The Scottish Cardiovascular Disease Policy Model

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Author Declaration

I hereby declare, that with the exception of explicit referencing, this following research is my own work and has not been submitted for the award of a different degree at the University of Glasgow, or any other institution.

Kenny Lawson

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Working papers and presentations

Working papers

The Scottish Cardiovascular Disease Primary Prevention Policy Model: Part 1 – statistical module
KD Lawson[1]*, JD Lewsey[1], I Ford[2], K Fox[3], LD Ritchie[4], H Tunstall-Pedoe[5], GCM Watt[6], M Woodward[7], AH Briggs[1]

The Scottish Cardiovascular Disease Primary Prevention Model: Part 2 – evaluating risk factor interventions
KD Lawson[1]*, JD Lewsey[1], I Ford[2], K Fox[3], LD Ritchie[4], H Tunstall-Pedoe[5], GCM Watt[6], M Woodward[7], AH Briggs[1]

Primary prevention of cardiovascular disease – who might benefit most in terms of life expectancy?
KD Lawson[1]*, JD Lewsey[1], I Ford[2], K Fox[3], LD Ritchie[4], H Tunstall-Pedoe[5], GCM Watt[6], M Woodward[7], AH Briggs[1]

Health related quality of life (HRQoL): to what extent does "quality adjusting" life expectancy reveal greater health inequalities?
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The quality of life impact of CVD events in a general population
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From Framingham to ASSIGN - who are the winners and losers?
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Are targeted primary prevention programmes cost effective in reducing CVD? Scotland's Keep Well programme
KD Lawson[1]*, JD Lewsey[1], I Ford[2], K Fox[3], LD Ritchie[4], H Tunstall-Pedoe[5], GCM Watt[6], M Woodward[7], AH Briggs[1]

Primary prevention of CVD: do population health interventions increase or decrease health inequalities

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Presentations

Developing the Scottish CVD Policy Model, *European Society for Social Medicine*, Hall, Austria 2009

Disseminating the Scottish CVD Policy Model, *Chief Scientist Office for Scotland (CSO)*, Edinburgh, Scotland, 2011

The Scottish CVD Policy Model: Rapid evaluation of primary prevention interventions, *Invited seminar, Mailman School of Public Health, Columbia University*, New York, 2011

Economic projections of Keep Well Scotland's primary prevention programme, *Greater Glasgow and Clyde Health Board*, Glasgow, Scotland, 2012

The Scottish CVD Policy Model: making effective use of national routine data, *University of Glasgow-University of Columbia Symposium, University of Glasgow*, Glasgow Scotland, 2012

The Scottish CVD Policy Model: Evaluating targeted and population interventions, *European Society for Social Medicine, Oslo, Norway 2012*

Developing optimal combinations of targeted and population interventions: The Scottish CVD Policy Model, *European Society of Cardiology, Rome*, 2013

Abstract

This thesis is concerned with economic evaluation in the primary prevention of cardiovascular disease. Policymakers are increasingly focussed on reducing the health and economic burden of CVD and to reduce health inequalities. However, the approach to primary prevention suffers from fundamental weaknesses that this research intends to help address.

There is general lack of effectiveness and cost effectiveness evidence underpinning current primary prevention interventions. First, there is a policy impetus towards mass screening strategies to target individuals at high risk of developing CVD when more focussed approaches may be more cost effective. Second, clinicians prioritise individuals on the basis of 10-year risk scores, which are strongly driven by age, and not the potential benefits (or costs) from treatment. Third, targeted and population interventions are often still treated as competing approaches, whereas the key issue is how they might best combine.

The key premise of this thesis is that the aims of primary prevention are the avoidance of premature morbidity, mortality and to close health inequalities - subject to a budget constraint. A CVD Policy Model was created using the same nine risk factors as used in the ASSIGN 10-year risk score, currently used in clinical practice in Scotland, to estimate life expectancy, quality adjusted life expectancy and lifetime hospital costs. This model can be employed to estimate the cost effectiveness of interventions and the impact on health inequalities. The model performed well in a comprehensive validation process in terms of face validity, internal validity, and external validity. Life expectancy predictions were re-calibrated to contemporary lifetables. This generic modelling approach (i.e. using a wide range of inputs and producing a wide range of outputs) is intended to avoid the need to build bespoke models for different interventions aimed at particular risk factors or to produce particular outputs.

In application, the CVD Policy Model is intended to assist clinicians and policymakers to develop a more coherent approach to primary prevention, namely: to design more efficient screening strategies; prioritise individuals for intervention on the basis of potential benefit (rather than risk); and to assess the impact of both individually targeted and population interventions on a consistent basis. Using the model in these ways may enable primary prevention approaches to be more consistent with guidelines from health sector reimbursement agencies, which may result in a more efficient use of scarce resources.

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List of Abbreviations

ASSIGN	Assessing cardiovascular risk using SIGN guidelines
CBVD	Cerebrovascular disease
CBA	Cost benefit analysis
CEA	Cost effectiveness analysis
CHD	Coronary Heart Disease
CHOICE	Choosing Interventions that are Cost Effective
CPD	Ciggarettes per day
CVD	Cardiovascular disease
CUA	Cost utility analysis
DALY	Disability adjusted life year
EQ-5D	Euroqol 5 Dimension score
HDL	High Density Lipoproteins
ICD	Internatinoal Classification of Disease
IND	Index of Multiple Deprivation
ISD	Information Service Directorate
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
JBS2	Joint British Societies 2
MI	Myocardial infraction
NHS	National Health Service
NICE	National Institute of Clinical Excellence
ONS	Office for National Statistics
PDG	Programme Development Group
QALE	Quality adjusted life expectancy
QALY	Quality adjusted life year
QRISK2	QResearch risk score 2
RCS	Restricted cubic splines
RISC	Rotterdam Ischemic Heart Disease and Stroke Computer model
RMSE	Root Mean Square Error
RRR	Relative risk reduction
SBP	Systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation
SF-6D	Short-Form 6 Dimension score
SF-12	Short-Form 12 Dimension questionnaire
SHeS	Scottish Health Survey
SHHEC	Scottish Hearth Health Extended Cohort
SIMD	Scottish Index of Multiple Deprivation
SMC	Scottish Medicines Consortium
SMR	Scottish Morbidity Records
TC	Total Cholesterol
WHO	World Health Organisation

Chapter 1 Introduction

Purpose

This thesis is concerned with the development and application of the Scottish Cardiovascular Policy Model. The intention is to assist policymakers by developing a single comprehensive model that can be used in the development and evaluation of primary prevention interventions, including those targeted on individuals deemed to be at high risk of a CVD event, and also interventions that impact on the entire population.

The introduction chapter provides a relatively detailed overview of the key issues with respect to the primary prevention of cardiovascular disease (CVD). In summarising the clinical and economic burden of CVD, the chapter then discusses the policy approaches to primary prevention and the extent of the current evidence. The overall aim to identify key research gaps that the thesis is then intended to help address.

The burden of cardiovascular disease

Cardiovascular disease (CVD) is associated with substantial burden of disease(1), is a leading cause of inequality(2) and results in substantial economic costs(3). CVD is a global issue and it is a particular issue in Scotland, where it is the leading Western European country in terms of coronary heart disease (CHD) mortality(4). In line with other countries, premature mortality due to CVD has been falling, with the incidence becoming more concentrated in more socially deprived communities(5).

CVD also results in substantial morbidity and economic costs. Estimates are not published for Scotland, however for the UK as a whole the estimate of the health service and wider economic costs is in excess of £31billion per annum(6). Yet, between 80% and 90% of premature CVD is preventable(7).

The aims and approaches of primary prevention

The causes of CVD are well researched. Known risk factors can be divided into modifiable and non-modifiable categories(8). The former include variables such as age and family history, while the latter include cholesterol and smoking. In effect, the entire population is at risk, and most people could benefit from changes to modifiable risk factors. Efficacy evidence suggests that the potential impact of interventions could be hugely significant(9).

There is a vast array of interventions that may influence CVD, including 'downstream' interventions delivered to individuals (e.g. pharmaceuticals, lifestyle advice), to 'upstream' interventions that influence health directly (e.g. legislation) or health behaviours by changing the social determinants of health (e.g. employment, housing)(10).

Policymakers are embarking on major primary prevention initiatives in an attempt to avoid the premature incidence of CVD, reduce health inequalities and avoid the downstream financial consequences(11-12). There are two main strands to primary prevention. First, there is the targeted approach where a pre-defined population are screened and then individuals deemed to be at high risk are referred onto a range of interventions. Second, there is the population approach where interventions are intended to impact on everyone in a defined population without the need for screening to assess baseline risk (13-14).

A targeted approach is based on clinical guidelines which recommend individuals aged 40-74 year olds who are asymptomatic are screened for known CVD risk factors using a 10-year risk score(8). High risk individuals are identified as those with a ≥ 20% risk of a CVD event over the following 10 years, and prioritised for a series of intensive interventions. Clinical guidelines list a menu of possible interventions, including pharmaceutical and lifestyle interventions. There are various risk tools in use across the developed world such as the Framingham score(15) which is used in the United States and England, and SCORE which is used in many European countries(16).

In Scotland, the SIGN clinical guidelines(9) recommend that clinicians use the ASSIGN 10-year score which was developed in 2007 to be used specifically in Scotland. This was intended to replace the Framingham score which was previously used (17). In particular, the ASSIGN score includes a measure of socioeconomic deprivation as an independent risk factor that detects the underlying social gradient in CVD, particularly prevalent in Scotland. The Framingham score does not include deprivation as a risk factor, and consequently may actually increase inequalities if socioeconomic gradient in CVD risk is not considered when calculating risk and prioritising individuals for intervention(17).

In 2007 Scotland launched Keep Well, a targeted primary prevention programme focussed on the most deprived communities, and those aged 45-64 years(12). This is in contrast to clinical guidelines that recommend screening all individuals aged 40-74 years every 5 years. To date,

there has not been a rigorous economic evaluation of the impact of the Keep Well programme. In 2009 England launched a primary prevention programme following clinical guidelines, in contrast to Scotland. Similarly, an economic evaluation is not planned. The mass screening approach underway in England is now under consideration in Scotland.

The second approach to primary prevention is a population approach. The intention is to impact on the whole population, rather than only affecting individuals at high risk over 10-years. Interventions most commonly refer to changes to legalisation and regulation, such as a reduction in saturated fat in processing food, a ban on smoking in enclosed public spaces, and mass media campaigns. Further, while a targeted approach focuses on those aged 40 years and above, it is also the case that the onset of risk behaviours and incidence of inflated risk factors can occur in young adults, including teenagers, and especially in deprived areas(18). For instance, policymakers are increasingly concerned regarding a possible obesity epidemic and prevalence of sedentary lifestyles from an early age(19-21).

Evidence gaps and uncertainties regarding the approaches to primary prevention

Overall, there are serious (and often similar) concerns raised by the clinical, public health and economic communities regarding primary prevention. These are outlined before detailing how these concerns represent an excellent opportunity for health economists to fully engage with the primary prevention effort, and perhaps have an influence over both the development and evaluation of interventions.

There are four broad concerns. First, it is unknown what the most (cost) effective screening approaches are to identifying high risk individuals. While Scotland has a screening programme currently focussed on deprived communities; there is however a policy impetus to screen the entire population. This is in recognition of the seriousness of the CVD issue and perhaps in response to England's national programme. However, a feasibility study regarding whether primary care is able to take on a large influx of patients does not appear to have been conducted. It may be the case that identifying individuals through routine primary care databases could avoid the need for mass screening(22). Further, there are concerns that a mass screening approach places equality of access over equality of outcomes and that such a policy may actually increase health inequalities(23). Programmes which require individual voluntary uptake tend to engage less well with deprived communities, and the "inverse care law" has demonstrated that deprived practices are also less well equipped(24).

Second, the rationale behind using 10-year risk scores to discriminate between and prioritise individuals for intervention is increasingly questioned(25-26). Risk is not a measure of the potential benefit from treatment, as risk is influenced by both modifiable and non-modifiable factors. For instance, everyone is at high risk over a certain age given inevitable mortality. Yet, younger individuals with inflated modifiable risk factors can actually be excluded from interventions. However, it is younger people who may have the most to gain from early intervention, in terms of avoiding premature events.

Further, while CVD is the leading cause of death, there are other competing causes of death (e.g. cancers). There are concerns whether interventions prevent CVD only for individuals to die of other causes(27). Consequently, there is a need to focus on modifiable risk, think more clearly regarding competing causes of death and make explicit the potential benefits of interventions. Most individuals, clinicians and policymakers would agree that the aims of prevention are the avoidance of premature mortality and morbidity(15). Given these aims discrimination and prioritisation of individuals may best be made explicitly on the basis of benefit, not risk. This is not to suggest that clinicians do not have potential benefits in mind when treating individuals, but rather the process is not as explicit or formalised as it could be.

Third, there is considerable doubts regarding whether the targeted approach taken together (screening, prioritisation interventions) is likely to be value for money(28). There is robust evidence regarding the impact of single interventions, especially pharmaceutical (29-30) and certain lifestyle interventions, in particular smoking cessation interventions(31). However, there is little evidence with regards to the efficacy, effectiveness and cost effectiveness of the multi-factorial interventions being rolled-out in Scotland and elsewhere. Particular concerns, relate to the long run compliance behaviour of individuals from both pharmaceutical and lifestyle interventions. The complex issues of implementation and context may also be important in attempting to transferring learning between locations(32). Economic evaluation has been relatively poor at conditioning estimates on such contextual issues(33).

Fourth, the targeted and population approaches to primary prevention have traditionally been seen as a competing, with advocates running the risk of polarising the debate(13-14). Perhaps, part of the reason for polarisation is that it can be (implicitly) assumed that the targeted approach favours pharmaceutical interventions(13) and the population approach favours lifestyle interventions. However, this is needn't be case. Mass administration of drugs

has been recommended in the literature(34) and lifestyle interventions can be targeted on individuals. As will be argued in the thesis, a targeted and population approach can be quite compatible, and indeed be used strategically to reinforce impacts. Modelling exercises have indicated the huge potential impact that could result from legislative changes on reducing CVD and extending life expectancy(35); although the actual evidence supporting these exercises is still lacking.

Overall, policymakers are intent on responding comprehensively to mitigate the incidence and burden of CVD; however, there is a lack an equally comprehensive evaluation effort to influence the choice of approaches and interventions. The objectives of primary prevention are clear, but there are major question marks regarding whether current initiatives can best meet these objectives, given limited resources. Policymakers are using a dual approach of targeted and population wide interventions, but not necessarily in an explicit or coordinated manner. The recent emphasis has been on funding and implementing targeted approaches: to screen, identify and prioritise individuals for a wide mix of multi-factorial interventions.

Informing primary prevention approaches: the role of modelling

Economic evaluation is intended to build upon clinical evidence to consider both the benefits and resource costs from interventions. Consideration of available budget is essential given scarce public resources, and the inherent opportunity costs in decision making. The aim of economic evaluation is to help policymakers choose the best buys and make the most of scarce budgets.

The key feature of economic evidence is the development of a common outcome measure to enable different types of interventions to be compared directly and consistently. There are different forms of economic evidence however(36), such as cost benefit analysis, cost utility analysis and cost effectiveness analysis. The first is the traditional approach of economics and, in taking a societal perspective, attempts to value all outcomes that result from an intervention. The latter two, as applied in health economics, are a particular forms of economic evaluation developed for the health sector. A health perspective is taken where evidence is tailored to what decision makers (are assumed) to consider when allocating sector budgets. The outcomes considered are restricted to health (and personal social services)(37). This thesis takes a health perspective, and consequently the intention is to compare targeted and population intervention on health outcomes and health service costs.

Economic information can be part of a pragmatic trial design to help ensure relevant information is collected, such as an appropriate measure of health benefits, to generate quality adjusted life expectancy (QALE), and estimate the impact on health service costs, net of intervention costs(38). However, trials and evaluation studies are subject to a wide range of limitations. Key amongst such limitations is that studies in general can only detect short run impacts whereas the impacts on health may only be fully realised over the long term. This is particularly the case for prevention and when interventions are extended from the elderly to younger adults. Therefore, there is an important role of economic modelling to project long term impacts of 'within-trial' evaluations, that are often necessarily conducted over the short term(38), and especially to sensitise assumptions regarding compliance over the longer term. Further, many interventions can be evaluated against a 'do-nothing' scenario(31). However, what is clear in that the policy direction in the prevention of CVD is to 'do something'. Therefore, there is also an important role for modelling to simulate head-to-head comparisons, given interventions essentially compete for scarce public budget.

Limitations of current economic models

From first principles, it would be ideal if a single economic model was wide enough in scope to evaluate the range of targeted and population interventions and had the ability to produce outcomes commensurate with the aims of primary prevention. This generic approach to modelling is in a sense an extension of the rationale for a generic approach to economic evaluation. That is, there could be a consistent modelling approach, in addition to a consistent outcome measure. Such consistency may help to foster additional confidence by policymakers in comparing evidence from different interventions.

A major application of an economic model is to inform the targeted approach to prevention, where perhaps the greatest uncertainties are with respect to economic evidence. It is desirable that an economic model is congruent with the clinical risk scoring models that are used to prioritise individuals for interventions in the first place. Building a model using the same wide range of variables employed in 10-year risk scores would enable greater congruence between how individuals are prioritised and how interventions are evaluated. Consequently, this approach may help align economic models with clinical models, and perhaps further encourage the acceptance of economic models and model outputs in clinical and policy circles.

Further, it is also important to develop a model that can help assess the impact of population interventions also to provide consistency in comparing both targeted and population interventions.

In considering existing policy models, the phrase: “[a]ll models are wrong but some are useful” is a helpful starting point(39). Experts have developed best practice guidance which is periodically updated(40-44). It is evident that certain modelling approaches and features can help enhance the credibility of models. Models should be as simple as possible, fully reported and validated, including: (i) face validity, that the model represents a medical issue properly; (ii) internal validity, which is a check on whether the model can estimate the outcomes from the dataset(s) from which it was constructed; and (iii) external validity, which tests whether the model can predict outcomes in a dataset not used in the construction of the model. Further, it is important that models are calibrated to the population of interest. This is particularly important if the model has been built using historical data and /or is intended for use in a different context (e.g. a different country). Overall, following best practice guidance is important so that both analysts and peers have confidence in using models, and decision makers trust the outcomes produced.

There are a range policy models in existence which will be reviewed in the thesis. All have considerable merits, and several have been used persuasively to estimate the impact of mainly population wide interventions. However, no model is ideally suited to estimate the impacts of both targeted (especially, multi-factorial programmes) and population wide interventions. Three models use the same variables used in 10-year risk scores, but only estimate the impacts of interventions on reducing CVD events (and consequent life years saved) over 10 years. No models estimate the full lifetime impact of interventions on CVD or all cause mortality taking into account the fact that same risk factors also drive other conditions such as cancers and respiratory diseases. Also, no model estimates the full impact of interventions on health service costs from interventions that may extend life expectancy. The later is important as interventions essentially postpone events or change the cause of eventual death(27), and meanwhile individuals incur greater co-morbidities as life expectancy increases(45-47). Further, few models quality adjust outcomes to take into account the morbidity impacts of avoiding non-fatal events. Sensitivity analysis can also be limited and validation is usually restricted to tests of internal validity. Finally, of key importance for Scotland, is that no model uses the same variables in the ASSIGN score. This is notable

given Scotland suffers from a pronounced social gradient in CVD. Overall, no current policy model is ideally placed for use in Scotland.

Purpose of thesis I: to build the Scottish CVD Policy model

The overall purpose of the thesis was to develop the Scottish CVD Policy Model to build upon the strengths and limitations of current exiting policy models in an attempt to help address the perceived weakness of current approaches to primary prevention.

A generic model was developed using the same set of nine variables employed in the ASSIGN risk score and used to estimate the impact of changes to modifiable risk factors on quality adjusted life expectancy (QALE), lifetime costs and health inequalities. In this sense, the model is intended to be a 'natural extension' to 10-year risk scores and have the capacity to inform the development and evaluation of the targeted approaches to primary prevention. In addition, the model is developed using data sources and statistical methods that are intended to be generalisable to the Scottish general population. Following best practice guidance, the model building process and resultant outputs are intended to be transparent and validated on the Scottish population. In application, the model is intended to be used by policymakers to help inform and evaluate both targeted and population interventions.

Purpose of thesis II: applying the model to address key research questions

Overall, the intention was to develop a new and comprehensive Scottish CVD Policy Model to help inform primary prevention and address certain key uncertainties as discussed, which are formulated into the following specific research questions:

(i) If the current approach to prioritising individuals for intervention is to use 10-year risk scores, can the model be used to identify optimal screening approaches to identify high-risk individuals?

(ii) Given the weaknesses in 10-year risk scores, can a new approach to prioritising individuals be developed based upon individuals' potential to benefit rather than risk?

(iii) Can the model be used consistently to assess the cost effectiveness of both targeted and population interventions?

In addressing these issues pragmatically, an important observation is that policymakers are intent on forging ahead with primary prevention interventions, despite a relatively weak evidence base. Consequently, the immediate decision context for policy makers is which interventions to choose; rather than a willingness to delay decisions before further research is available. As a consequence, the focus of the thesis was to demonstrate the application of the model to evaluate interventions by generating mean estimates, and focus on heterogeneity; rather than also provide a full uncertainty analyses. In other words, given the policy context, at present, there is an "irrelevance of inference"(48). Nonetheless, it is important to note that the model is capable of conducting a full uncertainty analysis which will also be discussed, including probabilistic sensitivity analysis and value of information analysis in order to inform decisions regarding funding further research(49).

Structure of thesis and chapter outline

The thesis is divided into three parts, building upon one another. Each part begins with an overview section to help orientate the reader, and is composed of particular chapters.

Part 1 - Part 1 aims to provide the background for the thesis. Chapter 2 illustrates the health and economic burden resulting from CVD, before describing the targeted and population approaches to primary prevention. In summarising the existing literature, there appears to be a general lack of evidence underpinning the practice of primary prevention, particularly regarding the impact of the targeted multi-factorial programmes which is the key policy focus in Scotland.

The aim of Chapter 3 is intended to make the case for the Scottish CVD Policy Model to help inform clinicians and policymakers regarding the development and evaluation of interventions. The chapter introduces the rationale for economic modelling, to be used in tandem with evidence from clinical trials, to produce cost effectiveness evidence. The chapter collates best practice guidance regarding how to build an economic model, and uses this to appraise current policy models, which are identified through a systematic review. The key strengths and weaknesses of existing models are discussed, before further developing the rationale for building the Scottish CVD Policy Model to help address the research questions.

Part 2 - Part 2 forms the main empirical element of the thesis and describes how the model was developed. Chapter 4 details the approach to creating and populating the model drawing upon the best practice guidance. Importantly, access was granted to the Scottish Heart Health Extended Cohort (SHHEC) and consisted of approximately 16,000 individuals who were free of CVD. In linking this dataset to Scottish Morbidity Records (SMR) all hospitalisations incurred by individuals could be tracked. This was the dataset employed in the development of the ASSIGN 10-year risk score used in clinical practice within Scotland, thus providing an opportunity for the policy model to be developed using the same variables that serve as risk factors. This approach is intended to provide consistency between the clinical model used to screen and prioritise individuals, and the policy model that may then be used to evaluate the impact of interventions intended to modify risk factors. The policy model was comprehensively validated, in terms of face validity, internal validity and externally validity; and life expectancy predictions were also re-calibrated to the latest Scottish lifetables, at the time of writing.

Chapter 5 then builds upon the statistical modelling to generate and populate the model with economic information. This allows the model to generate QALE and lifetime hospitalisation costs. Quality adjustment consisted of background morbidity (population norms) and the negative impact of experiencing CVD events (utility decrements), including first and subsequent events. Estimates of lifetime costs include all hospitalised events, CVD and non-CVD. A key feature is that all estimates are generated directly (rather than using secondary sources) and using Scottish data sources. This is intended to enhance the applicability of outputs to Scottish decision makers, the (immediate) intended users of the model. The chapter ends with a brief demonstration of how the model could be used in evaluation to assess the impact of changes to risk factors on (quality adjusted) life expectancy and lifetime health service costs.

Part 3 - Part 3 of the thesis demonstrates how the model can be used to help address the research questions, identified above. Four short chapters follow to show how the model can be used to improve the approach to primary prevention. Chapter 7 uses the model to help identify optimal screening strategies by simulating the potential cost effectiveness of different approaches to detect the high risk in the general Scottish population. Chapter 8 uses the model to develop a new approach to prioritising individuals for intervention on the basis of the potential lifetime benefit from modifying risk factors. This approach could in principle replace current clinical practice which uses a 10-year risk score that is driven by age, which is non-

modifiable. The chapter simulates the potential impact that a switch from 10-year risk to potential benefit may have in the Scottish general population in terms of the reprioritisation of individuals, potential gains in population health, and the impact on health inequalities. Chapter 9 then illustrates how the model could be used to estimate the cost effectiveness of Keep Well. The Scottish Government has no immediate plans to undertake an economic evaluation. The expectation of policymakers is that, given the burden of CVD and the existence of robust efficacy evidence, the programme will be a good use of public resources. The policy model is used to challenge such assumptions and illustrate the huge uncertainty regarding whether the programme is cost effective, and the consequent need for a rigorous economic evaluation. Finally, chapter 10 simulates the potential impacts of a variety of population interventions concentrating on changes to regulation in smoking, and the reduction of the salt and saturated fat content in food. The final demonstration shows how the model can be used to inform the optimal mix between targeted and population interventions. The model demonstrates that utilising both approaches may make strategic sense to both increase population health and reduce health inequalities.

The concluding chapter completes the thesis and summarises the aims, approach and applications of the Scottish CVD Policy Model. The model is intended to be fit-for-purpose and ready for use. However, no model should ever be considered complete(43-44, 50-52) and there are also several limitations that a future research agenda could help address. The chapter ends by discussing a range of potential innovations that could be made to improve the current model, broaden its scope from CVD (e.g. to other chronic diseases), extend it focus (e.g. to younger adults and children) and consequently widen its potential policy applications. Overall, the hope is that the aims of the thesis have been fulfilled and that a fruitful agenda has been identified for future research.

Part 1: The burden of cardiovascular disease and the role of economic modelling

Overview

The first part of the thesis is intended to set the overall context regarding the burden of cardiovascular (CVD) disease in Scotland and the need for a Scottish CVD policy model to help inform both the clinical and policy approaches to primary prevention.

Two chapters follow. Chapter 2 provides a detailed discussion of the health and economic burden of CVD, the risk factors that drive CVD in the population and the current approaches to prevention that seeks to reduce modifiable risk. Primary prevention approaches can be classified into targeted approaches that focus on individuals identified as being at high risk of a CVD event, and population wide approaches that impact on the entire population. Notably, there is a general lack of economic evidence underpinning these approaches and, in particular, the targeted approach. The chapter identifies four key areas of uncertainty regarding current approaches to primary prevention, which are reformulated into associated research questions for the thesis to address.

Chapter 3 discusses the role of economic modelling to help generate the kind of cost effectiveness evidence that national reimbursement agencies, such as the Scottish Medicine Consortium (SMC) and the National Institute for Health and Care Excellence (NICE) require to approve new interventions. Economic modelling can be used to compliment trial evidence by, for instance projecting short term clinical outcomes such as changes in risk factors to generate outcomes such as quality adjusted life expectancy. However, modelling can be a complicated process, and may involve the use of complex data sources, assumptions and statistical techniques. Therefore, while economic models are necessary, a common criticism is that models can become “black boxes”(53). To enhance the rigor, credibility and trust by decision makers in model outputs, experts in economic modelling have developed best practice guidance. The chapter conducts a systematic review of existing policy models that can be used to inform primary prevention, and appraises identified models using these best practice guidelines. The chapter then makes the case that a new Scottish CVD Policy Model is needed for use in Scotland to address the four research questions identified in Chapter 2.

Chapter 2: The burden of cardiovascular disease and approaches to primary prevention

2.1 Introduction

Cardiovascular disease (CVD) is a major cause of mortality and is a leading cause of health inequalities across the world(1-2). In recent years, the primary prevention of CVD has become a key national policy priority in order to avoid the first instance of the disease and the downstream consequences in terms of premature mortality and the economic impact on the health service and the wider economy. The purpose of the chapter is to review the burden of CVD in Scotland and the policy approaches to primary prevention.

The chapter is structured as follows: Section 2.2 reviews the clinical burden of CVD, highlighting the socioeconomic inequalities in mortality and morbidity of CVD. Section 2.3 estimates the economic burden of CVD in Scotland on the health service, informal care and the wider economy. Section 2.4 then reviews the risk factors that are known to drive the incidence of CVD and describes how these are distributed across the general population in Scotland. Having illustrated the causes and consequences of CVD, the chapter reviews current approaches to primary prevention and the associated evidence with respect to modifying risk factors. Section 2.5 provides an overview of prevention strategies in general, before sections 2.6 to 2.9 discuss the targeted and population approaches to primary prevention in detail and the associated evidence base. Section 2.10 summaries the limitations in the evidence base, before section 2.11 develops four associated research questions. Section 2.12 concludes by emphasising that there is a need for (more) economic evidence to inform decision making in primary prevention and help ensure that funded interventions are actually value money.

2.2 The clinical burden of cardiovascular disease

2.2.1 Defining cardiovascular disease

Coronary heart disease (CHD) and cerebrovascular disease (CBVD) are the two main forms of cardiovascular disease (CVD). CHD is a disease of the heart and coronary arteries caused by the build-up of fatty materials in the blood vessels that supply the heart with oxygen. This can result in a range of events, the most common being: angina, irregular heartbeat (arthymia) heart attack (myocardial infarction) or heart failure. CBVD is where the blockage restricts blood to the either the brain resulting in a stroke, or in the extremities of the body resulting in peripheral arterial disease (intermittent claudication)(54).

The international classification of disease (ICD) is the accepted standard regarding the coding and grouping of events by disease area and particular events. The versions of ICD referred to in the thesis are ICD-9 and ICD-10, with the relevant codes with respect to CVD shown in Table 2-1. ICD-9 codes refer to the pre-2000 period, and ICD-10 codes refer to the post-2010 period. Events are grouped into the broad categories of non-fatal CHD, non-fatal CBVD, and CVD death, from CHD or CBVD. These groupings will be used when building the structure of the Scottish CVD Policy Model, in part 2 of the thesis.

Table 2-1: Defining cardiovascular disease

Event	ICD codes
CHD	ICD9 410-414; ICD10 I20-I25
CVBD	ICD9 430-438; ICD10 G45, I60-I69
CVD death	ICD9 390-459; ICD10 I00-I99

Source: World Health Organisation(55)

2.2.3 The mortality burden of cardiovascular disease

Cardiovascular disease (CVD) is a major cause of death worldwide and in 2010 resulted in 30% of all deaths before the age of 75 years(56). There can be wide variations across the world in terms of CVD mortality. For instance, in the United States in 2009 CVD accounted for

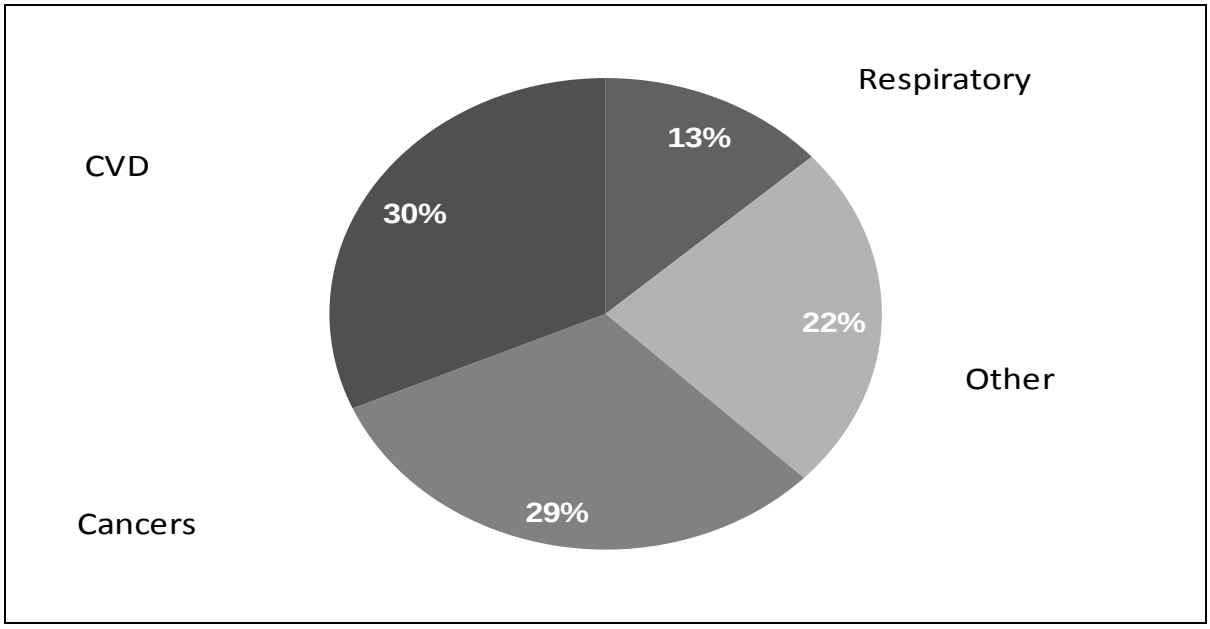
29.9% of all deaths before the age of 75 years, and equivalent figures in the European Union in 2010 ranged from 37% in Central and Eastern European Countries to 17% in France(1).

Within the European Union there is a clear North East-South West gradient in mortality rates, with Southern and Mediterranean countries having amongst the lowest rates. For instance, the age standardised mortality rates (SMR) for CHD was 89 for Portugal, Italy and Spain, whereas the SMR was UK, Ireland and Finland was 218(1).

Mortality rates have actually been falling rapidly in recent decades in most developed countries. In Western European countries, the annual percentage fall in CVD mortality was 1.8% in men and 2.1% in woman from 1970 to 2000 for those between 45 and 74 years(57).

Regarding Scotland, the main source for mortality statistics is the Information Service Directorate (ISD). In Scotland, CVD accounted for 30% of all deaths in 2011, with the other major causes of mortality being cancers and respiratory diseases, as figure 2-1 illustrates.

Figure 2-1 CVD as share of all deaths before the age of 75 years in 2011



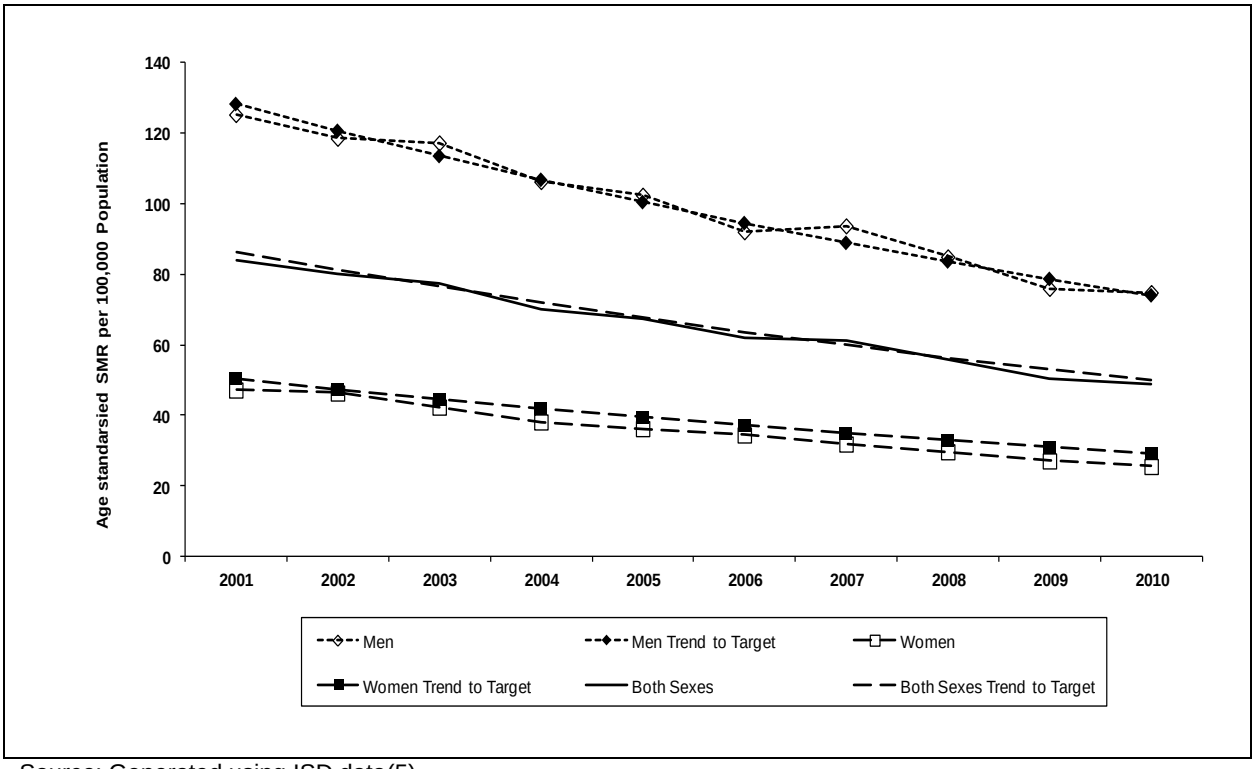
Source: Generated using ISD data(5)

Mortality reductions relative to Government targets

Figures 2-2 and 2-3 illustrate the fall in SMR per 100,000 for under-75 year olds between 2001 and 2010. The year 2001 to 2010 was chosen as this provides the longest time period over which ISD provides data consistently at both the general population level, and lower levels of aggregation, such as age group and socioeconomic deprivation status (discussed shortly). Further, trends are shown relative to the Scottish Government targets(58) for which ISD have generated annual trend targets.

Figure 2-2 is concerned with CHD mortality and illustrates a 40% reduction in CHD mortality for men relative to a target of 42% over this period. For exposition, this target was shown as a linear gradient to facilitate comparison with actual falls. The equivalent reduction for women was 46% relative to a target of 42%. Overall, in considering men and women together the combined target reduction of 42% was met. In comparing the levels of CHD mortality between men and women, the SMR rate was 2.7 times greater in men than women in 2001 and this rose to 2.9 in 2010.

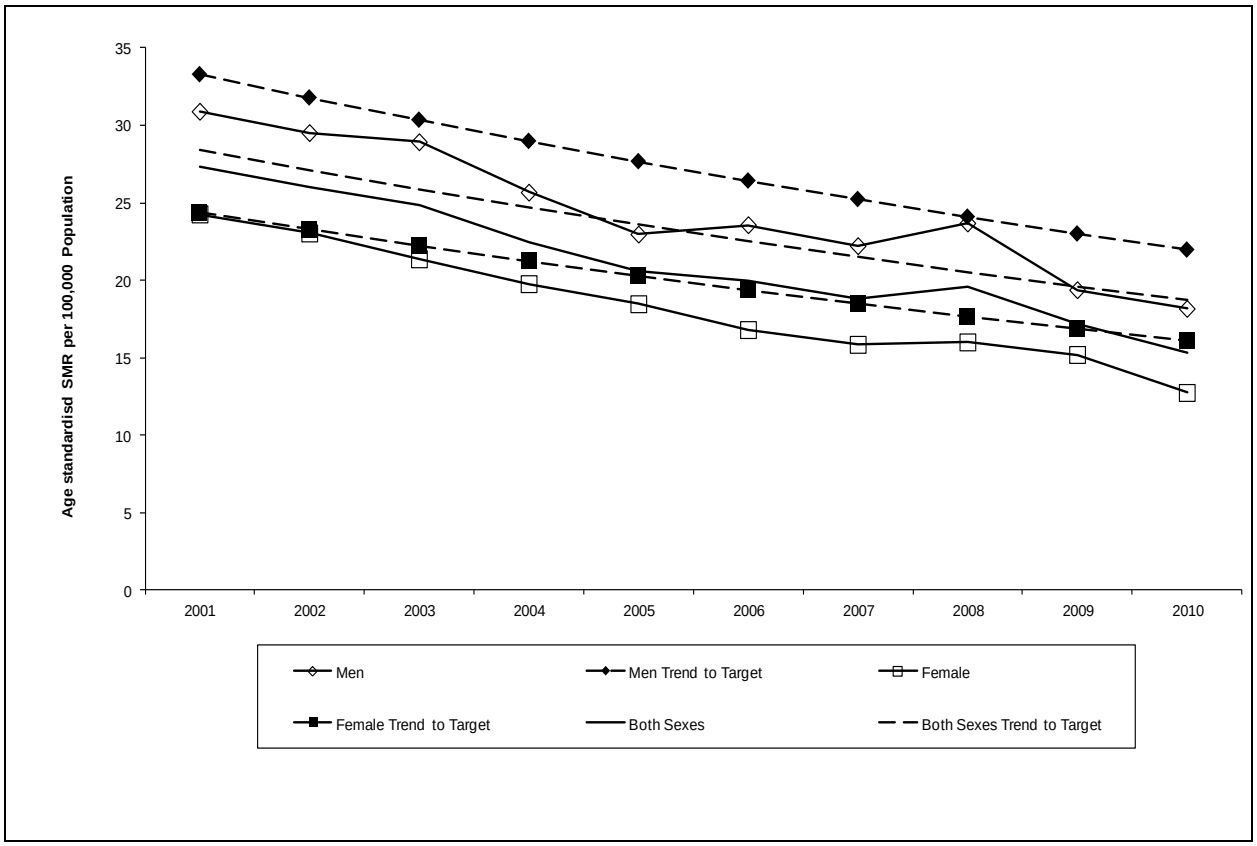
Figure 2-2 Reductions in CHD mortality relative to Government targets



Source: Generated using ISD data(5)

Figure 2-3 illustrates equivalent reductions in CBVD mortality. The target reduction was 34% for both men and women and this was surpassed with the reduction in mortality rate for males of 41% and 48% respectively, with a combined reduction of 44%.

Figure 2-3 Reductions in CBVD mortality relative to Government targets

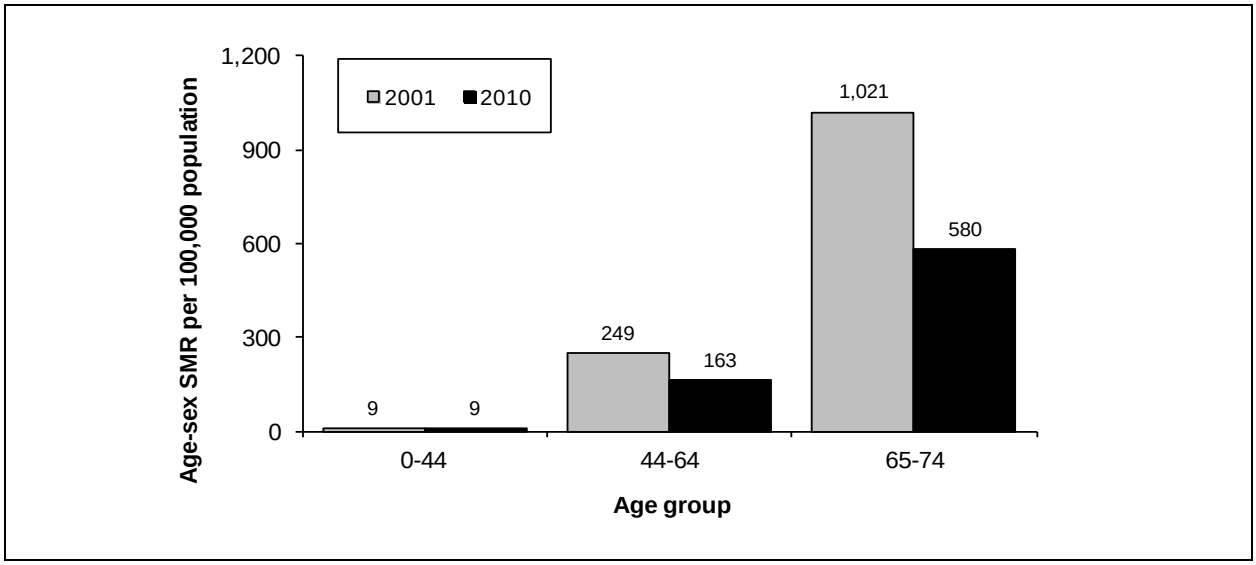


Source: Generated using ISD data(5)

Variation by age group

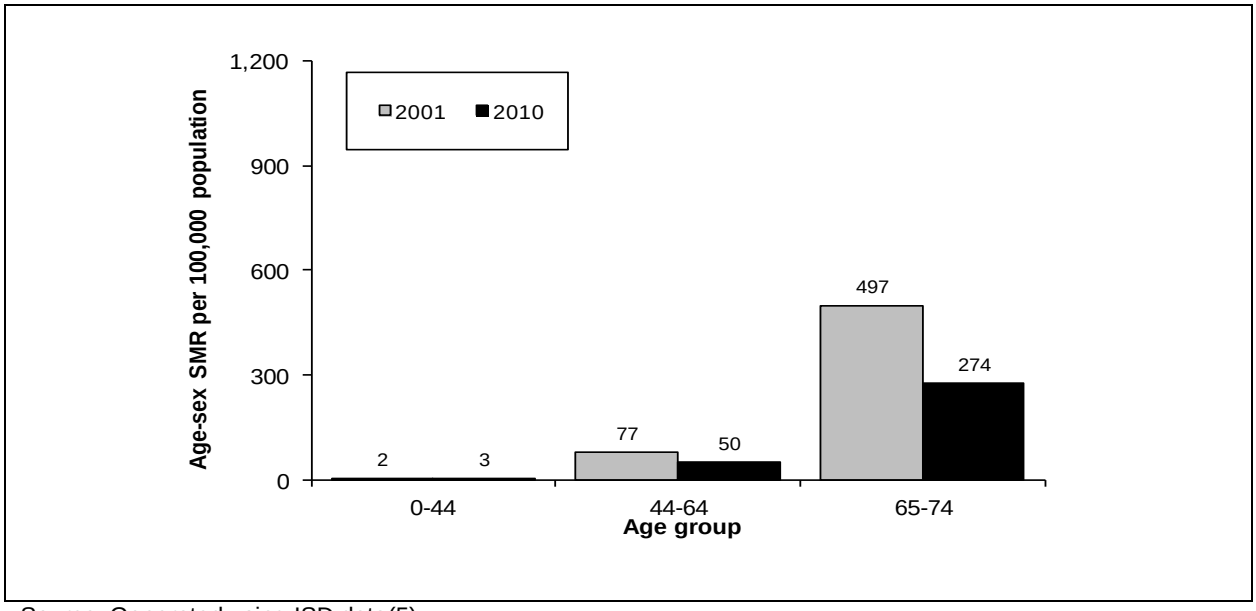
The reduction in CHD death varied across age groups (figures 2-4 and 2-5). These are the age groups that ISD report. For men, the reduction in CHD was 35% for 44-64 year olds and 43% those aged between 64-74 years between 2001 and 2010. There were similar variations across age groups for women and the reduction in mortality was also greatest in the 65-74 year olds, falling by 45%. The (age-sex) SMR was higher for men than women across all age groups, and this ratio was fairly constant between 2001 and 2010. In 2010, the SMR rate for men was 3.3 times higher than women for 44-64 year olds and 2.1 times higher for 64-74 year olds.

