decomposition matrix for model in Table A1b (fatal CVD)

	Age	SIMD sc.	Diabetes	Fam. his.	CPD	SBP	TC	HDL	Constant	Gamma
Age	5.22E-05									
SIMD sc.	-3.12E-06	4.91E-06								
Diabetes	-6.5E-05	-3E-05	0.056007							
Fam. his.	4.58E-05	-1.64E-06	0.000961	0.009241						
CPD	6.60E-06	-1.85E-06	3.83E-05	9.60E-06	1.48E-05					
SBP	-4.81E-06	-1.95E-07	-2.57E-06	-4.48E-06	4.62E-07	4.30E-06				
TC	-7.1E-05	1.13E-05	-0.00014	-0.00025	-2E-05	-5.45E-06	0.001614			
HDL	-4.1E-05	4.73E-05	0.002741	0.000329	5.4E-05	3.09E-06	-0.00069	0.015663		
Constant	-0.00173	-0.00012	-0.00286	-0.0045	-0.00049	-0.00032	-0.00528	-0.0204	0.241351	
Gamma	8.99E-06	1.83E-06	8.77E-05	2.29E-05	1.31E-06	4.95E-07	-5.91E-06	-5.4E-05	-0.00128	5.58E-05

Table A10: Cholesky decomposition matrix for model in Table A1b (fatal non-CVD)

	Age	SIMD sc.	Diabetes	Fam. his.	CPD	SBP	TC	HDL	Constant	Gamma
Age	2.61E-05									
SIMD sc.	-1.22E-06	2.61E-06								
Diabetes	-5.4E-05	-1.3E-05	0.103373							
Fam. his.	1.88E-05	-1.43E-06	0.000119	0.005609						
CPD	3.22E-06	-1.10E-06	1.32E-05	2.35E-06	8.98E-06					
SBP	-2.87E-06	-1.45E-07	-8.82E-06	-3.44E-06	2.02E-07	3.01E-06				
TC	-4.9E-05	5.38E-06	0.000137	-0.00016	-1.3E-05	-4.92E-06	0.00103			
HDL	-2.1E-05	2.4E-05	0.000733	0.000174	3.07E-05	7.74E-07	-0.00041	0.008691		
Constant	-0.0007	-7.7E-05	0.000422	-0.00161	-0.00022	-0.00022	-0.00277	-0.01125	0.118397	
Gamma	3.99E-06	1.10E-06	4.08E-05	8.37E-06	5.54E-07	1.90E-07	-4.73E-06	-2.5E-05	-0.00062	3.03E-05

Table A11: Cholesky decomposition matrix for model in Table A2a

	Age at event	SIMD score	Family history	Constant	Gamma
Age at event	3.95E-05				
SIMD score	1.29E-06	4.53E-06			
Family history	5.81E-05	-1.1E-05	0.01014		
Constant	-0.00275	-0.00023	-0.00676	0.202488	
Gamma	2.62E-05	2.19E-06	1.38E-05	-0.00246	0.000116

Table A12: Cholesky decomposition matrix for model in Table A2b

	Age at event	SIMD score	Family history	Constant	Gamma
Age at event	9.59E-05				
SIMD score	2.70E-06	9.60E-06			
Family history	0.000123	6.25E-07	0.027277		
Constant	-0.00685	-0.00052	-0.01452	0.513441	
Gamma	7.25E-05	4.20E-06	-7.7E-05	-0.00675	0.000379