Figure 2-4 CHD – Changes in CHD mortality - men



Source: Generated using ISD data(5)

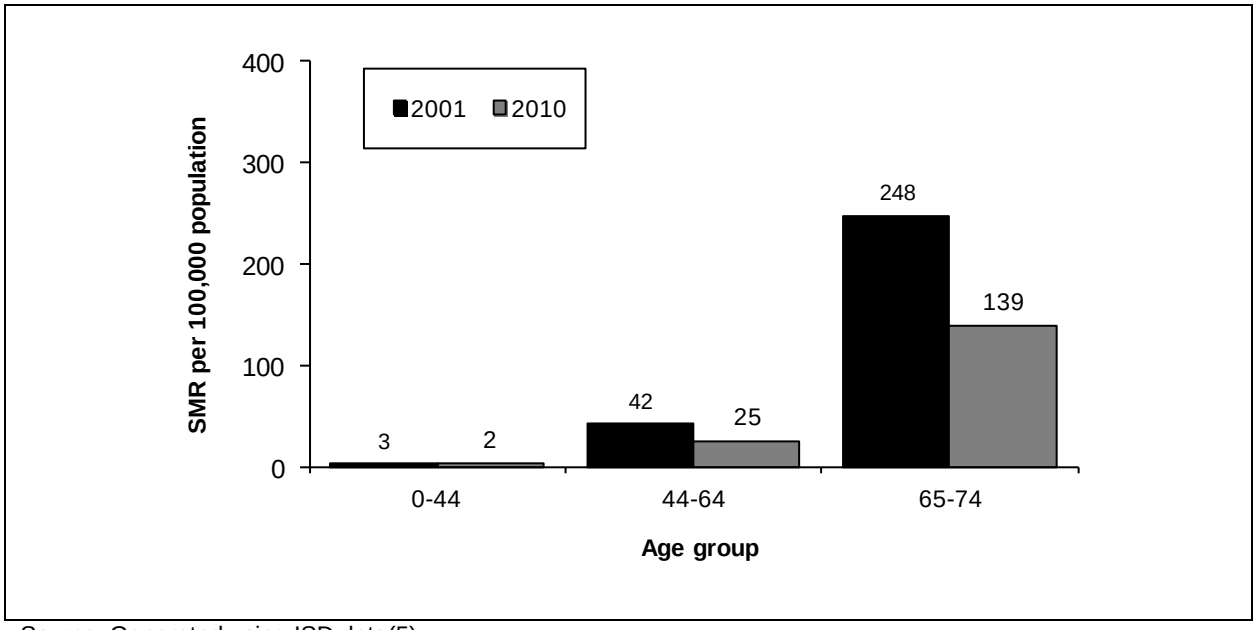
Figure 2-5 CHD – Changes in CHD mortality - women



Source: Generated using ISD data(5)

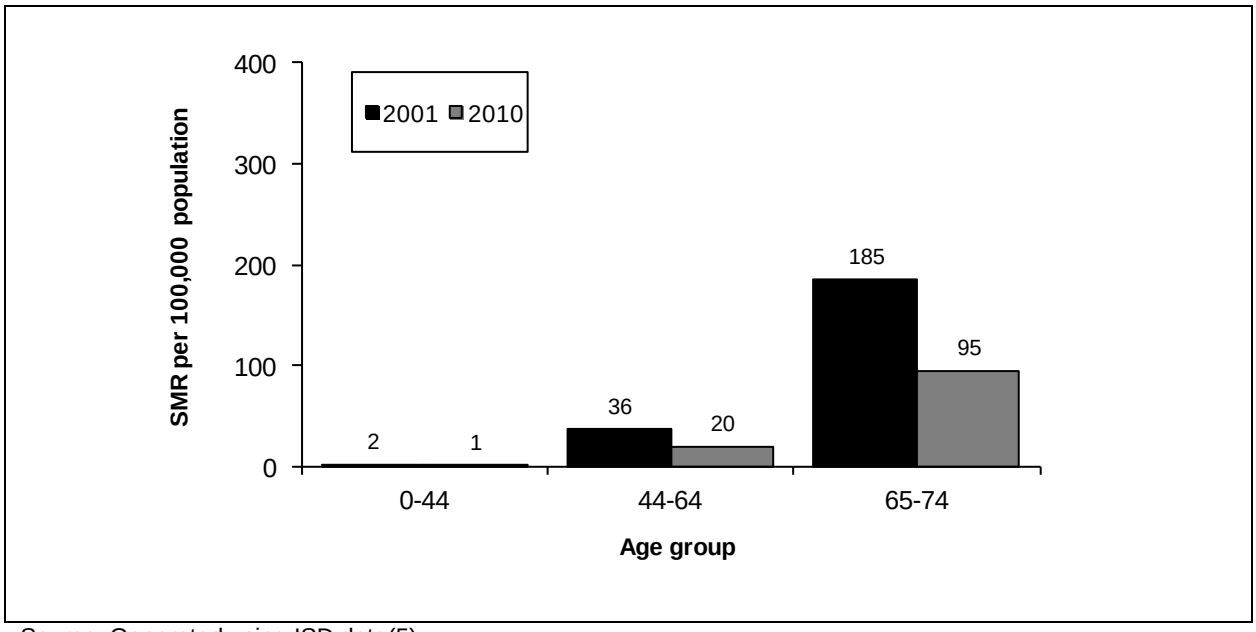
There were similar variations in SMR across age groups for CBVD as found for CHD, and for both men and women. The reduction in mortality was also greatest in the 65-74 year olds, falling by 44% and 45% for men and women respectively. The SMR was also higher for males than females across all age groups but the ratio increased slightly between 2001 and 2010. In 2010 males SMR rate was 1.3 times higher than women for 44-64 year olds and 1.5 times higher for 64-74 year olds.

Figure 2-6 Changes in CBVD mortality - men



Source: Generated using ISD data(5)

Figure 2-7 Changes in CBVD mortality - women



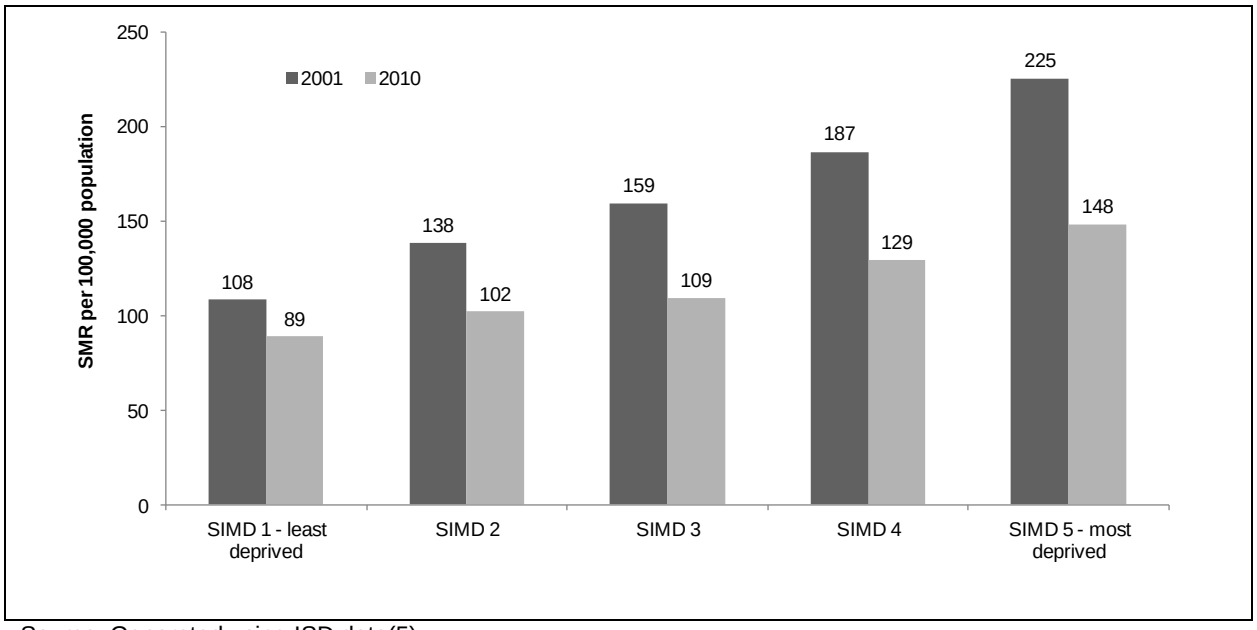
Source: Generated using ISD data(5)

Variation by deprivation

Figure 2-8 illustrates (age/sex) SMR CHD mortality by fifths of socioeconomic deprivation. The Scottish Government uses a measure of socioeconomic deprivation called the Scottish Index of Multiple Deprivation (SIMD). The SIMD score is an aggregated measure of material deprivation derived from 37 indicators in seven domains (income, employment, health,

education, access to services, housing and crime) and is determined at the data zone level (geographical areas with a median population of 769)(59). Equivalent statistics are not produced for CBVD mortality by SIMD.

Figure 2-8 Changes in CHD mortality by fifths of socioeconomic deprivation (SIMD)



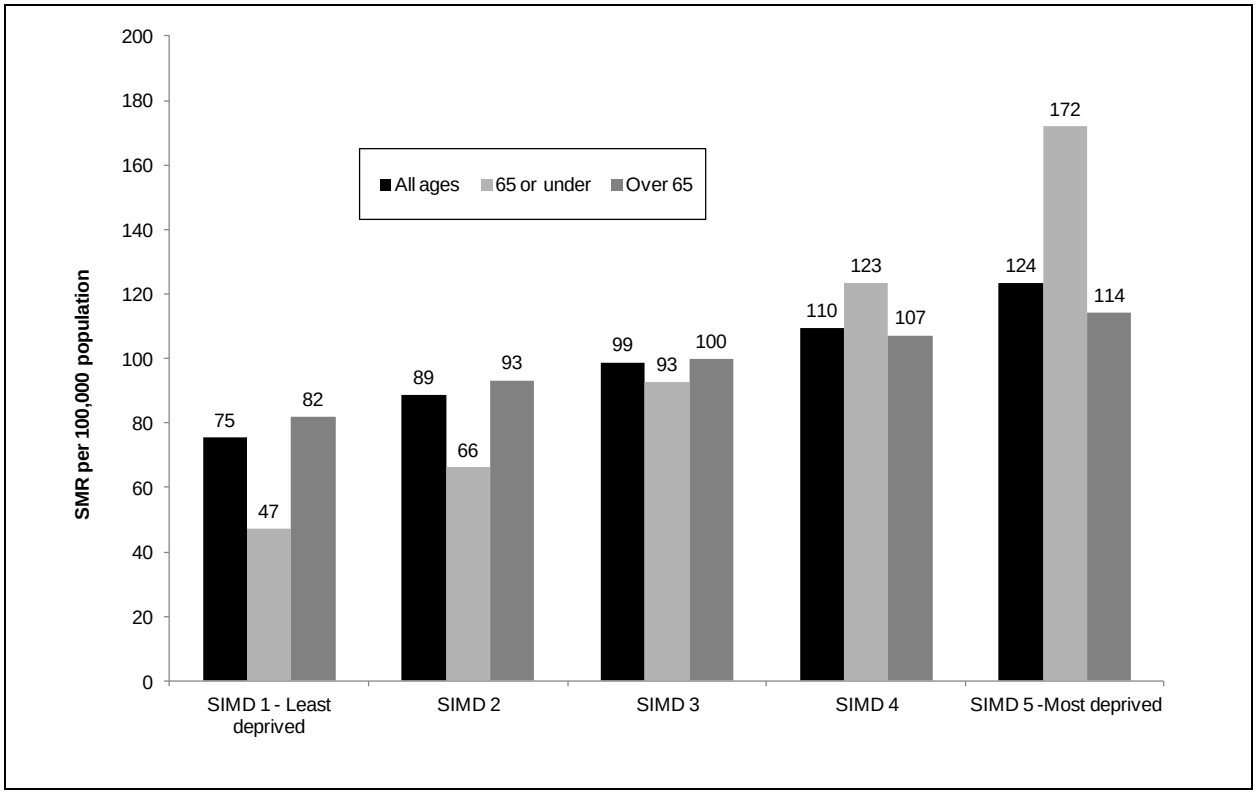
Source: Generated using ISD data(5)

Notably, inequalities in CHD mortality have been falling. While mortality rates across all fifths of SIMD fell markedly between 2001 and 2010, the reduction (34.1%) in the age-sex standardised CHD mortality rate among the most deprived fifth has been almost double the reduction observed in the least deprived category (18.1%). The most deprived fifth had a mortality rate which was 66% higher than the least deprived fifth in 2010 – almost half the gradient in 2001 (108%).

Variation by age and deprivation

Figure 2-9 illustrates the (age) SMR rate for CHD in men and split by those below and above 65 years in 2009 and across fifths of SIMD. Further, the bars represent average rates between 2004 and 2009. Equivalent statistics were not available for women.

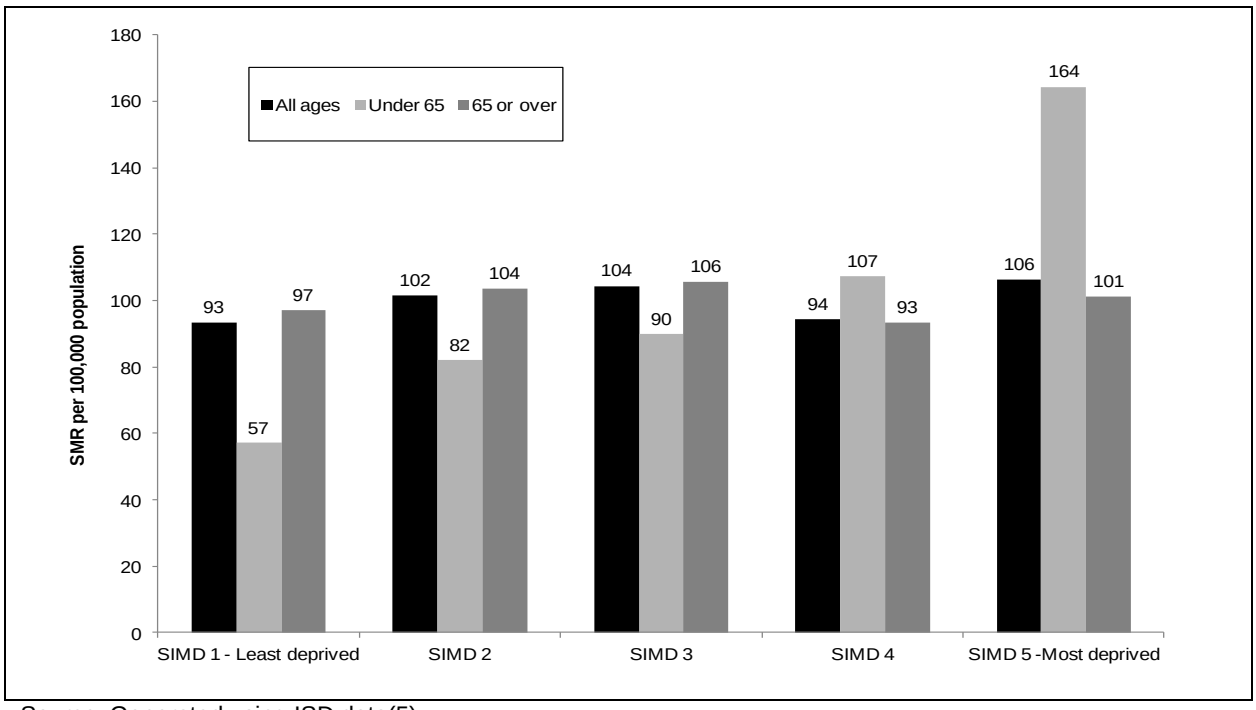
Figure 2-9 Five year average of CHD Mortality: 2004-2009



Source: Generated using ISD data(5)

The incidence of CHD mortality for those under 65 years is greater in the most deprived communities. Further, mortality rates are progressively higher for increasing fifths of socioeconomic deprivation. Mortality in SIMD 5 in the under 65s was over 3 times higher than in SIMD 1 (ISD, 2011) – compared to 50% higher for all age groups taken together. A similar relationship is also found for CBVD, although the SMR are on the whole slightly lower with the exception of SIMD 1.

Figure 2-10 Five year average of CBVD Mortality: 2004-2009

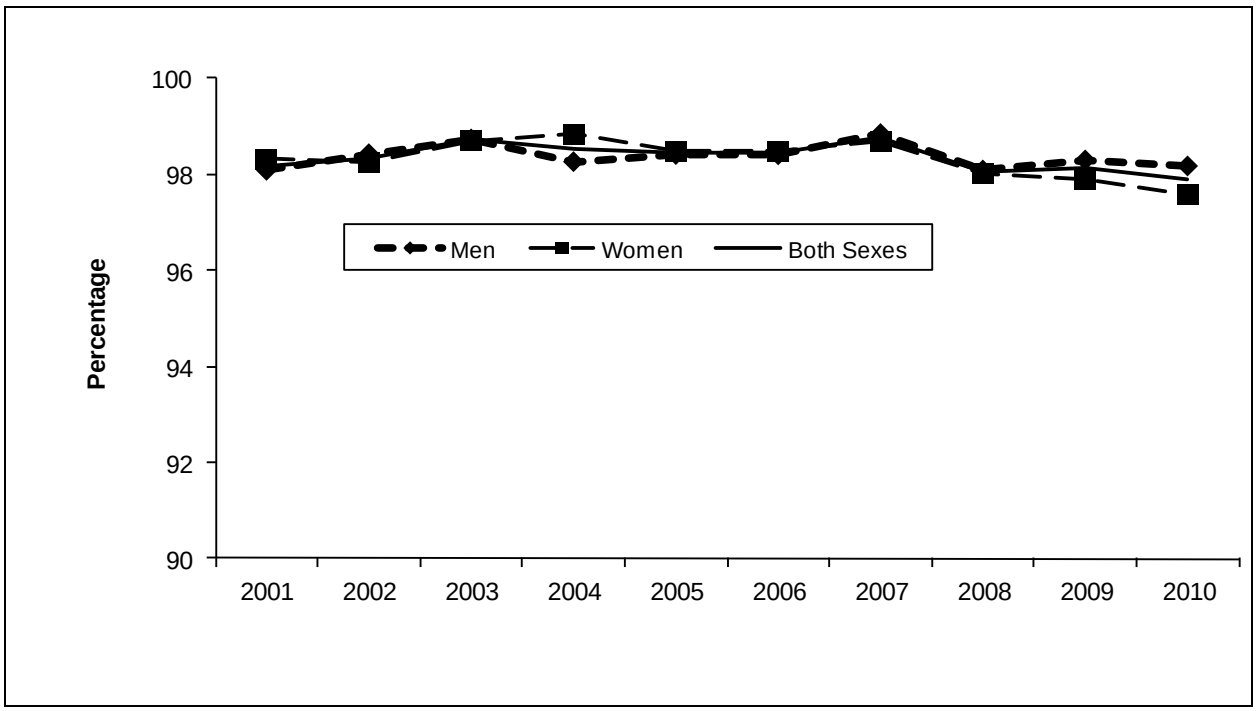


Source: Generated using ISD data(5)

Survival from CVD events

It is also important to estimate survival from events, as a means to help understand the morbidity and resource cost burden of CVD. Morbidity is discussed in detail in the next section. Figure 2-11 and 2-12 illustrates survival for those conditions that ISD report statistics for. In general, 30-day survival from acute myocardial infarction and unstable angina is high, around 98%; similar for both men and women and has been fairly flat since 2001. In contrast, 30 day survival post-stroke is lower than acute myocardial infarction, but has been rising steadily over the past 10 years. The survival rate for both sexes combined rose from 79% in 2001 to 83% in 2010. Males have a higher survival rate than women rising from 82% in 2001 to 86% in 2010.

Figure 2-11 Trends in 30 day survival post-acute myocardial infarction and unstable angina



Source: Generated using ISD data(5)

Figure 2-12 Trends in 30 day survival post-stroke

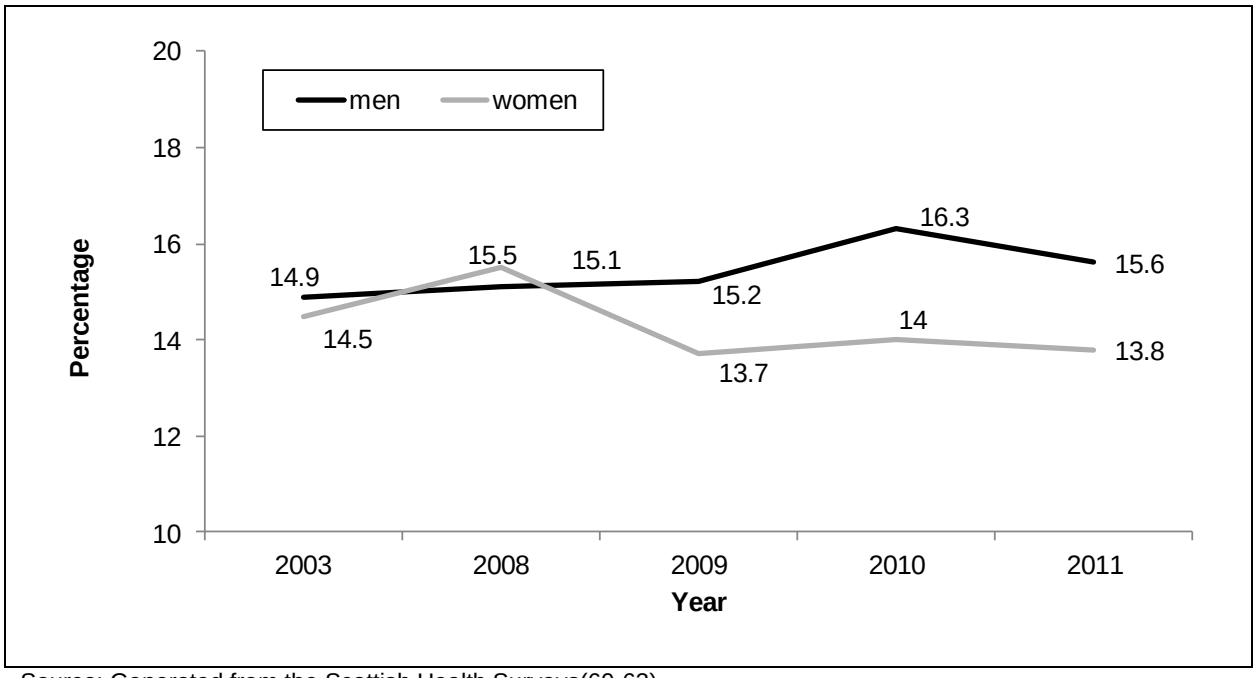
Source: Generated using ISD data(5)

2.2.4 Morbidity burden of cardiovascular disease

Figure 2-13 illustrates the prevalence of those living with CVD in Scotland, split by males and females. The source of this information is the Scottish Health Survey (SHeS). Individuals self-report having experienced events, including angina, heart attack, stroke, heart murmur, abnormal heart rhythm, or 'other heart trouble. The survey began in 1995, however the years 2003 to 2011 are shown as these are the earliest and most recent survey that contain prevalence rates.

The y-axis is truncated in an effort to illustrate variation between years. A wider range in the y-axis would have resulted in the trend appearing relatively flat. In 2003, 14.9% of men and 14.5% of women were living with CVD. By 2011, this proportion had risen to 15.6% for men and fell to 13.8% for women. However, these changes are within 1 percentage point, and the SHeS does not report expected sampling error.

Figure 2-13 Percentage of the population above 16 year living with CVD

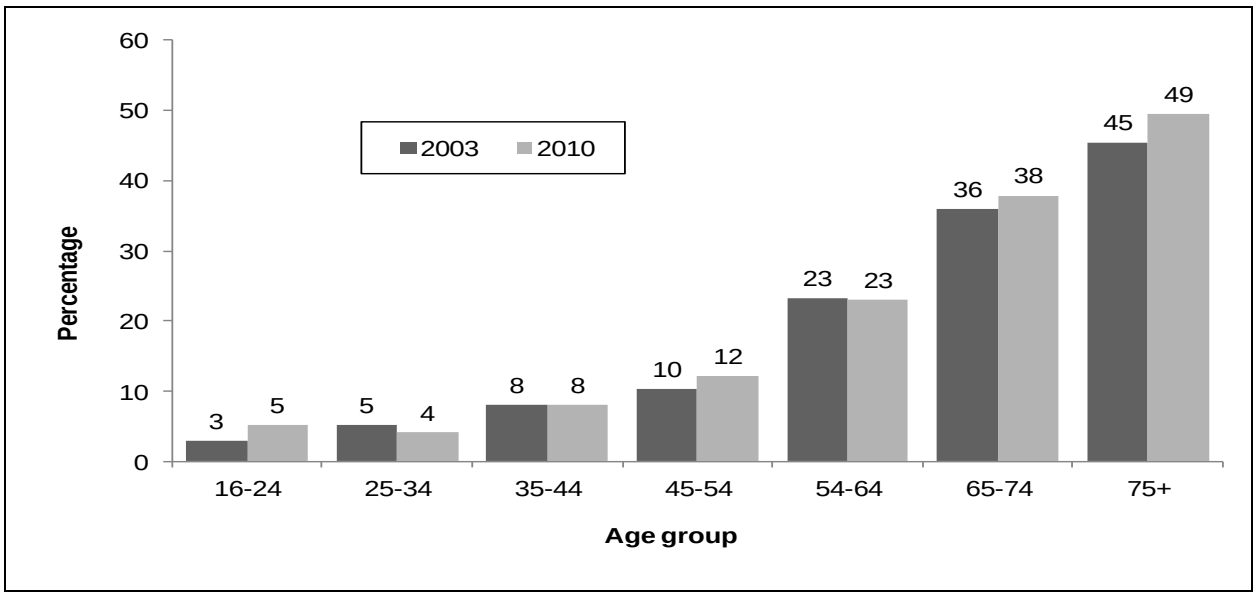


Source: Generated from the Scottish Health Surveys(60-63)

Morbidity by age

Figure 2-14 and 2-15 shows the percentage of those living with CVD by age group and sex.

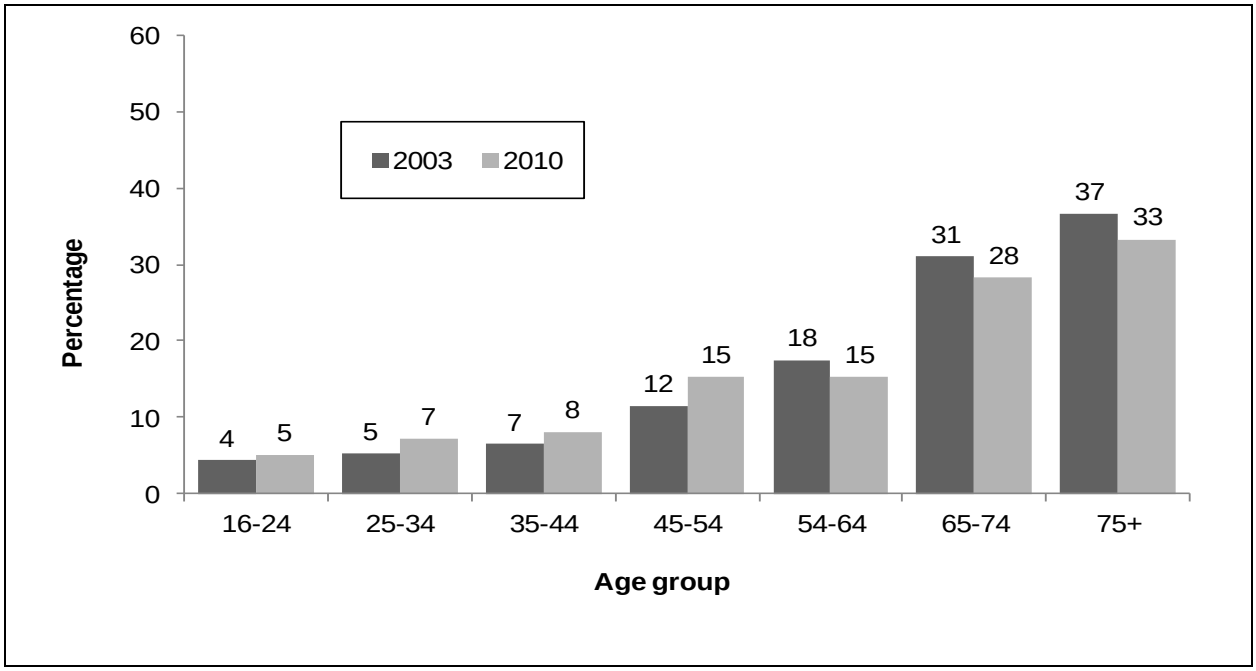
Figure 2-14 Percentage living with CVD by age group - men



Source: Generated from the Scottish Health Surveys(62, 64)

CVD events are: angina, heart attack, stroke, heart murmur, abnormal heart rhythm, or 'other heart trouble

Figure 2-15 Percentage living with CVD by age group - women



Source: Generated from the Scottish Health Survey(62, 64)

CVD events are: angina, heart attack, stroke, heart murmur, abnormal heart rhythm, or 'other heart trouble

As expected, prevalence increases with age. Most notably, however, CVD appears to be a significant problem across all ages, including the under-40 year olds. Also, while prevalence

rates have been falling in older age groups, it is rising in younger age groups and especially in men.

CVD is also responsible for substantial morbidity in the form of pain, disability and poorer quality of life(65-66). Economists attempt to measure the impact of living with a condition on reducing health related quality of life. Current estimates in Scotland are not available. This is a major gap in the evidence base however, and the discussion will be revisited in detail later in the thesis, in Chapter 3 and Chapter 5.

2.3 The economic burden of cardiovascular disease

It is important to estimate the economic impacts of CVD in addition to the health burden. There are no official statistics that estimate the economic costs of CVD to Scotland. The following analysis builds upon previous estimates made for the UK(6).

Table 2-2 illustrates the cost of CVD to the UK economy in 2011, which was estimated to be £35 billion. The estimates update previous research which had reported costs in 2006 prices, where the cost was estimated to be £31 billion(6). These were inflated 2011 prices by using

Table 2-2 Health service costs, UK 2011

	CVD		CHD		Stroke	
	£ million	% of total	£ million	% of total	£ million	% of total
Health care costs	16,453	46.9%	3,718	36.1%	3,631	38.2%
Productivity losses due due to mortality	5,056	14.4%	2,809	27.3%	883	9.3%
Productivity losses due due to morbidity	4,395	12.5%	1,652	16.0%	1,652	17.4%
Informal care	9,205	26.2%	2,120	20.6%	3,329	35.1%
Total	35,108	100.0%	10,300	100.0%	9,496	100.0%
Cost per capita	£574		£169		£155	

Source: Adapted from Luengo-Fernandez, R.(6)

the Consumer Price Index (CPI)(67) with the exception of health care costs which was inflated using the Health Service Cost Index (HSCI)(68).

Health care incurs the single most important expenditure representing 47% of the total cost, followed by productivity losses of 27% that are split by mortality (14.4%) and morbidity

(12.5%) and informal care 26%. The estimates are also disaggregated for CHD and stroke, with the former accounting for the greatest costs, with the exception of health service costs. Overall, it is estimated that CVD results in a per capita cost of £574.

An estimate of Scottish costs were made based upon Scotland's percentage share of those in UK living with CVD and those dying due to CVD causes. These percentage shares, or weights, are estimated before applying them to the UK cost estimate of Table 2-3.

To estimate Scotland's share of those living in the UK with CVD, it was necessary to first estimate the actual numbers of people in Scotland and the UK with CVD. To do this national statistics were accessed for each home nation (England, Scotland, Wales and Northern Ireland), providing estimates of the number of people alive and who are aged 16 and over(69). Then, using health surveys which are particular to each home nation the percentage of 16 years and over living with CVD was estimated. By applying the percentages of those living with CVD to the numbers in the population, an estimate of the actual numbers living with CVD across all four home nations was generated.

Second, by summing across the four nations, an estimate of the total number in the UK living with CVD was made. This was estimated to be 6.5 million people. Scotland's share of this total was estimated to be 9.8% by dividing the number living with CVD in Scotland by the UK total. This is a disproportionate share, given that Scotland's population is 8.7% of the UK as a whole.

Table 2-3 Estimating Scotland share of the UK's CVD morbidity, 2011

	Population	Prevalence		% share of UK total
	(16+ years)	Number	% of population	
Scotland	4,361,484	639,955	14.7%	9.8%
England	41,805,100	5,285,377	12.6%	81.0%
Wales	2,507,100	383,473	15.3%	5.9%
N. Ireland	1,423,234	220,001	15.5%	3.4%
United Kingdom	50,096,918	6,528,807	13.0%	100.0%

Sources: Office for National Statistics(69), Scottish Health Survey(62), Health Survey for England(70), Welsh Health Survey(71), Health and Well-being Survey, Northern Ireland(71)

Next, Scotland's share of UK mortality from CVD was made for 2011. The number of CVD fatalities for each of four country's was taken directly from the ONS(72). The number of events for CBVD was not available, and the sub-category of stroke is shown instead. Table 2-4 provides the resultant estimates with Scotland representing 9.4% of total UK mortality from CVD.

Table 2-4 Estimating Scotland's share of the UK's CVD mortality, 2011

	Total	%	CHD	%	CBVD	%
Scotland	13,539	10.4%	8,941	11.0%	4,598	9.4%
England and Wales	113,559	87.2%	70,196	86.6%	43,363	88.4%
Northern Ireland	3,060	2.4%	1,966	2.4%	1,094	2.2%
United Kingdom	130,158	100.0%	81,103	100.0%	49,055	100.0%

Sources: Office for National Statistics(73)

With Scotland's share of UK morbidity and mortality estimated, these were applied as weights applied to Table 2-5 an estimate of Scotland's share of the UK cost burden. First, Scotland's share of UK health service costs was estimated. Morbidity and mortality shares were averaged [(9.8% + 9.4%)/2] to obtain 9.6% and then applied generate an estimate of £1.6 billion. Second, to estimate, productivity costs the weights of mortality and morbidity were applied respectively, generating estimates of £495 million to mortality, and £413 billion due to morbidity. Finally, to estimate informal care costs, Scotland's morbidity share was applied to the UK total which resulted in an estimate of £865 million. Overall, the economic burden of CVD in Scotland was estimated to be £3.4 billion in 2011, at a per capita cost of £769 - compared to a UK per capita cost of £574.

Given the total spend by NHS Scotland was £11.7 billion(74) in 2011, spending on CVD accounts for approximately 30%, which is equivalent to the percentage share of all deaths due to CVD (Figure 2-1).

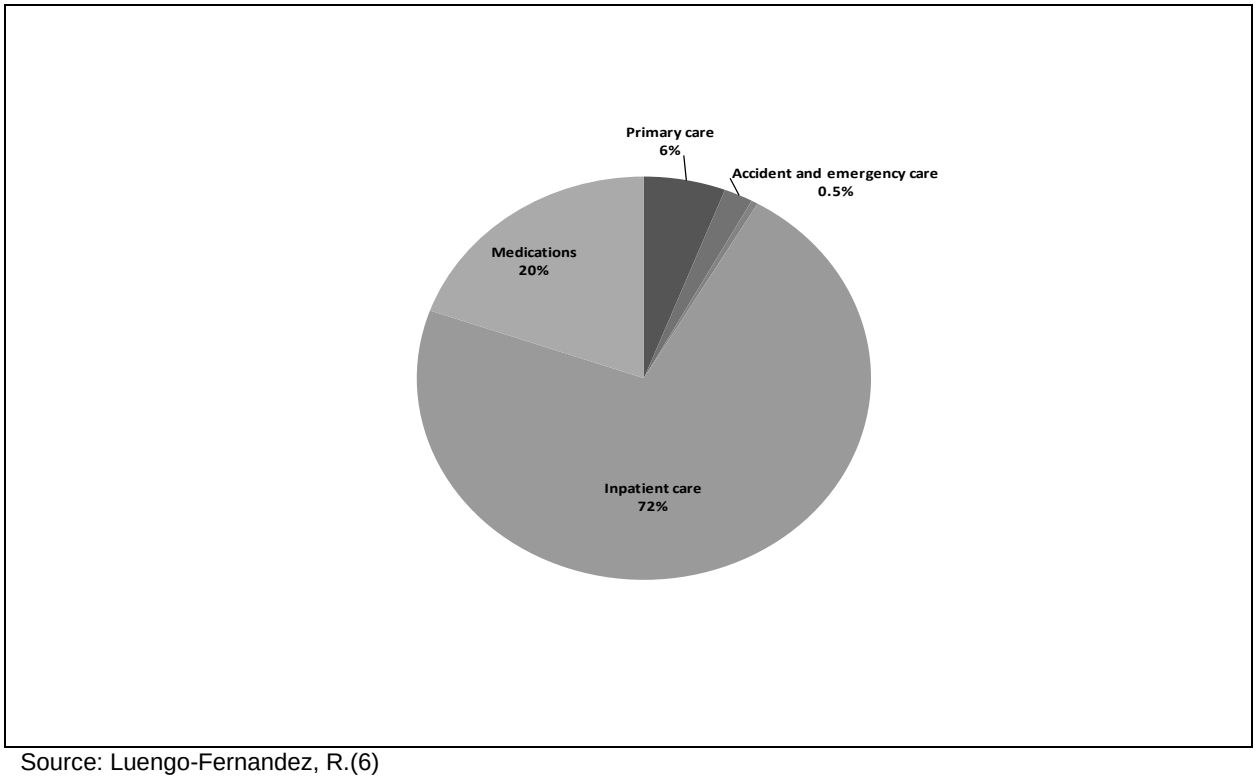
Table 2-5 Estimating Scotland's share of economic costs due to CVD

	CVD		CHD		Stroke	
	£ million	% total	£ million	% total	£ million	% total
Health care costs	1,579	47.1%	357	35.9%	349	38.6%
Productivity losses due to mortality	495	14.8%	284	28.5%	87	9.6%
Productivity losses due to morbidity	413	12.3%	155	15.6%	155	17.2%
Informal care	865	25.8%	199	20.0%	313	34.6%
Total	3,353	100.0%	996	100.0%	903	100.0%
Cost per capita	769		228		207	

Source: Estimated using Tables 2- 4

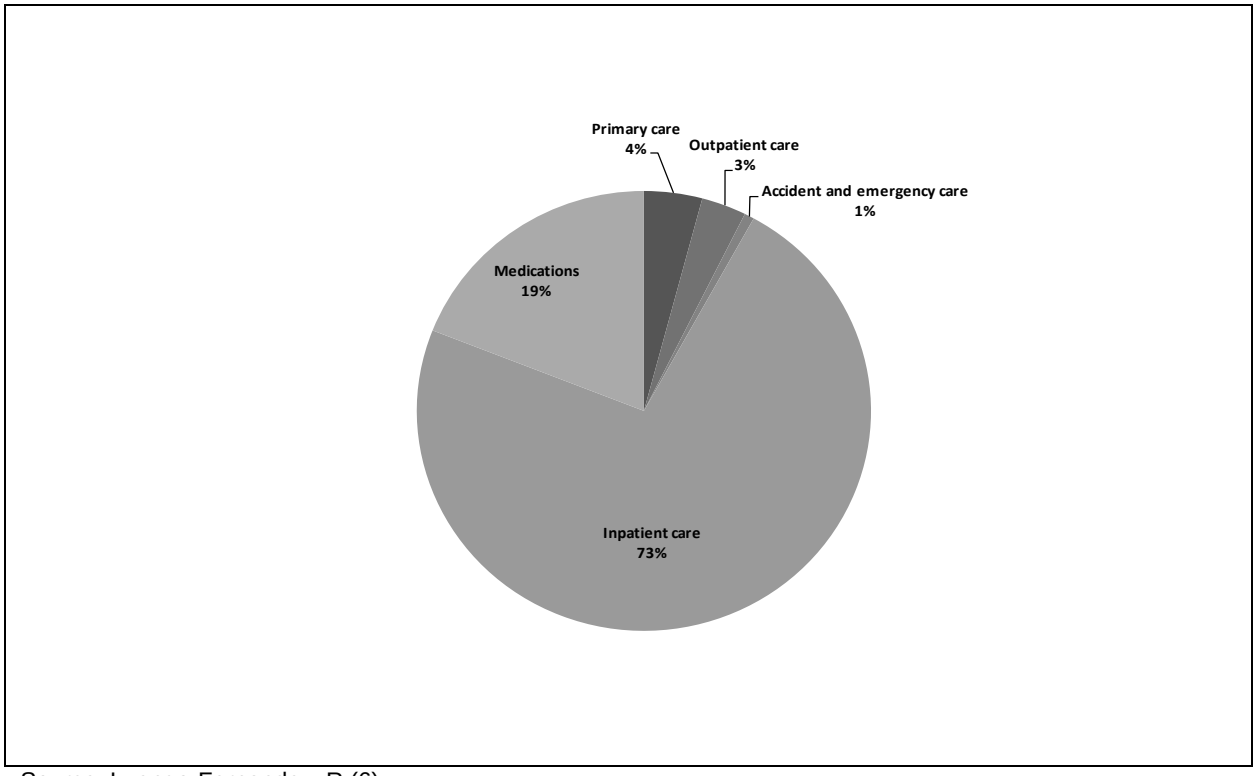
In terms of health care costs, it is also possible to have a further disaggregation to understand how the NHS spends its resources regarding CVD. This is illustrated in Figures 2-16 to 2-18. These figures are for the UK, as equivalent figures for Scotland are not available. For CVD as a whole, most spend by the health service is on inpatient care (72%) and medication (20%). In contrast, primary care accounts for just 6%. In considering stroke in isolation approximately 92% is on inpatient care, with just 2% on medications.

Figure 2-16 Health care costs of CVD



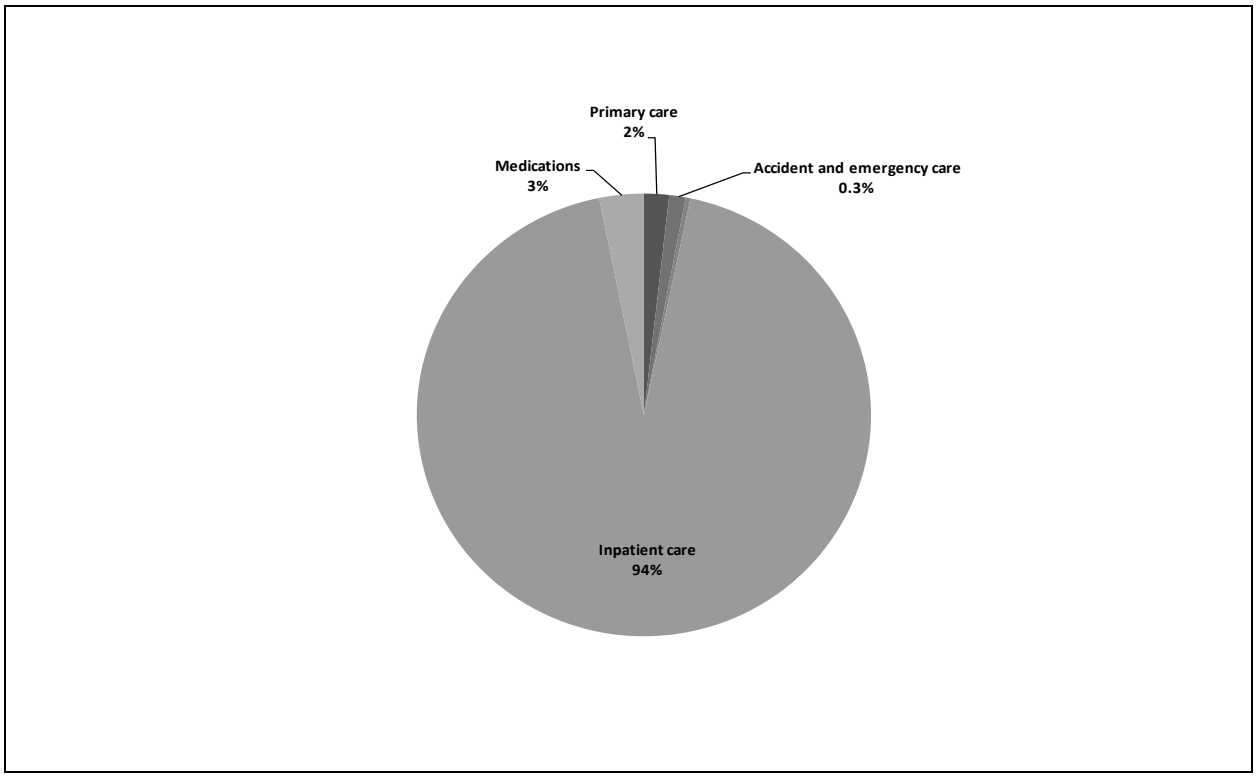
Source: Luengo-Fernandez, R.(6)

Figure 2-17 Health care costs of CHD



Source: Luengo-Fernandez, R.(6)

Figure 2-18 Health care costs of stroke



Source: Luengo-Fernandez, R.(6)

2.4 Risk factors for cardiovascular disease

2.4.1 Identifying risk factors

The incidence of CVD is determined by a complex interaction of risk factors acting over the lifecourse(75). A large number of international and UK epidemiological studies have identified multiple risk factors that are important to explain CVD incidence(76-78). Risk factors can be classified into demographic, biomarkers, lifestyle, social and genetic factors. Demographic factors include age and sex; biomarkers include variables such as cholesterol; lifestyle variables include smoking and diet; and social variables include measures of deprivation, which in turn is driven by such factors as income, employment, housing and education(59). To date, while work is on-going to identify genetic risk factors, there have not been a breakthrough in identifying risk factors that provide clinically meaningful additions to more traditional risk factors(8).