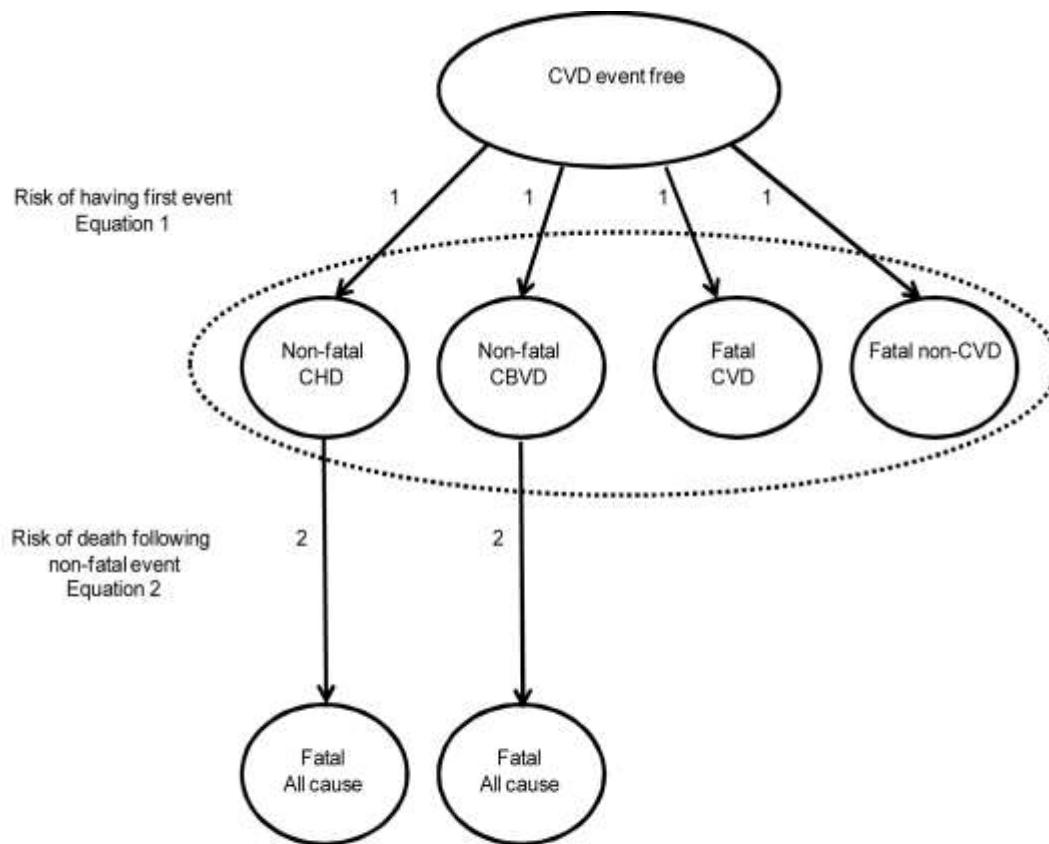
Table A13: Cholesky decomposition matrix for model in Table A2c

	Age at event	SIMD score	Family history	Constant	Gamma
Age at event	6.08E-05				
SIMD score	8.05E-07	6.06E-06			
Family history	5.03E-05	-4.91E-06	0.014259		
Constant	-0.00437	-0.00026	-0.00863	0.3313	
Gamma	4.5E-05	4.42E-07	-6.3E-05	-0.00411	0.000197

Table A14: Cholesky decomposition matrix for model in Table A2d

	Age at event	SIMD score	Family history	Constant	Gamma
Age at event	0.000106				
SIMD score	-2.60E-06	1.41E-05			
Family history	0.000242	-2.6E-05	0.028796		
Constant	-0.00775	-0.00031	-0.02781	0.604536	
Gamma	9.8E-05	7.31E-07	6.96E-05	-0.00917	0.000503

Figure A1: Structure of the state transition model



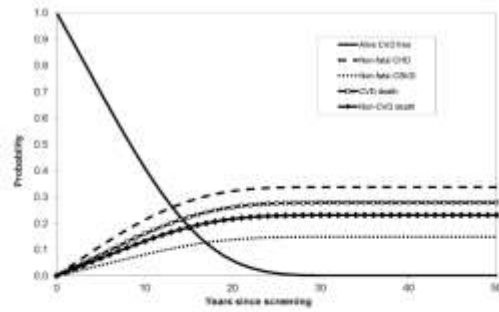
Equation 1: Function (age at survey, SBP, TC, HDL, CPD, family history, SIMD)

Equation 2: Function (age at first event, family history, SIMD)

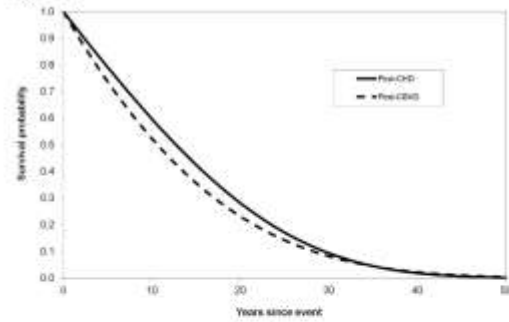
Notes: SBP = systolic blood pressure (mm Hg), TC = total cholesterol (mmol/l), HDL = HDL cholesterol (mmol/l), CPD = cigarettes per day, SIMD = Scottish Index of Multiple Deprivation

Figure A2: Cumulative incidence of first four events and survival probabilities after first non-fatal events

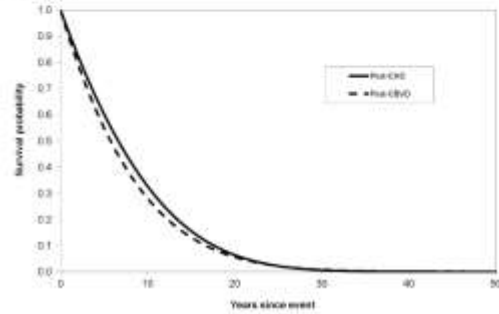
a) Cumulative incidence of first events



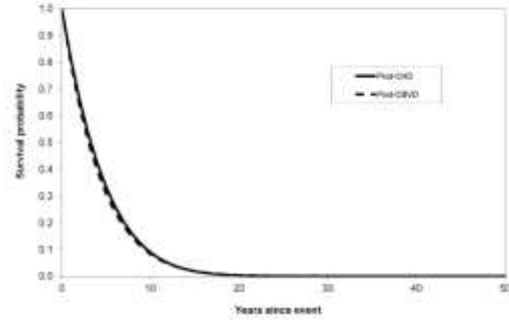
b) Survival probabilities after first non-fatal event (event occurs at age 60)



c) Survival probabilities after first non-fatal event (event occurs at age 70)



d) Survival probabilities after first non-fatal event (event occurs at age 80)



## REFERENCES

1. **Lewsey JD**, Lawson KD, Ford I, *et al.* A Cardiovascular Disease Policy Model that predicts life expectancy taking into account socio-economic deprivation.
2. **Tunstall-Pedoe H**, Woodward M, Tavendale R, *et al.* Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study. *BMJ* 1997;**315**:722-9.
3. **Tunstall-Pedoe H**, ed, for the WHO MONICA Project. *MONICA monograph and multimedia sourcebook*. Geneva: World Health Organization, 2003:124.
4. **van Buuren S**, Boshuizen HC and Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Statistics in Medicine* 1999;**18**:681-694.
5. **Kleinbaum DG**, Klein M. *Survival Analysis – A Self-Learning Text*, 2<sup>nd</sup> edition. New York: Springer, 2005, p285.
6. **Briggs A**, Claxton K, Sculpher M. *Decision Modeling for Health Economic Evaluation*. Oxford: Oxford University Press, 2006, p95.
7. **Putter H**, Fiocco M and Geskus RB. Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* 2007;**26**:2389-2430.
8. **Gray AM**, Clarke PM, Wolstenholme JL, Wordsworth S. *Applied Methods of Cost-effectiveness Analysis in Health Care*. Oxford: Oxford University Press, 2012, p72.
9. **ScotPHO** Public Health Information for Scotland. Measuring Socio-Economic Inequalities in Health: A Practical Guide, 2007.  
[http://www.scotpho.org.uk/downloads/scotphoreports/scotpho071009\\_measuringinequalities\\_rep.pdf](http://www.scotpho.org.uk/downloads/scotphoreports/scotpho071009_measuringinequalities_rep.pdf) (accessed 13th May 2014).
10. **Harrell FE**, Lee KL and Mark DB . Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Statistics in Medicine* 1996;**15**:361–387.
11. **Shepherd J**, Cobbe S, Ford I, *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine* 1995;**333**:1301-1308.
12. **The Scottish Government**. Scottish Health Survey.  
<http://www.scotland.gov.uk/Topics/Statistics/Browse/Health/scottish-health-survey> (accessed 30th October 2012).
13. **General Register Office for Scotland**. Life Expectancy at Scotland Level – Scottish Interim Life Tables. <http://www.gro-scotland.gov.uk/files2/stats/life-expectancy-at-scotland-level/table2-le-2009-2011.pdf> (accessed 30th October 2012).



Supplementary Table: Predicted life expectancies for men and women residing in areas of low and high levels of socio-economic deprivation