It is important to identify risk variables as either modifiable or non-modifiable. Identifying which risk factors are modifiable can then focus decision makers on interventions that may influence the risk of CVD. Modifiable risk factors include those amenable to change by interventions. Biomarkers, lifestyle behaviours, and social variables that ultimately driven behaviour are modifiable(8). Demographic and genetic risk factors are not modifiable, though research in the latter is on-going.

A large international study, of high and low income countries, found that nine risk factors (biomarkers and lifestyle variables) may explain up to 94% of the CHD risk within populations(76). These risk factors included: smoking, history of hypertension or diabetes, waist hip ratio, dietary pattern, physical activity, alcohol consumption, blood apolipoproteins and psychosocial factors were identified as the key risk factors. The effect of these risk factors was consistent in men and women across different geographic regions and by ethnic group. Other studies have focussed on a narrow set of risk factors. A UK study found that three risk factors accounted for at least 80% of the attributable risk of CHD in men(79). A WHO report found that declines in total cholesterol may have accounted for more than 50% of all reductions in CHD events(80). Considered differently, there may be diminishing marginal returns to the inclusion of additional risk factors when attempting to infer the risk of CVD events(81).

Risk factors tend to be continuously distributed in the population(82) following a bell shaped distribution. Most of the population have low levels of risk factors, but some individuals have particularly inflated factors (in the right tail) putting them at a high risk of events. The chapter will shortly describe approaches to the primary prevention of CVD to reduce risk factors. A targeted approach focuses on the right hand tail of the bell shaped curve, whereas a population wide approach attempts to shift risk in the entire population.

High risk individuals tend to cluster and are not evenly spread across the general population. For instance, the elderly are at high risk due to age and are at risk of all major causes of mortality. However, age itself is not modifiable by intervention. Of particular policy interest is that biomarkers, social context and poor health behaviours that can lead to inflated risk factors also cluster in certain groups(83) and are in principle modifiable by intervention,

Importantly, health behaviours do not develop in a vacuum but are influenced over the lifecourse by the environment that individuals develop within, which determine opportunity (e.g. access to healthy lifestyle) and define cultural norms (e.g. the behaviours that are exhibited)(75). There is a significant research effort with regard to the wider determinants of health, investigating the influences for instance of income, employment, housing, education, and the physical environment. These influences may have direct impacts on psychological well-being and also shape the opportunities and norms that individuals and communities face(84-85).

The chapter now turns to describing in more detail how risk factors are distributed in the Scottish population, before detailing how risk factors have been embedded into scores to predict future CVD events, and identify individuals who may be most at risk.

2.4.2 The prevalence of risk factors in Scottish general population

Table 2-6 describes how the prevalence of modifiable risk factors has changed over time within the Scottish general population aged 16 years and above. The data was collated by accessing the full range of the Scottish Health Surveys (SHeS) which date from 1995, and were repeated intermittently with the most recently available pertaining to 2010 (at the time of thesis submission). The information in the SHeS is self-reported by survey respondents and the table concentrates on those risk factors where there are sufficient information to generate a time trend of two points or more. The focus of the table is on behavioural risk factors or BMI. The SHeS has had a lack of good response rates from survey respondents giving

permission for bloods to be taken, to estimate cholesterol, or even for blood pressure readings to be taken. In particular, missing data can be as high as 80% for such biomarkers.

Overall, the prevalence of risk factors has generally fallen which is consistent with falls in CVD mortality rates seen earlier. In particular, smoking prevalence has decreased the most with a drop of 8 percentage points, followed by hazardous alcohol consumption with a drop of 6 percentage points. In stark contrast, however, the percentage of the population considered overweight or obese was estimated to be 63 percent in 2010, an increase of 11 percentage points since 1995.

Table 2-6 Change in risk factors over time

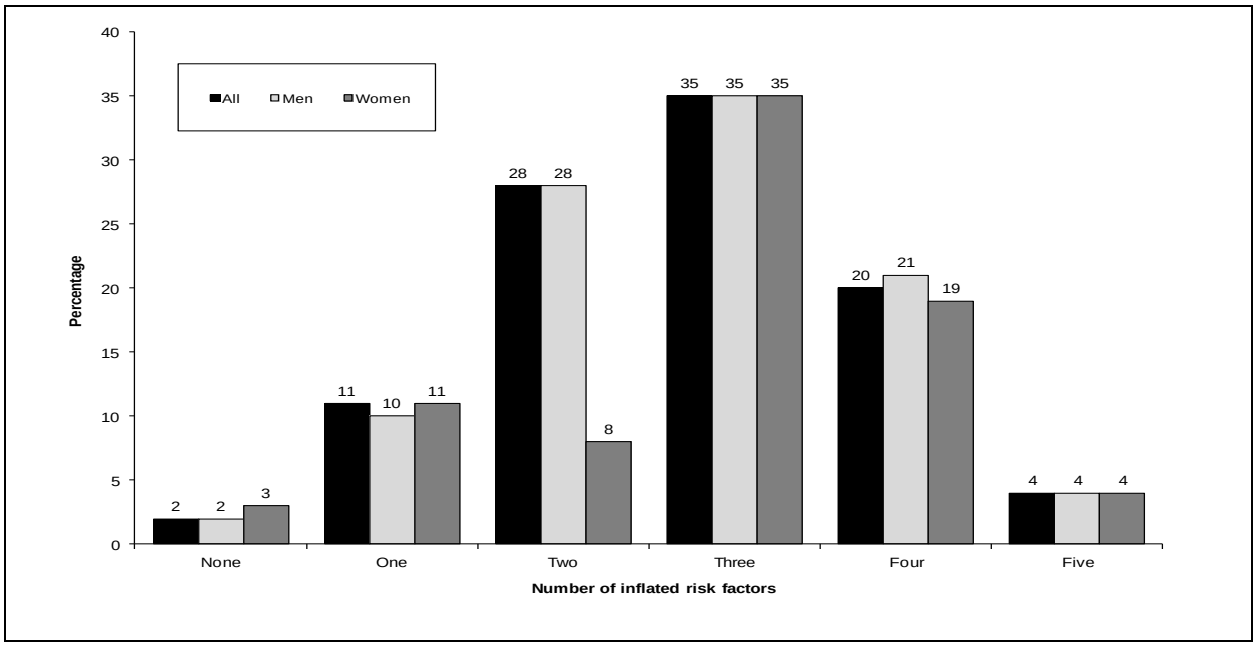
	1995	1998	2003	2008	2010	% point change
Smokers						
All	35	35	31	29	28	-7
Male	34	36	32	29	29	-5
Female	36	33	31	28	28	-8
Low physical activity <30 mins per week						
All	-	-	-	32	31	-1
Male	-	-	-	28	29	1
Female	-	-	-	33	33	0
Fruit & vegetables < 5 a day						
All	-	-	79	78	78	-1
Male	-	-	80	80	80	0
Female	-	-	79	78	78	-1
Alcohol Hazardous						
All	-	-	28	25	22	-6
Male	-	-	33	30	27	-6
Female	-	-	23	20	18	-5
BMI 25 + Overweight/ Obese						
All	52	57	61	63	63	11
Male	56	61	64	66	66	10
Female	47	52	57	60	60	13

Source: Scottish Health Surveys. Note there was insufficient detail in the early release version of 2011 to include it.

Figure 2-19 illustrates the percentage of the total Scottish population with one of more of the risk factors identified in table 6. This is shown for both men and women. The distribution of

the risk factor count approximates a normal distribution. Just 2% have no risk factors, with nearly 60% having 3 risk factors or above.

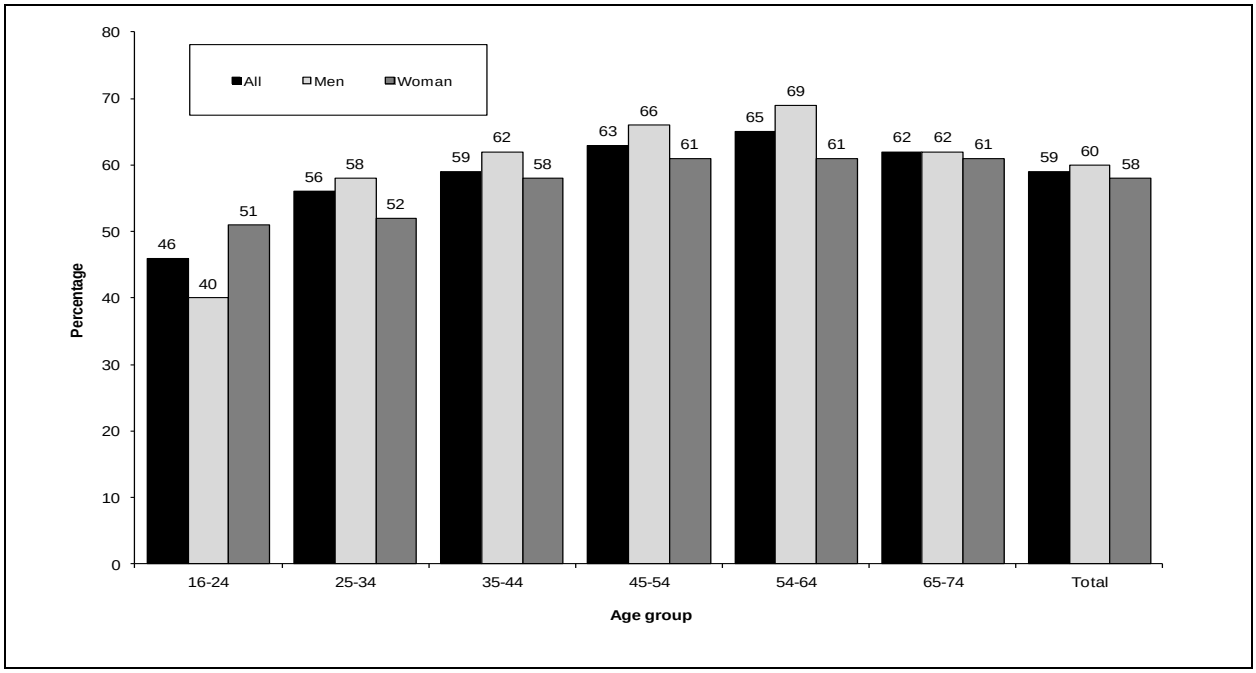
Figure 2-19 Distribution of risk factors in the Scottish general population



Source: Adapted from Scottish Health Survey 2010

Figure 2-20 illustrates the distribution of those living with multiple risk factors using the 2010 SHeS. Multiple risk factors are defined for exposition as having three risk factors or more. The distribution of modifiable risk factors is high across all age groups and increases with age.

Figure 2-20 Prevalence of three risk factors or above by age group



Source: Adapted from Scottish Health Survey 2010

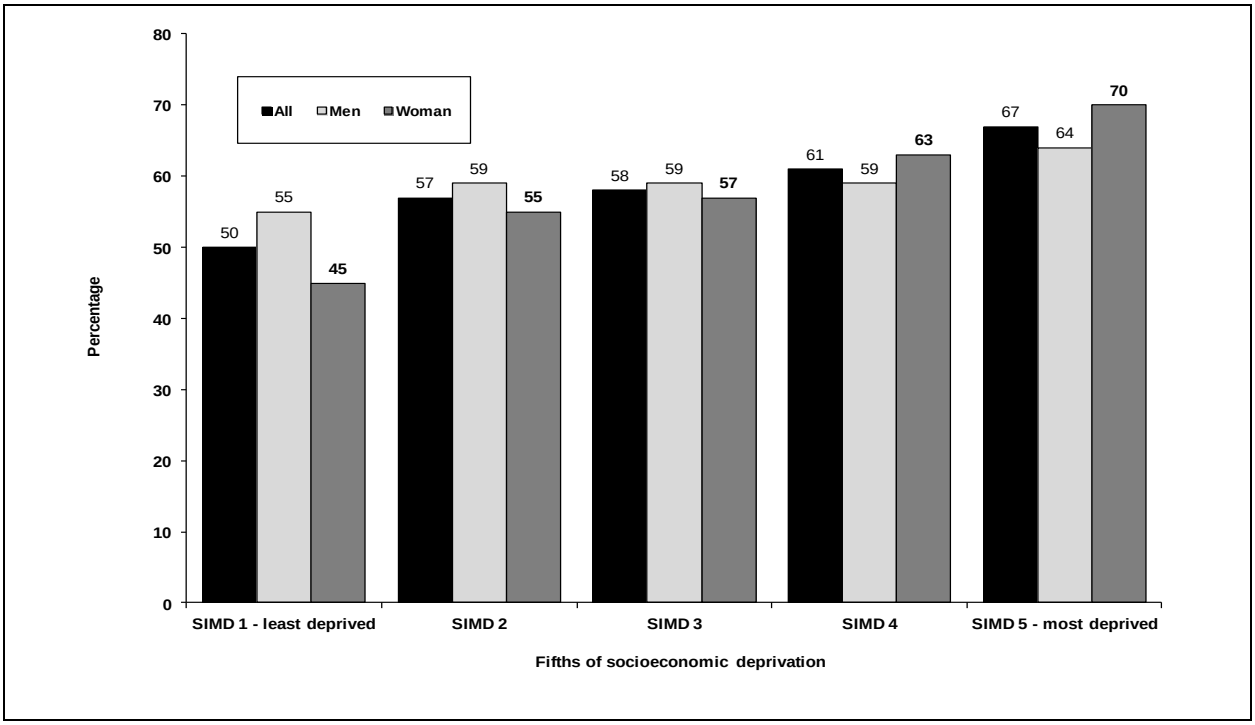
Notably, the prevalence of risk factors in young people aged between 16-24 years appears to be relatively high, with 46% having 3 or more inflated risk factors. It was not possible to generate a time series for the Scottish population. It has been noted elsewhere that there is a dearth of survey information for younger adults 16-25 regarding risk behaviours(86).

There is a growing body of evidence that many risk behaviours in youths tend to cluster together, particularly in young people from the most deprived backgrounds. There is also evidence that early initiation of a particular behaviour, such as smoking or alcohol use for example, is associated with other risk-taking behaviours in later adolescence and early adulthood, including sexual risk taking, binge drinking, teenage pregnancy and delinquency. For instance, the Scottish Schools Adolescent Lifestyle and Substance Use Survey (SALSUS) found that in 2008 alcohol was consumed in the week prior to the survey by 11% of 13-year-olds and 31% of 15-year-olds, with no differences between genders(87). Among those who reported drinking in the previous week, 15-year-olds boys consumed on average 17 units and girls consumed an average of 12 units. Further, 14% of girls and 16% of boys aged 15 are regular smokers, with the rates for both genders having decreased since 1998; and among 15-year-olds, 21% of boys and 12% of girls reported illicit drug use in the past month.

Risk factors are also associated with a deprivation gradient, consistent with observed event rates – figure 2-21. An analysis of the Scottish Health Survey 2010 revealed that smoking prevalence in SIMD 5 is 45% compared to 14% in SIMD 1(78). Such differences in behaviour are key reasons behind the deprivation gradient in prevalence of CVD mortality and morbidity.

Figure 2-21 illustrates that the prevalence of individuals with three inflated risk factors or above increases steadily as deprivation status worsens. For instance, 50% of those in the least deprived fifth have multiple risk factors, which increased to 67% in the most deprived fifth.

Figure 2-21 Prevalence of three risk factors or above by deprivation status



Source: Adapted from Scottish Health Survey 2010

Survey data on the interaction of age group and deprivation status is lacking; however, it is broadly known that the deprivation gradient in risk behaviours begins at an early stage in the lifecourse(86). The Scottish Collaboration for Public Health Research and Policy(88) commissioned the Medical Research Council's Social and Public Health Science Unit to analyse health behaviours in young adults aged 18/19 years old within the West of Scotland, a region known to have amongst the highest deprivation rates in Scotland(89). Using the 20-07 study(90), the risk behaviours of young adults aged 18/19 years were analysed over

time(86). For males and females, rates of current smoking changed very little between 1990 and 2003 whereas rates of heavy smoking (defined as 70+ cigarettes per week) dropped by over a third. Among males, rates of drinking more than the government recommended maximum units of alcohol in the previous week increased only slightly between 1990 and 2003, while the rates of ever having used illicit drugs increased by about 50% between 1990 and 2003. The most striking increase in risk behaviours were among females, where at age 18–19: drinking more than the weekly recommended maximum units of alcohol more than doubled between 1990 and 2003; binge drinking doubled between 1990 and 2003; experience of illicit drugs more than doubled between 1990 and 2003; and sex at age <16 years more than trebled between 1990 and 2003. In terms of earlier adolescent risk behaviour, rates of smoking initiation at age <14 years was similar in both cohorts for both genders, whilst rates of monthly drinking at age 15 more than doubled in males between 1990 and 2003, and increased by more than four times among girls between 1990 and 2003.

2.5 The prevention of cardiovascular disease: overview

In taking stock of the chapter so far, CVD has been falling in the Scottish general population; however, it remains the number one cause of death, results in large numbers of people living with CVD, and has considerable resource costs on the health service and wider economy. Also, while known modifiable risk factors have in general come down, the clustering of multiple risks remains high across the whole population, but especially in more deprived groups where it was seen that mortality in the under-65s was particularly high (Figures 2-9 and 2-10). Further, there is concern regarding the onset of risky behaviours and risk factors in younger adults and the increasing problem of obesity in society in general. Consequently, policymakers are increasingly intent on responding to the tackling the causes of CVD to prevent a potential rise in the incidence and prevalence of CVD.

2.5.1 Four levels of prevention

The different approaches of prevention are well developed conceptually, and there are essentially four levels: primordial prevention, primary prevention, secondary prevention and tertiary prevention.

Primordial prevention is focussed on preventing the emergence of the risk factors themselves by encouraging healthier lifestyles, behaviours and environments. This approach tends to focus on children and young adults, to encourage healthy lifestyles. This can manifest itself in

a number of different types of interventions, from general health promotion interventions in schools directly focussed on children(91), to interventions in adults with risky behaviours (e.g. smoking) that may lead to indirect influences on children, such as adults that quit smoking may influence children not to take up smoking(92). Given the manifestation of risky behaviours at early age groups, as discussed previously, Scotland is increasingly looking more systematically at developing interventions that can be described as primordial prevention(93).

Primary prevention is where interventions seek to control exposure to risk factors. The intention is to prevent or postpone the first instance of an event in individuals who are asymptomatic, but considered at risk. Interventions may include regular screening for risk factors, and lifestyle and pharmaceutical interventions, as will be described in detail when considering evidence for each type of intervention.

In contrast, secondary prevention is designed to prevent or postpone subsequent CVD events following a first event. Interventions may include surgery, and lifestyle and pharmaceutical interventions. Individuals may be regularly screened for signs of elevated risk factors as a means to gauge the intensity of prescribed interventions(94).

Tertiary prevention is the application of measures to reduce or eliminate long-term impairments and disabilities, minimising suffering caused by existing departures from good health and to promote the patient's adjustments to his/her condition. Interventions are typically palliative in nature(95).

2.5.2 Strategies for primary prevention: targeted and population approaches

Strategies for primary prevention include an individual-centred 'high-risk' strategy, termed here a targeted approach; and a population 'average-risk' strategy, termed here a population approach – see table 2.7. These approaches have been in existence for some considerable time, and each is associated with certain well-defined pros and cons. The following section describes these two approaches in general terms, without specific mention of CVD. The reason is that such approaches are common in most areas of primary prevention irrespective of the disease focus(96-98). The subsequent discussion in the chapter details the approaches as applied to CVD.

The targeted approach to prevention generally consists of screening a population to identify individuals at high risk of a disease and to then offer a range of interventions tailored to the individual in an effort to reduce risk. This is most commonly associated with the clinical approach to prevention focussed on individuals. The generic advantages include: that interventions are more likely to be appropriate; individuals who realise they are high risk are more likely to change behaviour; have agreement from clinicians who are trained to focus on individuals who are seen as current cases, and high risk individuals may gain more from interventions than low risk individuals. However, there are also disadvantages. These include the likely expense of identifying the high risk; the dangers of developing crude cut-off points between high and moderate risk, where the latter may still be a significant clinical risk; that most events in a population actually occur in the non-high risk; and that the underlying aetiology of the disease may not be addressed (e.g. offering pharmaceutical may reinforce unhealthy behaviours); and that individuals may not be sufficiently incentivised to reduce risky behaviours if the consequence is being on the outside of local social networks.

An alternative approach to primary prevention is a population approach, which is most commonly attributed to Geoffery Rose as formalising the approach(99-100). He first observed that risk is distributed across the entire population, approximating a normal distribution; and that the high risk are essentially a small proportion of the population represented by the tail-end of the normal distribution. Further, it was argued that most event rates occurred in those at moderate risk as they constitute the largest group in the population. The inference is that a small shift in the mean risk of the entire population could lead to a greater reduction in the burden of disease compared to a high risk approach to prevention, which concentrates on an extreme tail of the distribution. Consequently, it is argued that “the only strategy with the potential to greatly increase the proportion of the population at low-risk status is the population-wide approach to primary prevention”(101).

Interventions may include legislative changes, mass media campaigns and offering lifestyle advice to all groups. Further, even mass administration of pharmaceuticals has been proposed as a possible intervention(34). The population approach is argued to be more comprehensive, encompassing those at any risk and can extend to primordial prevention by preventing the onset of risky behaviours. However, such approaches are not without possible disadvantages, including that the benefits of interventions may be outweighed by risks for certain individuals, and this may especially be the case for mass administration of pharmaceuticals. The approach may be an inefficient use of resources, given that most

Table 2-7 Comparison of targeted and population approaches

	Individual-centred 'high-risk' strategy	Population 'average-risk' strategy
Advantages	• Intervention is appropriate to the individual. • People who learn that they are at high risk may be more likely to change behaviour • Physicians feel justified in reducing risk factors in high-risk patients. • High-risk individuals are likely to gain more benefit than lower-risk individuals.	• Intervention aimed at roots of problem reduces illness in the whole population, including those at low or average risk. • Tackles condition in its early stages when interventions may be more effective. • A small change in the level of a risk factor in a population can improve the health of a large number of people
Disadvantages	• Difficulties and costs of identifying high risk groups and individuals. • Dividing line between average and high-risk is often arbitrary, and many 'average-risk' people can still be at significant risk. • Little impact on the disease burden in society. Most cases of disease occur in people at low or moderate risk. • Palliative and temporary—the determinants are not addressed. • A change of behaviour sufficient to reduce risk may put the individual outside the norms of the particular social circle.	• Small benefit to most individuals may be outweighed by the risk of the intervention. • Potentially inefficient: demands change by a large number of people who would not have developed the disease at all. • Little motivation for low-risk individuals to change behaviour. • Danger of increasing inequity in health. Unless specifically designed strategies are used, • Intervening in apparently healthy people is ethically more sensitive that intervening in people with problems.

Source: Adapted from Rose(102)

people may not have developed the disease and, depending on the intervention proposed, there may be limited incentives for low-risk people to change behaviour.

A key distinction needs to be made regarding population health interventions that are offered to the whole population where individuals are free to engage or not; and those interventions that are essentially paternal where individuals are passive recipients. The former would include screening programmes and media campaigns, and the latter would include legal and regulatory changes. It has been shown that where the impacts of interventions require individual engagement and compliance health inequalities can widened(23). Further, when interventions are offered to everyone irrespective of the underlying risk profiles then inequalities can also widen, given it is also known that more socially disadvantaged individuals have greater prevalence of risk factors.

This parallels what Tudor Hart described as the “Inverse Care Law”: that the availability of good medical care tends to vary inversely with the need for it in the population served(102). Thus, the people in the poorest health gain the lowest net health benefit from the interventions. Disadvantage can occur at every stage in the process, from the person's beliefs about health and disease, and actual health behaviour, to presentation, screening, risk assessment, negotiation, participation, programme persistence, and treatment adherence. This effect has been usefully described this cumulative inequality as the “staircase effect”(103). Finally, from a libertarian perspective, it may be ethically less tolerable to intervene in people who do not have health problems, if this restricts or coerces behaviour(104-105).

The next two sections detail the targeted and population approach as it is applied to the primary prevention of cardiovascular disease, at present.

2.6 The targeted approach to primary prevention of cardiovascular disease

2.6.1 General approach

There is an increasing focus on primary prevention with the aims to reduce the premature incidence of CVD and the associated health and economic burdens. To date, the clinical and policy focus has been on the adult population. However, it is recognised that the scope of preventative interventions should include children and younger adults, as discussed earlier. In particular, the widening focus of prevention is due to concerns regarding a potential obesity epidemic, with increasingly sedentary lifestyles and the rise of unhealthy lifestyles(19-21, 106-109). The next two sections describe both the targeted and population approach to the primary prevention CVD, and the associated evidence base.

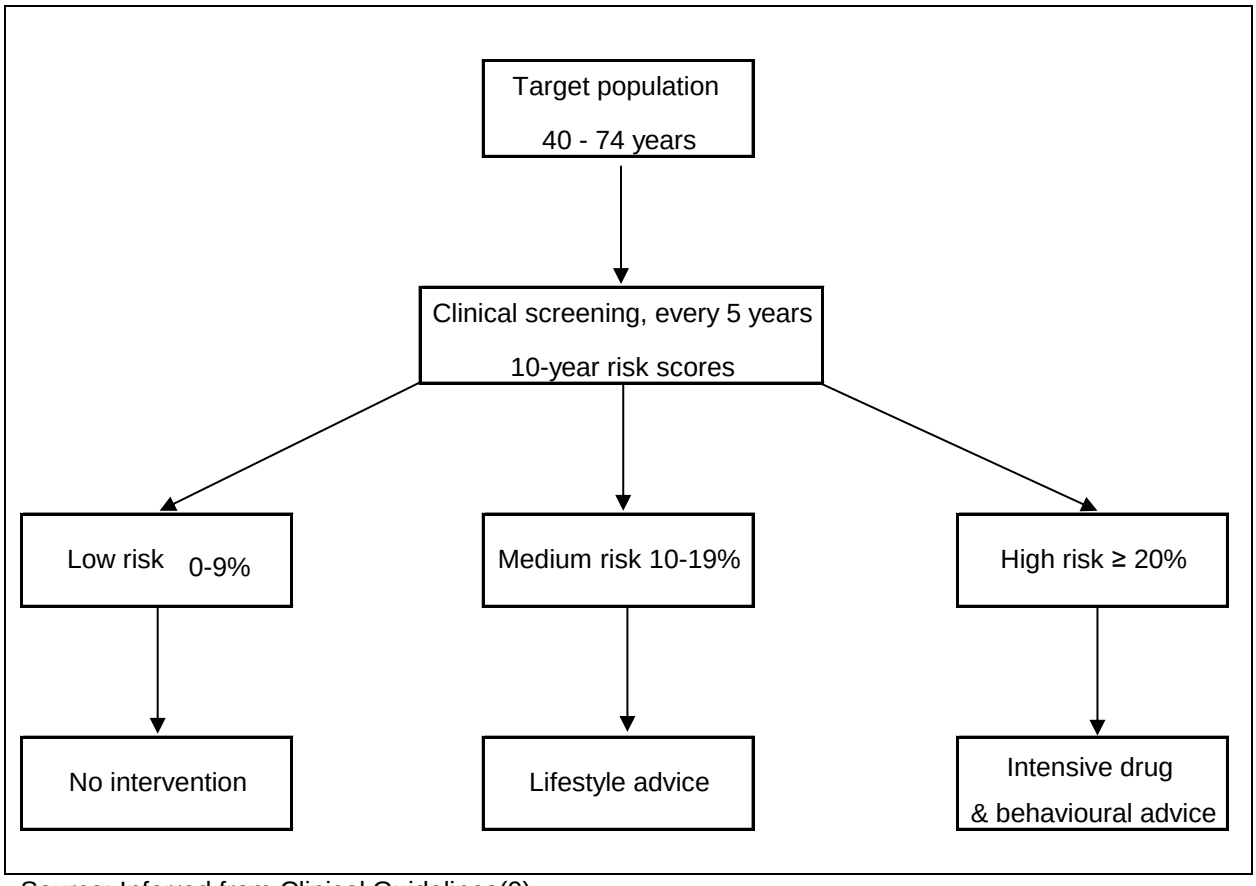
The targeted approach to the primary prevention of CVD requires identifying and treating relevant risk factors. The clinical understanding of how best to measure and respond to the risk of CVD has evolved over a number of years(8). Historically, clinical guidelines recommended that individual risk factors, such as systolic blood pressure and cholesterol were measured and managed in isolation(8). Threshold levels of risk factors were identified which defined the cut-off point regarding normal levels. If an individual exceeded a threshold

level they were then referred onto particular treatments with the aim to reduce the risk factor to below the threshold level.

There is now a wealth of supporting evidence that major CVD risk factors like blood pressure or blood lipid levels are not only individually poor predictors of a patient's CVD risk but also of a patient's potential to benefit from treatment(25).

Clinical guidelines now recommend screening all individuals from 40 -74 years old every 5 years using a risk tool to assess multi-factorial risk over 10-years(15-16), Figure 2-22 illustrates the process. Such 'global' risk scores use both non-modifiable risk factors (such as age and sex),

Figure 2-22 Overview of a high risk approach: screening and tailored interventions



Source: Inferred from Clinical Guidelines(9)

and modifiable risk factors (such as smoking status and blood pressure). Risk calculators are now routinely embedded into administrative software packages and readily available in general practice(8). High risk individuals are identified as those with a risk score of ≥ 20%

and are referred onto a range of intensive drug therapies (such as statins and anti-hypertensives) and behavioural advice (such as smoking and diet advice). Individuals with any symptomatic manifestation of CVD, including diabetes, are assumed to be at high risk of cardiovascular events and do not require formal risk estimation.

Those with a risk score of between 10-19% are classified as medium risk and are offered the behavioural advice only. Low risk patients are those with a risk score of 0-9% are not offered specific interventions. In this respect, a high risk approach embeds primary prevention in general practice, as the 'gatekeepers' to onward intervention.

2.6.2 The targeted approach in Scotland

Scotland introduced a primary prevention programme called Keep Well in 2007(12). While clinical guidelines recommended screening the entire population aged 40-74 years, Keep Well is focused on 45-64 year olds living in the 15% most deprived areas as identified by the Scottish Index of Socioeconomic Deprivation (SIMD). The explicit policy aim of the programme is to reduce health inequalities.

The Keep Well programme consists of the standard process as outlined in Figure 2-22. Individuals are invited to attend clinical screening and general practices are recommended to follow the SIGN Guidelines to then screen individuals using the ASSIGN score. The ASSIGN score, and other risk scores, will be described in detail shortly. The score was developed for specific use in Scotland and uses SIMD as a risk variable which accounts for the social gradient in CVD. Individuals who are identified as high risk are then referred onwards to an intensive set of pharmaceutical and lifestyle interventions.

The Keep Well programme began as a pilot in Glasgow and has been rolled-out gradually to other deprived areas in Scotland, achieving national coverage in 2011. The Keep Well programme will be revisited in Part 3 where the pilot will be evaluated.

2.6.3 Developing risk tools: an overview of modelling approaches

Before reviewing the main risk scores that are in use in clinical practice, this short section provides an intuitive overview regarding how risk scoring tools are created, and tested for accuracy.

The approach of survival analysis

The key defining characteristic of risk scores is that they predict the risk of event over a period of time. Survival analysis is defined as a term used to describe a set of methods designed specifically for analysing a longitudinal dataset where time to event is an explicit marker for individuals who are followed over time. The output of the survival analysis is to estimate both a survival function and a hazard function. The survival function, St, gives, for every time period, the probability of surviving (or not experiencing the event) up to that time.

$S(t) = Pr(T>t)$

The hazard function, h(t), gives the instantaneous probability that the event will occur, per time unit, given that an individual has survived up to the specified time.

$\lambda(t) = f(t) / S(t)$

The role of censoring

In developing regression models for survival analysis to estimate survival and hazards the straightforward application of multiple regression techniques is inappropriate for two main reasons. First, normality cannot typically be assumed as empirical observation will usually show that survival times are not normally distributed. Second, there is the issue of censoring. Observations are censored when the information about their survival time is incomplete(110).

Censoring can manifest in three forms: Left censoring, interval censoring and right censoring. Left censoring is when an individual experiences the event of interest before the beginning of the study period. Interval censoring is when an individual is lost to follow-up for a period of time and then returns to the dataset. The most commonly encountered form is right censoring. This occurs when the individual does not experience the event with the study period; when an individual is lost to follow-up permanently within the period of observation; when an individual experiences the event of interest after the study period; and finally multiple censoring when the individual experiences the event multiple times after the observation period.

Intuitively, censoring represents a particular type of missing data, which standard multiple regression techniques cannot address. Survival analysis seeks to incorporate information from both censored and uncensored observations in estimating model parameters. Censoring

that is random and non informative is usually required in order to avoid bias in a survival analysis. Conveniently, this is most often assumed to be the case.

There are three main approaches to survival analysis: non-parametric, semi-parametric and parametric approach. Each is outlined described in turn.

Non-parametric approaches

This approach relies solely on the observed data to estimate survival relative to an exposure of interest. No distributional assumptions are imposed on the data. The objectives are to compare relative survival times between different groups (e.g. male and female).

Lifetable or actuarial approach: This used in situations where it is known that for a group of interest, a number of events occurred over a long observation period, but it is unknown when an event occurred. A lifetable or actuarial approach estimates the time to event in a relatively crude fashion by first dividing the observation period into a series of equally spaced intervals and assumes that the number of events are spaced equally across all periods. The result is that the probability of event is the same in each period. However, this approach isn't appropriate in developing risk scores given that it is known that risk is not uniform in time, and for instance increases with age. More refined methods are available.

Kaplan-Meier (KM) approach: A KM approach is the most popular non-parametric approach and is sometimes referred to as a product limit estimator. It can be used when it known when the event of interest occurred. The application of a KM approach is when time is not continuous, but rather the distribution is discrete with the incidence of events defining consecutive time periods. Again, the assumption of independent censoring is made such that remaining survivors over time are representative for all subjects.

Let di be the number of deaths at $t_{(i)}$, and let n_i be the number alive just before $t_{(i)}$. The hazard is:

$$\lambda (t) = (n_i - di) / n_i$$

However, this approach is also not appropriate in the estimation of risk scores, where the objective is to estimate the relationship between risk factors (measured continuously or categorical) and the hazard of events. Therefore, a regression approach is necessary.

Semi-parametric approach

The most popular regression model for the estimation of risk scores is the Cox proportional hazards regression model. The Cox regression model is a semi-parametric model, which makes no assumptions about the shape of the baseline hazard function, but assumes that the hazard ratio comparing any two observations is constant over time in the setting where the predictor variables do not vary over time. This is the proportional hazards assumption. This shown in log for expositions, as it defaults to a linear equation:

$$In\lambda(t) = In\lambda(t) * (b_1 X_1 + b_2X_2 + ... + b_nX_n)$$

Parametric approach

These models assume that the underlying distribution of survival over time follows a certain probability distribution. The risk of event(s) is composed of two-parts. First, by a linear predictor, the sum of the products of covariates and the estimated coefficients; and secondly the use of an ancillary parameter resulting in event risks changing in time.

There are several distributions that are commonly used. The exponential distribution assumes that the hazard is a function of the linear predictor and does not vary with time. This is shown in logs for consistency with other possible model choices:

$$In\lambda\ (t) = In\lambda$$

The Weibull distribution is described by a scale parameter λ and shape parameter p.

If p is less than 1 then the instantaneous hazard monotonically decreases with time; if p equals 1 instantaneous hazard is constant over time (equivalent to the exponential distribution); and if p is greater than 1 instantaneous hazard increases with time.

$$In\lambda\ (t) = In(\lambda^{p}{}_{pt}{}^{p-1})$$

The Gompertz distribution is given by

$$In\lambda\ (t) = In(xb)In(\gamma t)$$

Where xb is the linear predictor from the regression and γ is the ancillary parameter estimated from the data. The Gompertz distribution is commonly used when predicting mortality, predicting rates consistently well(110).

Validation of risk score predictions: discrimination and calibration

It is important to test how good a risk score is to enhance its credibility to be used in clinical practice(111-112). There are two main tests commonly used to assess risk scores: discrimination and calibration(113). Discrimination is the ability of the risk score to differentiate between patients who do and do not experience an event during the study period. The most widely reported measure of model discrimination for CVD risk prediction models is the C-statistic. The C-statistic is a function of both the sensitivity and specificity of the model across all of its values, and it represents the ability of the score to discriminate (future) cases from non-cases(114). The sensitivity of a test is the probability of a positive test result, or for a value above a threshold, among those with disease (cases). The specificity is the probability of a negative test result, or a value below a threshold, among those without disease (non-cases). The Receiver Operator Curve (ROC) is a plot of sensitivity versus 1-specificity (often called the false-positive rate) that offers a summary of sensitivity and specificity across a range of cut points for a continuous predictor.

The C-statistic is quantified by calculating the area under the ROC; a value of 0.5 represents chance and 1 represents perfect discrimination. A C-statistic of between 0.70 and 0.80 is considered adequate and between 0.80 and 0.90 is considered offering excellent discriminatory ability(114). In short, the C-Statistic is a simple measure to test whether a model can rank order individuals: that the probability that the measure or predicted risk is higher for a case than for a non-case.

Strengths of the C-Statistic are in its simplicity to combine sensitivity and specificity in a single measure, and the ability to discriminate between higher and lower risk cases. However, this is also its weakness. That is, it is a measure of relative ranking, not the probability that individuals are classified correctly or that a person with a high test score will eventually become a case. This is a key weakness for using the C-Statistic to judge 10-year risk scores, which are prognostic models with the intention to predict absolute risk. Cook(115) provides an illustration that in a prospective cohort that is considered generally low risk (such as many population-based cohorts) there may be a small proportion of individuals who are at high risk, with most at low or very low risk. The C-statistic does not take this distribution into account.

For instance, differences between two individuals who are at very low risk (e.g. 1.0% versus 1.1%) have the same impact on the C-statistic as two individuals who are at moderate versus high risk (e.g. 5% versus 20%) if their differences in rank are the same. For prognostic risk tools this would appear to be a major issue as the prioritisation of individuals and treatment decisions are based on classifications of absolute risk. Therefore, while discrimination is important it is a weakness if models are assessed solely using the C-Statistic(114).

The C-statistic is also limited when a risk tool considers whether to add additional risk variables. It has been shown that the addition of key risk factors, such as cholesterol can makes a substantive difference to absolute risk, but can make very little difference to the C-Statistic if the risk model already included certain other variables, including age and blood pressure. In short, the C-statistic is useful, but is not ideal - on its own at least - to assess the performance of risk models(115).

Calibration, on the other hand, directly assesses the ability of a risk prediction model to predict accurately the absolute level of events that are subsequently observed. When the average predicted risk within defined subgroups of a prospective cohort matches the proportion that develops the event of interest the model is described as well-calibrated(115). Calibration can be assessed by dividing the population at risk into deciles of predicted risk and plotting the predicted risk versus the observed event rate. The statistical metric often used to test for the calibration of a risk model is the Hosmer-Lemeshow test(116). A p-value of ≥ 0.05 indicates that

the null hypothesis (that there is a lack of fit) can be rejected in favour of the alternative that there is good agreement between observed and predicted results for such a test.

When good model fit is not achieved in the original estimation of the model it can be recalibrated to the population of interest. Recalibration can be a simple and pragmatic exercise, and for risk models this may simply involve inserting an intercept, adjusting the slope coefficient, or adjusting the ancillary parameter is a parametric model is used (discussed shortly). Overall, recalibration is likely to be important in prognostic models that are generated using historical data, and where the relationship between risk factors and outcomes may have changed over time; or when attempting to use a model developed in one setting in another setting.

To reiterate, in current clinical practice, the performance of CVD risk scores is judged (at times only) using the C-Statistic(115). This is illustrated in the next section when we review the major risk prediction scores in use in the developed world.

2.6.4 Common risk scores used in clinical practice

This section reviews the most commonly used risk scores in clinical practice in the developed world. It is not intended to be a systematic review of all risk scores within the literature, but rather the key scores used in United States, Europe, England and Scotland (Table 2-8).

Framingham score – US Version

Population

The Framingham score was the first risk score in use and was developed in the United States. This was based on the Framingham Cohort, which began in 1948. The original cohort consisted of 5,209 individuals aged between 30-62 years old, who were predominately white Caucasians. Participants are rescreened every two years for a detailed medical history, physical examination, and laboratory tests(117).

Since the original cohort there have been five additional cohorts, including: (i) a second generation study (Framingham Offspring Study) in 1971. This consisted of the adult children of the original cohort and their spouses in 1971; (ii) a third generation study in 2002, the grandchildren of the original cohort; (iii) a study of the spouses of the second generation; (iv) a particular ethnic cohort in an attempt to diversify the cohort to be reflective of the changing ethnic mix of US, and finally; (v) there was also the addition of the first generation of this ethnic cohort.

Consequently, the Framingham cohort continues to be an evolving study with continued follow-up, though no new cohorts have been preannounced to date. Further, as the cohort has been updated, new variants of the score have been produced periodically, which vary accordingly to sample size, age range, risk factors, clinical end-points and time frame (e.g. 10-years and above, which is discussed at the end of the chapter).

The first CVD score was developed in 1991(118) and was focused on CHD event. The latest score developed for the US was published in 2008(119) widens the focus to CVD. This was based on a sample size of 8,491 individuals who were followed for an average 12 years. The

baseline (observation years) used in this particular study are staggered over several years, beginning in 1971 and combining observations from the original cohort and the second generation study.

Risk factors / clinical end-points

Sex-specific multivariable risk functions were derived that incorporated age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetes status. Other variables such as diastolic blood pressure, body mass index, and triglycerides also were considered, but they were not statistically significant. The clinical end-points included coronary heart disease, stroke, peripheral artery disease, or heart failure.

Modelling approach

A Cox-proportional hazards model is used, with different versions for men and women.

Validation: Discrimination and calibration

Tests of discrimination and calibration were conducted. The score demonstrated good discrimination with C-statistics of 0.763 for men and 0.793 for women. Further, the model showed reasonable calibration. Of those identified as being at high risk (top quintile of predicted risk) 49% of men and 60% of women had a CVD event. The model also demonstrated good specificity. Of those identified not at high risk 85% and 84%, of men and women respectively did not have an event.

Application

The score has been developed for use in the United States.

Table 2-8 Summary of dominant risks used in clinical screening

	Population (baseline screening)	Risk Factors / intervention threshold	End-points	Modelling approach	Validation / calibration	Application
Framingham	United States 1971 - Mean follow-up 12 years 8,491 30-74 years	Age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetes status. Separate equations for men and women 20% + denotes high risk	Coronary heart disease, stroke, peripheral artery disease, or heart failure	Cox proportional hazards model	C-Statistic:0.763 men, 0.793 women. No calibration	US
Framingham	United States 1971 - Mean follow-up 12 years 8,491 30-74 years	Age, sex, smoking status, systolic blood pressure, and the ratio of total cholesterol to HDL cholesterol 20% + denotes high risk	Fatal and non-fatal myocardial infarction, new angina fatal and non-fatal stroke, cerebral haemorrhage and transient cerebralischaemia	Cox proportional hazards model	Re-calibrated to the UK population. Factor of 1.3 for family history Factor of 1.4 for Asian ethnicity	England
SCORE	Europe - 12 countries 1972 - 1987 Mean follow-up 13 years 205,178 19 to 80 years	Age, sex, total-HDL cholesterol ratio, smoking, systolic blood pressure 5% + denotes high risk	CVD mortality	Weibull proportional hazards model Separate models for CHD death and stroke death	C-Statistic: ranged from 0.71 - 0.84, across risk straum No calibration	Europe-wide
ASSIGN	Scotland 1984 - 1995 Mean follow-up 18 years 16,000 30-74 years	Age, SBP, total cholesterol, HDL cholesterol, diabetes, family history, socioeconomic deprivation, cigarettes per day Separate equations for men and women 20% + denotes high risk	Deaths from cardiovascular causes coronary heart disease cerebrovascular disease coronary artery interventions	Cox proportional hazards model	C-Statistic: 0.727 men, 0.765 women. No calibration	Scotland
QRISK2	England and Wales 1994 - 2008 Mean follow-up 12 years Over 2 million 30-74 years	Age, sex, SBP, ratio total cholesterol/HDL cholesterol, diabetes, family history, socioeconomic deprivation, smoking status, ethnic status, BMI, treated hypertension, rheumatoid arthritis, chronic renal disease, atrial fibrilllation 20% + denotes high risk	Myocardial infarction, angina, coronary heart disease, stroke, and transient ischaemic attack.	Cox proportional hazards model	C-Statistic: 0.792 men, 0.765 women. Calibration: from 0.92 -0.95 across deciles	England

Framingham score – UK Version

Population

The Second Joint British Societies (JBS2) clinical guidelines recommend using a modified version of the score that uses the risk factors in the original 1991 study(15, 120). The population dated from 1971 and was comprised of 8,491 individuals.

Risk factors / end-points

The score uses the risk factors of age, sex, smoking status, systolic blood pressure, total cholesterol and HDL cholesterol. The CHD end-points used were fatal and non-fatal myocardial infarction and new angina, and the CBVD end-point includes fatal and non-fatal stroke, cerebral haemorrhage and transient cerebralischaemia. Some primary cardiovascular events, such as aortic aneurysm or lower limb ischaemia, are not included. However, on their own these represent a small proportion of all CVD events.

JBS2 recommends that the risk score is adjusted for Asian individuals and those with a family history of premature CVD, defined as < 55 for men and <65 for woman. The score for Asian individuals is multiplied by a factor of 1.4, and for those with family history the multiplicative factor is 1.3. For those who are Asian and have a family history these factors are applied simultaneously.

Modelling approach

A Cox-proportion hazard model was used.

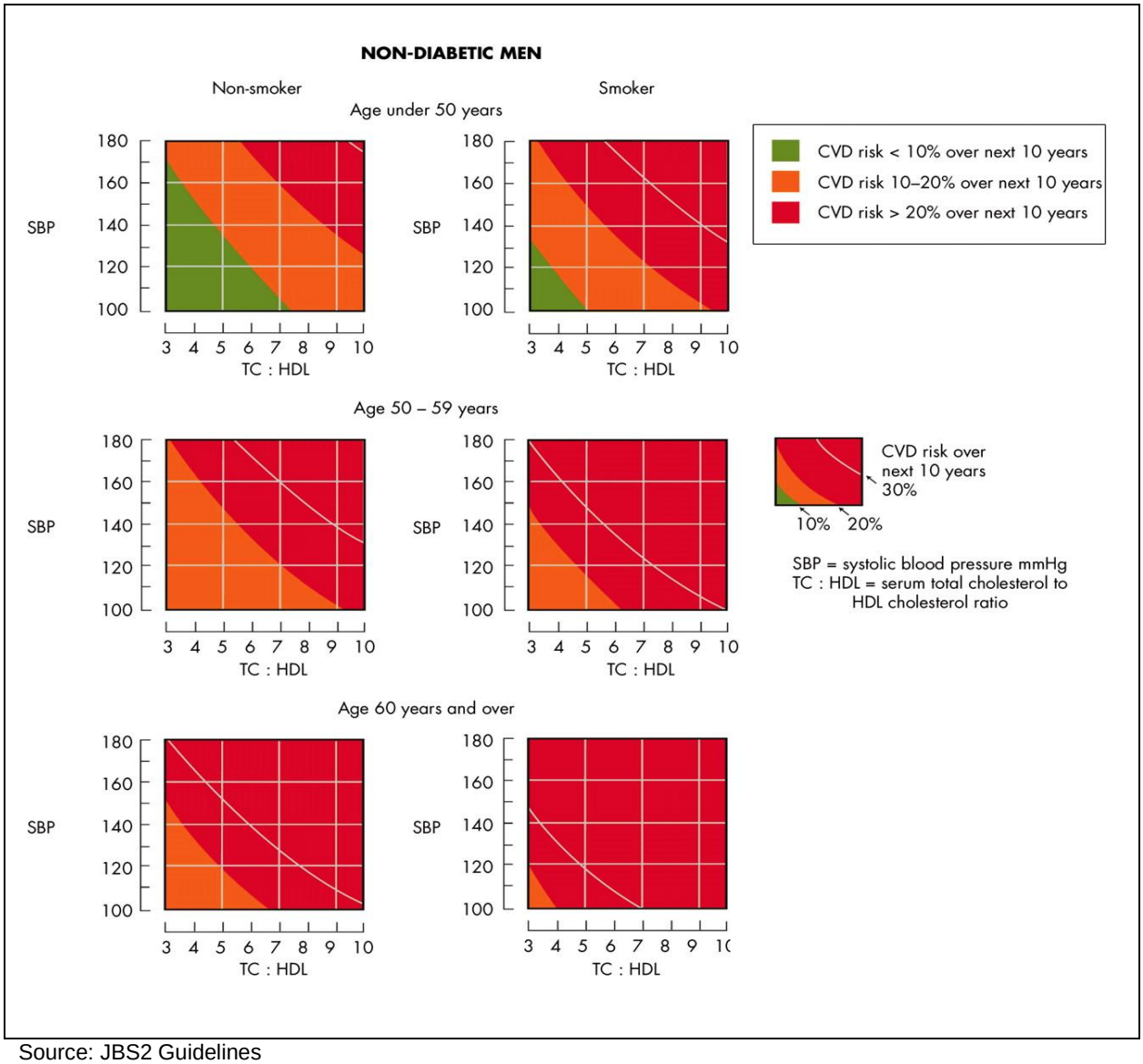
Validation: Discrimination and calibration

A specific validation and calibration exercise of the score in the UK was not conducted as part of JBS2 guidelines. However, a large systematic review of cardiovascular risk assessment in primary prevention has shown that the performance of Framingham risk scores varies considerably between populations, and that accuracy relates to the background risk of the population to which it has been applied(28). There is a general agreement that Framingham over predicts absolute risk in populations with low observed CVD mortality and under predicts in populations with high CVD mortality(121). The adjustments described above for Asian communities and those with family history attempts to calibrate the score accordingly.

Application

In England, the Framingham score is still the recommended by Department of Health(122). JBS2 recommends the use of risk charts, to communicate how risk factors translate into 10-year scores, as an aid to comprehension for both clinicians and individuals(15, 120). Figure 2-23 provides an illustration for non- diabetic men. Separate charts are shown for 10-year age bands, and smoking status.

Figure 2-23 JBS2 10-year risk charts



Source: JBS2 Guidelines

Profiles towards the top right corner denote the highest systolic blood pressure and total to HDL cholesterol values, resulting in the highest risk. A key driver of risk is age. For equivalent risk profiles, the risk of CVD increases with age, and by aged 60 almost all profiles is denoted

at high risk. The presence of this age gradient is revisited in later in the discussion, in the context.

The National Institute for Health and Care Excellence (NICE) has withdrawn its recommendation that general practioners (GPs) should use Framingham exclusively. Rather, GPs have the liberty to use Framingham or QRISK2, which is discussed shortly.

Systematic COronary Risk Evaluation (SCORE)

Population

SCORE(123) was developed by the European Society for Cardiology (ESC) and recommended for use in ESC Clinical Guidelines(16). The datasets used in creating the score originated from 12 countries, over a staggered baseline period of 1972- 1987 and there as with an average follow-up of 13 years. In total, 205,178 individuals were included in the study aged between 18 and 80 years old.

Risk factors / end-points

The risk factors of age, sex, ratio of total to HDL cholesterol, smoking status and systolic blood pressure were used. The end point is CHD death and stroke death. The score adds these two together to have an overall risk of CVD.

Modelling approach

A Weibull proportional hazards model was used. Separate equations are estimated for CHD death and stoke death. The total CVD death risk is calculated by simply adding the risk of CHD death and stroke death together.

Validation: Discrimination and calibration

Internal validation was conducted using the age range of 45-64 years, and separately for certain high and low risk countries. The former included Russia, Scotland, Sweden and the UK. The latter included France and Germany. Validation was conducted for the risk thresholds of 3%, 5%, 7%, and 10%. The C-statistic ranged from 0.71 to 0.84 demonstrating good discrimination. However, the variability in sensitivity was marked, ranging from 20% to 87%; and specificity 19% to 95%. This wide range reflects the fact that the tests were done for 4 thresholds, with event predictions for the higher thresholds performing better. There were no tests of calibration.

Application

SCORE is used across European countries where it was derived, with the exception of Scotland and England. England uses Framingham mainly, and Scotland has being using the ASSIGN score, discussed next.

ASsessing cardiovascular risk using SIGN guidelines (ASSIGN)

Population

A Scottish specific risk score was developed in 2007 to replace the Framingham score which had previously been widely used. It was found that the Framingham score overestimated the observed CHD risk in the cohort as a whole, and it seriously underestimated the large gradient in risk by socioeconomic status(17). Therefore, application of the Framingham score as a basis for preventive treatment may have resulted in relative under-treatment of the most socially deprived.

The ASSIGN score (ASsessing cardiovascular risk using SIGN guidelines to ASSIGN preventive treatment) was developed to include social deprivation as a risk factor(124). ASSIGN score is based on the Scottish Heart Health Extended Cohort, a series of population studies from the 1980s and 1990s followed up until the end of 2005. The Scottish Heart Health study recruited men and women across 25 districts of Scotland in 1984-87 and the Scottish MONICA Project recruited in Edinburgh and Glasgow in 1986 and in Glasgow alone in 1989, 1992 and 1995. In total, this involved collecting baseline data from 6,419 men and 6,618 women

Risk factors / clinical end points

The ASSIGN score estimates sex specific equations using the variables age, family history, diabetes, socioeconomic deprivation, systolic blood pressure, total cholesterol, HDL cholesterol, and the number of cigarettes smoked per day. Risk factors were measured continuously where possible (with dichotomous variables for sex, family history, diabetes).

Socioeconomic deprivation was measured by the Scottish Index of Multiple Deprivation (SIMD), as introduced previously. Family history of cardiovascular disease is defined as coronary disease or stroke in parents or siblings below age 60 or in several close relatives.

Modelling approach

A Cox-proportion hazard model was used. Separate models were generated for males and women, following significant interactions between sex and SIMD, which persisted following adjustment for other covariates.

Validation: Discrimination and calibration

The ASSIGN score and Framingham score (the version reviewed under Framingham England) were tested together using the SHHEC dataset(121). The results were similar when taking the population as a whole, slightly favouring ASSIGN. The predicted high risk was 14.4% for ASSIGN and 16.0% for Framingham, where the observed incidence was 11.7%. The C-statistics for ASSIGN was 0.727 versus Framingham 0.716 for men and 0.765 versus 0.741 for women – both in favour of ASSIGN. In averaging across sex, the sensitivity of the scores was 46.3% for ASSIGN and 45.6% for Framingham. Specificity was 82.5 and 82.6% for ASSIGN and Framingham respectively. These results might be expected given that the dataset used to conduct the tests was the same used to construct the ASSIGN score. The real added value of ASSIGN over Framingham is the ability to detect the underlying social gradient in the incidence of events. However, there were no calibration tests.

Application

The SIGN97 Guidelines recommended using ASSIGN as the risk score of choice in Scotland, given it was developed for specific use in Scotland and detected the underlying social gradient in the incidence of CVD. SIGN recommends that all adults aged 40 years to 74 years are screened every five years. In addition, SIGN recommends that screening is widened to individuals at any age with a first-degree relative who has premature atherosclerotic CVD or familial dyslipidaemia. In practice, however, this is not done routinely. The important of family history in detecting high risk individuals will be revisited in Part 3.

QRISK2

Population

QRISK2(125) was developed in East Anglia in the UK, and is a rapid update of the preceding QRISK(126-127). The 10-year risk score was developed in East Anglia, with a patient group of over two million patients aged 30 to 84 years from 1994 to 2008.

Risk factors / end-points

A very wide range of risk factors are used including age, systolic blood pressure, the ratio of total to HDL Cholesterol, diabetes, family history, socioeconomic deprivation, smoking status (five levels, including former smoker), BMI, treated hypertension, rheumatoid arthritis, chronic renal disease, and atrial fibrillation. Socioeconomic deprivation was measured by the Townsend score, which is similar to the SIMD score (used in ASSIGN). Family history is slightly more restrictive than ASSIGN defined as coronary heart disease in a first degree relative. Notably, up to 80% of risk factor information is missing in the baseline screened dataset, and extensive multiple imputation was undertaken. The end-points in the score include myocardial infarction, angina, coronary heart disease, stroke, and transient ischaemic attack.

Modelling approach

A Cox-proportional hazards model was used to estimate the 10 year event risk.

Validation: Discrimination and calibration

The performance of the QRISK2 model was compared with the original Framingham score(125) using the QResearch database. QRISK2 performs well in terms of discrimination with C-statistic is 0.792 for men versus 0.779 for Framingham. The model is also well calibrated to the population. Individuals were scored, divided into tenths of predicted risk and then the ratio of observed risk to predicted risk was estimated. This was called the calibration slope and ranged from 0.92-0.95. QRISK2 did not find any socioeconomic deprivation gradient in the incidence of CVD unlike ASSIGN.

Application

The score is not specifically recommended by any Guidelines at present, but general practioners are at liberty to use QRISK2 if felt appropriate.

Overall, there a variety of different risk scores in use across the developed world. Most notably, Scotland has developed a particular risk score, called ASSIGN which in particular includes a measure of socioeconomic deprivation: the more deprived an individual is the deemed to be the great the risk of event. In application this score detects an underlying social gradient in the risk of events that accord with the gradient in event rates.

An additional issue of note is the range of risk factors that can be included. For instance, SCORE has six, ASSIGN has nine, and QRISK has 11. However, when comparing the performance of risk score directly, it makes very little difference to the overall proportion of the population found to be at high risk. This is consistent with the finding of law of diminishing marginal returns to risk factor inclusion(81) . These observations raise three issues. First, in choosing a risk score the main concern should be whether a particular risk factor aids discrimination between individuals – this is the necessity of using ASSIGN in Scotland. Second, in considering whether to add or replace risk factors key issue are not only whether it adds to predictive capacity and discrimination but also whether information on risk factors is available. QRISK2 includes more than double the risk factors of the Framingham score it is seeking to replace in England. However, it is difficult to see the added value, and this adds to the burden of the collection of risk factor information and potential for missing data. Third, from an economic perspective it is also important to assess the cost effectiveness of including additional risk factors, rather than saturating models with additional biomarkers, behaviours, genetic factors, and social variables. There is lack of research regarding the latter(8).

Notably, no risk tool includes physical activity as an independent risk factor despite inactivity being a known independent risk factor(128). Regarding ASSIGN the reason is that physical activity was not reported within the baseline screening survey. It is unclear as to the reason for its exclusion, is perhaps related to measurement issues. We return to the issue of physical activity later, and the potential challenges this poses in evaluating intervention effects.

2.7 Targeted approach: review of the evidence

2.7.1 Categories of evidence

The previous sections outlined the approaches to screening and identifying individuals deemed to be at high risk of a CVD event, and who are then subsequently referred onto a range of interventions. Section 2.7 as a whole is concerned with reviewing the evidence underpinning this approach. This particular sub-section defines the different types of evidence used in the chapter. There are three main categories of evidence: efficacy, effectiveness and cost effectiveness, as Table 2-9 outlines.

Table 2-9 Types of evidence

Type of evidence	Working definition
Efficacy	The maximum impact of an intervention detected under clinical conditions.
Effectiveness	The impact of an intervention in a real world setting.
Economic evidence	The value for money of an intervention.

Efficacy evidence

Efficacy refers to the maximum capacity of an intervention to result in changes in clinical outcomes. Clinical epidemiology had developed a hierarchy of evidence which essentially ranks the rigour of alternative study designs.

One of the difficulties in using efficacy evidence, as will be illustrated when reviewing the evidence for CVD interventions, is that the nature of outcome chosen can be particular to a study. For instance, efficacy evidence can relate to changes to a risk factor, events, disease mortality or all cause mortality. Further, studies can vary widely regarding the time period over which evidence is measured. From a particular study perspective, this is perfectly rational when the aim is to test efficacy on a particular medical outcome. However, from a policy or decision maker perspective that may need to collate a range of evidence and

choose between interventions, such an array of outcomes can inhibit comparability across interventions. This issue will be revisited shortly under the approach to economic evaluation.

Effectiveness evidence

Effectiveness evidence refers to the impact of the intervention under real world settings where, for instance, individuals' uptake and compliance behaviour with the intervention may vary between settings. Further, such effectiveness studies should report possible side effects and intolerance from medications where relevant.

The approach of economic evaluation

The basic premise of economic evaluation is that resources are scarce, and decision makers need to prioritise resources to achieve a set of explicit aims. Economic evidence essentially builds upon efficacy and effectiveness estimates, to look at both the benefits of an intervention and also the resource impacts, including the costs of an intervention and knock-on cost impacts from events saved, or incurred. Drummond defines economic evaluation as the 'comparative analysis of alternative courses of action in terms of both their costs and consequences"(p9)(129).

Economic evaluation is intended to produce the evidence that can allow decision makers to prioritise resources according to economic first principles. There are two important first principle concepts that determine the kind of information economic evaluation is required to produce(130). The first is 'opportunity cost': when investing resources in one area, the most relevant cost for the decision maker to consider is the opportunity for benefit that is forgone because those resources are not invested elsewhere. The second is that of the 'margin': when changing the resource mix, the most relevant costs and benefits for the decision maker to consider are the marginal costs and benefits resulting from the proposed change in the resource mix, rather than the average or total costs and benefits of all the historical resources used.

There are three main approaches to economic evaluation used in health economic evaluation: cost effectiveness analysis, cost utility analysis and cost benefit analysis(129, 131-132). The first two approaches are the most common. Each is outlined in turn, and with respect to how resources can be prioritised using the information generated.

According to McGuire (p76), a cost effectiveness analysis is employed when '…there is a fixed benefit or health effect to be achieved, and the objective is to seek the most technically efficient—i.e. least cost—way(131). For instance, if drug B is seeking to replace drug A, and both have the same health effect yet drug B is cheaper, then choosing drug B is the most technically efficient option. Further scenarios encountered in cost effectiveness analysis are where a new intervention is seeking to replace an existing intervention, and both costs and the level of health effect are different(37). The decision to adopt (reject) the new intervention is straightforward if the new intervention both costs less (more) and the effects are more (less). Here the new intervention is said to 'dominate' the existing intervention. In cases where the new intervention cost more (less) and the benefits are higher (lower) then the adoption decision is less straightforward. Here an incremental cost effectiveness ratio (ICER) is calculated which is the ratio of the additional costs to the additional outcomes generated. The ICER essentially generates a cost per unit of outcome. The decision to adopt the new intervention is conditional upon whether the ICER is below the maximum amount that the health sector is willing to pay (WTP) for an additional gain in health effect. This maximum WTP is termed the threshold value, and is driven (among other things) by the health sector budget. Where there are multiple independent interventions competing with one another for adoption then a cost effectiveness table can be constructed to rank order interventions, using the methods of 'dominance' and 'extended dominance'(37). Using this approach to prioritise resources between alternatives to achieve a common outcome can lead to what is termed 'productive efficiency'; defined in a health care context as '...the maximisation of health outcome for a given cost, or minimisation of cost for a given health outcome(133).

Cost utility analysis is a second form of economic evaluation that requires benefits to be comparable across interventions and patient groups(134). 'Utility' is a term used to define a measure of health outcome using the preferences of individuals or society(129). To create utility a two-stage process is conducted. First, a condition-specific(134-136) or more commonly a generic health related quality of life (HRQoL) questionnaire is administered, such as Short Form 12 (SF-12)(137), EuroQol-5D (EQ-5D)(138) or Health Utilities Index (HUI)(139). Responses are then weighted by preferences regarding the desirability of different health states. This then generates preference-weighted HRQoL scores which are essentially a linear index of possible utility scores. The range of the index can vary depending on the initial HRQoL questionnaire used. The SF-12 can be converted to utilities using the SF-6D algorithm, producing a score than can range from 0.29 to 1. The EQ-5D can be converted to utilities producing a score that can range from -0.54 to 1, where negative values

indicate states worse than death. The utility score can be used itself as the measure of health effect, and it is common for the utility scores to be used to weight expectations of length of life generating a more comprehensive generic outcome measure called Quality Adjusted Life Years (QALYs). These approaches to generate utilities will be described in much more detail later in the thesis. Alternative metrics to QALYs, but based on a similar approach, include Disability Adjusted Life years (DALYs)(140), and Healthy Years Equivalent (HYE)(141). To estimate whether a new intervention represents value for money a similar process as described under cost effectiveness analysis is undertaken to then improve the productive efficiency of the health service(37).

The third approach of economic evaluation is cost benefit analysis (CBA). The standard approach in CBA is to value all outcomes (including health and non-health outcomes) in financial terms by asking recipients of the intervention (or the general public) their willingness to pay for outcomes. The underlying premise is that the social value of an intervention can be measured legitimately in financial terms. Given outcomes and costs are in enumerated in financial terms, a CBA is intended to estimate the net social impact of an intervention(s) i.e. outcomes in financial terms minus costs in financial terms. Positive net values represent an improvement in social welfare, negative values represent a net reduction in social welfare and a zero value is neutral.

The approach of CBA takes what is termed a 'societal perspective', by attempting to incorporate all costs and benefits resulting from an intervention. In contrast, the approach of cost effectiveness analysis and cost utility analysis take a narrower 'health perspective' by restricting the scope of the evaluation to collect information on the costs and benefits (health only) to the health sector, and in the UK this extends to personal social services(37). The approach of CBA develops the widest generic outcome measure that is intended to represent social welfare (including heath and non-health outcomes). The rationale is to help decision makers to allocate resources between alternative uses to improve social welfare and improve the allocative efficiency of resource use. Allocative efficiency is achieved when resources are allocated so as to maximise the welfare of the community(133).

CBA is the traditional approach of welfare economics, whereas the practice of cost effectiveness analysis and cost utility analysis is the dominant approach of economic evaluation in the health sector. The general argument made for using cost effectiveness/cost utility analysis is that the health sector budget has been apportioned to deliver health

outcomes, and decision makers may be only interested in the health benefits and costs that accrue to the sector. Arguments that can be made for CBA is that health sector decision makers may be interested in more than utility or QALYs(142) and perhaps the role of economic evaluation is also to challenge decision makers and influence the health sector budget itself, rather than begin from an assumption that policy makers adopt the heath perspective(143).

Approach of economic evaluation in the United Kingdom

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) has guidance recommending the approach of cost utility (or cost effectiveness) analysis when undertaking economic evaluation(37, 144). The resource costs considered are those that fall on the health sector and also personal social services. An evaluation should ideally account for both the intervention costs and further impacts on health sector costs, such as events avoided or delayed. HRQoL impacts should be measured by surveying patients (or carers). To generate utilities, the valuation of HRQoL should reflect the preferences of the general population, and the recommendation is that the EQ-5D should be used to promote standardisation of preference elicitation across economic evaluations. Further, a key feature of cost effectiveness analysis is that outcomes and costs should be discounted at 3.5% to reflect the lower value placed on distant outcomes. Also, an equity judgement is taken that the value of an additional QALY is equal regardless of the recipient. NICE recommends that an intervention is cost effective is the cost per QALY is below £20-30,000(37, 144). In Scotland, while health policy is devolved, NICE's methodology is generally accepted by both the Scottish Medicine Consortium (SMC) and NHS Scotland.

It is important to note, however, that guidance is evolving over time. An important issue is the price that the NHS pays for pharmaceuticals. The current approach is that prices are negotiated through the Pharmaceutical Price Regulation Scheme (PPRS) which is a voluntary agreement between the Department of Health (DH) and the pharmaceutical industry. The PPRS determines profit rates from drug sales to the National Health Service (NHS) every 5 years utilising price and profit controls(145). Therefore, the current NICE guidance on economic evaluation treats prices as exogenous inputs to the economic evaluation and then generates a cost per health gain (e.g. cost per QALY), with the adoption decision made relative to the willingness to pay threshold of £20-30,000. However, the PPRS scheme expires in January 2014, and the Department of Health announced that NICE will thereafter play a key role in price setting; where the price set is intended to reflect the social value that

the pharmaceutical is expected to produce. The pricing system is called ‘Value Based Pricing’ and the general concept is that prices should reflect the value created, and should include considerations of the burden of illness, unmet need, future innovation, and wider social benefits. This system has been introduced in Sweden, for instance(146). The implications for the role of NICE and the approach to economic evaluation going forward will be important to observe. The intention of this section is not to rehearse differing views but to make the point that approach to economic evaluation is subject to on-going innovation.

Further, NICE’s recent Public Health guidance(147) recommends that economic evaluation takes a broader perspective by considering non-health outcomes alongside health outcomes. It is recommended that where appropriate a societal perspective is adopted to consider all major costs and outcomes. It is suggested that a cost consequence analysis (CCA) be conducted, which is essentially a social accountancy exercise, listing all major outcomes in natural units. To then value outcomes in economic terms, it is recommended that health outcomes are valued as Quality Adjusted Life Years (QALYs) to permit direct comparability of public health interventions with other interventions. Similar to the previous guidance, a QALY is valued equally regardless of the recipient.

It is also recommended that evaluators consider undertaking a cost benefit analysis (CBA), when evaluating public health interventions. In practice, this would entail valuing all outcomes in the CCA in economic terms (health and non-health) to estimate the overall social value of an intervention, where health is one component. The guidance also recommends that the discount rate for costs and benefits should be 1.5%. This is in contrast with guidance for the economic evaluation of health technology which recommends a discount rate of 3.5% for both cost and benefits. A potentially interesting issue is whether within the CBA the WTP survey includes valuing QALYs. This may then allow for the social valuation of a QALY to vary dependent on the recipient and, if so, this would contrast with guidance in for the economic evaluation of health technology. Again, the purpose of this discussion is descriptive rather than evaluative as to the merits of one approach over another. Overall, the key point is that the first principles of economic evaluation are clear; however, the particular approach adopted may be tailored to the decision problem at hand, and methods are evolving over time.

Quality of evidence

Understanding the risk factors of CVD, and which interventions may impact on modifiable risk requires scientific attribution. For health researchers, it is standard practice to refer to a hierarchy of evidence, as illustrated in Table 2-10 where there are 6 'levels'.

In short, the randomised control trial is considered as the most rigorous study design to compare the impact of a treatment on an intervention group relative to control group, where the act of randomisation is intended to evenly distribute all known covariates, leaving the difference between groups as the intervention itself. These studies designs can vary, for instance with respect to the extent blinding such as study participants (single blinded), physicians (double blinded) and study administrators (triple blinded). Systematic reviews of RCTs, where the conclusions are aligned, provide the most robust evidence (Level 1), followed by a single or multiple RCTs without conducting a formal systematic review (Level 2).

Table 2-10 Hierarchies of evidence

Level	Description
One	Systematic review(s) of well designed randomised control trials
Two	Evidence from at least one well designed randomised controlled trial
Three	Evidence from well designed observation studies, such as matched-control cohort studies
Four	Evidence from well conducted natural experiments
Five	Expert opinion elicited under scientific conditions
Six	View of peers

Source: adapted from Evidence Based Nursing Practice(148)

Non-RCTs designs are essentially different forms of either observational studies (level 3), such as matched controlled studies which may require statistical adjustment for known confounders to infer treatment estimates. Natural experiments (Level 4) are where it may be possible to develop attributable evidence of a policy change that proceeded in the absence of explicit experiment. For instance, econometric techniques such as interrupted time series or where changes in the outcome of interest may be traced back to the introduction of legislation.

Level 5 is where expert opinion is collated by convening an expert/stakeholders group to elicit opinions systematically through tools such as Delphi Panels. Level 6 is simply the view of peers, and while not evidence may be important when considering the need to conduct trials or studies.

Additional challenges in generating and generalising from evidence

In general terms, it is more straightforward to generate evidence for drugs rather than lifestyle interventions. The use of RCTs is relatively straightforward when assessing the impacts of drugs. However, there can be additional challenges in both generating and generalising from service based interventions. This is particularly the case when interventions are programmatic and need to be implemented through a delivery system. This can lead to interventions being termed 'complicated' and 'complex'.

Interventions are complex where there are multiple components and where causal chains are long term. These features make it difficult to identify active ingredients and to distinguish between a good intervention and poor implementation(72, 73).

Further, interventions may also be 'complex' in the sense that they can interact with local context (e.g. past and present interventions). In effect, context is an effect-modifier(149). For instance, perhaps 'upstream' interventions that focus on improving the living conditions of communities live (e.g. housing, regeneration) are prerequisites for sustained 'downstream' interventions that attempt to change health behaviours directly(36).

These common features can cause difficulties in establishing both causality (e.g. the opportunity for randomised trials is limited) and the generalisability of evidence, given that context can vary substantially between settings. Evidence synthesis is a particular challenge(150). The interaction of economic evidence with context provides an opportunity for interdisciplinary research in the future in order to improve both the generation and generalisability of evidence(51-52, 151).

The practical consequence of this is that even if evidence is found that lifestyle interventions have made significant impacts and are cost effective, it can be more difficult to assess how to transfer the intervention between settings. It has been suggested that rather than preserve the absolute fidelity of an intervention, the steps of the intervention are maintained but how it

is delivered is adopted for local context in order to suit local resource ability and cultural practice(152).

The role of modelling

Of particular concern in this thesis is the role of modelling to help generate economic evidence. As will be discussed in detailed throughout the thesis, preventative interventions may have the greatest impact over the long term. Experimental studies, often conducted over relatively short time periods, can detect short term or intermediate outcomes, such as changes in risk factors or events. However, as discussed previously economic evaluation is concerned with 'final outcomes' such as (quality adjusted) life expectancy and impacts on health service costs. In generating economic evidence, modelling is undertaken. Chapter 3 discusses the rationale for modelling in detail.

In addition, modelling studies may be undertaken in the absence of any evidence. First, such exercises can be done to either analyse historical data for the purpose of investigating the associations between events and interventions that occurred. Second, modelling exercises can be used to predict future events and the potential for (further) event reductions. Third, modelling can also be undertaken to highlight uncertainties in the evidence base and need for economic evaluation.

Modelling is now undertaken routinely to evaluate health interventions. However, given its widespread use and application there is a need for good modelling practices to ensure the best opportunity for achieving robust and transparent result open to peer review. Chapter 3 discusses the latest guidance on how to build and disseminate economic models. For the time being, this chapter will simply summarise the evidence available.

2.7.2 Approach taken to identify studies

There is a significant on-going effort by researchers to undertaken new studies and perform periodic systematic reviews. Rather than undertake a new systematic review this section is essentially a summary and interpretation of key studies. It is not intended to be exhaustive, but rather to provide a valid interpretation of the overall body of evidence. Further, only interventions directly focussed on particular risk factors were considered, and those delivered by the health sector. Therefore, interventions excluded include those where CVD is not the main aim, but may nonetheless have knock-on effects on relevant behaviours, such as mental health interventions that seek to enhance an individuals' general sense of self-efficacy

that may then lead to healthier lifestyle choices. Also excluded are the wider determinants of health that may influence lifestyle choices indirectly, such as housing and regeneration. Further, interventions designed to 'nudge' behaviour are also not considered(153).

Efficacy, effectiveness and cost effectiveness evidence is reviewed. In reviewing the clinical evidence, clinical guidelines were drawn upon. Specifically, the Scottish Intercollegiate Guidelines Network (SIGN) developed the SIGN 97 guidelines for the primary prevention of cardiovascular disease(9). Within this document there was the collation of numerous systematic reviews of both pharmaceutical and lifestyle interventions, and was published in 2007. Further, the National Institute for Health and Care Excellence(NICE) Programme Development Group (PDG) for the primary prevention of CVD undertook an extensive review of the literature which related to population health interventions, and mainly included lifestyle interventions, rather than a focus on pharmaceuticals(154-156). This review was published in 2009. In an effort to update these evidence reviews, a literature search for more recent systematic reviews was also conducted by reviewing Cochrane Libraries and also a general search of the literature using PUBMED dated from 2008 to the end of 2012.

A similar approach was adopted to search for effectiveness and cost effectiveness evidence. The research by the NICE PDG is heavily drawn upon. Further, PUBMED was searched for more recent evidence relating to singled drugs and multi-factorial interventions that combine drugs and perhaps also with lifestyle interventions.

2.7.3 Targeted prevention: efficacy evidence /modelling studies

In reviewing relevant studies a distinction is made between evidence derived from evaluations and estimates derived from modelling studies.

Pharmaceuticals

As discussed, cholesterol is a key risk factor; though more specifically it is low density lipoprotein (LDL) which is the harmful component which comprises 60-70% of total cholesterol. Guidelines recommend that high risk individuals (whether raised cholesterol or not) be given a 40 mg dose of a statin drugs daily. There is also a log-linear relationship between the statin dosage and reductions in LDL, with each doubling of the dose being associated with a fall in LDL of 6%. A meta-analysis found that a reduction LDL of 1.6 mmol/l halves the CHD event risk after 2 years(9).There are a variety of different types of statins.

Guidelines recommend a dosage of 40 mg per day and trials have found this reduces LDL by between 29% (pravastatin) to 53% (rousuvastatin).

Further, there is also evidence that statins increase high density lipoprotein, which then improves health outcomes. The West of Scotland Coronary Prevention Trial (WOSCOPS) found that pravastatin increased HDL Cholesterol(157). Table 2-11 summarises mean estimates, providing a range where possible.

A Cochrane systematic review of fourteen RCTs in 2011 found no evidence of significant harm(158-159). At present, statins are not recommended for those at CVD risk below 20%(29-30). However, there is on-going debate. A recent systematic review of 27 RCTs found that statins could be safety prescribed to those at lower risk(160). However, previous studies have concluded that statins should not be prescribed to individuals below a 1% annual all-cause mortality risk or an annual CVD event rate of below 2%(159). This is aligned with treating individuals with a risk score of 20% or greater 10-year risk of developing CVD.

Table 2-11 Evidence of efficacy - pharmaceuticals

	Benefits	Risks
Statins	- LDL of 29-53% + HDL of 5%	Controversy: possible + risk stroke
Anti-hypertensives	- CHD by 15-25% - Stroke by 30-40%	None reported
Aspirin	- MI 15-25%	+ risk bleeding 70% + stroke 40%

"+" denotes increase; "–" denotes decrease; "M" denotes myocardial infarction

Anti-hypertensives are prescribed to reduce blood pressure. There are five main types of anti-hypertensives, namely: thiazides, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor-II antagonists, calcium channel blockers and beta-blockers. All have approximately equivalent impacts and when combined appear to have additive impacts. The SIGN97 clinical guidelines also report that anti-hypertensives can reduce the risk of CHD by 15-25% and stroke by 30-40%. There is an approximate linear relationship between dosage of anti-hypertensive and CVD risk between the values of 115/70 and 170/100 mm Hg, with the numerator denoting systolic blood pressure and the denominator diastolic blood pressure.

Clinical guidelines recommend that individuals are treated where systolic blood pressure (SBP) is ≥ 140 mmHg and diastolic blood pressure is ≥ 90mmHg; or where the risk of CVD calculated by the ASSIGN score is ≥ 20% over 10 years. The relationship between lowering blood pressure and CVD outcomes is approximately linear: the higher the baseline risk: the greater the reduction(9). The target level for SBP is 100-115 mm Hg, however there is no evidence that lowering below this has harmful effects.

SIGN Guidelines also recommend that asymptomatic individuals at high risk be given a daily dose of aspirin of 75mg as anti-platelet therapy. Pooled RCT results estimate a reduction in the risk of myocardial infarction of 30%. However, there can be serious side-effects with the relative risk of stoke increasing by risk of 40% gastrointestinal bleeding by 70%. There was no impact on all cause mortality. Guidelines recommend not extending aspirin to those not at high risk. However, there is a renewed debate regarding the safety of prescribing aspirin to any individuals eligible under primary prevention. The most recent paper found that the risk of bleeding outweighed any benefits(161-162).

There is also on-going interest in combining medications into a single polypill. In a modelling study(34), it was estimated that the incidence of coronary heart disease could be reduced by 80% if all men and women over the age of 55 took a “polypill” of six low dose drugs. The assumption being that this is an age threshold most individuals would benefit. However, the study also assumed compliance of 100%. There is also no trial evidence as yet in a Cauasian population, although several studies are on-going(163). Positive impacts were found in a trial conducted on an Indian population(164).

In summary, there is relatively robust evidence of the benefits of certain pharmaceuticals. While there can be a risk of side effects, clinical guidance recommends offering statins, anti-hypertensives and aspirin to patients found to be at high risk of a CVD event. There remains controversy that non-high risk patients should be offered similar treatment. Further, a key observation is that the outcome measures reported are not consistent, consisting of risk factors or events. This is a recurring theme in the evidence base, and can make it difficult to directly compare the effects of different interventions; and inhibits an assessment of the impact of interventions against the ultimate objectives of prevention which is to avoid premature mortality.

Lifestyle interventions

The following summarises the evidence of dietary, physical activity and smoking interventions, as these are the main focal points for primary prevention. A variety of dietary interventions have been reviewed, in the literature both in terms of additions and abstinence from certain food stuffs. A systematic review of 27 studies found that reductions in dietary fat intake reduced CVD events by 16%, but had a small insignificant impact on total mortality(165). SIGN Guidelines recommend diets low in saturated fats. Table 2-12 provides mean estimates with ranges from different studies for illustration, where possible.

It is also recommended that individuals with hypertension should reduce salt intake as much as possible. A Cochrane meta analysis of 28 studies found that for individuals with SBP of ≥ 160 a daily reduction of salt intake of 6mg resulted in a reduction in SBP of 7.11/3.88 mmHg(166).

Table 2-12 Evidence of efficacy – lifestyle changes

	Risk factor
Saturated fat reduction	- 15-35% CVD events
Salt reduction (6mg reduction)	- 7.11 mm Hg (SBP) - 3.88 mm Hg (DBP)
Fruit and vegetables (400 g per day)	- 14-23% CHD events
Physical activity (sedentary to moderate)	- SBP 3.8 mmHg - DBP 2.8 mmHg. - MI 26-30%
Smoking cessation	- RRR death x3

MI = myocardial infarction; RRR = relative risk reduction

Further, it is also recommended by SIGN97 that all individuals should consume 400g of fruit and vegetables each day. Such diets are also associated with low fat intake. Two systematic reviews of cohort studies found that the reduction in CHD events was between14% to 23%.

There is strong evidence that physical inactivity has been shown to be independent risk factor, after adjusting for other known risk factors; however, it is argued that it remains unclear to what extent increasing activity levels reduces CVD risk(128).

Nonetheless, there are a wide range of studies estimating the impact of physical activity on other known CVD risk factors that do point to positive impact. A meta-analysis of 54 RCTs found that previously sedentary adults who undertook moderate aerobic exercise of 30 minutes and three times a week could decrease SBP 3.8 mmHg and DBP by 2.8 mmHg(167). No dose response was reported.

The impact of exercise on lipids levels was inconsistent. Of 51 trials, 24 showed that HDL increased, which is protective of CVD events. However, the range across the 51 trials showed that the HDL varied from -5.8% to +24%(167). The Interheart study found that HDL levels increased by 5% (76). No dose response was reported. In terms of event risk, the Interheart study found that moderate exercise compared to sedentary reduce the risk of myocardial infarction by 14% (26% – 30%, CI 95%).

Importantly, it can be difficult to draw general inferences regarding the particular type of interventions that may work best. The impact of interventions can differ widely by type of activity, frequency, duration and intensity; and also report different outcomes. It appears that energy expenditure and frequency of activity are the key drivers of risk rather than type or duration of activity(168).

The evidence regarding smoking is relatively unequivocal. SIGN97 reports that there is a strong and dose response relationship between smoking and all CVD events and overall mortality. For instance, male smokers are three times more likely to die between 45-64 years, and twice as likely to die aged between 65-84 years, than non-smokers. Risks increase with the number of cigarettes smoked per day, with the risk of a myocardial infarction 10 times higher for those who smoke 40 per day.

Overall, there is relatively strong evidence that adopting healthy lifestyles can have significant impacts on risk factors and the incidence of CVD events. The major areas of uncertainty relates to multi-factorial programmes, either in terms of a polypill or combination of drugs and lifestyle changes. In particular, there is a lack of knowledge regarding the compliance rates

and how the impacts of interventions interact in terms of the combined reduction in risk factors and events.

2.7.4 Targeted approach: effectiveness evidence /modelling studies

The key difference between efficacy and effectiveness is compliance behaviour. That is, whether individuals, under real world settings, take the appropriate medicines and in the appropriate doses. Further, when considering effectiveness of lifestyle interventions it is important to recognise that interventions can vary enormously in the intervention design (e.g. staff specialities), delivery (e.g. setting), target group (e.g. age, socioeconomic background), and evaluation methods (e.g. outcomes, time, information collected). This makes synthesising extremely difficult(51).

Pharmaceutical interventions

There are few studies that have assessed the real world effectiveness of pharmaceuticals over the long term. In general terms, it appears that compliance behaviour for asymptomatic patients is relatively low for any medications. For instance, studies find that compliance rarely will exceed 50%(13). This suggests that the efficacy estimates previously reviewed should be at least halved when estimate effectiveness over the long term.

With regards to a polypill there is also uncertainty about how the benefits that where identified for single intervention (e.g. stains) might combine when collated into a single pill. Even optimistically assuming a hypothetical combined risk reduction of 40% (that is, 15%+25%), over half the cardiovascular risk will remain. If compliance was say 50% on average in the population, then the risk reduction would be halved. Nonetheless, clinical guidelines infer that these impacts are sufficient to maintain that screening and prescribing should continue for high risk individuals.

Lifestyle interventions

The evidence base regarding the effectiveness of interventions to promote healthy lifestyle is mixed. Clinical guidance recommends that such interventions are not rolled-out routinely without an accompanying study, and ideally to assess long term compliance. Counselling to stop smoking is an exception. There are a wide number of studies assessing the effectiveness of smoking initiatives. Smoking interventions are varied, and can include one or a combination of medications (including patches), one-to-one counselling, and group therapy, combined with general lifestyle advice. As such, it can be difficult to draw general inferences.

Despite, high relapse rates, with long term compliance falling to as low as 5%(169), decision makers have deemed this sufficient to continue funding such programmes. The cost effectiveness evidence will be summarised shortly.

The major areas of uncertainty in the evidence base relates to multi-factorial programmes that combine pharmaceutical and lifestyle interventions. Table 2-13 details key studies gathered from the NICE PDG which extended to 2008, which was then combined with a more recent search of the literature. There were two studies that reviewed the effectiveness of multifactorial interventions that were targeted on high risk individuals – following a screening of the whole population. The interventions were Seeze District Control which began in 1983 and had a 10-13 year follow-up and Oxcheck in 1995 which had a 4 year follow-up. There were significant changes in key risk markers, such as BMI and dietary behaviours. However, it is difficult to interpret the clinical significance of changes to certain risk factors and event rates are often not reported. A more recent study published in 2012 was of the EUROACTION intervention. This was a clustered RCT of 6 practices from across Europe and for the asymptomatic population there were positive changes in blood pressure and cholesterol, after a 1-year follow-up.

More recently, a Cochrane Review in 2011 focused on counselling and educational interventions included 55 trials aimed at modifying one or more cardiovascular risk factors in the adult general population(170). The review concluded that there is no evidence that such interventions to change behaviour reduce total or coronary heart disease mortality or clinical events in general populations. The review found that effects were only found when individuals had pre-existing disease such as hypertension or diabetes.

Table 2-13 Efficacy/effectiveness evidence - multi-factorial interventions

Programme	Interventions	Study design	Outcomes / results
The Sezze District Control Italy 1983 20-69 years old	Population screening programme assessing 10-year risk High risk offer intensive lifestyle and behavioural interventions	Controlled before and after study Matched intervention and control area Baseline screening in 1983 and follow-up screening in 1993-1996 10 - 13 year follow-up	BMI - 10% (women), blood fasting glucose -15% (men)
OXCHECK Luton and Dunstable England 1995 35-64 years old	Screening for CVD risk factors, 11,090 invited for randomisation Individuals with high risk factors invited to nurse appointment in 1st year (1989-90) and attendees invited to further check in 4th year (1992-93) Comparison of screening strategies to find those at high risk 6 risk factor identified: (i) SBP > 140 mmHg (ii) smoking (iii) BMI > 28 (iv) fat intake 110g/day (v) family history CVD first degree relative <60 years (vi) TC > 7.5mmol/l Comparing mass screening on population for all risk factors against different targetted approaches that first screen for one risk factor initially and then for the high risk screening for other risk factors	RCT Control attended health check in 4th year Four year follow-up	TC - 0.19 mmol/l, SBP - 2.5 mm/Hg, diastolic - 1.1 mm/Hg BMI - 0.38 kg/m2, physically active +3.3%, consumption of full cream -7.5%, consumption of butter -8.7 %
EUROACTION Mistry H et al 2012	Screening and treatment of high risk patients with individualised lifestyle counselling and medications. Europe-wide.	Clustered RCT: 6 pairs of general practices in 6 countries 1019 intervention patients; 1005 control patient	Hypertensive patients(> 140 SBP/90 DBP); - 17%; total cholesterol -13%

2.7.5 Targeted approach: cost effectiveness evidence / modelling studies

From an economics perspective, the important issue is whether the observed changes in risk factors and events are enough to justify the cost the interventions themselves. This is the rationale for taking a cost effectiveness approach, as described earlier.

Pharmaceutical interventions

The evidence regarding the cost effectiveness of single pharmaceutical interventions appears to be robust for individuals defined as high using 10-year risk scores. There is strong evidence that medications including statins(NICE)(171), anti-hypertensives (NICE)(172) and aspirin (NICE)(173) are cost effective, with the incremental cost effectiveness ratio below £20-30,000 recommended by NICE and followed by SMC – table 2-14. The uncertainty is not whether to prescribe a drug but rather which should the first line intervention, as the extent of benefits and costs of different drugs may differ(172).