a) Men – least deprived fifth

Systolic Blood Pressure (mm/Hg)	Non-Smoker					Smoker					
	Age 70 years					Age 70 years					
	180	83.9	83.7	83.7	83.6	83.6	80.8	80.9	81.1	81.2	81.3
	160	84.7	84.5	84.5	84.4	84.4	81.4	81.6	81.8	81.9	81.9
	140	85.3	85.3	85.3	85.2	85.2	81.9	82.2	82.4	82.5	82.5
	120	85.9	86.0	86.1	86.0	85.9	82.3	82.7	83.0	83.1	83.1
	100	86.4	86.6	86.7	86.7	86.6	82.6	83.1	83.4	83.6	83.6
	Age 60 years					Age 60 years					
	180	81.4	81.1	81.2	81.2	81.1	77.6	77.9	78.3	78.5	78.5
	160	82.2	82.1	82.1	82.0	82.0	78.3	78.7	79.0	79.2	79.2
140	83.0	82.9	83.0	82.9	82.8	78.9	79.4	79.7	79.9	79.9	
120	83.7	83.7	83.8	83.7	83.6	79.4	80.0	80.3	80.5	80.5	
100	84.2	84.4	84.5	84.4	84.4	79.8	80.4	80.8	81.1	81.1	
Age 50 years					Age 50 years						
180	80.0	80.0	80.2	80.2	80.2	76.2	76.7	77.3	77.6	77.7	
160	81.1	80.9	81.1	81.1	81.0	76.9	77.5	78.0	78.3	78.4	
140	81.9	81.8	81.9	81.9	81.8	77.6	78.2	78.6	78.9	79.0	
120	82.6	82.6	82.7	82.6	82.5	78.0	78.8	79.3	79.5	79.6	
100	83.2	83.4	83.4	83.4	83.3	78.5	79.2	79.8	80.0	80.1	
Age 40 years					Age 40 years						
180	79.9	79.9	80.2	80.4	80.4	76.1	76.9	77.6	78.1	78.3	
160	80.8	80.8	81.0	81.0	81.0	76.8	77.5	78.2	78.6	78.8	
140	81.6	81.6	81.7	81.8	81.8	77.3	78.1	78.8	79.1	79.3	
120	82.3	82.3	82.4	82.4	82.4	77.8	78.7	79.3	79.6	79.8	
100	82.9	83.0	83.1	83.1	83.0	78.2	79.1	79.7	80.1	80.2	
		3	5	7	9	10	3	5	7	9	10
Total/HDL cholesterol ratio											

b) Women – least deprived fifth

Systolic Blood Pressure (mm/Hg)	Non-Smoker					Smoker				
	Age 70 years					Age 70 years				
	3	5	7	9	10	3	5	7	9	10
180	85.5	85.3	85.1	85.1	85.0	81.1	81.2	81.2	81.3	81.3
160	86.6	86.4	86.1	86.1	86.0	82.0	82.1	82.2	82.2	82.2
140	87.6	87.4	87.2	87.1	87.0	82.9	83.0	83.0	83.1	83.1
120	88.6	88.5	88.2	88.0	88.0	83.8	83.9	83.9	83.9	83.9
100	89.6	89.4	89.1	88.9	88.9	84.5	84.8	84.7	84.7	84.7
	Age 60 years					Age 60 years				
180	82.8	82.7	82.5	82.4	82.4	77.7	77.9	78.0	78.1	78.2
160	84.0	83.9	83.7	83.5	83.5	78.8	79.0	79.1	79.1	79.2
140	85.2	85.1	84.8	84.6	84.5	79.8	80.1	80.1	80.2	80.2
120	86.3	86.2	85.7	85.6	85.5	80.8	81.1	81.1	81.1	81.2
100	87.3	87.1	86.8	86.5	86.5	81.7	82.0	81.9	82.0	82.0
	Age 50 years					Age 50 years				
180	81.2	81.2	81.0	81.0	81.0	75.8	76.1	76.3	76.5	76.6
160	82.5	82.4	82.2	82.1	82.1	76.9	77.4	77.4	77.6	77.7
140	83.7	83.5	83.3	83.1	83.1	78.1	78.4	78.5	78.6	78.7
120	84.8	84.6	84.3	84.1	84.0	79.1	79.4	79.5	79.5	79.6
100	85.8	85.7	85.2	85.0	85.0	80.0	80.4	80.4	80.5	80.5
	Age 40 years					Age 40 years				
180	80.4	80.4	80.3	80.3	80.4	74.9	75.4	75.7	76.0	76.1
160	81.6	81.6	81.4	81.3	81.4	76.1	76.6	76.8	77.1	77.2
140	82.8	82.7	82.4	82.3	82.3	77.2	77.7	77.8	78.1	78.1
120	83.8	83.7	83.4	83.2	83.1	78.1	78.7	78.7	78.9	79.0
100	84.9	84.6	84.3	84.1	84.0	79.1	79.6	79.6	79.7	79.8