Table 2-14 Cost effectiveness evidence - pharmaceuticals

Type	Cost per outcome
Statins	Cost saving and has same or greater effectiveness; to £2,500 per QALY
Anti-hypertensives	Cost saving and has same or greater effectiveness; to £1,976 per QALY
Aspirin	Cost saving and has same or greater effectiveness; to £22,000 per QALY

Overall, NICE recommends that such medications should be used in the primary prevention of CVD, but only when individuals are found to be at high risk. This is consistent with clinical guidelines.

A recent systematic review of the cost effectiveness of statins found that the key driver was cost, and as cost falls so statins become cost effective even for low risk groups(171). This closely matches the clinical literature with regards to the efficacy and effectiveness of medications of the low risk. Prices have tended to come under downward pressure as drugs have come off-patent and generic versions have entered the market. However, treating the low risk remains a source of controversy. It has been argued that medicalising low risk

individuals may create perverse incentives if healthy behaviours become unhealthy as a result(174). Further, it is unclear whether potential side-effects had been accounted for in most studies.

Notably, however, there are no cost effectiveness studies of polypill to date. However, a recent modelling study also showed that a combination of different interventions may be cost effective(175).

Lifestyle interventions

The cost effectiveness evidence for certain lifestyle interventions is also strong(31), In particular, the evidence for smoking is unequivocal. This is even the case when compliance rates (abstinence from smoking) falls as low as 5% as found by a recent modelling study that extrapolated trial results to the longer term(169). Importantly, individual studies that make up these guidance documents have relied on the use on important assumptions, with respect to the long run compliance with healthier lifestyles. However, even following scenario analysis where assumptions around compliance are sensitised the inferences can remain robust; that such interventions appear to be cost effective.

In terms of the international evidence base, a recent modelling study(175-176) which drew upon the ACE-Prevention study, a large scale review of the literature of effectiveness estimates to then estimate cost effectiveness, found that certain physical activity intervention scan be cost effective. Notably, the exception was for multi-factorial programmes referred through general practioners. A study from the Netherlands also suggested that the particular form of the interventions and local context are key factors driving whether interventions are cost effective(177).

There are few cost effectiveness studies assessing of multi-factorial interventions, combing pharmaceutical and lifestyle interventions. The Oxcheck study, British Family Heart Studies, and EUROACTION interventions, previously summarised, found positive changes in certain CVD risk factors. Following these studies, economic modelling was conducted to infer whether these programmes are also cost effective – table 2-15. This required modelling to be undertaken to extrapolate trial results. It is inferred that the Oxcheck and the British Family Heart Studies could be cost effective if changes in risk factors found in trial were sustained for at least five years and tend year respectively(178). On the other hand, the inference was that EUROACTION was likely to be cost effectiveness over 10 years(179).

The Department for Health for England, created an economic model to project the impacts of the Vascular Screening Checks programme that began to roll-out nationwide from 2009(122), as discussed earlier. It was reported that the modelling found that the programme is likely to be very cost effective, with estimates of £7,000 per quality adjusted life year gained, below the cost effectiveness threshold of £20-30,000(180). However, it is difficult to assess how robust these estimates are. The model itself is not available for external review, and certain modelling assumptions that were reported appear to be very optimistic. For instance, within the detail of the report, the most notable assumption was regarding long term compliance. Regarding statins for instance, it was assumed that asymptomatic individuals would be 70% compliant over the long term. However, previous research suggests compliance would be unlikely to exceed 50%(13). It is reasonable to expect that this compliance assumption would have had a major impact on the cost effectiveness results reported. However, no sensitivity on compliance rates was conducted.

In reflecting on the models used to estimate cost effectiveness, two main issues are apparent. First, bespoke models appear to be built for (almost) every new intervention encountered. This seems inefficient. A single model that estimates the risk of CVD using a wide range of risk factors could in principle be used repeatedly. This could enhance the direct comparability of the cost effectiveness of different interventions. The second issue that the economic models are not always well-reported to permit third parties to review. The next chapter reports on a systematic review of models that have adopted a generic approach in an attempt to model the impact of a range of different interventions.

Table 2-15 Cost effectiveness evidence – multi-factorial interventions

Programme	Interventions	Study design	Outcomes / results
Field et al 1995 Long term projections of OXCHECK	See table 2-11	Modelling study, using study finding after 4 years and projecting over lifetime	All strategies cost effective with mass screening least. ICER ranged from £97 to £503 measured in £/Lifeyears
Mistry et al 2012 Cost effectiveness of EUROACTION	See Table 2-11	Modelling study, using study finding after 1 year and projecting over 11 years using Framingham equations.	Not cost effective - most costly; fewer QALEs compared to usual care

Overall, the evidence base for the targeted approach to primary prevention is inconsistent. There is strong efficacy evidence that single interventions can have positive net impacts on risk impacts, but there is a lack of robust efficiency, effectiveness and cost effectiveness evidence for multi-factorial interventions. The challenge for researchers is to conduct rigorous and longer trials, combined with transparent modelling approaches to estimate the lifetime impacts of interventions.

Turning to Scotland specifically, it is now clear that there is no prior evidence that the targeted prevention programme called Keep Well, that is being rolled out nationwide, will have major impact and be cost effective. Further, the programme is being rolled out without a rigorous economic evaluation. Consequently, it would appear that while policymakers are justifiably concerned regarding the incidence of CVD and health inequalities, policy is being rolled out mainly on aspiration rather than expectation.

2.8 A population approach to the primary prevention of cardiovascular disease and evidence base

Population approaches are intended to impact on everyone in the population of concern, in contrast to a targeted approach on the high risk, as discussed earlier. This general approach has gained traction in policy circles regarding the primary prevention of CVD. It is argued that population approaches need to be at the centre of a comprehensive approach to combat the underlying aetiology of the disease, and that “all other strategies will, at best, only restrain the epidemics; they will not prevent them”(181). A population approach is endorsed by numerous bodies, including the European Heart Network(182), for instance.

Population interventions include a varied set of interventions, from mass media campaigns and lifestyle advice to legal and regulatory changes. The following now summarise the effectiveness and cost effectiveness of population wide interventions.

2.8.1 Population approach: effectiveness evidence/modelling studies

The landmark study was in North Karelia which was 5-year community intervention study in Finland, beginning in 1972 with the aim to reduce CHD risk factors(183). A combination of interventions were delivered simultaneously: including mass and local media campaigns; training of health service staff, engaging with volunteers and community leaders for health

promotion; environmental changes, such as smoking restrictions; and food processing and supply restrictions to use low-fat dairy and meat products. There were major falls in key risk factors, including smoking prevalence, cholesterol and blood pressure. Following a 25-year period (1972-1997) it was reported that CHD mortality declined in North Karelia by 73%, and compared to 65% in Finland as a whole over the same time period(184).

Table 2-16 details 19 major studies since North Karelia that was reviewed by the NICE NPD. Most studies tend to be observational matched-control studies, with interventions delivered to entire localities (e.g. state level) with a neighbouring location used as a control. In general, studies do not have the benefit of such a long follow up as in North Karelia and varied widely according to time period, setting (different countries), and the intervention(s) (e.g. mass media, screening). It can be observed that 15 studies report significant changes in one of more risk factors, and 4 studies had no significant changes.

It is difficult to assess to what extent the changes in risk factors would result in clinically meaningful outcomes regarding future events. In general the evidence base is promising, but far from comprehensive or convincing that a particular type of intervention is likely to lead to substantial reductions in primary events. Overall, the impacts seen in North Karelia, that inspired many such interventions around the world has not been replicated elsewhere.

Table 2-16 Effectiveness evidence of population interventions

Programme	Interventions	Study design	Outcomes / results
The Norsjo Project Whole community of Norsjo Sweden 5500 individuals 1985	Mix of lifestyle interventions, consisting of information provision from existing providers regarding education, diet,exercise. Risk factor screening offered to 30 to 60 year olds with individual counselling.	Matched controlled before and after study Control was region of Northern Sweden, Surveys: 1,893 individuals 7 year follow-up	TC - 0.8 mmol/l,
The North Karelia Project Rural county Whole community 180,000 individuals 1972	Comprehensive education programme integrated within existing health and social services, including: Mass media, training of staff in CVD prevention, information services, provision of healthy foods, smoking restrictions	Matched controlled before and after study Control was Kuopio similar size and socioeconomic indicators 3 surveys over 15 years of follow-up	Smoking prevalence - 28% (men), TC -3% (men), SBP -3% (men), -5% (women), DBP 3% (men), - 4% (women)
The Pawtucket Heart Health Program Rhode Island United States 71,204 individuals	Behaviour change promoted via local statutory, church and community organisations; then combined with mass media from TV adverts to newspaper ads and billbards	Matched controlled before and after study Matched community, Surveys, 1,255 individuals 10 year follow-up	BMI -0.62 kg/m2
The Stanford Five City Project Five cities 1980 Two cities with intervention 245,000 individuals	Two cities with interventions City wide mass media education campaigns: TV, radio, newspapers , combined with community level education campaigns distribution of media products (eg. Leaflets)	Matched controlled before and after study Three cities as controls. Surveys : 1,148 intervention individuals, 743 control individuals 6 year follow-up	SBP -3.8mmol/l, BMI -0.83 in intervention group
The South Carolina Cardivascular Prevention (Heart to Heart Project) Florence 46,227 individuals 1987	Mass media education campaigns (TV, radio, newspapers) Community levels cooking demonstrations, restaurant labelleing.	Matched controlled before and after study Survey: 1,130-1,259 individuals 4 year follow-up	% with TC > 5 mmol/L -3.7% (women), BMI >25 kg/m2 -2.9% Consumption of animal fats -4.9%, consumption of fruit & veg + consumption up 5.2%

Table 2-16 continued

Programme	Interventions	Study design	Outcomes / results
Action Heart 2 towns in England (Swinton and Wath) 13,000 households 1993	Mix of lifestyle interventions, including: Schools based activities such as health eating, anti-smoking, trained teachers to discuss heart health topics Whole community activities to delivery leaflets to all households to drink semi-skimmed milk	Matched controlled before and after study, with one control area similar in socioeconomic indicators 18-64 year olds 4 year follow-up	Smoking prevalence -by 3.5% pts, semi-skimmed milk consumption + 7% pts Execise in children (≥3 times per week) + with odd ratio of 1.76 versus control Wholemeal bread consumption + Odds ratio of 1.3
Coeur en Sante St Henri Canada 25,000 people 1995	Mix of lifestyle interventions, including: anti-smoking, diet (e.g. Health menu in restaurants), exercise (e.g. walking clubs), healthy living videos	Matched controlled before and after study Intervention participants 849 individuals, control 825 individuals from a chosen matched control area. 18-64 year olds Five year follow-up	No significant difference in any outcomes
The Dutch Heart Health Community Intervention Maastricht & four surrounding areas 180,000 people 1988	Mix of lifestyle interventions, including: anti-smoking campaigns, exercise (e.g. nutrition tours of supermarkets), exercise (walking and cycling clubs)	Matched controlled before and after study 2,414 in intervention group, 758 in control group 3 year follow-up	SBP -7.8 mmHg (men), -5.5 mmHg(women) BMI -0.36 kg/m (men), -0.25 kg/m (women) Blood glucose -0.33mmol/l (women)
Health and inequality in Finnmark Batsfjord (Arctic village) Norway Whole village - 2,500 people 1988	Mix of lifestyle interventions, including: Confining smoking to designated areas of buildings, Exercise (wide range of activities e.g. aerobics, skiiing, dances), diet (prepared healthy meals for fishermen for sea, healthy menus circulated), other (e.g, cholesterol screening in supermarkets	Matched controlled before and after study Intervention village (2,500 individuals), and three matched control villages in coastal areas 3 year follow-up	DBP -2.1 mmHg, SBP -2.1 mmHg (men), -2.5 mmHg (women) Physical active + 8% (men), Low fat milk consumption +7.9% (women)
Health and inequality in Finnmark North Cape (Arctic village) Norway Whole village - 4,000 people 1988	Aim to reduce MI risk score by 25% Individual counselling on smoking, diet, exercise,	Matched controlled before and after study 4,000 in intervention group , 5,000 in control group 6 year follow-up	TC - 0.1 mol/l, BMI - 0.9 kg/m2, MI risk score -0.5 pts (women) Smoking -4.6% (women)

Table 2-16 continued

Programme	Interventions	Study design	Outcomes / results
Heartbeat Wales 9 district health authorities 1982	Mix of lifestyle interventions, including: Mass media (regular adverts, news coverage), Diet (approval for certain catering establishment to have Heartbeat wales brand, Encourage farmers to produce low fat breeds), Exercise (sponsored programmes in communities, awards for exercise friendly employers, GPs(further training in prevention)	Survey, 13,045 interventions, 4,534 control. 5 year follow-up	No significant reductions
The Kilkenny Health Project Community health promotion programme 73,186 people 1985	Mass media to promote important of CHD as morbidity/mortality Health promotion activities in schools,counselling service for diet advice, annual anti-smoking 10k run	Matched controlled before and after study Survey: 792 in intervention, 604 in control 5 year follow-up	% with BMI > 25 kg/m2 - 13% (women)
The National Research Programm 1A on Primary Prevention of CVD in Switzerland Community wide - two town combined population of 28,000 1977	Mix of lifestyle interventions, but integrated into local health service provision, using mix of conselling for healthy behaviours	Matched controlled before and after study Health checks undertaken for risk factors 3 year follow-up	No significant reductions
The Otsego-Schoharie Heart Health Program Rural villages, combined population 158,000 1990	Mix of lifestyle interventions, including: Diet (promotion of healthy foods), mass media campaigns regarding healthy lifestyles, opportunity for risk factor screening,	Matched controlled before and after study Survey: 424 intervention and 424 for control 5 year follow-up 20-69 year olds	Smoking prevalence -9.6%,

Table 2-16 continued

Programme	Interventions	Study design	Outcomes / results
The Bootheel Project England Schools programme 6 counties Began 1994	Mix of lifestyle interventions, including: smoking cessation, exercise (e.g. walking clubs), diet (e.g. cooking demos), and media campaigns. Delivered by new programmes	Matched controlled before and after study 6 control counties Not randomised Survey: 1,501 individuals 18-64 year olds Five year follow-up	Smoking down 24%, low fat milk consumption up 42%, exercise up 76%, wholemeal bread consumption up 33%.
The British Family Heart Study England 15 towns Whole community	Screening for CVD risk factors Counselling and follow-up sessions, with number of session tailored to five particular risk strata (no exclusion)	Matched controlled before and after study General Practices were randomised to the intervention Matched control group on socioeconomic status Rescreening: 10,283 individuals 40-59 year olds One year follow-up	CVD risk score (Dundee score) - 16.1% (men), 15.7 (women) Smoking prevalence -4.1% (men), 3.5% (women) TC - 0.12 mmol/l (men), SBP -7.5 mmHG (men), -7.7 mmHg(women) % DBP < 100 mmHg -4.6% (men), 2.2 (women) BMI - 1.8% (men), 2.2 (women)
The Danish Municipality Project Slangerup (rural town) 8,000 people 1993	Mix of lifestyle interventions, including: smoking cessation, exercise (weekly classes), diet (healthy eating demonstrations)	Matched controlled before and after study with rural town of simiar socioeconomic status Survey: 567 intervention individuals; 629 control individuals 20-65 year olds One year follow-up	No significant outcomes
The German Cardiovascular Project Six regions in former West Germany Whole population 1984	Mix of lifestyle interventions, including: smoking cessation, exercise, diet. Increased access to existing service providers	Matched controlled before and after study Control was three independent samples of the West German population Surveys: 1,900 intervention individuals, 5,000 control individuals 25-69 year olds Seven year follow-up	Falls in smokers 7%pts, systolic blood pressure 2%, cholesterol 2%.
The Minnesota Heart Health Programme Three communities with interventions Whole population 1986	Mix of lifestyle interventions, led by community leaders Mass media campaigns, risk factor screening, adults education programmes, schools based programmes	Matched controlled before and after study 3 matched communities Surveys: 7,079 individuals in whole population, with 300-500 individuals (ages 30-74) included in rescreening of risk factors 5 year follow-up	Smoking prevalence - 1.4% (women)

A number of modelling studies have examined the causes of the substantial reductions in mortality observed over the last few decades. For example, in Scotland it has been estimated that changes in the three main risk factors (smoking, cholesterol and blood pressure) accounted for about 50% of the mortality reductions observed between 1975 and 1994, 10% was attributed to other risk factors, and 40% to clinical treatments(185-186). This is consistent with similar studies in England and Wales(187-191), and international studies(192-195).

2.8.2 Population approach: cost effectiveness evidence/modelling studies

Nine studies are summarised in Table 2-17. Notably, certain studies included a modelling component which was used to extrapolate trial results to then estimate economic outcomes. Most studies compared the impact of an intervention against no comparator. Overall, there is a wide range of estimates from cost saving to $240,000 per disability adjusted life year (DALYs).

Several important observations can be made with respect to how the economic evidence was developed. First, there were a variety of approach to reporting results, including the annual risk of events, event rates avoided, life years, or disability adjusted life years. This makes direct comparisons of the cost effectiveness of different interventions difficult. Given the rationale for economic evaluation is to have a generic measure of outcome (to improve upon the variety of ways efficacy evidence can be report), it is not ideal that there is such a wide distribution of outcomes used. Second, the discount rate used is not consistent across studies. This is understandable as different jurisdictions may have particular guidance. Third, not all studies used modelling, with some preferring to adopt ‘within-trial’ evaluations, where follow-up across studies was a maximum of 5 years(196). Fourth, when modelling is used to project evaluation findings the methods used are not always well reported. Overall, a lack of consistency in modelling approaches, time horizons, and final outcomes reported mean that a general conclusion regarding cost effectiveness is impeded.

Table 2-17 Cost effectiveness evidence – population interventions

Programme	Interventions	Study design / Modelling approach	Outcomes / results
Baxter et al UK Rotherham (18-64 years) Community coronary heart disease programme 1997	Mix of lifestyle interventions, including: smoking cessation clinics for blood pressure screening, weight control, leaflets.	Matched controlled before and after study Control without intervention	£31 per life year gained
Assman and Schulte 1990 Primary prevention programme Coronary Heart disease, West Germany	Potential impact of implementing Helsinki Heart Study Population divided into 5 groups with different in interventions received: Grp 1 - no therapy; Grp 2 - nutritional advice; Grp 3 - stringent diet; Grp 4 - nutritional advice + fibrate/nicotinic acid; Grp 5 - stingent diet + ion exchange resin / HMG CoA reductase inhibitor for group V	Use of Framingham risk equations Lifetime horizon (age and risk factors adjusted in time) Discount rate - 4% for benefits and costs	Cost per life year Men < 60 yrs: 30k DM Men 60-64 yrs: 40k DM Women < 60 yrs: 86k DM Women 60-64 yrs: 110k DM
Langham et al 1996 Cost effectiveness of OxCheck United Kingdom	See Table 2-14	Within trial evaluation (4 years) Discounting: Benefits 0%, cost 6% Authors say risk reductions reported by OxCheck resulted in drop in CHD risk by 20% of those attended check in 4th year and 13% of those not attending	Attending 4th year screening: ICER £1.22/1% reduction in CHD; (ii) Non-attenders 4th year screening: ICER £2.25/ in CHD;
Lasater et al 1991 United States, Rhode Island Community based programme to reduce obesity	10 week late weight programme, including: goal setting, record keeping.	No control 10 week horizon	ICER $1.30 per pound loss

Table 2-17 continued

Programme	Interventions	Study design / Modelling approach	Outcomes / results
Tosteson et al 1997 United States The cost effectiveness of populationwide educational approaches to reduce TC	Interventions estimated were those from Stanford Five-City Project, and North Karelia project.	25 year time horizon Discounting: Benefits 5%, cost 5% The Coronary Heart Disease Policy Model	Stanford Five-City Project: ICER $3,200/lifeyear North Karelia Project: ICER $6,100 Range of ICERs from cost saving to $400k/lifeyears
Wonderling et al 1996 United Kingdom Cost effectiveness of the british family heart study	see table X	Time horizon unclear Discounting: Benefits 0%, costs 6%	ICER worse case: $38k/lifeyear
Lindholm 1996 Cost effectiveness of community CVD programme	Wide range of interventions from mass media, keep fit classes, food labelling, screening and further advice for all	15 year follow-up, Estimated mortality from Framingham equation	ICER: £1,200 / life year Worst case £14,000 / life year
Lowensteyn et al 2000 Canada Cost effectiveness of aerobic exercise	Comparion of supervised and unsupervised aerobic exercise classes of 30 mins	Cohort of 1,000 35-74 years Time horizon 67 years Use of Cardiovascular Disease Life Expectancy Model	Unsupervised programme ICER: $11k/life year Supervised programme ICER: ranged from $9k/life year $87k/life year
Murray et al 2003 United Kingdom Population health impacts of interventions to reduce SBP and TC	Comparison of: (i) mass media, (ii) mass media + legislation to reduce salt in processed foods	Lifetime horizon, Discounting: Benefits 3%, cost 3%	(i) vs do nothing: $160 / DALY; (ii) vs (i) $250 / DALY

In addition, to these studies a recent review of NICE public health guidance was consulted(31). It appears that interventions to promote physical activity(197-198), mass media to promote healthy eating(199), and smoking(200-202) are very cost effective – table 2-18. Many smoking interventions are already implemented, and several new interventions were actually 'dominated' (cheaper and more effective) than existing services. Therefore, despite an apparent scepticism from the clinical community(9), lifestyle interventions do appear to be value for money. Perhaps the apparent difference of opinion is due the fact that seemingly small average changes in behaviour at the individual level may appear clinical insignificant; but when summed across the population results in a large population impacts. Given these interventions are typically cheap to implement they are also very cost effective.

Table 2-18 Cost effectiveness evidence – lifestyle interventions

Type	Cost per outcome
Physical activity	£84 to £900 per QALY
Mass media/health eating	£87 per QALY
Smoking	£50 to £6,000 per QALY

Further, a modelling study by the NICE PDG estimated the potential impact in the English population from implementing several legislative changes(35). The distribution of risk factors in the population was estimated using cross-sectional surveys. It was assumed that reduction in salt and trans-fats in processed foods could realistically result in reductions in SBP by 5% and TC by 5% respectively.

Looking internationally, similar kinds of modelling studies have found that the potential for public health interventions can be greatly in reducing CVD event costs effectively, including smoking, physical activity, diet, and regulation(203-210).

2.9 Combining targeted and population approaches

As discussed previously, the targeted and population approach to primary prevention each confers potential advantages and disadvantages. It remains commonplace for the different approaches to primary prevention to be pitted against one another, as if these were competing approaches(13-14). The, at times, polarised nature of such discussions can be predicated on false premises. For instance, a potential danger is equating a targeted approach with pharmaceutical interventions and a population approach with more lifestyle interventions. For instance, those concerned about medicalising the population(13) can ignore that a targeted approaches also includes lifestyle advice. Equally, advocates of a population approach can ignore that mass administration of pharmaceutical is also an option. Indeed Wald and Law have advocated medicalising everyone over the age of 55 years to receive a polypill. The key point here is that it is erroneous to make sweeping judgements regarding the relatively desirability of one strategy over another; rather the 'devil is in the detail' regarding what intervention is proposed.

Encouragingly, there is increasing recognition that the approaches can be complementary(211-212) The CHD and Stroke Strategy for Scotland recommends that local primary prevention strategies incorporate both approaches(58, 213). Further, the 2012 European Guidelines on prevention emphasises the importance of both population and individual strategies for reducing CVD(214). High risk patients provide clinicians with 'caseness' and an imperative to offer interventions. However, a high-risk strategy alone will not have a significant impact on the population. As Rose argues, this requires a shift in the distribution of risk in the population as a whole(215). However, if extending interventions to the entire population requires active engagement of individuals then this may result in widening inequalities, as more deprived groups tend to both engage less and health services tend to be less well resourced. A population strategy that can puts addition investment in areas of greatest need may offset such risks.

The key point is that both population and targeted approaches appear to be necessary to decrease the population burden of CVD and reduce health inequalities in particular groups where modifiable risk factors cluster. It is therefore rational for policy to consider tackling the societal factors that promote the development of unhealthy behaviours; and also to focus resources on those at greatest risk and where interventions may offer immediate benefits. In

this sense the approaches can be viewed as complimentary, as has been argued elsewhere(216).

In reviewing the evidence base regarding the effectiveness and cost effectiveness of interventions (Table 2-19) the search of the literature was similar as discussed previously. That is, the search began with the 2008 NICE Programme Development Group systematic reviews, and a new search was conducted using PubMed dating from 2008. The search looked for studies that compared the relative performance of targeted versus population approaches, in addition to studies that looked at the impact of combining approaches.

Four studies were found in the NICE PDG review: one effectiveness study and three cost effectiveness studies. In all cases, a population approach was more cost effective that a targeted approach. One study compared the cost effectiveness of a combination of population and targeted approaches against a targeted approached. The combination was more cost effective.

More recently, a modelling study estimated the contribution in the reduction of CHD mortality and morbidity in a Dutch population over a period of 40 years attributable to targeted and population interventions(216). The study found that population interventions such as legal changes (e.g. tobacco control) were responsible for the majority of observed declines in events.

Table 2-19 Effectiveness and cost effectiveness evidence – combining targeted and population approaches

Programme	Interventions	Study design / Modelling approach	Outcomes / results
The Stanford Three Communities Study Three towns, combined population of 42,000 1,972	Mass media campaigns on CVD risk factors. CVD risk scoring and intenstive one-to-one counselling with high risk individuals	Matched controlled before and after study Two towns were interventions, one was control One intervention town received media only, the other town received media and counselling for HR	For town that combined mass media and one to one counselling cholesterol fell from 20% (men) to 40% (women)
Hall et al 1998 Cost effectiveness of different prevention strategies Australia	(i) Whole population - mass media campaigns on health lifestyle (ii) High risk: screening and long term counselling for those in 15% distribution of overweight, smoking, SBP, TC, (iii) combined approach of i and ii	Modelling, using literature for potential impacts from interventions on risk factors 5-year time horison Discount rate 6% benefits and costs	(i) vs do nothing cost saving (ii) vs (i) ICER $28k, (iii) vs (ii) ICER $13k
Kinlay et al 1994 Cost effectiveness of two screening/treatment strategies New South Wales, Australia	(i) Screening and referral following CHD Guidelines (ii) Mass media dietary advice	Modelling, using risk profiles from Hunter, Australia using literature for potential impacts of interventions Discount rate 5% benefits and costs	(i) vs do nothing $44,667 per CHD case averted (ii) vs (i) $260,000 for high risk approach
Kristiansen et al 1991 Cost effectiveness of three cholesterol lowering strategies Norway	(i) Whole population approach: Mass media, tax incentives (ii) Screening for high TC, with dietary advice (iii) lipid lowering drugs and diet advice for those known to > 8.0 mmol/l	Modelling study	(i) vs do nothing: ICER £12/life years (ii) vs (i): ICER £101k/QALY (iii) vd (ii) ICER £126/QALYs

2.10 Summary and limitations of the evidence

It appears that population approaches have the opportunity to be most effective and cost effective. In particular, a recent modelling study(35) suggests that substantial outcomes could be achieved by legislative changes, rather than population approaches to changing lifestyles. However, few studies have directly assessed the impact of interventions on reducing inequalities in the population.

The evidence for individually targeted multi-factorial programmes has not been well-researched. However, there is strong evidence that particular interventions are cost effective. A major source of concern is whether extending screening to an entire population is cost effective and may result in widening inequalities.

Overall, the efficacy evidence base is inconsistent, particularly as different studies report different outcomes (risk factors, events, disease mortality, and all cause mortality). This can make it difficult to compare the impacts of different interventions. However, the economic modelling also appears to suffer from a similar criticism in that outcomes can include risk factors, events, life years, QALYs, DALYs. Further, there can be ambiguity regarding the modelling approaches taken to estimate such outcomes.

Generalising from the evidence regarding targeted and population approaches can be difficult. This is particularly the case for interventions aimed at lifestyle changes. These interventions are service-led, and there is not only variability in the actual results of the interventions, but also heterogeneity regarding the nature of the populations receiving interventions, delivery mechanisms and the outcomes reported. Further, much of the evidence was outwith a UK context. Returning to the previous discussion regarding generalisability, both how an intervention is delivered and the wider social and policy context may be vital in generating effect sizes. Therefore, an evidence synthesis and meta-analysis of studies was not feasible, as expected given the variation of interventions and context(51, 150).

Overall, while economic evidence is essential; it is assumed here that policy makers would ideally like an evidence base that is consistent in terms of outcomes produced in order to allow direct comparison of different interventions. Further, it is also inferred that outcome measures used should ideally be commensurate with the aims of primary preventions:

avoidance of premature mortality and morbidity, avoidance of associated health service costs, and the reduction in inequalities. This would then allow policymakers to compare interventions directly, and choose between interventions consistently. At present, such evidence and the approach to generating evidence in a consistent manner is quite limited.

2.11 Discussion: developing three research questions for the thesis to address

The chapter, so far, has been essentially reviewing and reporting. The purpose of this penultimate section is to interpret the findings of the chapter, and to assess gaps in the evidence base, especially with regard to the ultimate aims of prevention, as a means to develop research questions for the thesis.

The key premise of the thesis is that the aims of primary prevention are the avoidance of premature CVD and to improve life expectancy, quality adjusted life expectancy, and to reduce health inequalities. However, it is unclear whether the current approaches are aligned with these aims, especially given the reality of scarce resources and need to make efficient choices. Rather, the rationale and evidence base underpinning certain clinical and policy decisions is lacking, and may be misaligned with the aims of prevention. Three research questions are developed below. As a means to justify why these questions are considered key, relevant themes from the chapter are drawn together.

2.11.1 Question 1: Is it cost effective to screen the entire population or take a more focussed approach?

Clinical guidelines recommend screening everyone in the population from 40-74 years to detect high risk individuals. For instance, England since 2009 began to roll-out a national screening programme. In contrast, Scotland has decided to screen only the most deprived individuals and those aged between 45-64 years. It is not clear what evidence these decisions are based upon. Further, both England and Scotland claim that the respective screening programmes will lead to the closing of health inequalities.

It is important that there is a better understanding regarding optimal screening approaches. Population wide screening may have the best opportunity in detecting everyone at high risk, but the efficiency of such an approach is questionable as high risk individuals actually compose a small proportion of the population; and there is the potential for a negative impact

on health inequalities as more affluent groups are known to engage more with statutory services, as discussed. On the other hand, while Scotland has initially adopted a more focused approach, perhaps the screening criteria could be widened from the most deprived groups and have an opportunity to capture all (most) of the high risk in the general population, without having to screen everyone. Overall, it is important to investigate the coverage, cost effectiveness and impact on health inequalities of alternative screening approaches.

2.11.2 Question 2: How best to prioritise individuals for intervention?

Weaknesses of 10-year risk scores

(i) Age drives 10-risk: A major problem in the application of 10-year scores is that risk is driven mainly by age. For instance, the risk charts show previously illustrates that younger individuals with inflated risk factors may not be classified as high risk, purely because of age and yet may stand the most to benefit in terms of early prevention and potential lifetime benefits. In contrast, as age increases individuals can be automatically be classed as high risk even with individual risk factors are at normal levels according to clinical guidelines.

This issue is increasing recognised(25-26, 114). Further, it is important to note that this problem arises not primarily due to the risk score itself, but rather with the application of a universal threshold to denote high risk, which has been described as arbitrary and without evidence in terms of treatment benefits or cost effectiveness(25).

(ii) CVD risk score ignore competing risks: An important issue is that CVD risk scores do not consider the competing risk of non-CVD events, and death. For instance, treating the elderly for CVD risk may simply change the cause, not timing, of death(27).

Existing alternatives to 10-year risk scores

In recent years the literature has developed a range of responses to the perceived weaknesses of 10-year risk scores, with some responses more comprehensive than others.

(i) 30-year scores: In an effort to capture the long term risk of CVD the time frame over which risk is estimated has been increased by certain authors. For instance, the Framingham score now has a version that can estimate the 30-year risk of events(117). This is intended to be more relevant for younger patients to capture that while short term risk may be low, long term

risk is likely to be much higher. The idea is that by focusing on cumulative risk younger individuals would be seen as higher priority. This approach however does not address the fundamental issue that risk is driven by age, rather than modifiable factors. The score has not been used in practice, at present.

(ii) Lifetime scores: Researchers on the QResearch database have now developed lifetime CVD scores(217). This work is also in response to the age gradient inherent in 10-year scores. A practical challenge that has been identified is how to discriminate between individuals, given everyone is at high risk of CVD over a lifetime, and what an appropriate threshold would be to prioritise interventions(26). A further issue is that CVD is the sole focus, ignoring the competing causes that are also affected by risk factors. This approach may lead to counter-intuitive results. For instance, non-smokers live longer on average than smokers, given the competing risks of cancers; which results inhigher cumulative risks of CVD than smokers, and would be given priority(26).

The practical utility of lifetime scores has been questioned, with preference given to conducting 10-year risk scoring regularly rather than focusing of lifetime risk(26). The advantage of using shorter term risk scores may be to define caseness; that is, where patient of high risk may require intensive pharmaceutical interventions, as opposed to those with low short term risk who could be referred to lifestyle interventions to reduce longer term risk. This argument holds sway given that the reversal of the damage caused by risk factors is greater in younger individuals. However, this does not address the issue that risk is partially driven by non-modifiable risk factors. Given competing risks, concern remains that interventions may simply change the cause of death especially in the elderly(27).

(iii) Age defined risk scores: Norwegian Clinical Guidelines have attempted to respond to the problem of the age gradient which is inherent in the application of a universal threshold level of risk determining intervention. Specific thresholds have been developed for different 10-year age bands from 40 to 70 years(218). Underlying the choice of risk threshold is the expected cost effectiveness of treating an individual at that or above that risk level. The assessment of cost effectiveness is informed by literature reviews and expert clinical opinion. We discuss the nature of cost effectiveness, and the associated evidence, shortly.

However, the estimation of benefits is restricted to the avoidance of CVD death. There is no consideration of the wider benefits on avoiding CVD morbidity, or the avoidance of competing

events, that are driven by the same risk factors, including cancers and respiratory diseases. Further, if treatment guidelines were to be based on benefit rather than risk then it begs the question why the benefits are not made explicit, rather than returning to risk thresholds.

Need for a new approach: prioritising on the basis of potential benefit rather than risk?

Prioritising individuals on the basis of CVD risk scores is unlikely to result in the greatest treatment benefits. The fundamental problem is that risk scores are comprised of a mixture of modifiable and non-modifiable factors. This is true for 10-year, 30-year or lifetime risk. Risk is not a measure of the potential benefit from interventions.

If primary prevention has the objective to improve life expectancy and quality of life then perhaps it is more rational to prioritise individuals on this basis. It has also been argued that focusing on net benefits is more clinically interpretable than risk(219). In estimating potential benefits it is necessary to account for competing risks. SCORE has recently developed a tool that seeks to estimate the impacts of interventions on extending life expectancy by accounting for the impact of risk of CVD death and the competing cause of non-CVD death(220). The tool has just been developed and is undergoing validation tests before looking at the feasibility of using this in clinical practice. A switch to a potential benefit approach does begs the question what an appropriate benefit threshold should be, and whether this should be based solely on clinical benefit or (also) cost effectiveness. Note, that the tool does not produce estimates of the latter.

An ambiguity in the new SCORE approach is how the competing risk analysis was undertaken and the estimation of cause specific hazards for the end-point of CVD, CVD death and non-CVD death. Further, the datasets are not ideal. Rather than longitudinal cohorts of individuals, it appears that a variety of different country datasets are used rather than having a single cohort of individuals followed-up. Importantly, no account is made of socioeconomic deprivation, known to be an independent risk factor in Scotland, as discussed. Nonetheless, the use of a competing risk approach this is an important development in the evolution of CVD prevention.

Overall, it appears necessary to develop a new comprehensive tool that can estimate the potential benefit from changes to modifiable risk factors, as a means to prioritise individuals for intervention.

2.11.3 Question 3: How best to combine targeted and population approaches?

Traditionally, the literature has been polarised between a targeted and population approach. Nonetheless, there is recognition that the two approaches are not necessary mutually exclusive and perhaps a combination of approaches might be better to address the aims of prevention(221-222). Targeted and population-wide approaches may not only complement one another as independent strategies, but they can interact with each other to either enhance or inhibit the effectiveness and cost effectiveness of each other(10, 150).

From an economic viewpoint, it is contended that the extent to which one strategy is emphasised over another should depend on the evidence of impact: effectiveness, cost-effectiveness and overall budgetary considerations. Cost effectiveness evidence should also be used to develop complimentary strategies. It is contended that the extent to which one strategy is emphasised over the other should depend on the evidence of impact: effectiveness, cost-effectiveness and overall budgetary considerations. However, it is precisely this kind of evidence which is lacking, in general.

2.12 Summary

To summarise, cardiovascular disease is the number one cause of premature mortality and is a major cause of morbidity, health service costs and wider economic costs. Further, CVD is a leading cause of health inequalities and particularly in Scotland. In response, there is a significant clinical and policy response in the form of primary prevention initiatives in an effort to avoid or postpone the first incidence of CVD, and the consequent clinical and economic burden. There are two main approaches to primary prevention: a targeted approach on high risk individuals and a population wide approach. Both have advantages and disadvantages, and it seems sensible to consider how these approaches might best combine to address the aims of primary prevention.

However, there are important uncertainties regarding the impacts of current primary prevention initiatives, and policies appear to be predicted on aspiration rather than expectation. In particular, there is a lack of evidence regarding targeted multi-factorial interventions which is the main focus of primary prevention in the Scotland, and elsewhere. Overall, there are three main strategic weaknesses at present, which serve as research questions. First, there is uncertainty regarding appropriate screening approaches to detect

high risk individuals. Second, there is concern that prioritising individuals for intervention on the basis of risk will not lead to the greatest benefits, given 10–year scores are driven by age. Third, while targeted and population approaches can often be pitched as rival approaches, they are not mutually exclusive. A key uncertainty is how they might best combine.

The approach of cost effectiveness analysis offers the potential for a unified method for evaluating interventions and guiding decisions, at both the clinical and policy level. This would enable congruence with reimbursement agencies such as the National Institute for Health and Care Excellence (NICE). Cost effectiveness analysis essentially combines information regarding the clinical and resource impact of an intervention, offering a generic measuring stick whereby all intervention can be assessed consistently.

However, gaps in the evidence base cannot be resolved using trial information alone. For instance, it is infeasible for trial to be conducted over a lifetime. To help generate appropriate economic evidence there is an important role of modelling to project trial results on economic outcomes such as quality adjusted life expectancy and health service costs. The next chapter discusses the role of modelling and makes the case that a Scottish specific CVD model is required to help address the limitations in the evidence base.

Chapter 3: The need for a Scottish CVD Policy Model

3.1. Introduction

The previous chapter detailed the health and economic burden resulting from cardiovascular disease and current primary prevention approaches to avoid the premature onset of CVD. Notably, there is a lack of economic evidence concerning both the targeted and population approaches to primary prevention.

This chapter develops the rationale for the development of a Scottish CVD Policy Model which can help generate economic evidence of interventions and inform the approaches to primary prevention. The chapter is structured as follows: Section 3.2 and 3.3 introduces the rationale for and application of economic modelling. Section 3.4 then outlines the common criticisms that can be directed at economic models in general, before section 5 discusses best practice guidance that modellers can usefully follow to help ensure models that are fit-for-purpose and minimise potential criticisms. Section 3.6 then undertakes a systematic review of existing policy models and uses best practice guidelines to help critique the models. Section 3.7 collates and summarise the key strengths and weaknesses of the models that were reviewed, before Section 3.8 discusses the need for a Scottish Policy Model. Section 3.9 concludes.

3.2 The rationale for modelling I: generating economic evidence

As discussed in Chapter 2, the aim of economic evidence is to inform resource allocation decisions from across the health sector. The ultimate aim of economic analysis is to develop a consistent body of evidence to enable decision makers to fund interventions offering the best value for money.

There is an important role for modelling to both generate new economic evidence and synthesis existing evidence for the purpose of making decisions, which the following two sections discuss respectively.

It is important to provide a general definition of what a model is. A model is simplified representation of reality: "a logical mathematical framework that permits the integration of facts and values to produce outcomes of interest [to clinicians and] decision makers"(43).

For the purpose of generating economic evidence, modelling can be used in tandem with clinical trials to overcome the perceived shortcomings of trials. There are six main reasons where an economic analyst may wish to employ modelling(38, 40, 223-225).

First, as illustrated in Chapter 2, trials measure clinical efficacy where outcomes are necessarily short term studies often report short terms outcomes such as risk factor changes (e.g. blood pressure), or intermediate endpoints (e.g. myocardial infarctions). However, individuals, clinicians, policymakers and health economists may be interested in longer term impacts (e.g. mortality). Modelling can be used to extrapolate short term efficacy findings such as changes in blood pressure or events onto (quality adjusted) life expectancy.

Second, models can assist in estimating the generalisabiliy of trial results to other settings. Trial evidence is concerned with internal validity; however, economic evidence is ultimately concerned with external validity and generalisability - to provide advice to policymakers regarding the expected value for money in the intervention was to be delivered in the future and perhaps in different settings. The cost effectiveness of an intervention may be dependent on the nature of delivery, such as the skill set of those delivering the intervention, intensity and frequency. Modelling may be important to estimate the impact of changing resource costs and clinical effectiveness between settings.

Third, modelling can be used to estimate “head-to-head” comparisons of alternative competing interventions in the absence of trial evidence comparing two interventions of interest. Most trials compare an intervention against usual care. However, usual care may differ between settings. In this case, modelling can be used to synthesis evidence from different trials and infer what the head-to-head results are most likely to be.

Fourth, modelling can be used to incorporate information which may not be collected in trials, such as the quality of life impacts of non-fatal events, or resources costs. This information may either be generated from other primary studies or, more commonly, taken from secondary sources.

Fifth, models can be used to produce relevant information in the absence of hard data. For instance, it can be very difficult to conduct population wide experiments. This was illustrated in Chapter 2 regarding the variety of modelling studies that have been undertaken to estimate the potential impact of population interventions, for example legislative changes.

Six, modelling can be useful in order to explore uncertainty and undertake sensitivity analysis with respect to estimates of clinical and economic outcomes. In short, clinical evidence will also be subject to uncertainty in the estimates produced. Further, to produce economic evidence several sources of information will often be combined, the process of which may introduce uncertainty and may involve assumptions in the absence of data (e.g. long term compliance with medication). It is important that uncertainty can be fully articulated and that estimates, of for example effect sizes, are subject to a sensitivity analysis to explore the consequences on the economic outcomes produced. These issues will be more fully explored under the detailed discussion regarding best practice guidance.

Overall, there is a complimentary role for economic modelling to be used alongside trial evidence. Further, it is now commonly suggested that economists can usefully be involved in trial design themselves, to influence sample sizes, data collection and perhaps the length of trial themselves. These so-called 'pragmatic trials'(38) can then mitigate against some of the drawbacks of more orthodox clinical trials. Nonetheless, there is a limit to the length of trials (e.g. lifetime trials are infeasible), and there is a practical limit to the amount of information a trial can include. Consequently, it is likely that there will always be a role to be compliment trials and produce economic outcomes.

3.3 The rationale for modelling II: to help make decisions

The ultimate purpose of modelling is to act as a normative decision-making aid that can structure evidence on clinical and economic outcomes in a form that helps decision makers choose from among competing courses of action and the allocation of scarce resources(40).

The nature of the modelling should be conditional on the decision context at hand. Decision making in health care involves two sets of related decisions: those concerning appropriate service provision on the basis of existing information; and those concerned with whether to fund additional research to reduce the uncertainty relating to the decision(226).

If the decision maker needs to choose between interventions using existing information, then the decision should be based solely on a comparison of the expected or mean estimates of impacts. An assessment of uncertainty is irrelevant(48). However, where decision makers have flexibility to accept, reject or a delay a decision then modelling can be usefully employed

to generate both mean estimates of impacts, and whether decisions should be delayed in order to conduct further research.

Therefore, modelling can be an invaluable tool to help decision makers both structure the decision problem at hand, and inform the optimal decision given the information available. In general, modelling is recommended as both a 'tool of first and last resort' for economic evaluation(38, 225). In effect, there are three main stages where a model can be used(227). The first stage is to conduct pre-trial modelling. This is where an economic model can be used to help inform whether a trial is needed in the first place. That is, by using a model to synthesise all the available evidence a model can estimate whether the intervention under consideration is likely to be value for money.

The second stage is to use the model in the full scale evaluation of the intervention, to estimate cost effectiveness and provide a full assessment of uncertainty in the estimates made. If uncertainty is so great that there are doubts regarding the cost effectiveness of an intervention, then the model can also help pin-point where the most important areas are in terms the parameters that most impact on cost effectiveness estimates. This exercise then informs not only whether a trial should be conducted but also which areas of uncertainty the trial should focus upon. This exercise is termed value of information analysis(228), and will be discussed further in the chapter.

The third stage, is to then use the evaluation evidence from the trial, combine this with the pre-trial modelling exercise, and then recommend both the optimal decision option given existing information, and also reassess whether further trial evidence are required in the event decision can be delayed(48).

Regarding terminology, models that are built with the explicit purpose of generating evidence to inform a decision(s) are often termed decision analytic models(227).

3.4 Policy Models

Most often decision analytic models are constructed afresh to meet a specific decision problem, which is generally to assess the cost effectiveness of a single intervention such as a new statin drug. This practice is described in this thesis as a "bespoke approach" to modelling. In contrast, "generic approach" to modelling is where there is an attempt to

widening the scope of the model, with the intention to offer the opportunity to use a single model to inform a wider range of decisions. For instance, in the area of CVD it may be useful to have a single comprehensive model that could assess the cost effectiveness of a range of single and multi-factorial interventions, such as anti-hypertensive and statins drugs, and lifestyle interventions such as smoking and diet. Models that adopt such a generic approach are termed policy models in this thesis.

There are potential advantages of building policy models: they can be efficient if it avoids the need to build bespoke models for particular interventions aimed at certain risk factor(s); provide a consistent approach to assess the cost effectiveness of interventions that may be competing with one another for scarce resource; and conditional on a credible and transparent model, a policy model may enhance the opportunity for decision makers to gain familiarity and trust in using a model.

3.4 Common criticisms of models

While modelling is undertaken routinely there are common criticisms that the modelling process itself can introduce biases and lead to erroneous conclusions regarding cost effectiveness and decisions made(53).

First, decision analytic models are open to potential manipulation with respect to the data used to elicit a favourable result. This can extend to a choice of comparator, selection of evidence, and generation of effect estimates, for instance(229).

Second, there can be concerns regarding the potential for using inappropriate data. It has been expressed that insufficient attention can be paid to the quality of the clinical data used and that only when there are several well-powered trials reinforcing findings can there be confidence in the effect sizes used in models.

Third, there are general concerns regarding the extrapolation of clinical or intermediate outcomes. It has often been argued that extrapolations using only data collected in the short term, may omit potential longer term negative consequences. A key issue is to validate model predictions to test, for instance, whether intermediate outcomes are good predictors of final outcomes.

Fourth, there are more specific concerns when observational data is used to extrapolate findings. This may result in bias given the relative limitations in drawing causal inferences compared to trial evidence. Further, the observational data may be incomplete. As discussed shortly, it can be common for models in cardiovascular disease to estimate the life years saved and the resource impacts by simply estimating the impact on CVD events. However, by ignoring competing causes this may bias the estimates produced, both in terms of life expectancy and the overall impact on health services, beyond the avoidance (or postponement of a CVD event).

Fifth, in building a model there is the potential for intended and unintended biases, from inappropriate model pathways, syntax errors and failure to link variables. This raises the need for further validation regarding the integrity of the model structure and estimation of final outcomes.

It is important to recognise that many of these criticisms can also be applied to trials; such as choosing inappropriate comparators, or drawing erroneous inferences from short term results. However, the potential for manipulation and error is greater in modelling. The fundamental issue underlying most of these criticisms is a potential lack of transparency. Models can often be perceived as “black boxes” where third parties may find it difficult to follow a models causal structure, to evaluate decisions regarding the data sources used, and to evaluate the potential accuracy of model outputs.

Despite these potential pitfalls, modelling is unavoidable when decisions need to be made but there is lack of hard evidence and/or the decision is too complex to simply rely on human judgement. Models can never be a substitute for evidence and there is an important role for extended pragmatic trials to test an interventions’ effectiveness and cost effectiveness over time. However, lifetime trials are infeasible and there is a practical limit to the amount of information trials can incorporate. Consequently, there is a role for both trials and modelling.

Overall, "all models are wrong but some are useful"(39). In recognising the potential pitfalls and limitations of models, the next section discusses best practice guidelines for modelling regarding how to construct, use and disseminate models to help ensure that models can be as useful as possible to decision makers.

3.5 Consensus guidelines for building economic models

The importance of developing best practice guidelines to enhance the credibility and practicality of models has been recognised for some time by prominent authors(38, 44). Most notably there have been several guidelines developed through expert consensus from ISPOR in 2003(43), through the UK's Health Technology Assessment (HTA) Programme in 2004(42) and 2006(41), to guidelines from Canadian researchers in 2010 (230) and most recently ISPOR 2012(231). These guidelines have progressively built upon one another as new insights and consensus evolves.

The purpose of guidelines is to clarify the key generic stages within the modelling process, to guide modellers regarding appropriate choices within each modelling stage, and in general encourage greater clarity in the reporting of the model and model outputs. However, given that modelling problems may differ considerably, a rigid and prescriptive set of one-size-fits-all rules are inappropriate(41-42). Rather the emphasis on guidelines is on encouraging the use of criteria to make transparent modelling choices so that models and their outputs can be appraised, and ideally replicated, by third parties.

The following draws heavily upon the latest ISPOR 2012 Guidelines on best practice(231-236), which itself references, and may be regarded as building upon, previous guidance documents. Discussion is presented in the form of a checklist reminiscent of the format that Philips et al used in previous guidance developed 2004(42). The purpose of a checklist is to serve as an aid for the transparent appraising of existing models.

Five key modelling stages are identified and within each stage the best practice guidance is described. This is summarised in Table 3-1 and presented as if the development of a model is a "linear process" where a modeller completes one stage before moving to the next. This is a simplification for exposition purposes; in practice, there may be several iterations within and between the stages.

Further, models have value not only as prediction tools but also as explanatory and communication tools. That is, the value of a model lies not only in the results it generates, but also in its ability to reveal the logical connection between inputs (i.e. data and assumptions) and outputs in the form of valued consequences and costs(43). For this reason, a model

should not be a “black box” for the end-user but be as transparent as possible, so that the logic behind its results can be grasped at an intuitive level(43).

The following is a synthesis of expert guidance produced in recent years. These are referenced above, with the intention to repeatedly reference the same sources throughout this section.

3.5.1 Modelling stage 1: Conceptualising the problem

(i) Policy context: The policy context of a model is that it should be clearly stated, and this should include the strategic policy question at hand, the policy audience, whether the model has been developed bespoke for a single problem, or is intended to have multiple and/or on-going uses. It is also important to report how the model has been funded, as the model may be tailored to a particular decision maker’s priorities and values. Sponsorship bias may exist with respect to how models may be constructed and information presented. On the one hand, models funded by manufacturers run the risk of being skewed to represent a particular intervention in a favourable light. On the other hand, models funded by public sector decision makers may be skewed towards interventions that offer cost containment. Overall, the policy and funding context may influence the entire model building process.

(ii) Consultation of experts and stakeholders: To inform the understanding of the modelling problem and consequent model construction, it is important to consult relevant experts. For instance, clinicians and epidemiologists may be important in helping to define the clinical problem and its consequent representation in a model structure. Stakeholders such as patients and policymakers can inform the decision process behind which outcomes a model produces. Such consultation, if undertaken, should ideally be preceded by a review of relevant literature (including other relevant models) and then formally by convening an expert/stakeholders group to elicit opinions systematically through tools such as Delphi Panels.

(iii) Statement of the decision problem: The decision problem that the model is intended to address should be clearly stated. This may be an iterative process, such that an explicit statement offers that opportunity for focused discussion between the modeler, medical experts and policymakers. Once specified, the problem then determines how the modelling problem is considered and the subsequent construction of the model.

(iv) Statement of the model perspective: The model perspective determines which information inputs should go into a model, including which costs and outcomes. Alternative perspectives used in health economics include a health care decision maker perspective and a societal perspective, as discussed in Chapter 2.

In the UK, a health care decision maker approach is the standard approach that health economists have used and embedded in NICE guidance(144). This recommends in the 'reference case' for economic evaluation that costs and outcomes should be from the perspective of the National Health Service and personal social services. The rationale is that these sectors are mandated to improve population health and so, from a practical viewpoint, cost effectiveness (utility) analysis may be best at tailoring economic evidence to budget holder objectives.

However, guidance evolves. For instance, as discussed in Chapter 2, NICE's recent Public Health guidance recommends that the perspective of economic evaluation takes a broader societal perspective (beyond the health and personal social services)(147). It is recommended that an economic evaluation should consider all major costs and outcomes. It is suggested that a cost consequence analysis (CCA) be conducted, which is essentially a social accountancy exercise, listing all major outcomes in natural units. To then value outcomes in economic terms, it is recommended that health outcomes are values as Quality Adjusted Life Years (QALYs). This allows comparability of public health interventions with other interventions.

In addition, it is recommended that evaluators consider undertaking a cost benefit analysis (CBA), which would in practice mean using the CCA, and then values all outcomes, health and non-health and estimate the overall social value of an intervention, where health is one component.

(v) Statement of the model scope: Following decisions regarding the previous steps above, the requirements with respect to the models scope should be readily apparent. That is, the model should then be developed such that its inputs and outputs are relevant to the policy context, the modelling problem and the perspective taken of the economic evaluation.

(vi) Defining the target population: It is important to make clear the intended recipient population of the intervention(s). This should include both the intended geographical

coverage and also recipient medical characteristics. The former may extend to international or national uses (or lower forms of aggregation e.g. urban or rural). The latter may include the disease history of the individuals of interest (e.g. asymptomatic, comorbidity). Further, it should be clear whether the model is focused on individuals or cohorts, and if the latter what particular subgroups are of interest.

(vii) Health outcomes: The rationale for choosing to model outcomes should be justified. The focus of economic evaluation is on whether an intervention may have substantive impacts on final outcomes of interest, such as quality adjusted life expectancy. A model structure, discussed below, will typically link intermediate outcomes (e.g. risk factors) to final outcomes. The choice of these intermediate outcomes should be justified (e.g. only certain CVD event states).

(viii) Intervention strategies/comparators: The model problem will determine which intervention strategies and comparators should be compared. This should be made explicit. The problem that a model is intended to address may be specific to a particular intervention or may be more generic in the sense that the model may wish to consider multiple different interventions.

(viiii) Time horizon: The time horizon of the model should be long enough to reflect important differences between the long-run consequences and costs of alternative options and strategies. Lifetime horizons are appropriate for many models and are almost always required for models in which the options have different time varying survival rates. Shorter horizons may be justified if survival and morbidity does not differ among intervention options. Importantly, a lack of long-term follow-up data should not be used as a rationale for failing to extend the time horizon as long as is relevant to the decision under analysis.

(x) Cycle length: The cycle length of the model should be short enough so that multiple changes in pathology, symptoms, treatment decisions, or costs within a single cycle are unlikely. On this basis the choice of cycle length should be justified.

Table 3-1 Best practice guidance for building an economic model

Modelling stages	Elements with each stage	Best practice / transparent reporting of
Stage 1:Conceptualising the problem	Policy context	The sponsor / funder of model
	Consultation of experts and stakeholders	Comprehension of clinical and policy problem
	Statement of decision problem	Clinical and/or policy problem
	Statement of model scope	Spectrum of conditions considered
	Statement of model perspective	Societal, decision maker, individual
	Target population	Geography, individual characteristics
	Health outcomes	Events, QALYs, DALYs, other
	Intervention strategies/comparators	Nature of, frequency, intensity, duration
	Time horizon	Sufficient duration to reflect important difference in treatment options
	Cycle length	Consistent with natural history of the disease
Stage 2: Conceptualising the model	Converting the model problem into a model structure	Explicit process (e.g. written record, conceptual mapping)
	Choosing a model type	Key criteria: (i) individual vs cohort; (ii) static vs interactions; (iii) short vs long term horizons
	Tabular model	Spreadsheet, (hidden) cell formulas
	Decision tree	Cohort, static, short time horizons
	State transition	Cohort, health states/discrete time, static, long time horizons
	Discrete event simulation	Individual, continuous time, interactions, short or long time horizon
	Dynamic transmission model	Individual or cohort, continuous time, non-linear interactions, short or long time horizon
	Hybrid or novel models	Combines features, new features

Table 3-1 Best practice guidance for building an economic model - continued

Modelling stages	Elements with each stage	Best practice / transparent reporting of
Stage 3: Data identification and incorporation	Data identification	Transparency of methods used to identify, and justification, for choices of data sources
	Data modelling	Statistical and epidemiological techniques should be justified
	Baseline data	Either based on natural history of disease from epidemiological/observational study, or from control group of experimental study
	Costs	Consistent with perspective and in accordance with relevant guidance
	Quality of life weights (utilities)	Appropriate for disease states and decision problem
	Treatment effects	Systematic reviews/meta analysis to infer treatment impact and uptake/compliance assumptions
	Incremental cost effectiveness ratio	Difference in costs / difference in benefits
	Discounting	Consistent with guidelines (e.g. NICE/SMC recommends 3.5% for all outcomes)
Stage 4: Uncertainty analysis	Stochastic (first-order) uncertainty	Undertake either deterministic or preferably probabilistic sensistivity analysis
	Parameter (second order) uncertainty	Report means and standard errors; undertake either deterministic or preferably probabilistic sensistivity analysis
	Heterogeniety	Test model's ability to discrimate between unit of analysis
	Structural uncertainty	Consider structural sensitivity analysis reformulating model (modelling assumptions / model structure)
Stage 5: Validation and reporting	Face validity	Seek agreement by experts regarding consistency of model structure with current science
	Internal validity	Test model ability togenerate outcomes from the source data used in model development
	External validity	Test models ability to generate outcomes from a study not used in model development
	Cross validity	Test the consistency of outputs between different models
	Predictive validity	Test models ability to make forecasts
	Reporting and dissemination	Dissemination of model documentation to enable third party to assess and replicate model

3.5.2 Modelling stage 2: Conceptualising the model

(i) Converting the model problem into a model structure: It is recommended that the process of converting the model problem to the development of a model structure is made explicit. Various methods have been suggested, including expert consultation, influence diagrams and concept mapping. The use of model schematics to represent the model structure, functioning (e.g. disease process/interventions) and simplifying assumptions can then provide a focal point for interested parties to develop the model.

(ii) Choosing a model type: There are no prescriptive rules: almost any problem can be represented by any type of model. The general rule of thumb is that a model should be parsimonious: a simple as the modelling problem permits.

Three key specific considerations are identified: The first issue refers to the unit of representation; and whether the model problem is primarily concerned with individuals or cohorts. For instance, modelling the relationship between continuous variables and outcomes is more conducive to providing outputs specific to individual profiles defined by the variables used in the modelling. This would then enhance the discriminatory ability of the model. In contrast, the categorisation of variables means that individuals are assigned to a subgroup and treated as homogenous. The latter limits the ability of a model to explore heterogeneity.

The second key consideration is whether interactions between agents in the model are required. Interactions may be a feature of units of analysis (individuals or cohorts) co-evolving; or between the treatment and the unit of analysis. The former may be the result of constrained resources and the manifestation of queuing for instance. The latter may result from a treatment impact on how disease spreads in populations. Models without interactions are static in nature and can be consequently simpler.

The third key consideration is time: both the overall time horizon that the model runs for and the cycle length that a model needs to consider given the problem at hand. The longer the time horizon and smaller the unit of time the more complex a model can become.

The most popular model types are now described, and broadly ordered from the simplest to the most complicated. The discussion reflects how particular model types are most often associated with certain features (e.g. individual rather than cohort). However, it is important

to recognise that such demarcation is largely for exposition purposes. The models types discussed are stylised categories and there is room for continual innovation. For instance, the possibility of hybrid models that may draw upon features common to different stylised model types is also discussed. Indeed, the Scottish CVD Policy Model that is developed in this thesis may best be described as a hybrid model, combining particular features of different stylised model types.

(ii-a) Tabular models: The term tabular model is used to refer to a class of models that represent the decision problem as a series of cells within a spreadsheet. The relationship between variables and outcomes are embedded in cell formula. There is no time element represented to assess the consequences of changing variables on outcomes of interest over time. Rather, a tabular model is often chosen when the relationship between initial inputs and final outcomes is the key focus. This model type may be suitable when the decision problem is simple, cohorts are modelled and there are limited steps in the modelling process. As the modelling problem becomes more complex and the representation of transitions is important, then tabular models can lack transparency.

(ii-b) Decision trees: The decision tree visibly represents the transition of a cohort over time where there are no interactions. The model begins with a "root node" and the subject is faced with a series of branches each representing possible pathway (or scenario). Each branch may split into a sequential pathways defined by specific intermediate events towards a final end-node (e.g. death). Each end-node denotes the final pay-off (e.g. life expectancy) that an agent (e.g. individual) can expect if following a particular pathway (or scenario). The completion of each pathway is associated with a particular probability. It is often the case that from the starting node to the end-node there are a number of intermediate chance nodes where agents move in one direction or other. Therefore, often the probability associated with an end node is the product of a series of conditional probabilities. Importantly, the sum of probabilities associated with each possible pathway or scenario must equal 1; as the pathways are intended to be exhaustive of all model scenarios. Therefore, to solve the model, and estimate the 'expected' outcome, the model simply sums across the product of the probabilities of following a particular pathway and the pay-off associated the particular end-node.

Decision trees are a simple and transparent method of representing a decision problem. In principle, any decision problem can be represented by a decision tress, if the assumption of

independence between units of analysis is maintained. However, in practice there is a limit to the manageable size of a decision tree and so this model type is best suited to limited number of branches and short time horizons in each branch.

(iii-c) State transition: State-transition models are the most common form of modelling in health economics. The term is commonly used interchangeably with Markov models. They can be most often used to represent cohorts but can in principle be used to model individuals. No interactions between units of analysis are permitted. The emphasis of the model is in defining specific event states and time is modeled discretely, such that subjects transit between states at specific time points defined by the cycle length (e.g. 1 year increments).

The model functions such that as the time increases, the proportion of the cohort remaining in the starting state tends to zero and a higher proportion of the group filters through the model states to eventually reach the final state(s). This process is typically termed the “Markov chain” and movement through the model is termed the “Markov trace”. An important limitation of a Markov model is that is assumes that during a single cycle, each patient undergoes no more than one state transition. In reality, transitions occur continuously throughout each cycle. Therefore, counting the membership only at the beginning or at the end of the cycle will lead to errors. This error will be larger the longer the cycle length. To more accurately reflect the continuous nature of state transitions, a common assumption is that the transition occurs at the mid-point of the cycle. This adjustment is called a ‘half-cycle’ correction and is calculated as the average of survival at the beginning and end of a cycle(237).

This model type is often used when the disease process can be represented by a manageable number of states and over long time horizons where the use of decision trees may become unmanageable. A further key limitation of state transition models is that the probability of moving from one state to the next state is not conditional upon history, such as time in state or prior states. This “memoryless feature” is commonly known as the “Markov assumption”. This can become a particular problem when the need to model recurrent events is necessary and event history is important for determining future events. This loss of history can be resolved by developing extra (tunnel) states to represent history; however this can easily result in a model structure which becomes large and unmanageable. Overall, Markov models are typically simple to implement, and computations are typically straightforward; however, awareness of the limitations are necessary.

(ii-d) Discrete event simulations (DES): These models focus on the individual agent, interactions are permitted, and time to event is modelled continuously. The rationale is that the modelling may more accurately reflects the reality of the problem under consideration. Further, two forms of interactions are permitted both direct and indirect. Direct interaction most commonly refers to infectious disease transmission where individual agents' infect each other. Indirect interaction most commonly is the result of constrained resources where the consequence is that individuals compete for resources, which may then result in queuing for instance. In contrast, decision trees and state transition models do not model resource constraints endogenously within the model.

The result of these modelling features is that individuals can build-up complex histories which then determine future conditional probabilities. The overriding aim of DES is to attempt to more accurately reflect the underlying disease, event and policymaking process. The potential downsides are that the models can become very complex and are information intensive, which may require extensive assumptions in the absence of hard data. The key issue whether to choose a DES over a simpler model is whether the downsides are outweighed by more accurate predictions and better decision making.

(ii-e) Dynamic transition models: The structure of dynamic transition models can be very flexible. The description of these models in the latest ISPOR guidelines provides a very wide definition. These models can be used to model individuals, cohorts, populations or indeed health care systems as a whole. Time is most often modelled continuously and the models are often implemented with long time horizons. To model the risk of transmission, the use of differential equations are most often used to represent the interactions, and equations can either be static or stochastic.

These models can become very complex. Similar to DES the purpose of adopting such models rather than a simpler structure should be clear. Representing complex relationships may not necessarily aid explanation of the disease processes, and the key issue is whether the impact of an intervention is more accurately represented in changing outcomes of interest.

(ii-f) Hybrid models: This summary of the most common model types is stylised in the sense that particular modelling features (e.g. modelling time to event) may not be exclusive to

particular model types (e.g. DES). There may be an opportunity for continual model innovation, and there may be opportunities to combine features resulting in hybrid models.

When undertaking such an exercise and considering how to use the resultant information, the guiding principle is that a model should be parsimonious: as simple as possible, but no simpler. That is, it may not be necessary to model the full complexity of a disease, it relevant outcomes can be generated robustly by a more aggregated structure. If such structural simplifications are made, then these should be justified on grounds that they would be unlikely to materially affect the results of the analysis. Model choice itself is a judgment call by a consensus of stakeholders including clinicians, statisticians, and modelers. The issue of validating the model structure will be revisited under modelling stage five.

Overall, it is recommended that modellers should not choose a particular model type at the outset, but rather first define the model problem, and have awareness of the desirable features that a model could usefully contain. At the beginning of a modelling project there may be an opportunity to think afresh regarding whether innovations can be made, which may involve combining features normally associated with different models. In choosing or developing a model a key issue is how complex the model needs to be. This should be a product of the decision problem of concern. In decision analytical modelling in health economics the main purpose of the model is to produce accurate final outcomes (e.g. life expectancy) - not necessarily the details of causal processes - that allow an overall judgement whether an intervention is value for money. To inform the judgement whether a simple or complex model is more able to produce accurate outcomes, models should be subject to rigorous validation tests. The rationale and process of validation is further discussed shortly, under Modelling stage 4.

3.5.3 Modelling stage 3: Data identification and incorporation

(i) Data identification: Models require considerable data input and data sources need to be recent and credible. However, the availability of comprehensive high quality data remains a problem. The data may come from a variety of sources including clinical trials, meta-analyses, surveys, databases, medical records, audits, Delphi panels (expert opinion) and official tariff lists for health care resource use.

If secondary data sources are being used to create the model (structure and statistical estimation) then systematic reviews of the literature should ideally be conducted on key

model inputs. Evidence that such reviews have been done, or a justification for failing to do so based on the adequacy and generalisability of readily obtained data, should accompany the model(52).

If known data sources are excluded from consideration in estimating parameters the exclusion should be justified. Data sources and results should not be rejected solely because of a lack of comprehensiveness (e.g. not from a clinical trial). Further, in the absence of any or adequate data, expert opinion is a legitimate method for generating or assessing parameter estimates. If expert opinion is elicited, and the results are sensitive to the elicitations, then the process of elicitation should be disclosed in detail. Expert estimates derived from formal methods such as Delphi or Nominal Group techniques are preferred.

A model should not be faulted because existing data falls short of ideal standards of scientific rigor. Decisions will be made, with or without the model. The value of a model is that it can synthesis existing evidence, point to uncertainties and also make the case for postponing decisions until better evidence is found.

(ii) Data modelling: This refers to the statistical and/or mathematical steps that are taken to transform empirical observations into a form that is useful for modelling. The aim is to define how units of analysis (e.g. individuals or cohorts) transit through a model structure towards events of interest (e.g. CVD, death). For instance, the approach of survival analysis is used is when it is important to estimate time to event and appropriate longitudinal data is available. This approach was discussed in Chapter 2 when introducing CVD risk scores. Further, modelling may also be required to generate appropriate costs and the health related quality of life of units as the model cycles, as outlined below. Cross-sectional data sources can be used for this and the application of regression techniques such as ordinary least squares may be applicable. The model structure then harnesses this information to estimate how units of analysis transit through the model, incur events and accumulative costs and (quality adjusted) life expectancy,

(iii) Baseline data: This refers to the data used to initially populate the model to develop baseline results, in the absence of intervention. This information may come from the control group of a study, or from an observational dataset.

(iv) Costs: For the purpose of evaluation it is important that a model can estimate the cost of the intervention, events costs and wider cost implications. If a health perspective is taken then wider impacts are limited to health service costs. If a societal perspective is adopted then all substantive impacts are accounted for, such as intersectoral outcomes, productivity implications and so forth.

In practice, most evaluations are limited to assessing the intervention costs and event costs. For instance, the review of economic evidence for CVD interventions in Chapter 2 found that no study assessed the interventions impact on wider health service (e.g. from longer life expectancies, or the wider economic costs). In general terms, this could pose a serious limitation to such evaluations. For instance, if an intervention leads to increase life expectancy then the additional costs from the accumulation of comorbidities may outweigh any particular events cost avoided, or delayed. This may lead to erroneous conclusions that an interventions are cost saving, whereas in actual fact they may lead to increased costs from an older population.

(v) Health related quality of life: Conditional upon the modelling problem, such as modelling the impact of a particular disease event it is normally important to estimate health related quality of life in addition to length of life, if the event was non-fatal.

Health related quality of life (HRQoL) can be measured through the application of generic questionnaires where respondents self-assess their health status. Chapter 5 will discusses HRQoL in detail. There are a variety of possible questionnaires available. The most commonly used in the UK is EuroQol EQ-5D index(138) and the Short Form 12 or 6 (SF-12 or 36)(137, 238), which divides questions in physical and mental health. The “EQ-5D-3L” refers to there being three levels (3L) per question. This is the most commonly used version. The other version is called the EQ-5D-5L, where there are 5 levels (5L) of possible responses. SF-12 consists of 12 questions and SF-36 has 36 questions.

These questionnaires can generate a wide variety of different health states given the range of potentially different combination of responses. To measure overall HRQoL a single summary score is generated by applying weights to different question responses. These weights are derived from general population preferences regarding the desirability of different health states. This generates preference-weighted HRQoL which economists call utilities. Modelling can be used to then estimate the impact of experiencing an event on reducing utility. These

estimates are called utility decrements. This process of estimating utilities and utility decrements can then be used to weight length of life to generate quality adjusted life expectancy (QALE).

NICE recommends using the ED-5D; however, this doesn't necessarily preclude using alternative instruments. Previous studies have shown close correlation overall between measures in general(239). However, in healthy or sick individuals the scores can differ in terms of which tool is most sensitive. This will be discussed in chapter 5 when considering how to measure quality of life in the context of primary prevention of CVD where populations are asymptomatic. Further, NICE recommends that the valuation of outcomes should be equal regardless of who in the population is affected by the intervention.

(vi) Treatment effects: With the previous steps in place, the model can estimate the impact of interventions. For instance, interventions may slow the transition from one state to another (e.g. free of CVD to a CVD event). This will then change patient history and have impacts on (quality adjusted) life expectancy and costs.

In the context of policy models there may be challenges in modelling treatment effects when multi-factorial interventions are considered, that include a mix of pharmaceutical and/or lifestyle interventions that impact on different risk factors. The key issue is how these interventions interact to then lead to reductions in risk factors (or CVD outcomes directly). For instance, statins and dietary changes both impact on cholesterol. There nature of the challenge would depend on whether the model is used in trials or to conduct a purely 'what-if' analysis. If the model was used to extrapolate known trial results then it may not be necessary to understand the underlying interactions, and the combined impact on risk factors and/or event rates would be known. However, as discussed in the previous chapter while there is fairly substantial evidence of the impact of single interventions on reducing one (or more) risk factors, there is a lack of secondary literature on the combined impact of multiple interventions. This is despite the fact current CVD clinical guidelines recommend such multi-factorial intervention programs, which policymakers are following.

To model the impact of such multi-factorial programmes important assumptions would be required regarding how interventions interact. Possibilities include applying an additive relationship as discussed by Capewell(13), however this does not seem to make intuitive sense. As new interventions are included in a package of interventions, eventually adding

relative risk reductions would result in negative risk and implying immortality in the limit. This is clearly incorrect. An alternative approach may be to apply a simple multiplicative relationship where as new interventions are added to a package of interventions, the products of the relative risk reductions of individual interventions are taken.

A further potential challenge is modelling the impact of physical activity interventions. As discussed in chapter 2, physical inactivity is an independent risk factor in predicting CVD events, after adjusting for other known risk factors. This may present a challenge if a model estimates the impact of intervention through risk factors changes using the same variables employed in risk tools. A potential solution is to use trial evidence on the evidence of physical activity (in isolation or as part of multi-factorial package of interventions) and then adjust the risk factors to match the observe event rates. Nonetheless, this would represent a practical fix, rather than an elegant solution.

An additional challenge for modelling long term impacts is the sustainability of changes to risk factors / event rates over time. Sustainability is likely to be a function of lag effects between intervention and risk factors, and also patient compliance with particular interventions (e.g. statin use) over time. This is a challenge for both extrapolating trial results and for purely 'what-if' modelling exercises.

(vii) Generate incremental cost effectiveness ratio (ICER): Once the model has been created, populated and the interventions have been defined, it is then important to enable the model to generate cost effectiveness evidence. This is done through generating an ICER, where the numerator is the difference in the additional costs between 'new' intervention (to a 'comparator'); and where denominator is the difference in the effect between the intervention 'new' intervention (to a 'comparator').

(viii) Discounting: Further, it is important that outputs are discounted to account for societal time preference, to reflect that outcomes realised in the future are valued less in present day terms. The guidance from NICE is that benefits and costs should be discounted at 3.5%(144). However, the Public Health guidance recommends that the discount rates are 1.5%(147). Discounting then results in an ICER represented in net present value terms, and congruent with economic theory. Note that while the Scottish Medicines Consortium (SMC) makes adoption decision regarding new interventions, the methods used to undertake economic evaluation follow NICE guidelines.

3.5.4 Modelling stage 4: Uncertainty analysis

At all stages in the evaluation and modelling process uncertainty is prevalent(227). There is uncertainty in the: (i) sample data used (to assess efficacy or effectiveness); (ii) model structure (used to represent the modelling problem); (iii) analytical methods employed (e.g. the instruments used to estimate utilities); and (iv) generalisability of results to different settings. The consequence of the different forms of uncertainty is the assessment as to whether an intervention is value for money is also subject to uncertainty.

The systematic examination and responsible reporting of uncertainty are hallmarks of good modelling practice(43). There are two separate, but interrelated decisions: (i) whether to fund a particular intervention; (ii) whether to invest in further research to reduce uncertainty. However, the role and urgency of sensitivity analysis is, in part, conditional upon the modelling problem. If the model has been built to assist a decision maker and they must make a decision regarding resource allocation now, have no role in commissioning further research and a decision cannot be reviewed in the future then uncertainty analysis has a limited role and the decision should be based on the mean estimates.

There are four main types of uncertainty in estimates produced(49). The first type of uncertainty is stochastic uncertainty which refers to the random variability in the estimates produced. This is random variability not attributable to features of individuals, and is sometimes described as first order uncertainty. The second type of uncertainty is parameter uncertainty. This is represented by the error term in the beta coefficients of the estimates. This is sometimes called second order uncertainty. The third type of uncertainty is heterogeneity and the difference in estimates that can be attributable to characteristics of individuals. This can be represented by difference in the beta coefficients of the estimates. To explore parameter uncertainty, the reporting of estimates should include means and confidence intervals. It is also important to explore heterogeneity in model results to separate out natural variation explained by individual characteristics, from statistical uncertainty in the modelling results. This can be undertaken by conducting sub-group analysis consistent with the modelling problem under investigation. The fourth type of uncertainty is structural uncertainty and relates to the uncertainty surrounding the modelling assumptions, including the structure of the model (e.g. model type) and analytical methods employed, such as the choice of discount rates or estimation of inputs such as health utilities (e.g. whether EQ-5D or SF-6D is used). Structural uncertainty may be at least as important as parameter uncertainty. Therefore, where possible it is best practice to sensitise the model structure. This can be

done by reformulating the model, choosing different distributional assumptions in parameter estimations, and varying key exogenous inputs to the model such as the utility estimates, discount rates, and so forth.

Further, it is important that modelling undertakes sensitivity analysis to “stress test” the extent to which model outputs change due to change in key inputs, such parameter values or structural assumptions. This then allows the model to estimate not only mean impacts but also to present the uncertainty surrounding such estimates. Standard methods of sensitivity analysis in health economic models can be broadly divided into two categories: deterministic sensitivity analysis and probability sensitivity analysis (240). Deterministic sensitivity analysis is where parameters in the models are changed manually. This can be undertaken in four ways: (i) If one parameter is changed at a time while all others retain their base-case specifications, it is called “one-way sensitivity analysis”; (ii) if more than one parameter is changed at the same time then it is called “multi-way sensitivity analysis”; (iii) “Threshold analysis” is concerned with identifying the critical value of parameters above or below which the conclusion of a study will change; (iv) An “analysis of extremes” involves incorporating the best and worst estimates of inputs, and then generating extreme scenarios.

Probabilistic sensitivity analysis is an automated process where all parameters are varied simultaneously. This is undertaken by specifying a priori probability distributions (e.g. normal, log-normal, beta), which should be justified by the evidence based. It may be that parameters are not (or expected to be) independent. Where data permits, the covariance relationship between parameters should be estimated and used to inform the PSA, for instance through the development of a using a Cholesky decomposition matrix. If data is not available, independence need not be a default position but rather the process of choosing distributions need to be justified (e.g. secondary data, Bayesian synthesis, subject judgment)(228). This method involves exploring the parameters, but in running these multiple times and averaging across estimates this is intended to take into account stochastic variations. Monte Carlo simulation analysis is a convenient way to automate this process(241).

To represent uncertainty graphically, the standard approaches are to plot the estimates on a cost effectiveness plane and/or generate cost effectiveness acceptability curves (CEACs)(242). The former approach can show the range of ICER estimates and relative to a decision threshold which is represented as a line maximum willingness to pay for a unit of effect. However, when we don’t know the threshold then the approach of CEAC is a method

of illustrating the probability of cost effectiveness as the threshold value changes. Separate CEACs can be produced for different sub-groups if treatment decisions can be considered independent. Further, when considering multiple treatment options that are mutually exclusive the approach of using a cost effectiveness acceptability frontier (CEAF) is a convenient way of representing the optimal choice based on net benefit(227-228).

Decisions based on existing information will be uncertain, and there will always be a chance that the 'wrong' decision will be made. As discussed in section 3.3 if an adoption decision is required then decisions should be taken on the basis of mean expectations of outcome; the uncertainty surrounding mean estimates is irrelevant. However, although we make the correct decision now based on our current estimate of expected net benefit, there is a chance that another alternative would have had higher net benefit once our current uncertainties are resolved. If our decision based on current information turns out to be 'wrong', there will be costs in terms of health benefit and resources forgone. Where there is the opportunity to delay an adoption decision in order to undertake further research then the approach of value of information analysis can assess whether conducting further research is value for money(243). That is, the extent to which to invest in further research to reduce the possibility of making a wrong decision given the economic impacts. With estimates of the probability of error and the opportunity costs of error we can calculate the expected cost of uncertainty or the expected opportunity loss surrounding the decisions. The expected costs of uncertainty can be interpreted as the expected value of perfect information (EVPI), since perfect information can eliminate the possibility of making the wrong decision(227). Total EVPI is commonly expressed in net monetary benefits. The higher the EVPI the greater the opportunity cost of an incorrect decision, and consequently the rationale for delaying a decision to undertake further research increases. This provides an assessment of the overall uncertainty in the model output. It may also be beneficial to explore which particular parameters are driving this uncertainty to guide the research effort. An analysis of expected value of partial perfect information is designed to identify single or multiple parameters whose uncertainty most materially impacts on a decision(49).

Implementing probability sensitivity analysis and conducting a full uncertainty analysis, as described previously, may provide particular challenges for policy models. To reiterate, the rationale for a policy model is to have a single generic model that can be used to evaluate and model a wide range of interventions; both individually and together as part of package of interventions. The crux of the issue is that as the number of modelling variables used within a

policy model increases it may be more difficult to know the covariance structure between variables in order to implement PSA.

The first challenge is to understand the underlying relationship between risk factors and outcomes of interest. We saw in the previous chapter that current epidemiological research has used anywhere between 6 and 14 variables (as risk factors) when attempting to predict the risk of future CVD events. An economic model with aspirations to be a policy model would ideally need access to such a wide range of variables and know the underlying covariance structure. As we will discuss shortly, when reviewing existing policy models, that this is rarely the case.

The second challenge is modelling the uncertainty in estimating the impact of multiple intervention(s) that are delivered simultaneously as part of CVD prevention programmes. A particular challenge in implementing PSA in modelling exercises is the lack of trial evidence regarding how interventions interact, and so the treatment effect on reducing risk factors. To explore uncertainty, there would need to be evidence (or less satisfactorily, reliable expert opinion) regarding the potential covariance relationship between interventions to explore uncertainty. At present, this knowledge is largely absent. Consequently, a sensitivity analysis may best default to an analysis of extremes prior to trial evidence becoming available. The assumptions regarding how interventions combine to reducing overall risk can be sensitised as part of a structural sensitivity analysis. Indeed using an analysis of extremes to articulate such uncertainties of impact may be a valuable output from a policy model to make the case for trial evidence.

Therefore, there are challenges in implementing PSA in policy models. However, the fundamental issue is the lack of trial evidence regarding the impact multi-factorial programmes, rather than any intrinsic weakness of the rationale for, or application of, a policy model. To reiterate, clinical guidelines and policymakers are intent on continuing to roll-out multi-factorial programmes nationwide. These programmes need to be evaluated. Therefore, the rationale for a policy model in this context remains essential. The uncertainty regarding the predictions represents a challenge to the modelling, but the model can be used at least in a ‘pre-trial’ phase (as discussed previously) to articulate best guess and inform the need for policy to invest in actual trial evidence.

3.5.5 Modelling stage 5: Validation and reporting

There are five different types of validity: (i) face validity is achieved when experts in the area corroborate that the model structure and the assumptions used are consistent with the problem at hand; (ii) internal validity is achieved if the model can reproduce outputs from the source data used in the construction of the model. This is sometimes referred to as verification and is a check on the coding used to generate the model; (iii) external validity is achieved if the model can accurately reproduce outcomes in a dataset and context not used in the construction of the model; (iv) predictive validity is where the model can accurately predict future outcomes. If a model doesn't accurately predict outcomes in a different context and / or time period, this does not necessarily invalidate the model. Recalibration can be undertaken to adjust model parameters systematically to allow predictions to match observations in a population of interest. In principle, there is a wide variety of ways to recalibrate a model, and no formal guidance exists. It is suggested here that a pragmatic and parsimonious approach may be best. For instance, if a regression is used to estimate key model parameters then perhaps the addition of an intercept may be sufficient, with the expectations that the slope coefficients are accurate. More sophisticated forms of recalibration should be clearly explained, such as multiplicative factors to parameters values. Finally, (v) cross-validity is the extent of agreement in the outcomes generated by different models using the same input datasets. If a model's outputs differ appreciably from published or publically available results based on other models, the modelers should make a serious effort to explain the discrepancies(44). If possible, it would be important to distinguish between the discrepancies due to differences in model structure or input values.

Within this process of validation it is important that the model's ability to discriminate between individuals is carried out. The most common approach is to generate the C-Statistic and Hosmer-Lemenshow tests. These were discussed in Chapter 2 when reviewing CVD risk scores. To briefly reiterate, the C-Statistic is measure of how well the model discriminates between those incurring an outcome from interest from those who do not. The Hosmer–Lemeshow test specifically identifies subgroups as the deciles of fitted risk values. Models for which expected and observed event rates in subgroups are similar are called well calibrated.

Overall, it is strongly recommended that modelers make every effort to fully report how the model was constructed, and ideally provide enough information to enable third parties to replicate the model. To these ends, the dissemination should be easily accessible and comprehensible. This may encounter limitations, such as commercial property rights if the

model was built for the purpose of profitability rather than knowledge dissemination and reporting may need to be updated over time if protocols and best practice guidance changes. External and predictive validity should be an on-going process where necessary, such as exploring whether the model can be used on a population not involved in constructing the model.

Overall, the process of building a model can be complicated task conducted over a considerable period of time. Also models should never be regarded as complete. That is, models should be repeatedly updated, and sometimes abandoned and replaced, as new evidence becomes available to inform their structure or input values(43-44).

3.6 Cardiovascular disease policy models: systematic review

3.6.1 Approach taken for the systematic review

An approach was taken to build upon a previous systematic review which covered the literature until 2003 and included models with a focus on CHD(244). This review searched MEDLINE and PUBMED, and found 6 models. Rather, than simply update the previous review using the same terms the review conducted here, was informed by, but sought to widen the search strategy.

A search of the MEDLINE, PUBMED and EconLit electronic databases was undertaken from 1970 to 2011. To decide on a suitable approach the important observation is that there are three relevant categories of search terms: ‘disease area’, model type’ and ‘economic evaluation’. Within each of these categories there were two options identified of relevance to the search. First, within the category ‘disease area’ certain economic evidence concentrates on ‘CVD’ and ‘CHD’. Second, within the category ‘model type’ the search included ‘policy model’ and ‘generic model’. The rationale being that a generic modelling approach (i.e. incorporating a wide range of risk factors) was the key approach that allows a policy model to inform wide range of prevention interventions focussed on different risk factors (independently or simultaneously). Third, the category ‘economic evidence’ includes the terms ‘economic evaluation’ and ‘cost effectiveness’, the former being the generalisable approach to generate economic evidence and the latter the specific approach developed by

health economics to generate evidence for health service interventions. Table 3-2 summarises the search terms used.

Table 3-2 Search terms used in Systematic review of policy models

Disease area	*Model type*	*Economic evidence*
CVD	Policy model	Economic evaluation
CHD	Generic model	Cost effectiveness

An iterative approach was taken, where different searches were conducted sequentially rather than inputting all terms. In each round of searching a term was chosen from each of the categories, and so three terms in total were included in a single search. An exhaustive set of searches was undertaken with all combinations of these terms were combined (one from each category). In total 5 searches were conducted. The expectation was that there would considerable overlap in the articles picked up between specific searches; but that this approach would provide a comprehensive attempt at detecting all relevant models in peer reviewed journals.

The search was restricted to terms in the title and abstract only. In total the searches identified 4,261 articles. All records were imported to 'End-note'. Figure 18 summarise the review process. Articles were excluded in two stages. First, models were excluded if they did not relate to human beings, or focussed on single risk factors/interventions, as these cannot be described as policy models following the definition made previously. There were 118 articles retained. Second, articles were excluded if either the models description was unclear to give at least an overview of its characteristics relative to best practice guidance; or articles referred to an application of the model, rather than a description itself.

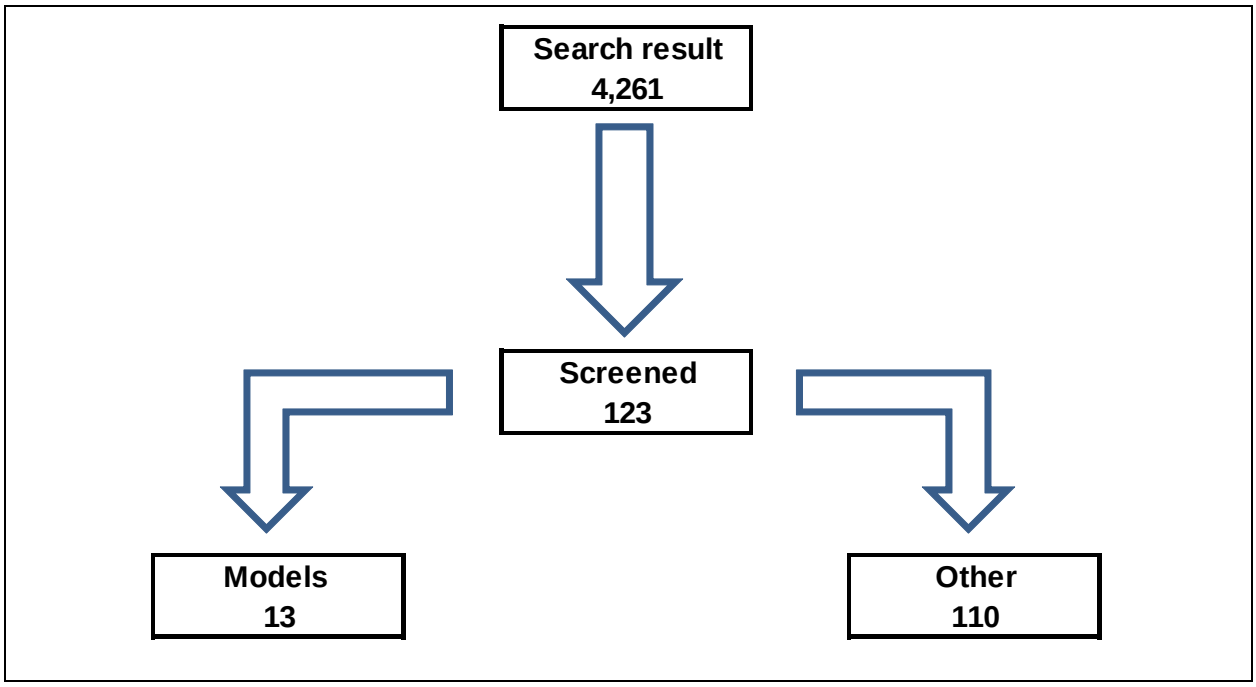
A final list of thirteen models was identified for critical appraisal. This is in contrast to the six models detected in the previous systematic review outlined above, published in 2010. The contrast in findings appears to confirm the comprehensive nature of the search, as several of the models identified could have been detected by the published review given the model pre-date the search that had been undertaken.

The following provides a detailed description of twelve models. A model that was developed in Australia is essentially a replica of a previously published model developed by the NICE

PDG, but was populated with local data. This is a perfectly valid approach, and the Australian model is briefly discussed when reviewing the NICE PDG model.

The extent of the reporting of the models was inconsistent, with certain models being extremely transparent and others less so. This is reflected in the review in terms of the detail that can be conveyed. An additional model is discussed that was detected in the review that while not an economic model, provided an interesting approach to converting risk profiles into estimates of life expectancy. This was influential in conceptualising the approach taken to estimate life expectancy in the Scottish CVD Policy Model.