c) Men – most deprived fifth

Systolic Blood Pressure (mm/Hg)	Non-Smoker					Smoker				
	Age 70 years					Age 70 years				
	3	5	7	9	10	3	5	7	9	10
180	80.5	80.2	80.1	79.9	79.8	77.8	77.7	77.8	77.8	77.8
160	81.1	80.9	80.8	80.6	80.5	78.3	78.3	78.4	78.3	78.3
140	81.7	81.5	81.5	81.3	81.2	78.6	78.8	78.9	78.9	78.9
120	82.1	82.1	82.1	82.0	81.9	79.0	79.2	79.4	79.4	79.3
100	82.5	82.7	82.7	82.6	82.5	79.2	79.6	79.8	79.8	79.8
	Age 60 years					Age 60 years				
180	76.8	76.4	76.2	76.0	75.9	73.3	73.3	73.4	73.4	73.4
160	77.6	77.2	77.1	76.8	76.7	74.0	74.0	74.1	74.1	74.1
140	78.3	78.0	77.9	77.7	77.6	74.5	74.6	74.8	74.8	74.8
120	78.9	78.8	78.7	78.5	78.4	74.9	75.2	75.4	75.4	75.4
100	79.4	79.4	79.4	79.2	79.1	75.2	75.7	75.9	76.0	75.9
	Age 50 years					Age 50 years				
180	74.6	74.1	73.9	73.7	73.6	70.7	70.8	71.0	71.0	71.0
160	75.6	75.0	74.9	74.6	74.5	71.5	71.6	71.7	71.7	71.7
140	76.3	75.9	75.8	75.5	75.4	72.1	72.3	72.4	72.4	72.4
120	77.1	76.8	76.6	76.4	76.3	72.6	72.9	73.1	73.1	73.1
100	77.6	77.5	77.4	77.2	77.0	73.0	73.4	73.7	73.7	73.7
	Age 40 years					Age 40 years				
180	73.6	73.1	73.0	72.8	72.7	69.7	69.8	70.1	70.2	70.3
160	74.6	74.0	73.9	73.6	73.5	70.4	70.6	70.8	70.9	70.9
140	75.3	74.9	74.7	74.5	74.3	71.0	71.2	71.5	71.6	71.6
120	76.1	75.7	75.6	75.3	75.1	71.6	71.9	72.1	72.2	72.2
100	76.7	76.5	76.4	76.1	75.9	72.0	72.4	72.7	72.8	72.7

d) Women – most deprived fifth

Systolic Blood Pressure (mm/Hg)	Non-Smoker					Smoker				
	Age 70 years					Age 70 years				
	3	5	7	9	10	3	5	7	9	10
180	83.0	82.9	82.7	82.6	82.6	79.4	79.5	79.5	79.5	79.6
160	83.9	83.8	83.5	83.4	83.3	80.1	80.2	80.2	80.2	80.2
140	84.8	84.6	84.3	84.2	84.1	80.8	80.9	80.8	80.9	80.9
120	85.6	85.4	85.1	85.0	84.9	81.5	81.6	81.5	81.5	81.5
100	86.4	86.2	85.9	85.7	85.6	82.1	82.2	82.1	82.1	82.1
	Age 60 years					Age 60 years				
180	79.9	79.7	79.5	79.4	79.3	75.5	75.7	75.7	75.8	75.8
160	80.9	80.7	80.4	80.2	80.2	76.4	76.5	76.5	76.6	76.6
140	81.8	81.6	81.3	81.1	81.0	77.1	77.3	77.3	77.3	77.3
120	82.7	82.5	82.2	82.0	81.8	77.9	78.1	78.0	78.0	78.1
100	83.7	83.4	83.0	82.7	82.7	78.7	78.9	78.8	78.7	78.8
	Age 50 years					Age 50 years				
180	77.9	77.8	77.6	77.5	77.5	73.1	73.4	73.6	73.7	73.7
160	79.0	78.7	78.5	78.3	78.3	74.0	74.4	74.4	74.5	74.5
140	80.0	79.7	79.4	79.2	79.1	74.9	75.2	75.2	75.3	75.3
120	80.9	80.6	80.3	80.0	79.9	75.8	76.0	76.0	76.0	76.0
100	81.8	81.5	81.0	80.8	80.7	76.5	76.8	76.7	76.7	76.8
	Age 40 years					Age 40 years				
180	76.9	76.8	76.6	76.5	76.5	72.0	72.4	72.6	72.9	72.9
160	77.9	77.7	77.4	77.3	77.2	72.9	73.3	73.5	73.6	73.7
140	78.8	78.6	78.3	78.1	78.0	73.8	74.1	74.2	74.4	74.4
120	79.7	79.4	79.1	78.8	78.8	74.5	74.9	74.9	75.0	75.1
100	80.6	80.3	79.8	79.6	79.5	75.3	75.7	75.6	75.7	75.8