Figure 3-1 Systematic review of CVD or CHD policy models



To review the models, the best practice guidance described earlier was used. The order that the models are reviewed is with reference to the model type employed, beginning with the simplest types. Of note, is that models perform quite differently relative to the criteria. The prose concentrates (mainly) on what the model does relative to best practice, rather than what is omitted. An accompanying table summarises how the model performs against all best practice criteria.

3.6.2 Review of existing policy models

The order in which the models are reviewed is an attempt to begin with the simplest model and end with the most complicated, consistent with the earlier discussion on model types. There is no value judgement associated with the term simple in this context, but rather refers to the model structure and transparency of the approach used to estimate transition risks. Indeed, as will discussed later simplicity is considered here as a virtue, conditional upon a model being capable of producing the outputs required commensurate with the decision problem.

NICE Programme Development Group: "Modelling Strategies for the primary prevention of cardiovascular disease"

(i) Conceptualising the model problem: The NICE Programme Development Group commissioned and developed a model to inform the potential cost effectiveness of population-wide interventions(35). This model formed part of the (on-going) response by NICE to a request by England's Department of Health for NICE to developed guidance on a public health programme aimed at the primary prevention cardiovascular disease.

The perspective taken by the model was from the health service and the objective was to predict the gains in life expectancy from changes to modifiable risk factors from a range of legislative interventions including salt reduction and a ban on trans-fats. The time horizon of the model was 10-years. This is very conservative, given impacts will be expected over a lifetime. Nonetheless, this is a long enough to illustrate that the huge potential benefits from population wide interventions, and that even over a short horizon these interventions are likely to be very cost effective.

(ii) Conceptualising the model structure: The analysts built what they termed a "cell-based" model which is reclassified here as a tabular model for consistency with best practice guidelines. The model uses the Framingham 10-year risk score with risk factor information and estimates the risk of CVD event. This 10-year estimate is then interpolated to generate annual event risks. The model then estimates the particular type of CVD event which included 7 different events (including different severities of angina and stroke). The event predictions in turn determines the relative risk of subsequent death which is used to adjust the background life expectancy estimates of an individual profile, defined by age and sex (taken from national lifetables). Event predictions are also used to quality adjust life expectancy

estimates of a non-fatal event; however, no account is taken of background quality of life (population norms). The model does not estimate the health service costs associated with the incurrence of fatal and non-fatal events.

(iii) Data identification and incorporation: The model is then populated with the English population risk factor distributions using cross-sectional surveys. First, the population is divided into sex and 10-year age bands. The average risk profile for each subgroup is then taken from a separate survey. Each subgroup (number and risk profile) is then inserted into the model and estimates baseline life expectancy, quality adjusted life expectancy and health service costs. The model then simulates the effect of the intervention (e.g. salt reduction) by reducing the relevant risk factor (e.g. blood pressure) by a certain amount and estimating the impact on extending life expectancy and avoiding event costs. All outcomes were discounted at 3.5%.

(iv) Uncertainty analysis: The model only takes into account the mean values from the Framingham parameters coefficients when estimating the impact on CVD events.

(v) Validation and reporting: No internal or external validation was conducted of the model predictions as the interventions considered were speculative. The accuracy of the Framingham equation itself has already been tested separately and recalibrated for an English population (see Chapter 2). The model is well reported, with on-line technical appendixes and third parties could easily replicate the model.

(vi) Applications: The model has been used to simulate the impact of population interventions, including potential reductions of systolic blood pressure, cholesterol and salt(35). This exercise has shown the potential of population interventions. However, the benefits may be an underestimate given the 10-year horizon of the model and that the total impact on health service costs may be underestimated also if longer life expectancy results in higher cost in the long term.

Strengths of the model are the simple approach, that it can rapidly simulate intervention and can be communicated simply. The model could, in principle, be used to inform the targeted approach to primary prevention, by estimating the potential economic impacts of prioritising different groups. In this case the time horizon of 10-years would become a serious weakness as it would be important to compare the impact of prevention in the young and old.

Weaknesses of the model include the absence of quality adjustment to account for non-fatal events avoided, costs saved only include the avoidance of CVD events, and the time horizon of the model is just 10-years rather than a lifetime.

This modelling approach has been replicated in Australia, with the only differences being that the Framingham score was then calibrated to an Australian population, and that local cost data are used to estimate intervention costs and events costs(175-176). This version of the model has been used to identify what may be the most cost effective interventions, including drugs and diet. The most notable finding is that a shift away from lifestyle counselling to legislation and drugs was estimated to be more cost effective(175). However, the difficulty in generalising from this finding is that the model is only estimated over 10 years, and it could be argued that lifestyle intervention deals with the underlying aetiology.

Markov model to estimate cost effectiveness of EUROACTION

(i) Conceptualising the model problem: An economic evaluation was conducted of the EUROACTION intervention that was reviewed in Chapter 2. The aim was to extrapolate the one-year trial results and assess the likely cost effectiveness of the intervention over a longer time horizon(179).

(ii) Conceptualising the model structure: A Markov model was constructed that estimated event risks over an 11–year period, within annual cycles and final outcomes reported in quality adjusted life years and event costs (net of interventions). From a CVD free state an individual can incur one of 7 events: stable angina, unstable angina, myocardial infarction, CHD death, transient ischaemic attack, stroke, CVD death and non-CVD death. Following a non-fatal first event, individuals can then move to any of these states in subsequent years within the model.

(iii) Data identification and incorporation: The Framingham study was used to define risk factors and the risk of incurring a CVD event over 10-years. The risk factors used were: age, sex, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, smoking status and diabetes. The 10-year risk was interpolated to estimate annual risk. To apportion global CVD risk between events a variety of different sources were used, and used to also estimate how individual transit between different types of non-fatal events. The utility decrements associated with events were taken from a UK study. The cost estimates were particular to EUROACTION. All outcomes were discounted at 3.5%.

(iv) Uncertainty analysis: To account for sampling variation in the original EUROACTION trial. Using non-parametric bootstrapping; the model sampled individuals from the study with replacement and generating 10,000 replications. The final results report 95% confidence intervals and the model reports results by different subgroups.

(v) Validation and reporting: The Framingham risk prediction was calibrated to the EUROACTION observed event rates. The model was very clearly reported within its single application to date.

(vi) Applications: The model was built for the evaluation of HEARTSCORE. However, the generic structure means it can be applied to any risk factor intervention that impact on the Framingham risk factors.

The IMPACT model

(i) Conceptualising the model problem: The IMPACT model was first developed in Scotland in the mid-1990s and now several country specific versions exists, such as England(190), Canada, China(245). The general method is to use historical data on risk factors and event trends to explain the decline in CHD prevalence.

(ii) Conceptualising the model structure: IMPACT is a tabular model which estimates the relationships between risk factors, CHD events and life expectancy. The scope of the model is comprehensive. For primary prevention, the model includes smoking, cholesterol, blood pressure deprivation, obesity, diabetes and physical activity.

(iii) Data identification and incorporation: The model was estimated from cross-sectional data sources which were collated over time. The model then uses trends in these risk factors to explain historical trends for a very wide range of specific CHD events (e.g. cardiopulmonary resuscitation and thrombolysis). The authors outline that multivariate regression was used to estimate a range of beta coefficients for each risk factor's contribution to the historical declines in CHD prevalence. However, the estimation procedure is unclear. The underlying epidemiological relationships between risk factors and events appear to have taken from individual studies in the literature. What is unclear is how these estimates were all combined and then calibrated, or not, to match historical observations. Further, no quality adjustment is

made, the impact of risk factors on CBVD and non-CVD outcomes are not considered, and the cost impact of longer life expectancies are not included

(iv) Uncertainty analysis: Uncertainty in the model outputs is represented by confidence intervals in the reported results. Sensitivity analysis is undertaken via an analysis of extremes.

(v) Validation and reporting: Internal validation was performed for the models in each of the settings that variants were created, and the authors qualitatively report accuracy in findings. It is unclear how validation was conducted. While technical appendices are available on request there is a lack of transparency in how data was modeled, and whether (how) predictions in events and life expectancy were calibrated to official sources.

(vi) Applications: A wide range of publications has been generated to explain historical declines in CHD prevalence, and distinguish between risk factor reductions and secondary prevention interventions. In particular, the model makes a powerful case for primary prevention and for population interventions, such as incremental reductions in risk factors.

Table 3-3 Appraisal of policy models

Modelling stages	Elements within each stage	NICE Programme Development Group	Brunel / EuroAction	IMPACT	DisMod II	CHD policy model	RISC	RIVM	POHEM	Coronary heart disease policy analysis model	Cardiovascular life expectancy model	PREVENT	PRISM	Archimedes
Stage 1:Conceptualising the problem	Policy context	√	√	√	√	√	√	√	√	X	X	X	√	√
	Consultation of experts and stakeholders	√	√	√	√	√	√	√	√	√	√	X	√	√
	Statement of decision problem	√	√	√	√	?	√	√	√	√	√	√	√	√
	Statement of model scope	√	√	√	√	√	√	√	√	√	√	X	√	√
	Statement of model perspective	√	√	√	√	√	√	√	√	√	√	X	√	√
	Target population	√	√	√	√	√	√	√	√	√	√	√	√	√
	Health outcomes	√	√	√	√	√	√	√	√	√	√	√	√	√
	Intervention strategies/comparators	√	√	√	√	√	√	√	√	√	√	X	√	√
	Time horizon	√	√	√	√	√	√	√	√	√	√	√	√	√
	Cycle length	√	√	√	√	√	√	√	√	√	√	√	√	√
Stage 2: Conceptualising the model	Converting the model problem into a model structure	X		X	X	√	√	√	X	X		√	√	?
	Choosing a model type													
	Tabular model	√		√	√									
	Decision tree					√	√	√						
	State transition		√						√	√	√	?		
	Discrete event simulation													
	Dynamic transmission model											√		√
	Hybrid models													

Key: √ = done; X = not done;? = unclear or partially done

Table 3-4 Appraisal of policy models - continued

Modelling stages	Elements within each stage	NICE Programme Development Group	Brunel / EuroAction	IMPACT	DisModII	CHD policy model	RISC	RIVM	POHEM	Coronary heart disease policy analysis model	Cardiovacular life expectancy model	PREVENT	PRISM	Archimedes
Stage 3: Data identification and incorporation	Data identification	√	√	√	√	√	√	√	?	√	?	?	√	√
	Data modelling	√	√	√	√	√	√	√	?	√	?	?	√	√
	Baseline data	√	√	√	√	√	√	√	?	√	?	?	√	√
	Costs	√	√	√	X	√	√	√	√	√	√	?	√	√
	Quality of life weights (utilities)	X	X	X	X	X	√	?	√	?	√	?	X	√
	Treatment effects	√	√	√	√	√	√	√	√	√	√	?	√	√
	Incremental cost effectiveness ratio	X	X	X	X	√	√	√	√	√	√	?	X	√
	Discounting	√	√	√	√	√	√	√	√	√	√	?	?	√
Stage 4: Uncertainty analysis	Stochastic (first-order) uncertainty	√	√	√	√	√	√	√	√	√	X	√	√	√
	Parameter (second order) uncertainty	√	√	√	√	√	√	√	√	√	X	√	√	√
	Heterogeniety	X	X	X	X	√	√	√	√	?	X	?	√	√
	Structural uncertainty	X	X	X	X	X	X	X	X	X	X	X	X	X
Stage 5: Validation and reporting	Face validity	√	√	X	X	X	X	X	X	√	X	X	?	?
	Internal validity	X	X	X	X	X	√	X	X	?	X	X	√	√
	External validity	X	X	X	X	X	X	X	X	X	X	X	?	√
	Cross validity	X	X	X	X	X	X	X	X	X	X	X	X	X
	Predictive validity	X	X	X	X	X	X	X	X	X	X	X	√	√
	Reporting and dissemination	√	√	√	?	?	?	?	?	?	√	X	√	√

Key: √ = done; X = not done;? = unclear or partially done

WHO Global Burden of Disease Model

(i) Conceptualising the model problem: WHO Global Burden of Disease (DisModII) was created to model the burden of premature mortality and disability by all major diseases at the global level and across 14 regions or the world(246). CVD was a sub-section of the model.

(ii) Conceptualising the model structure: A tabular model was developed which estimates the relationship between 25 risk factors and the incidence, prevalence, duration, and case fatality of over 200 disease and injuries. In all, DisMod consists of 500 cells to calculate the relationship between risk factors and disease outcomes, for age ranges between 0 to 85+ years.

(iii) Data identification and incorporation: To identify the risk factors, expert working groups conducted a comprehensive review of published literature as well as other sources (government reports, international databases, etc) to obtain data on the prevalence of risk factor exposure and hazard size (relative risk or absolute hazard size) for 14 sub-regions of the model.

The criteria for the selection of risk factors included were: likely to be among the global or regional leading causes of disease burden; not too specific (e.g. chemical exposures) or too broad (e.g. environment or food); high likelihood of causality based on scientific knowledge; reasonably complete data on exposure and risk levels or methods for extrapolation when needed; potentially modifiable. The risk factors used to drive cardiovascular events are blood pressure, cholesterol, body mass index (BMI), fruit and vegetable intake and physical inactivity. These were dichotomised and relative risk applied to the proportion of the population with high risk factor levels.

To use the model, country or regional population statistics (numbers, ages and sex) are inputted and the model develops projections of mortality and non-fatal health outcomes over the next 30 years. The model then contains active cells for the user to insert relevant interventions and costs, with the latter including intervention and event costs. The model generates life expectancy estimates and produces Disability Adjusted Life Years. However, it is unclear how the weights were derived or applied in the model.

(iv) Uncertainty analysis: Uncertainty in the model outputs is represented by confidence intervals in the reported results. Sensitivity analysis is undertaken via an analysis of extremes

using the upper and lower bounds of the confidence intervals for the relative risk ratios. This generates scenarios analysis of expected, best and worst case scenarios.

(v) Validation and reporting: The model undertakes internal validation with mortality predictions calibrated to lifetables each region or country. No validation of its predictions appear to have been undertaken; however, the model literature makes clear that users of the model should validate predictions relative to the local geography. The model is also available freely on-line as a web based tool.

(vi) Applications: The model is intended for use by supra-national and national governments. Overall, the model is comprehensive, transparent and is used in WHO-CHOICE (CHOosing Interventions that are Cost Effective) research. This research attempts to generate a central resource regarding cost effective interventions in three ways: by collating economic evaluation from across the world; generating economic evidence of new interventions; tailoring results from previous economic evaluation to local conditions by for instance changing unit costs or compliance assumptions The model has been used by the Millennium Development Commission for instance, to convert burden of disease estimates into health service costs, and also to estimate the macroeconomic impact of disease in terms of productivity loses and resultant losses in Gross Domestic Product.

The Coronary Heart Disease Policy Model

(i) Conceptualising the model problem: The Coronary Heart Disease Policy (CHDP) Model was the first model developed in this area and was self-titled as a policy model(205). The model was constructed in the 1980s with the aim to forecast population trends in CHD mortality and the associated costs in the United States. The perspective taken is from the health service. Overall, the CHD Policy Model was the seminal policy model that others have since taken a lead from.

(ii) Conceptualising the model structure: The model is described as a state-transition model. The model seeks to estimate the transition of the US population from a CHD free state to eventual death. The model was constructed using several cross-sectional datasets representative of the US population. It is comprised of three main parts. First, there is what the authors call a “demographical/ epidemiological model”, which represents the disease-free population aged 35-84 years. The population to be simulated is first stratified by sex, age groups and four cardiovascular risk factors including smoking status, total cholesterol, DBP

and relative weight (as a ratio of the population average). Age was split into 5 year bands and the other risk factors are inputted as categorical variables with three levels.

The second stage of the model is the “bridge model”, which covers subjects for the first 30 days after developing coronary disease. Using a CHD incidence data from Minnesota, the model initially determines whether the first event is angina, myocardial infarction or cardiac arrest.

The third stage of the model is the “disease history model”, which includes the survivors after the first 30 days. Individuals surviving are then apportioned to one of 12 CHD events, including the post-intervention states of CABG and PTCA. Separate cells and risks are estimated for males and females, and also specific to different 5-year age bands. The risk of non-CHD death is included which is estimated from national lifetables.

Overall the model uses over 5,000 separate cells to stratify the US population, with a CHD-free population then moving between cells as the model cycles on an annual basis. The model can simulate the life expectancies of the CHD-free population for up to 30 years, and also the impact of interventions. Primary prevention interventions are simulated by changing the modifiable risk factors to slow the population transition from a CHD-free state into the bridge model. Secondary prevention interventions are then used to slow the transition to CHD-death, with background life expectancies (defined by national lifetables) unchanged by any risk factor adjustment. In other words, changing risk factors such as smoking only affects CHD events.

(iii) Data identification and incorporation: The model uses a very wide range of cross-sectional data sources, both national and at state level. The model then predicts the annual incidence of CHD events from each of the population cells using relative risk estimates from the Framingham Heart Study population. A proportion of each of the subgroups then experienced an event. While all individual parameter estimates are provided it can be unclear if and how these are combined to determine transition risks. Overall, the cost effectiveness of interventions is then estimated at the overall population level by looking the benefits of greater life expectancies from the costs of prevention interventions (net of the hospitalisation costs). No quality of life adjustments are made.

(iv) Uncertainty analysis: Confidence intervals are given for all parameters and the model can undertake analysis of extremes sensitivity analysis.

(v) Validation and reporting: The model has been calibrated to the 1980 census statistics on mortality, the year in which the model was built. Authors do describe the intention to test the model to forecast future CHD trends, which is in a sense a form of external validation. However, this has not been reported. The model is relatively well described in published model appendixes.

(vi) Applications: The model has been widely used mainly to forecast CHD events in whole populations, including the US(204, 247), Argentina(203) and China(207). It has not been used in patient level cost effectiveness analysis. This appears to be due to the nature of the model where is limited scope to assess patient heterogeneity, given limited risk factors have been grouped into broad categories.

The Rotterdam Ischemic Heart Disease and Stroke Computer model (RISC)

(i) Conceptualising the model problem: The Rotterdam Ischemic Heart Disease and Stroke Computer model (RISC) is an economic model designed to predict the risk of CVD and the cost effectiveness of primary and secondary prevention initiatives from the perspective of the health sector(248). It is unclear how the model development was funded.

(ii) Conceptualising the model structure: The model was developed from the Rotterdam Study a 7-year cohort follow-up of individuals aged 55 years and over. A sample of 3,501 individuals was used to construct the model. A Markov state transition model was developed where the model predicts the risk of fatal CVD, non-fatal IHD, non-fatal stroke and CVD death within a competing risk analysis and using Cox-proportional hazards. Recurrence of non-fatal events is possible for up to 4 times, with a fifth event programmed to be fatal. The model cycles every 0.1 years and extends for 50 years. While the study data was for 7 years, estimates were made for how risk factors changes with age. In turn, as individuals age in the model the risk of events increase.

(iii) Data identification and incorporation: There were 24 risk factors included in the Rotterdam study and different risk factors were selected to predict different events. Step-wise hazard analysis was used to include risk factors, with additional variables added following a tests

using the Akaike Information Criteria AIC, which considers the trade-off of predictive accuracy from increasing the number of variables from the loss in efficiency. The model can then be populated with utilities and event costs taken from secondary sources. This has not been published yet, but the appendix to the RISC model details the capability to produce QALE and costs saved from CVD events avoided.

The key weaknesses of the model are that the follow-up data is only for 7 years, the model does not consider the impact from interventions on extending life expectancy on health service costs.

(iv) Uncertainty analysis: Parameter uncertainty is represented by confidence intervals in the reported results. The model is programmed to undertake Monte-Carlo analysis. To model uncertainty regarding the transition probabilities, 100 bootstrap samples of the study population was undertaken. For each model simulation a mean and confidence interval can be generated. The model also allows heterogeneity to be explored in terms of how individual risk factors affect the cost effectiveness of outcomes.

(v) Validation and reporting: The internal validity of the model was tested by visually comparing the predicting cumulative incidence of events against observed rates, and there was found to be close match. This was done for the whole sample, rather than testing the models ability to discriminate between individuals.

It is unclear how representative the Rotterdam study is of the Dutch population and therefore the validity of the model to be used at a national level. A full on-line appendix details the modelling assumptions and in principle the model appears that it could be replicated using the appendix.

(vi) Applications: Overall, the RISC model is a rigorous and transparent model that can simulate the impact of a wide range of interventions. The model has been used only on one occasion to date, including modelling the cost effectiveness of statin therapy(249). In corresponding with the senior author the model was being updated and external validation was underway.

Dutch Chronic Disease Model (RIVM)

(i) Conceptualising the model problem: The RIVM is a chronic disease policy model that was commissioned and held by the Dutch Ministry of Health(250). The model is comprised of 28 disease models, including COPD, CVD (with CHD and Stroke modelled separately), diabetes, and 15 forms of cancer. The aims of the model are to simulate the impacts on life expectancy and costs from population interventions aimed at risk factor changes.

(ii) Conceptualising the model structure: The model is a Markov model which predicts the proportion of the population that reside in different disease states. The risk factors used in the model include age, sex, smoking, blood pressure, cholesterol and BMI. These are categorised into three levels and the model first estimates how risk factors change over time in the absence of interventions. Overall, the model predicts how risk factors change in the population and therefore predicts the proportion of the population that resides in each risk disease state of CVD free, CHD, stroke and death. The CHD and stroke states allow for three recurrences before an individual must transit to death. The model cycles on an annual basis, and runs for 50 years.

(iii) Data identification and incorporation: The model combines cross-sectional and longitudinal sources. It is not straightforward to follow how the modelling was undertaken. The relationship between risk variables and different disease states are specified as relative risks and taken from multiple sources. The model appendix states that the event risks are linear and time-invariant.

Further, it appears that no competing risks are included, where the probability of being in one state influences the probability of being in another. This would appear to be a major omission given the breadth of states included. It is unclear whether and how a ‘fix’ is applied to account for competing risk. It is also unclear how predictions are calibrated.

The model simulates the impact of changes to risk factors in terms of incremental life expectancy. Adjustments are made for quality of life; however it is unclear how utility weights were either derived or taken from the literature. The model also includes the cost of residing in different disease states. Given the breadth of co-morbidities that are included perhaps the model accounts for the impact on health service from longer life expectancies from CVD primary preventions. This isn’t made explicit in the model literature however.

(iv) Uncertainty analysis: Parameter uncertainty is represented by confidence intervals in the reported results. The model is also programmed to undertake Monte-Carlo analysis.

(v) Validation and reporting: It is unclear whether any validation has been conducted; however, model outputs have been calibrated to national health survey data.

(vi) Applications: The model has been used to estimate the cost effectiveness of a wide range of preventive interventions, including diet, exercise, smoking and estimating the impact on a range of chronic conditions going beyond simply CVD outcomes(251-252).

Coronary Heart Disease Policy Analysis Model

(i) Conceptualising the model problem: The Coronary Heart Disease Policy Analysis Model, was developed 2004 at the London School of Hygiene and Tropical Medicine. The aim was to estimate the cost effectiveness of population-wide prevention strategies. The model was commissioned by England's Department of Health(253).

(ii) Conceptualising the model structure: The model is closely resembles the CHD Policy Model developed in the US. There are three-parts: a primary prevention model and a secondary prevention model that was estimated independently, and "linked model" which brings the primary and secondary components together. The primary and secondary parts of the models exist independently at present. The perspective of the model was from the health service with the aim to predict the impact on prevention strategies on quality adjusted life expectancy and event costs avoided.

The primary prevention component of the model includes four risk factors, namely systolic blood pressure, total cholesterol and smoking. The authors had access to the Framingham cohort. However, rather than taking the Framingham coefficients over 10-years as some other models have done, they estimated coefficient afresh. A parametric approach was used to estimate risk factor coefficients and the authors assumed a Gompertz ancillary parameter to allow estimation of CVD risks to change in time. Annual global risk estimates are then apportioned to 3 non-fatal CHD events (myocardial fraction, stable angina and unstable angina) and two death states (CHD and stroke). Further, the model literature reports that a competing risk was undertaken; however, it is unclear how this was done.. Nonetheless, this was a very interesting approach and influenced the modelling used within the Scottish CVD

Policy Model. Overall, the model cycles until all-patients reach 85 years and is truncated thereafter.

Following a non-fatal event the model then estimates the transition to 6 subsequent states, including the treatment states of angiogram, angioplasty, bypass graft, unstable angina admission, myocardial infarction and sudden death. Patients can remain within or move between any states. The transition risks and distribution were taken from various datasets from national and regional datasets. The treatment arm of the model includes primary and secondary care interventions, waiting times, lag times in treatment effects. The model also includes intervention specific estimates of treatment uptake and compliance. Estimates are all taken from a wide variety of the secondary sources.

(iii) Data identification and incorporation: The model is then populated with a range of English sources. Event costs are taken from various English sources for primary care (e.g. GP visits) and secondary care (e.g. cost of CABG). Utility adjustments are made for incurring non-fatal events, where one utility adjustment is made for any CHD event and another for a stroke event. Model predictions are calibrated to the Health Survey for England for 1998.

(iv) Uncertainty analysis: All parameters have associated confidence interventions, and the model can undertake an analysis of extremes.

(v) Validation and reporting: Model predictions over 5 years were then validated against the Framingham cohort, British Regional Heart study, and a population survey of Bromely. Calibration to English lifetables in 1988 was reported, though it is unclear how this was done. The authors state that there was reasonable accuracy but that more will be done in the future. In particular, there is no validation of treatment impacts, and there is no test discrimination for individual risk profiles.

Model appendices are available on request; however, the justification of the complexity of a discrete event simulation is unclear. Overall, the model is potentially very policy relevant and appears to be extremely comprehensive. However, the modelling can be quite opaque.

(vi) Applications: To date, the model has not been used and through correspondence with the senior author there are no immediate plans to do so. Given calibration is to 1998, the model does not appear equipped at present to be used in contemporary settings.

NorCaD

(i) Conceptualising the model problem: The Norwegian Cardiovascular Disease Model (NorCad) was developed in 2008(254). The aim was to estimate the cost effectiveness of primary and secondary prevention strategies

(ii) Conceptualising the model structure: A Markov model was built simulating individuals aged between 30 to 100 years, and cycles annually. Individuals begin from an asymptomatic state and are at risk of myocardial infarction, stroke, angina and heart failure. Post first event, individuals can transit between any these states or directly to death. Transition risks are specific to first and subsequent events, with the latter using tunnel states. The perspective of the model was from the health service with the aim to predict the impact of prevention strategies that change risk factors on life expectancy and event costs avoided.

(iii) Data identification and incorporation: A wide range of national and international data sources are used. The risk factors used to determine transition between states are age, sex, smoking status, cholesterol, systolic blood pressure, and diabetes. Transition probabilities rely mainly on international registries (longitudinal data) and trials. The relationship between individual risk factors and particular event rates is taken from different sources, mainly RCTs. However, the method used to calibrate the impact of the complete risk factor set on event rates is unclear. Unit costs are derived from Norwegian sources and include primary care and secondary care costs. The impact of event rates on resource utilisation (e.g. length of stay) was determined by expert opinion. Overall, data incorporation is very complicated, and nearly 200 parameters are used to estimate baseline risk of events. The model is intended to estimate the impact of changes to risk factors on event rates. All outcomes are discounted at 4% in line with guidance from the Norwegian Ministry of Finance.

(iv) Uncertainty analysis: The model provides confidence intervals and conducts heterogeneity analysis by sub-group (ranges of different risk factors). The model can undertake extensive sensitivity analysis including one-way, multi-way and probabilistic sensitivity analysis.

(v) Validation and reporting: Internal validation was conducted and outputs of life expectancy calibrated to Norwegian life tables where 10 year age bands were used. The model has been disseminated and available on-line.

(vi) Application of the model: The most comprehensive application of the model was to estimate the cost effectiveness of a range of individually administered drugs for primary prevention, including aspirin, statins and anti-hypertensives(172). The model has not been used to evaluate behavioural interventions, nor multi-factorial interventions.

Cardiovascular Life Expectancy Model

(i) Conceptualising the model problem: The model was developed in Canada to examine the cost-effectiveness of the primary prevention of CHD (rather than also CVD)(255).

(ii) Conceptualising the model structure: A Markov model was constructed where from a CVD free state an individual can transit to fatal CHD, non-fatal CHD and non CHD death. Following, a non-fatal event an individual can incur CHD death or non-CHD death. The model cycles annually and for individuals aged between 35 and 84 years. End-points of interest are CHD events and life expectancy.

(iii) Data identification and incorporation: An early version of the Framingham risk scores was used that includes the risk factors of age, sex, diastolic blood pressure, total cholesterol, HDL cholesterol level, left ventricular hypertrophy, glucose intolerance and smoking status. Further, risk is project over 8 years, within annual risks an eighth of the global risk score. Non-CHD death was estimated from life tables. Following a first CHD event, the Framingham risk score was applied again to estimate further event risks. It is unclear how competing risk of events are accounted for, especially given CHD risk and non-CHD death come from different sources.

(iv) Uncertainty analysis: Parameter uncertainty is represented by confidence intervals, as are final outcomes. An analysis of extremes can be undertaken.

(v) Validation and reporting: The model was not subject to internal validation, but it was tested for external validation. The model performed well in external validation predicting outcomes observed in Helsinki Heart Study, Multiple Risk Factor Intervention Trial (MRFIT), and the Lipids Centre Clinics Coronary Prevention Trial. This was done by comparing observations and predictions across predicted deciles.

(vi) Applications: The model has been used to widely to simulate the potential benefits for statins, and diet and exercise for instance by using efficacy evidence in the wider

literature(206, 255-258). Outcomes were life years free of CHD and life years saved. It has not been used in recent years, and appears to have been replaced by an alternative model POHEM, discussed next.

POpulation HEalth Model (POHEM)

(i) Conceptualising the model problem: POHEM was built by Statistics Canada, with the aim of identifying key drivers in the causes of multiple chronic diseases (including CHD, cancers, dementia and arthritis)(259).

(ii) Conceptualising the model structure: A discrete event simulation model was developed. However, it is unclear how the model was built e.g. statistical estimation, and therefore how the model functions e.g. interactions between individuals, disease incidence. This lack of transparency may be a function of how complicated the relationships are assumed to be.

(iii) Data identification and incorporation: The variables used in the modelling as risk factors for future disease incidence are demographic factors (age, sex etc), socioeconomic status variables (e.g. education, marital status, labour force participation, income), more orthodox risks factors (e.g., smoking cholesterol, blood pressure, obesity, disease history), health system variables (e.g. service delivery) and include a range of health sector costs for events and services. The aims are to predict the incidence of events for both individuals and populations in continuous time.

The model has been created using multiple longitudinal and cross-sectional datasets; and can simulate the cost effectiveness of different interventions, and aims to look at the impact of risk factors and disease incidence across the health sector as a whole. Outcomes include disease events, life expectancy and disability free life expectancy. Quality adjustment is made using the Health Utilities Index III(260).

(iv) Uncertainty analysis: The model can undertake Monte Carlo microsimulation. This generate a distribution of the impacts of an intervention(s) and associated mean and confidence intervals.

(v) Validation and reporting: There does not appear to have been any validation of the model outputs, although it seems reasonable to assume that the model has been calibrated to national statistics regarding disease prevalence.

Overall, the model appears to be comprehensive in its inputs and intended outputs; however but it is equally as complicated. The rationale for building such a complicated structure is unclear.

(vi) Applications: The model has used to simulate the economic impacts of several cancers(259, 261-265). There are no publications regarding CVD. However, in conversation with authors of POHEM a module is being developed specifically to predict the relationship between risk factors and myocardial infarction.

PREVENT Model

(i) Conceptualising the model problem: The PREVENT Model(266-267) was developed in the Netherlands, and pre-dates the RISC model previously reviewed. It is a model that simulates the impacts of prevention on CHD, cancers and respiratory diseases. The model is not particularly well-reported and in particular it is difficult to verify the model type and how it functions.

(ii) Conceptualising the model structure: The model is described as a microsimulation. However, it is unclear what the authors mean by this definition. The model cycles annually and events are incurred discretely; where individuals transit from states defined by risk of exposure to an event and then consequent death.

(iii) Data identification and incorporation: To inform how individuals transit in the model the estimates between exposure to risk factors and events are estimated using a population attributable fraction (PAF). However, there are several ambiguities including the data sources used to estimate the PAF; the unit is analysis (individuals or cohorts) and how heterogeneity is modelled, rather than applying a single PAF to all units. It appears that individuals are divided into 10 year age bands where the risk exposure varies between age bands, rather than (also) the transition risks to events. It is unclear how costs are incorporated into the model. Estimated life years gained from prevention are not quality adjusted.

(iv) Uncertainty analysis: It does not appear that the model estimates uncertainty in predictions. However, presumably in estimating PAF confidence intervals could be estimated, and it should be straightforward to undertake one way sensitivity analysis or an analysis of extremes.

(v) Validation and reporting: No formal validation tests have been reported, including corroboration of model structure through face validity checks.

(vi) Applications: Simulations of the model have been conducted; however the model does not appear to have been used in evaluation. There have only been two studies that were found regarding the application of the model, one to validate its predictions(268), and another to simulate the potential benefits of prevention(195).There are no publications in recent years, and perhaps other more recently created Dutch models (i.e. RIVM and RISC) may have superseded PREVENT.

Prevention Impacts Simulation Model (PRISM)

(i) Conceptualising the model problem: The PRSIM model was developed in the United States for use initially in Texas, and broaden to the US. The model was developed by a Homer Consultancy((209), jointly with the Centres of Disease and Control (CDC). The model was developed specifically to inform the prevention of CVD, both primary and secondary.

(ii) Conceptualising the model structure: The model is described as a Systems Dynamics (SD) model, and simulates multiple risk factors, direct and indirect impacts on behaviour, the impacts on mortality and consequent impacts on health service costs. It is not clear why a SD model was used, as the advantages of using this approach do not seem to have been taken advantage of. That is, the modelling framework can be intuitively appealing to model non-linear relationships, continuous-time interactions, feedback loops and tipping points. None of these features appear to have been used to date.

(iii) Data identification and incorporation: The model uses cross-sectional data sources dating from the early 1990s, in order to specify the US population of risk factors and proportion of population who have CVD. The model uses a wide range of risk factors and estimates of the relationship between risk factors and events are taken from the literature, and include the Framingham score from 1991 (the first score developed for primary prevention, as discussed in Chapter 2), and add other variable such as exposure to second hand smoke and access to junk food, though its less clear how transmission risk were estimated for these variables. Individuals in the model are grouped by age category and sex, and simulated as units that age in the model. While not explicitly stated, it is assumed here that the model also simulates

demographic changes so that cohorts are renewed by the next generation. Only intervention CVD events costs were included.

(iv) Uncertainty analysis: In the one demonstration of the model to date(209), mean estimates are varied in a scenario analysis. However, no reporting of stochastic or parameter uncertainty is given. The focus of the model is to simulate impacts on the population, rather than investigating heterogeneous impacts.

(v) Validation and reporting: The model is has not been validated before use. The model reports that calibration has been performed, however it is unclear how or on which outcomes. The absence of an appendix means that reporting is limited.

(vi) Applications: The model was used to simulate the potential impacts of 19 interventions on the population as a whole; including improved air quality, improve mental health services, regulation changes. The model found that 15 interventions could be cost saving.

Archimedes

(i) Conceptualising the model problem: The Archimedes model was developed in the United States, and is owned by a Kaiser Permanente, a private Managed Care Organisation. The model was developed over a period of five years and involved a wide number of specialists in term of academic background (including natural scientists, computer programmers, mathematicians, economists), and professions (including medics to health service managers, policymakers). The ambitious aim is to create a 'virtual world' and simulate the entire US health care system, including the future disease rates and health services implications(269). The model is in continual evolution.

(ii) Conceptualising the model structure: The Archimedes model is a large-scale simulation model that attempts to simulate the whole health care system in the United States. The model essentially operates as a series of interrelated modules, including physiology, disease, and health care systems. The model simulates individuals and is incredibly detailed. The physiology model is detailed down to the organ and chemical level when simulating risk factors. Currently, the model includes coronary artery disease (CAD), stroke, diabetes and its complications, congestive heart failure, obesity, smoking, asthma, and the metabolic syndrome in a single integrated model. The health care systems model also models individuals and individual events to then predict downstream clinical events, utilization, and

costs, including signs and symptoms; patient encounters with the health care system (e.g. emergency room visits, office visits, and admissions); protocols and guidelines; tests and treatments; patient adherence to treatment recommendations; and clinical events that affect logistics, utilization, and financial costs.

While there are three modules there are inter-relationships between modules and between different risk factors, diseases and health care utilisation. Relationship are estimated in continuous time through a set of ordinary and differential equations that represent the physiological pathways pertinent to diseases and their complications. The model is run on a network of computers.

(iii) Data identification and incorporation: The model uses person-specific data from real populations (e.g. the National Health and Nutrition Education Survey [NHANES]) to create simulated populations that match the real populations, person by person. Each individual can be matched to variables such as demographics, risk factors, biological variables, current and past medical histories, and current treatments.

(iv) Uncertainty analysis: The model reporting to date is for mean estimates, and heterogeneity rather than parameter uncertainty. However, given the authors of the model, it is assumed that a full parameter uncertainty analysis is feasible.
(v) Validation and reporting: The model's accuracy is checked by using it to simulate clinical trials that have been conducted in the real world and comparing the predicted results with the real results. This has been done successfully for several hundred treatments and outcomes in 48 randomized controlled trials thus far.

(vi) Applications: The model appears to be used (or is at least reported) on the sub-model defined by disease areas. For example, the diabetes model has generated a range of publications(270-271). There is one publication to date with respect to the impact of statin treatment on asymptomatic individuals(272).

3.8.3 Additional modelling approaches of relevance

In addition, to identifying policy models capable of economic evaluation, the systematic review also identified an important paper that was influential to inform the approach that was taken ultimately creating the Scottish CVD Policy Model, discussed in the next chapter. This

was a model developed in the UK in 2004 with the aim of developing a clinical tool that could predict the life expectancy based upon CVD risk factors(273). The rationale was to replace 10-year risk scores and identify individuals at risk of premature death. Further, the aims of the model were to respond to perceived weaknesses in other models that the impact of smoking should be modelled using the competing risk of non-CVD death; and should have the ability to discriminate between individuals rather than modelling the impact of interventions at the population level.

A Markov model was constructed that used the Framingham 10-year risk score CVD and is intended to be used for subjects aged between 35 and 85 years. First, linear interpolation was used to estimate the annual risk of CHD, and this was divided equally into four first events, namely myocardial infarction, other CHD, stroke and other CVD. All cause death was modelled conditional upon incurring one of the first four events rather than as a competing first event risk. Post-first event individuals either remain in the current state (no secondary events were modelled) to transit directly to death. The annual risk of death was taken from various secondary sources. Adjustments for death risk conditional upon smoking status was estimated using relative risk estimates from the US Cancer Society's 4 year follow-up. Relative risks were applied on an annual basis. The model cycles until all individuals are 85 years old. The model generated predictions of life expectancies using the Health Survey for England (1998)

The model was not designed to generate economic information in terms of quality adjustments to life expectancy estimates or costs. Further, the model also does not illustrate the benefits from changes to modifiable risk in terms of additional life expectancy. However, this could easily be done using secondary sources that other models have used (e.g. Barton et al) and simply simulate the impact of changes to say smoking status. The life expectancy predictions have been externally validated using the Wickham study (from the 1970s) which was nationally representative survey of adults 18 years and over, where asymptomatic individuals were followed-up for 20 years. The model accurately replicated the results from this survey and showed an ability to discriminate accurately between 35 different covariate subgroups.

Overall, the key strength of the model was in creating a model using a risk score in current practice in England and having an ability to predict life expectancy at both the population and individual level. The model is also simple and the estimation procedure was very clear. A

weakness was that model could have taken an extra step and estimated the potential lifetime benefits from changes to risk factors. Further, the scope of the model could have been widened to develop a full economic model and simulate the cost effectiveness of primary interventions.

In referring back to the model's developed by NICE PDP and EUROACTION these groups could have developed similar methods to estimate the lifetime impact of the intervention. The cost in not doing so may have led to the EUROACTION team concluding that the intervention was not cost effective.

3.8.4 Relevant models found in the grey literature

In addition, an opportunistic search of the grey literature was undertaken for policy organisations that may not have published in academic journals (or not yet). These models are not reviewed in detail, but it is important that chapter acknowledges their existence, development and possible applications. The search included website of the World Bank, WHO and OECD. Further, the search of the UK database 'Idox', which collates UK based policy documents, was made. There was prior awareness of England's Department of Health economic model that was used to simulate the potential cost effectiveness of England's mass screening population to identify high risk individuals for intervention.

WHO / OECD Chronic Disease Prevention Model

The OECD, in collaboration with the WHO, developed a dynamic micro-simulation model named the Chronic Disease Prevention to assess the health outcomes, impact on health expenditure, and cost-effectiveness at the population level. The structure appears to be a microsimulation model designed to simulate the behaviours and life histories(19-20). The models scope is global, and the associated literature suggests that the model simulates 4 billion individuals from 30 countries and across all 5 continents. The model is information intensive requiring information on demographic and socioeconomic conditions, health-related behaviours, and current and past disease history. The interaction between risk factors and disease is modelled dynamically and in continuous time. The intended application of the model is to be the first model to address obesity and chronic diseases as a global issue.

PRISM – Prevention Impacts Simulation Model

PRISM is a system dynamics (SD) simulation model for evaluating multiple approaches to preventing and managing cardiovascular risks, developed by Centers for Disease Control and

Prevention and the National Institutes of Health (Homer et al. 2010; Homer et al. 2008). SD models help decision makers anticipate the likely effects of interventions in dynamically complex situations, where the pathways from interventions to outcomes may be indirect, delayed, and possibly affected by nonlinearities or feedback loops. PRISM has been used in the US by public health leaders at the national and local levels to inform strategic planning, and will soon be broadly available as a web-based tool. It is also being used by the US government for evaluation of the half-billion dollar, 50-community stimulus program known as Communities Putting Prevention to Work.

PRISM, like most SD models, is compartmental, operating at the level of population subgroups rather than individuals, and consists of hundreds of interconnected differential and algebraic equations. PRISM incorporates data from many sources to represent leading cardiovascular risk factors in adults, including key chronic disorders (hypertension, hyperlipidemia, and hyperglycemia), smoking (and former smoking), obesity, diet, exercise, and psychological distress. It also represents obesity, diet, and exercise in children. Dynamic stock (state) variables are used to model changes in the prevalence of many of these risk factors and in the total population. The population is subdivided by gender, age group (children ages 2-5y, 6-11y, and 12-17y; adults ages 18-29y, 30-64y, and >65 y), and cardiovascular disease status (non-CVD, post-CVD).

Multi-level Modular Agent-based Modelling for the Study of Childhood Obesity

This is a multi-level modular individual-based model currently in development by the Center on Social Dynamics and Policy at The Brookings Institution(106-107). It is motivated by the complex set of drivers that are implicated in the obesity epidemic. Increasing calls for multilevel studies and systems approaches to obesity reflect a widespread perception that research paradigms focused on single factors in isolation have failed to provide the insights needed to stop the growing epidemic. The goal of this project is the development and application of a novel modular agent-based modelling approach for the multilevel study of childhood obesity. The technique of agent-based computational modelling (ABM) offers unparalleled flexibility to incorporate individual heterogeneity, complex social structures, and a range of dynamic adaptive behaviours. Our multi-level modular approach permits modelling of multiple mechanisms simultaneously, across several levels of scale, with inclusion of important sources of diversity. This effort is part of the newly assembled Comparative Modelling network of the National Collaborative on Childhood Obesity Research (a joint venture of the National Institutes of Health, the Centers for Disease Control, the US

Department of Agriculture, and the Robert Wood Johnson Foundation). In addition to directing modelling on the Brookings/McGill project, Hammond serves on the steering committee of this innovative network which is applying diverse systems approaches to the common topic of childhood obesity.

3.7 Summary of the strengths and weaknesses of existing policy models

The models that were reviewed all have merits. There purpose of this section is to attempt to collate common themes in terms of strengths and weaknesses that can be used to inform the development of the Scottish CVD Policy Model.

All models share take a health sector perspective to assess the cost effectiveness of interventions, with the exception of DisMod and the CHD Policy Model that estimate the broader macroeconomic consequences from risk factor changes. However, quite how this is done is not clear.

The modelling approaches differed considerably; with respect to risk factors used, event focus (CHD or CVD), model structure (Markov models, discrete event simulations and tabular models), datasets used (cross sectional, longitudinal), reliance on secondary data sources, the final outcome focus (life expectancy, QALYs, DALYs, disability free years), the extent of sensitivity analysis and validation undertaken.

Notable strengths of the NICE PDG and Australian CVD Model were that the models are simple and transparent; and to estimate the transition from an asymptomatic to a CVD state they used the Framingham risk coefficients that are used in clinical screening. The model developed by the authors evaluating EUROACTION also used the Framingham score. However, the projections of outcomes for all three of these models were limited to the 10 years. A key strength of the CHD Life Expectancy model was the extensive external validation that was conducted on three trials. This was the only model to have done so.

All models share key weaknesses. No model estimates the impact of extending life expectancy on health service costs. That is, the costs considered are only the avoidance of the particular event, net of any intervention costs. However, prevention should really be termed the prevention of premature events, as interventions essentially delay mortality and

most individuals will eventually die of CVD, cancers or respiratory diseases. Further, extending life expectancy tends to result in a rise of co-morbidities and an increase in use of health sector resources. This presents a genuine challenge for the health sector, on a par with fears of an obesity epidemic(45). The co-morbidities that accumulate include the 'big killers' (see figure 2-1) of CVD, cancers, and respiratory diseases (e.g. COPD), but extend to a wide number of other conditions including musculoskeletal to mental health problems (e.g. depression) which can also greatly affect quality of life(45-46).

Health care systems are in general set up to detect and respond to single diseases(46), and yet as the population ages it is increasing recognised that, it is multimorbidity, defined as 2 + conditions(47), that it is greatest concern to health service planners(45). In Scotland, the prevalence of multiple morbidity quadruples from 8% in the 20-44 year old to 33% in those 65 years and over(47). Further, there is a stark deprivation gradient(46-47). The onset of multimorbidity occurred 10–15 years earlier in people living in the most deprived areas compared with the most affluent, with socioeconomic deprivation(46).

Overall, it is contended here that economic evaluation needs to account for the impact of longer life expectancy on patient quality of life and the impact of health service costs when assessing the cost effectiveness of primary prevention interventions. Put another way, primary prevention may be part of a solution to address an obesity epidemic, but in so doing a potential consequence is to contribute to the concern of ageing populations and multimorbidity. Otherwise, it may be erroneous of economic evaluation to infer that an intervention is cost effective with respect to health sector resources if the impact of longer life expectancy is not considered. An integrated systems approach to prevention, service planning and evaluation may be a more productive approach rather than a traditional focus on disease silos(45-46).

Economic modelling can help inform this exercise. The risk factors that CVD prevention seeks to address are also important in explaining the onset of a full range of chronic disease, including cancers and respiratory diseases etc. There is a need to inform CVD policy, but also use a model to help inform wider chronic disease policy, including the implications of interventions beyond CVD.

Finally, a common weakness is that external validation and predictive validation is rarely done. No models, even those that have been in existence for some time, have undergone

cross-validation checks. Further, the practice of fully reporting and disseminating the model and assumptions is inconsistency done.

3.8 The need for a Scottish CVD Policy Model

To reiterate, policymakers are presently focused on a dual approach to primary prevention which includes a population policies and more recently the focus has been on a targeted approach on screening population to identify and treat high risk individuals. Chapter 2 formulated three key research questions that remain, namely: (i) how to identify the optimal screening approach if 10-year risk scores continue to be used? (iii) how to develop an approach to prioritisation based on potential benefit rather than risk? and; (iii) how best to combine targeted and population wide interventions to reduce premature mortality, morbidity, reduce health inequalities. Existing policy models are not ideally placed to address these issues, and this is particularly the case for Scotland.

For a model to inform both the targeted and population approach to primary prevention it needs to use the same risk factors as employed by clinicians to screen and prioritise individuals. In Scotland, the ASSIGN risk tool is used, and no existing models use these variables.

It is important that the policy model can also estimate the lifetime impacts of interventions on life expectancy, quality adjusted life expectancy, health inequalities and health service costs. No existing model can produce all of this information.

Further, in considering how a Scottish CVD Model should be built the approach can usefully follow the latest ISPOR Guidelines. From the literature review of existing models the major weakness concern validation and reporting. Most models perform internal validation, however external and predictive validity is rarely performed. Yet, this is vital if there is to be confidence in model predictions. Finally, it is important to attempt to produce comprehensive outputs from a model that is simple to understand and disseminate. Existing models perform inconsistently. There tends to be a relationship where as the demands on a model increase the more complicated and less transparent it becomes.

Overall, there is a need for a Scottish CVD Policy Model that can provide congruence between clinical practice in the way individuals are prioritised, and with evaluation and policy

in the way interventions impacts are judged and decisions made. In developing the model there is scope to learn from the strengths and weaknesses of existing models in an attempt to follow the latest ISPOR Guidelines as well as possible.

3.9 Summary

The chapter was focussed on the role and application of modelling, and how these can be applied to help generate the economic evidence required by health technology agencies to help inform value for money decision making.

Models are not a substitute for trials, but rather best used hand-in-hand. Trials are often short term and focussed on internal validity, and models can be used to extrapolate findings and help generalise findings. Whereas models are unavoidable in many situations in order to produce economic information, there are many potential pitfalls in developing a model. Best practice guidance exists to help the modeller design, populate and disseminate models that are fit for purpose, user friendly and encourage peer review. There are a dozen policy models in existence and they vary quite markedly, such as the type of model employed, and the evidence produced. Most models have been used to help inform primary prevention either through undertaking evaluation using trial evidence, or conducting what-if simulation exercises. Judged by best practice guidelines these models perform inconsistently. All have strengths, but also share common weaknesses such as lack of assessment of lifetime health service costs from prevention that extends life expectancy.

No existing policy model is ideally suited for use in Scotland. A key policy concern is health inequalities and the ASSIGN risk tool was developed that includes socioeconomic deprivation as a risk variable to detect the underlying social gradient in CVD incidence. It is important that a policy model builds upon this work to use the ASSIGN variables also in the underlying projections. This would then provide a degree of congruence between policy aims, clinical practice and how interventions are evaluated. Further, in attempting to build a Scottish CVD Policy Model there is scope to develop, test and communicate a model that can meet the latest standards of best practice.

Part 2 – Building the Scottish Cardiovascular Disease Policy Model

Overview

In taking stock of the thesis so far, the Scottish Government has made the primary prevention of cardiovascular disease (CVD) a national priority; with the overall objectives to reduce the premature morality, morbidity, avoid associated downstream resource costs and tackle health inequalities. Chapter 2 identified uncertainty regarding three key issues, including: what is the optimal screening strategy is to identify high risk individuals; how to move away from risk scores to develop a screening approach where individuals are prioritised for intervention on the basis of potential benefit; and how to choose between or rationally combine targeted and population interventions. It was contended that economic evidence should underpin all three issues, however this evidence can be lacking. Chapter 3 then discussed the key role of modelling to help develop the economic evidence base, but that there was a need for a new comprehensive economic model that could be used in Scotland to address the key issues above, and inform the development and evaluation of interventions.

The purpose of Part 2 of the thesis is to develop the Scottish CVD Policy Model in an effort to influence the approach to primary prevention in Scotland. Chapter 4 details how the model structure was developed and the statistical approach to estimating individuals' life expectancy from a set of risk factor variables. Crucially, the model uses the same variables employed in the ASSIGN 10-year risk score, which is used in Scotland to screen and prioritise individuals for intervention. This approach is intended to provide a degree of congruence between clinical and economic models, such that the same variables used to prioritise individuals can now be used evaluate interventions aimed at modifying risk factors to extend life expectancy. Chapter 5 details how estimates of life expectancy are quality adjusted to generate quality adjusted life expectancy (QALE), and also how lifetime hospitalisation costs are estimated. The chapter ends by illustrating how the model can be used to undertake economic evaluation to estimating the impact of changes to modifiable risk factors on life expectancy, quality adjusted life expectancy, life hospital costs and the impacts on health inequalities. Estimates can be undiscounted or discounted. The overall intention of Part 2 is to describe that the model is fit-for-purpose and ready to be used to inform the development of and selection of interventions that may produce best value for money.

Chapter 4: Estimating life expectancy from risk factors

4.1 Introduction

The overall objective of the Chapter is to describe the statistical approach to building the Scottish CVD Policy Model and how life expectancy estimates are generated. The structure of the chapter largely follows the five stages to building and reporting an economic model that were discussed under best practice guidelines in Chapter 3. The conceptualisation of the model is discussed in section 4.2, followed by section 4.3 which describes the model structure. Section 4.4 then details the main dataset used to develop the model, and discusses the statistical approach taken to convert risk factors into lifetime risk of CVD and estimates of life expectancy. The ability of the model to investigate uncertainty in predictions is discussed under Section 4.5, before the chapter describes how predictions were validated and recalibrated to contemporary Scottish lifetables. Finally, section 4.6 concludes with a discussion of the main strengths and limitations of the approach adopted.

4.2 Modelling stage 1: Conceptualising the model problem

The policy context and rationale behind creating the model was to respond to the perceived need for a Scottish specific model (as discussed in Part 1 of the thesis) capable of influencing the entire approach to primary prevention. Existing policy models vary in terms of their comprehensiveness and transparency, and none can fully assess the impact of interventions on reducing inequalities. The main funds that were used to help develop the model came from the Chief Scientist Office (CSO) of Scotland that funded a two-year project. The CSO project included funds to help bring together a team of experts and stakeholders on 4 occasions over the 2-year period. This enabled on-going discussion among experts regarding the focus, structure and functioning of the model problem.

The decision problem under consideration was to help guide clinicians and policymakers to develop and chose interventions offer best value for money in the primary prevention of CVD. The CSO did not put any restrictions on the modelling process. The model scope was the primary prevention of CVD and on adults.

A key objective was to build the policy model using the nine risk factors employed in the ASSIGN 10-year risk score that is used in clinical practice in Scotland to screen individuals and prioritise the high risk (≥ 20% risk of a CVD event over 10 year) for intervention. The aim was to access the underlying data sources that were used to create ASSIGN and re-estimate the coefficients for the nine risk factors to predict lifetime CVD risk, (quality adjusted) life expectancy and lifetime health service costs by predicting all events, CVD and non-CVD. Consequently, the model is intended to estimate the impact of changes to modifiable risk factors on lifetime CVD risk, (quality adjusted) life expectancy and lifetime health service costs.

This approach to building the policy model uses the ASSIGN risk factors then provides consistency between how individuals are identified and prioritised in clinical settings for interventions, and then approach to estimate the impact of interventions over an individual's lifetime. By taking a generic modelling approach (i.e. using a wide set of risk factors to predict a comprehensive set of outcomes) the intention is that the policy model could potentially inform the entire approach to primary prevention and to function as a: clinical screening tool and as an evaluation tool to assess the cost effectiveness single and/or multi-factorial interventions and those that are targeted on high risk individuals and/or the whole population.

The perspective taken was that of the health sector. Consequently, the model assesses the impact of interventions on health outcomes and costs incurred by the health service. This is the standard approach of cost utility and cost effectiveness analysis. However, this is a restricted set of outcomes compared to a societal perspective that attempts to account for all impacts, extending beyond health sector considerations, such as the impact on carers and estimating knock-on productivity impacts. A cost effectiveness approach assumes that health sector decision makers are only interested in outcomes that impacts on patients and health sector budgets.

The target population in terms of the recipients of the interventions was asymptomatic adults, both men and women. The key policy focus in Scotland is on a targeted approach from 40 to 74 year old individuals and the illustration of model also focuses on these groups for exposition. However, an important aim was to develop a model that could estimate the impact of both individually targeted and population interventions.

The intention was that the model should produce outcomes consistent with the aims of prevention, namely: to reduce premature morality, morbidity, avoid associated downstream resource costs and tackle health inequalities. Consequently, the model is intended to estimate the impact of changes to modifiable risk factors on life expectancy, quality adjusted life expectancy, lifetime hospital costs and the how these outcomes differ by individuals identified by socioeconomic deprivation. Estimates are intended to be either undiscounted or discounted. Producing these outcomes prepares the model to be used in economic evaluation.

The time horizon of the model is over an individual's lifetime, in an attempt to project the full impact of interventions. The aim was also to build a model that can cycle on an annual basis. Annual cycles with a half-cycle correction was felt sufficient by the advisory group to estimate the risk of events and life expectancy. The key application of the model, as will be discussed, is how to estimate the cumulative life expectancy (and costs) at baseline screening, and how this changes if risk factors are modifiable. It was felt that a time step of 1 year with half cycle correction was sufficient to enable cumulative life expectancy estimates, and these were calibrated to contemporary lifetables.

4.3 Modelling stage 2: Conceptualising the model structure

In conceptualising a model structure the guiding principles where the delivery of the outcomes discussed above but parsimony: that is, to build a model that is fit for purpose but also as simple as possible relative to these objectives. The model structure that was developed was the result of an iterative process between clarifying the modelling problem and exploring the available datasets. Consistent with the best practice guidelines discussed in Chapter 3, the structure of the resultant model is presented first, before discussing data sources and statistical approaches to populating the model. This presentation order is intended to set the direction of travel regarding intended model outputs, and to develop rationale regarding the decisions taken in choosing source data and statistical methods.

To build the model four features were of key importance. First, there was the need to estimate the risk of a first CVD event and the consequences for life expectancy. Second, in estimating the first event the expert panel advised disaggregating CVD into non-fatal and fatal events. The expectation was that incurring a particular type of event has different consequences for subsequent life expectancy. Third, to estimate overall life expectancy there

is a need to take into account the competing risk of death from non-CVD events. The risk factors that drive CVD are also in common with the other main mortality causes such of cancers and respiratory diseases. Fourth, a key simplifying feature of the model is that once an individual has incurred a first event the model directly predicts the consequences for life expectancy. This feature is congruent with primary prevention and avoids the need to model recurrent events and the consequences for life expectancy conditional upon the number of events incurred. The key is having an adequate dataset to enable the generation of accurate event and life expectancy predictions. As will be discussed shortly, the modelling was done using a longitudinal dataset with lifetime patient histories, thus providing the opportunity to estimate life expectancy direct from the first event.

Figure 4-1 illustrates the structure of the resultant policy model. A state transition model was developed, where individuals enter the model at screening and are CVD event free. Subsequent event states are represented by ovals and transitions between states are denoted by arrows and the model cycles on an annual basis.

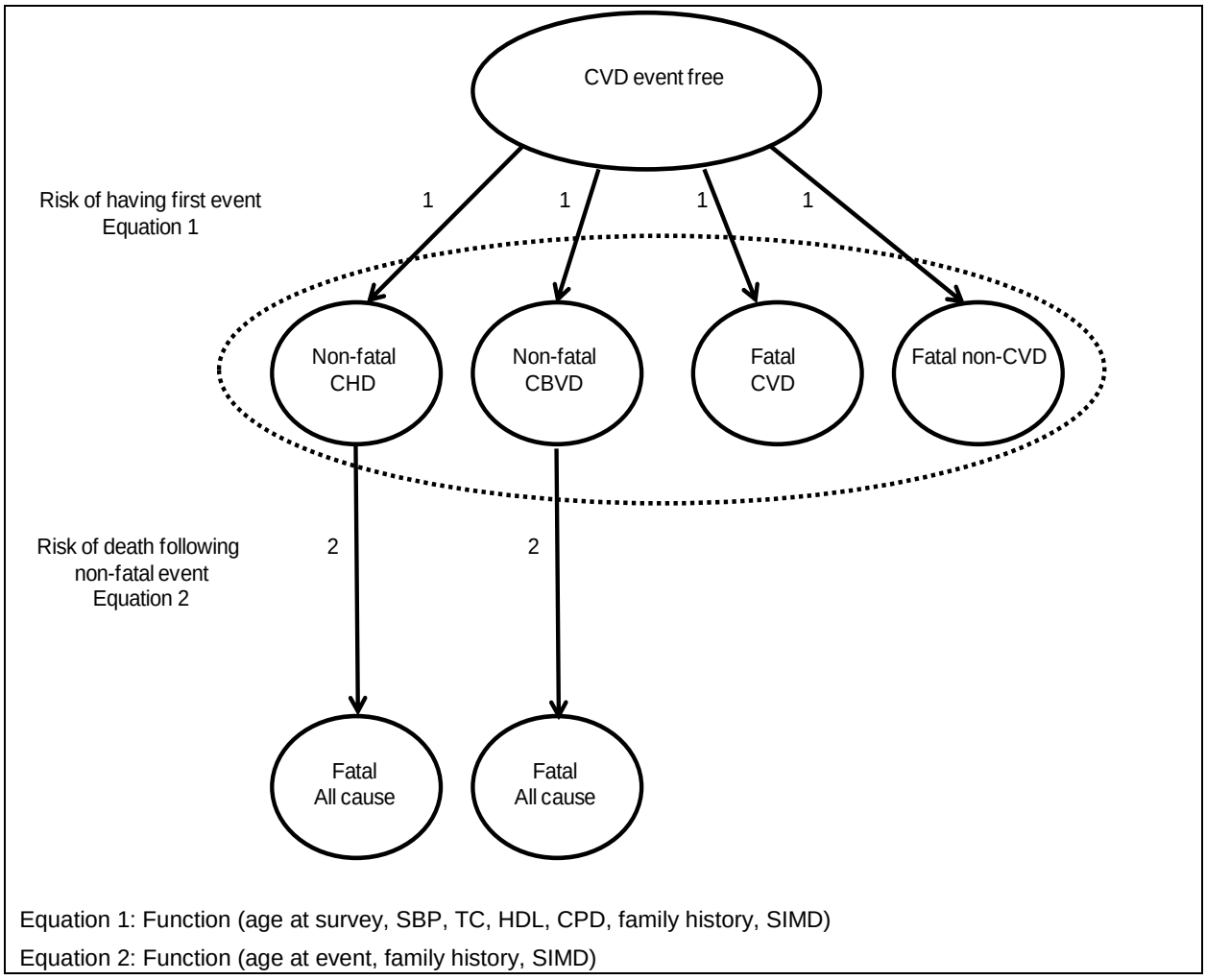
An individual enters the model CVD-free and in each annual cycle of the model the individual has five options: to remain in a CVD-free state or move to one of the four first events: non-fatal Coronary Heart Disease (CHD), non-fatal Cerebrovascular Disease (CBVD), fatal Cardiovascular Disease (CVD), and fatal non-CVD. If the first event was non-fatal, then an individual transits directly to death (from all cause).

The nine ASSIGN risk factors were divided into non-modifiable and modifiable risk factors. The distinction refers to which risk factors can be directly augmented via intervention with the expectation of delaying the onset of events and improving life expectancy. Non-modifiable risk factors include; age, sex, diabetes, family history and SIMD. Modifiable risk factors include: systolic blood pressure, total cholesterol, HDL cholesterol and cigarettes per day were defined as modifiable. The risk of first events is driven by all nine ASSIGN risk factors, and the risk of death post first event is driven by non-modifiable risk factors. This will be further explained shortly. Finally, separate models were built for men and women, in the sense that while the structure of the model was retained equation 1 and 2 were estimated conditional upon sex.

In general, a simple state transition model structure was developed. However, it is not a Markov model which is often used interchangeably with the term state transition model. As

will be discussed in detail as the chapter progresses the model combines the transparent structure of a state transition model with features most commonly associated with certain other models in terms in terms of how the model functions. In effect, a 'hybrid model' was developed using the terminology of the best practice guidance that was discussed in Chapter 3.

Figure 4-1 Scottish CVD Policy Model – estimating life expectancy



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

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

4.3 Modelling stage 3: Data identification and incorporation

The dataset that was used was an extended version of the longitudinal dataset used in creating the ASSIGN 10-year risk score. The dataset consists of two separate parts, which were combined into one longitudinal dataset: a baseline dataset containing CVD risk factors for individuals free of CVD linked to dataset that recorded all hospitalisations (CVD and non-

CVD events) and death. Each dataset is described in turn before discussing the data linkage that was made.

4.3.1 Data identification

Scottish Heart Health Extended Cohort (SHHEC) – baseline screening:

The baseline dataset was called the Scottish Heart Health Extended Cohort (SHHEC). SHHEC recruited from overlapping random samples of the Scottish population in the 1980s and 1990s. The Scottish Heart Health Study(124, 274). recruited random samples of men and women (aged 40–59 years) across 25 districts of Scotland from 1984 to 1987. The Scottish MONICA Project(275) which recruited in Edinburgh and north Glasgow in 1986, (ages 25–64) and North Glasgow again in 1989 and 1995 (ages 25–64), and 1992 (ages 25–74).

All individuals in SHHEC attended a survey clinic. Individuals were identified as “CVD free” if they did not report having had CVD events in the past. To reiterate, nine cardiovascular risk factors were recorded. These included age at survey, sex, self-reported diabetes, self-reported family history of heart disease, residential postcode, systolic blood pressure (mm Hg), total cholesterol (mmol/l), HDL cholesterol (mmol/l), and cigarettes smoked per day. Family history was defined as whether either parent or any siblings had developed heart disease below age 60. The postcode was used to give an individual a deprivation score. Deprivation in Scotland is measured through the Scottish Index of Multiple Deprivation (SIMD). This is an aggregated measure of material deprivation derived from 37 indicators in seven domains (income, employment, health, education, access to services, housing and crime). This is determined at datazone level (postal geographical areas with a population of 769). Overall, an important feature of the data is that the modifiable risk factors were all measured on a continuous scale. This is important when considering a modelling approach, discussed shortly.

Scottish Morbidity Records (SMR) – all hospitalisations

Patient records: The Information Services Division (ISD) of National Health Service (NHS) Scotland maintains an electronic database called the Scottish Morbidity Records (SMRs). This records all hospitalised events, cancer registrations and discharges from NHS hospitals in Scotland. Each individual in the dataset is given a unique patient identifier. SMR hold information including the reason for the visit, up to five secondary diagnoses, length of stay

and waiting time. Emergency, transferred and elective admissions are included in total hospital admission. The SMR are collated into 7 categories defined by the primary reason for contact (admission or discharge) – see Table 4-1

Table 4-1 Scottish Morbidity Records

SMR Scheme Code	**Record type**
SMR 00	Outpatient
SMR01	General/acute inpatient/day case
SMR02	Maternity
SMR04	Mental health inpatient/day case
SMR05	Geriatric (long stay)
SMR06	Cancer register
SMR11	Neonatal discharge

Source: Scottish Morbidity Records

Specific hospital events with each SMR scheme code are defined according to the International Classification of Disease (ICD). ISD provide guidance as to which codes refer to which diseases to enable continuity in tracing incident cases. ISD hold records from 1980.

Process and timeliness: Hospital records are first collated at the regional level by the 14 Scottish Health Boards. Records are submitted to ISD every 6 weeks (or 42 days).

Completeness: Historically, audits have shown 99% completeness on average over time. The latest set of data available was for 2009 and showed 100% completeness(276).

Accuracy: ISD maintains a high degree of accuracy of SMR records by applying a set of validation rules to all SMR records, both locally, prior to submission to ISD. Each SMR record is checked against the validation criteria and, should errors and/or queries be found, appropriate messages are generated to indicate the cause of any error or query(277).

Validation includes both simple and more complicated checks. Simple validation includes checking whether a recorded postcode exists on the U.K. national postcode directory. Complicated validation includes performing a cross-check of several data fields such as checking whether the consultant attributed to an episode worked in the provider at the time of

admission). Further, checks can require additional calculations (e.g. whether patient age at admission was consistent with the diagnosis).

4.3.2 Data incorporation: Linking SHHEC and SMR

ISD Linkage facility

ISD's Record Linkage (RL) team(278) provides a specialist data linkage service to clinical and academic staff and their researchers. ISD regularly produce linkages between baseline datasets such as the Scottish Health Survey(78) and the SMR. In addition, the RL team are also remitted to consider requests from researchers to link other source dataset with SMR records

Previous linkage

SHHEC participants then gave permission to be followed up through routine record linkage. ISD subsequently, linked SHHEC to SMR. Previous linkages of SHHEC-SMR occurred in 1993, 1997 and 2006, keeping the same baseline but updating with new hospital records. This latter dataset was used to develop the ASSIGN score.

Opportunity for further linkage

At the time of developing the model and identifying SHHEC-SMR as the key data source, the latest SMR records available were until end-2009. This provided the opportunity for a linkage that was three years more that the linkage made by the creators of the ASSIGN score.

An application for updating the SHHEC-SMR linkage until end-2009 was then made to the Privacy Advisor Committee (PAC), in collaboration with Professor Hugh Tunstall-Pedoe, one of the original creators of ASSIGN. Unlike the application made to create the ASSIGN score which only linked to CVD event, a request was made to SHHEC patients for all admissions, recorded in SMR01 (general/acute), 04 (mental health) and 06 (cancers) – see Table 4-1 above.

Managing the dataset

The dataset was received in STATA 11. All manipulation and analysis of data was also done using STATA 11. Each individual had a unique identifier within SHHEC and SMR. To identify a first CVD event any diagnosis of CVD was taken whether this was the primary reason for

admission, a secondary diagnosis or an event within a hospital episode. If death occurred within 28 days of a CVD event this was classified as fatal, otherwise this was classified as a non-fatal event.

Manipulating the dataset I: events of interest

Consistent with the model structure (Figure 20) individuals within the dataset were stratified according to what the first event was: non-fatal CHD, non-fatal CBVD, fatal CVD, fatal non-CVD. The corresponding ICD codes are shown in Table 4-2.

Table 4-2 ISD codes used in the model

Event of interest	ICD codes
CHD	ICD9 410-414; ICD10 I20-I25
CVBD	ICD9 430-438; ICD10 G45, I60-I69
CVD death	ICD9 390-459; ICD10 I00-I99
Non-CVD death	Any death except: ICD9 390-459; ICD10 I00-I99

A first CVD event was defined as the first recording of CVD in any diagnostic position, whether the primary cause for entering hospital (1st diagnostic position), and also CVD events experiencing within a single length of stay, or events incurred outside of hospital and recorded by SMR as a comorbidity.

Manipulating the dataset II: Missing data

The ISD records were complete. However, there was missing data in the ASSIGN risk factors for 24% of individuals, in one of more of the ASSIGN risk factors. Missing data were primarily limited to cholesterol (total and HDL) as a result of SHHEC participants refusing bloods to be taken by the nurse.

Missing data was addressed by using the multiple imputation of chained equations technique (MICE) (279). Intuitively, this method estimates the relationship between risk factors variables, by setting up a series of regression equations where each risk factor in turn is a dependent variable and regressed on all the others variables. The process then cycles through all estimates of the missing variables and averages over the estimates. The subsequent analysis to determine how risk is associated with events proceeded using the imputed dataset.

Final dataset used

Table 28 outlines the baseline SHHEC population using the ASSIGN risk factors. A total of 16,560 SHHEC participants were free of cardiovascular disease at baseline. There was approximate balance between males (7,949) and females (8,611) with an average age of 49 years. Most notably, there were elevated levels of total cholesterol and a high prevalence of smokers. Further, a third of the study population were classified within the lowest fifth of socioeconomic deprivation, defined by the Scottish Index of Multiple Deprivation (SIMD 5). The distribution of risk factors was similar between men and women although of those who smoked men reported, on average, a higher number of cigarettes smoked per day and a higher proportion of women had reported family history of heart disease.

Table 4-3: Demographics of SHHEC participants free of cardiovascular disease at baseline

	Men	Women
Cohort size	7,949	8,611
Age (years)	48.6 (9.3)	48.6 (9.3)
SIMD groups (fifths), n (%):		
1 (least deprived)	1,390 (17.5)	1,467 (17.0)
2	1,197 (15.1)	1,214 (14.1)
3	1,264 (15.9)	1,364 (15.8)
4	1,479 (18.6)	1,675 (19.5)
5 (most deprived)	2,619 (32.9)	2,891 (33.6)
Diabetes, n (%)	125 (1.6)	117 (1.4)
Family history, n (%)	2,061 (25.9)	2,788 (32.4)
Cigarette smokers, n (%)	3,083 (39.2)	3,317 (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)

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

Table 4-4 illustrates observed events when following-up SHHEC participants using SMR. The total follow-up period possible was 25 years, with an average follow-up of 21 years. A total of 7,270 people (43.9%) had a first event observed during the follow-up period with more events observed for men than women.

Table 4-4 Follow-up hospitalised events

	Men		Women	
	Number	% of baseline cohort	Number	% of baseline cohort
Alive and "CVD free"	4,450	57%	5,935	69%
First events				
CHD hosp	1,354	17%	985	11%
CBVD hosp	463	6%	382	4%
fatal CVD	696	9%	469	5%
fatal non-CVD	986	13%	840	10%
2nd events in model				
Death post CHD	455	6%	293	3%
Death post stroke	200	3%	147	2%

The most common first event was CHD hospitalisations – men 17%, women 11%, followed by fatal non-CVD (13%, 10%), fatal CVD (9%, 5%) and CBVD hospitalisation (6%, 4%). Overall, 655 males and 440 females subsequently died following non-fatal CVD events, representing 9% and 5% of the baseline study population.

4.3.4 Data modelling I: estimating the risk of having first event

Key considerations

In choosing an appropriate statistical approach two considerations were important. First, in estimating risk of the four first events, there was a need to take into accounting competing risks of non-CVD death. Second, the modelling should adjust for an individuals' time to event, as age at event is likely to be a key determinant of which event is incurred and whether an event was fatal.

Given these considerations, Gompertz parametric regression survival analysis was used to model the cause specific hazards of the competing first events, where age at event was a covariate(280). Gompertz is the standard choice when modelling the risk of death(110). The cause specific hazards are modelled continuously as a function of time to give the instantaneous probability of incurring a particular event, taking into account the risk of other events of interest.

Cause Specific Hazards (CSH) approach

$h_k(t_j)$ is the cause specific hazard (CSH) 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 γ is the ancillary parameter estimated from the data.

Table 4-5 details the CSH for each of the first four events for men. The CSH vary between events, providing justification for splitting CVD into component parts. Coefficients above 1 mean that for continuous variables a unitary change in the risk factor is associated with an increased (instantaneous) risk of event; and for binary variables (e.g. diabetes, family history) a positive identification results in higher instantaneous risk of events. Notably, the coefficients for diabetes, family history and cigarettes per (CPD) are the consistently the greatest across all four events. The exception is the relationship between family history and non-fatal CHD, which is just below 1. The coefficient for the hazard of total cholesterol and fatal non-CVD event is also below 1, suggesting a protective effect of fatal non-CVD. This result for cholesterol seems at first to be counter-intuitive. However, research elsewhere also showed a protective associative between total cholesterol and non-fatal CVD(281-282). Nonetheless, the expert panel advised that these relationships were unlikely to be causal. For example, an increase (decrease) in total cholesterol (HDL) is unlikely to lead to reductions (increases) in fatal non-CVD events.

Several estimates were not significant. Nonetheless, all estimates are used in the modelling as these are known risk factors in CVD. The key issue is the combined impact (and statistical uncertainty) of the covariates taken together in predicting events and life expectancy. The model will be extensively tested in comprehensive validation checks which are discussed later in the chapter.

The C-statistics were above 0.7 suggesting the model has good discriminatory ability: being able to distinguish case and non-case using the ASSIGN risk factors as covariates. However, as discussed in Chapter 3, the C-statistic is not a complete test for prognostic models, despite its widespread use in risk models. Later in the chapter we will test model predictions further by including calibration tests.

Table 3 details the CSH for women. The hazards signs remain the same, however the magnitude can differ. In particular, the impact of smoking is much stronger in increasing the hazards of all four events. For instance, the hazard of cigarettes per day (CPD) for CVD death is 2.62 for women and 1.87 for men. Regarding non-CVD death, the protective effect for total cholesterol remained. Again there were several estimates that were not significant, but to reiterate the modelling uses all estimates and that key test of the model is the ability to generate accurate event life expectancy predictions. The C-statistics for women also convey good discriminatory ability, with typically higher values than for the model developed specifically for men. A comprehensive validation and calibration check for the model constructed for women will be undertaken similar to the model built for men.

Tables 3 and 4 show the mean and confidence intervals, and to prepare the model for probabilistic sensitivity analysis the covariance relationship between the variables in the estimating the hazards was also estimated. Appendix 2 provides the associated Cholesky Decomposition matrixes. In application, this allows the model to vary the hazard and explore the uncertainty in event predictions of the model.

To iterate these estimates were derived in the model that used multiple imputation to adjust for missing data. As an internal verification check, Appendix 1 compares the CSH derived from the imputation compared to a complete case analysis. Minimal differences in the hazards were found.

Table 4-5: Modelling cause specific hazards of first event and survival following non-fatal first event

a) Men - cause specific hazards of first event

Covariate	Non-fatal CHD (1354 events, 17.0% of cohort)		Non-fatal CBVD (463, 5.8%)		Fatal CVD (696, 8.8%)		Fatal non-CVD (986, 12.4%)	
	HRs	p value	HRs	p value	HRs	p value	HRs	p value
Age	1.05 (1.04, 1.05)	<0.001	1.07 (1.06, 1.08)	<0.001	1.10 (1.09, 1.11)	<0.001	1.10 (1.09, 1.11)	<0.001
SIMD.	1.04 (1.01, 1.07)	0.002	1.10 (1.05, 1.15)	<0.001	1.07 (1.03, 1.10)	<0.001	1.10 (1.07, 1.13)	<0.001
Diabetes	1.93 (1.34, 2.76)	<0.001	3.22 (1.94, 5.33)	<0.001	2.37 (1.48, 3.81)	<0.001	1.40 (0.84, 2.31)	0.2
Fam. his.	1.50 (1.34, 1.69)	<0.001	0.98 (0.79, 1.21)	0.8	1.18 (1.00, 1.39)	0.05	0.99 (0.85, 1.14)	0.8
CPD	1.42 (1.31, 1.55)	<0.001	1.61 (1.40, 1.86)	<0.001	1.87 (1.67, 2.10)	<0.001	1.84 (1.68, 2.02)	<0.001
SBP	1.08 (1.05, 1.11)	<0.001	1.12 (1.08, 1.17)	<0.001	1.16 (1.13, 1.20)	<0.001	0.99 (0.95, 1.02)	0.4
TC	1.29 (1.23, 1.35)	<0.001	1.09 (1.00, 1.18)	0.06	1.13 (1.05, 1.21)	0.001	0.95 (0.90, 1.01)	0.09
HDL	0.68 (0.62, 0.75)	<0.001	0.94 (0.82, 1.07)	0.4	0.93 (0.83, 1.04)	0.2	1.21 (1.11, 1.32)	<0.001
c-statistic	0.70 (0.69, 0.71)		0.73 (0.71, 0.75)		0.77 (0.76, 0.79)		0.74 (0.72, 0.75)	

b) Women - cause specific hazards of first event

Covariate	Non-fatal CHD (985, 11.4%)		Non-fatal CBVD (382, 4.4%)		Fatal CVD (469, 5.4%)		Fatal non-CVD (840, 9.8%)	
	HRs	p value	HRs	p value	HRs	p value	HRs	p value
Age	1.06 (1.05, 1.07)	<0.001	1.08 (1.07, 1.10)	<0.001	1.11 (1.09, 1.12)	<0.001	1.09 (1.08, 1.11)	<0.001
SIMD	1.09 (1.06, 1.12)	<0.001	1.14 (1.09, 1.19)	<0.001	1.04 (1.00, 1.09)	0.05	1.08 (1.04, 1.11)	<0.001
Diabetes	2.07 (1.41, 3.03)	<0.001	3.01 (1.81, 4.99)	<0.001	3.14 (1.97, 5.00)	<0.001	0.96 (0.51, 1.81)	0.9
Fam. his.	1.68 (1.48, 1.90)	<0.001	1.43 (1.16, 1.75)	0.001	1.27 (1.05, 1.53)	0.01	0.98 (0.85, 1.14)	0.8
CPD	1.51 (1.34, 1.71)	<0.001	1.71 (1.41, 2.08)	<0.001	2.61 (2.24, 3.03)	<0.001	2.14 (1.91, 2.41)	<0.001
SBP	1.06 (1.03, 1.10)	<0.001	1.15 (1.09, 1.20)	<0.001	1.19 (1.14, 1.24)	<0.001	1.03 (0.99, 1.06)	0.1
TC	1.21 (1.15, 1.27)	<0.001	0.95 (0.86, 1.05)	0.3	1.06 (0.98, 1.15)	0.2	0.93 (0.87, 0.99)	0.02
HDL	0.69 (0.63, 0.76)	<0.001	0.84 (0.73, 0.97)	0.02	0.92 (0.81, 1.04)	0.2	0.98 (0.89, 1.07)	0.6
c-statistic	0.74 (0.73, 0.75)		0.76 (0.73, 0.78)		0.80 (0.78, 0.82)		0.72 (0.70, 0.74)	

Cumulative incidence approach

Further, by summing cause specific hazards over time the cumulative incidence function (CIF). This is simply the (cumulative) probability of incurring a particular event before a particular time.

The predicted cumulative incidence estimates of the first events can be obtained from the Gompertz regression as follows:

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

i.e., the cumulative incidence at time t, $CI_k\ (t_j)$, is the cumulative sum of the unconditional probabilities of having event type k at time t_j, $\Sigma\ p_k(t_j)$, 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 γ is the ancillary 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:

$S(t) = \Pi(1 - \Sigma\ h_k(t_j))$

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

Illustrating the cumulative incidence approach

Figures 4-2 and 4-3 illustrate the cumulative incidence curves for men within the highest and lowest quintiles of deprivation. Given modifiable risk factors were able to be modelled continuously this means that different predictions result from different risk profiles. The result

is that the model can estimate and discriminate risk by individual profiles, rather than for sub-groups which is a common feature in Markov models.

The profiles selected was that of a 60 year old, residing in SIMD 1 (SIMD score = 4) or SIMD 5 (SIMD score = 4 or 60), with no family history, no diabetes, a smoker of 20 cigarettes per day, total cholesterol of 7 and HDL Cholesterol of 1.2.

In comparing figures, the deprivation gradient is apparent with the probability of remaining alive and CVD free higher for the least deprived male. Notably non-CVD death is the event with the highest risk, which underlines the importance that the model estimates the impact of the risk factors beyond CVD. Further, the order of events in terms of probability also varies slightly between profiles. For the least affluent, non-fatal CHD carried the higher risk; and for the most deprived it is non-CVD death.

Figure 4-2 Cumulative incidence of first events – male, least deprived fifth

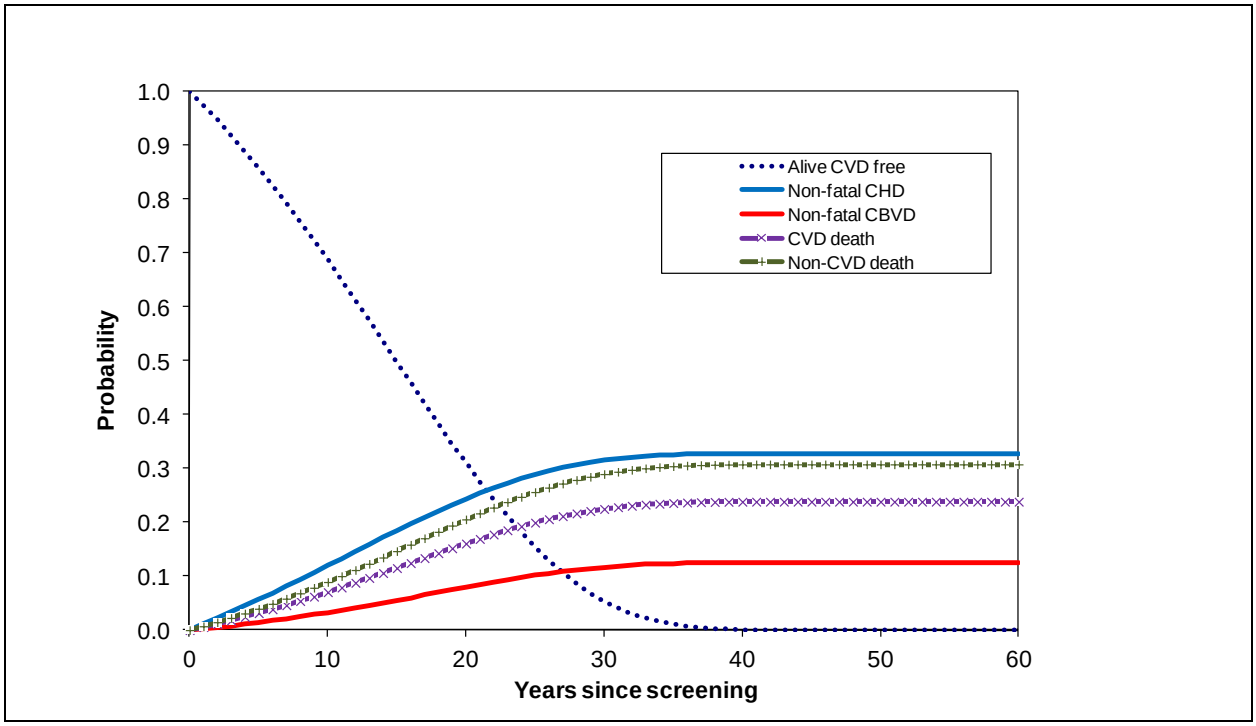
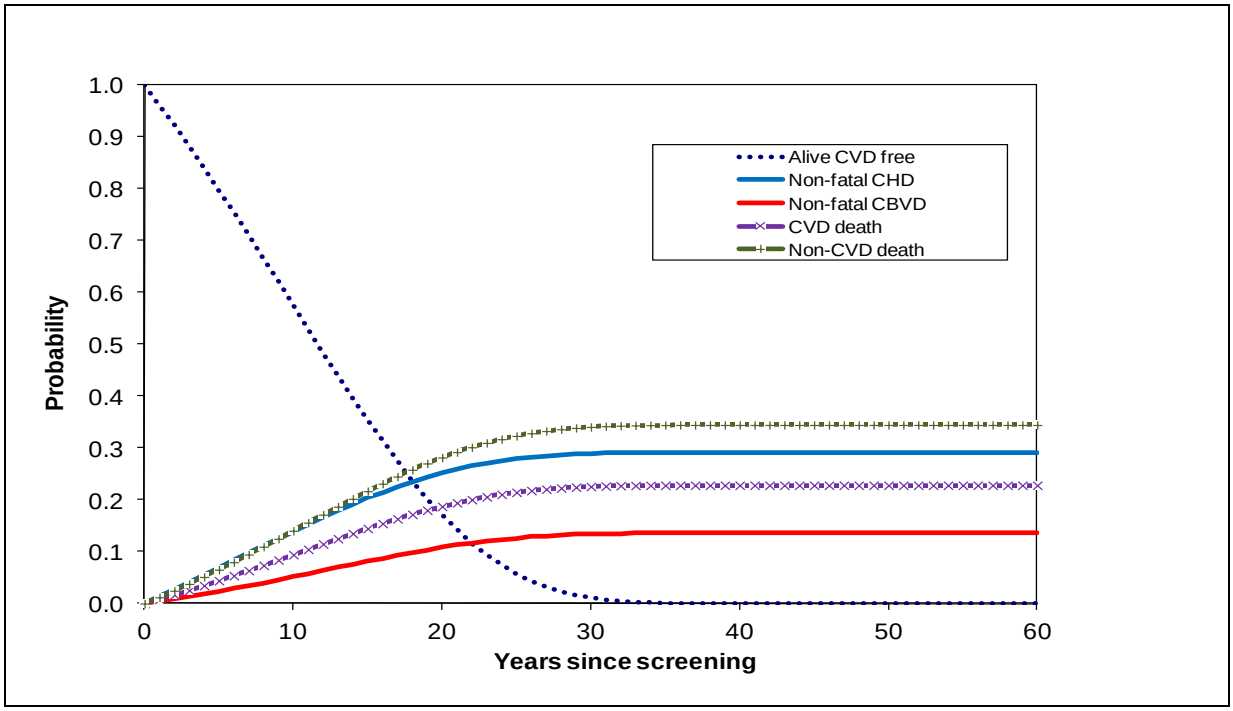
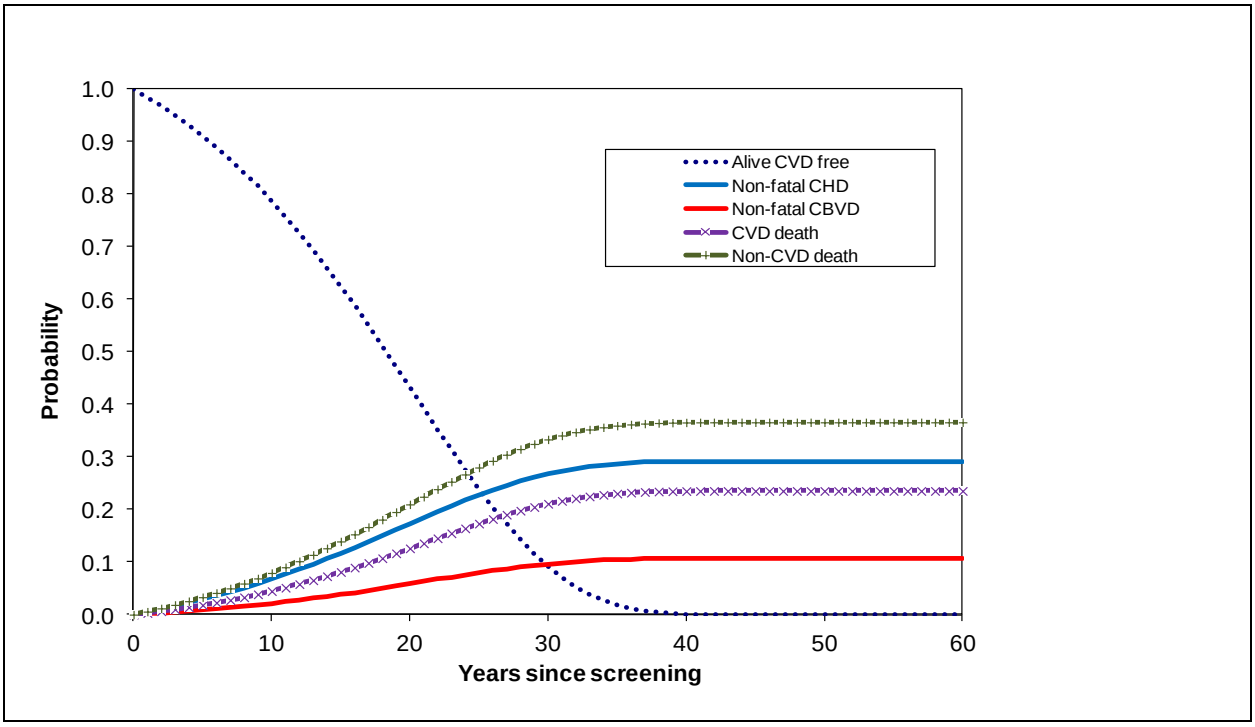


Figure 4-3: Cumulative incidence of first events – male, most deprived fifth



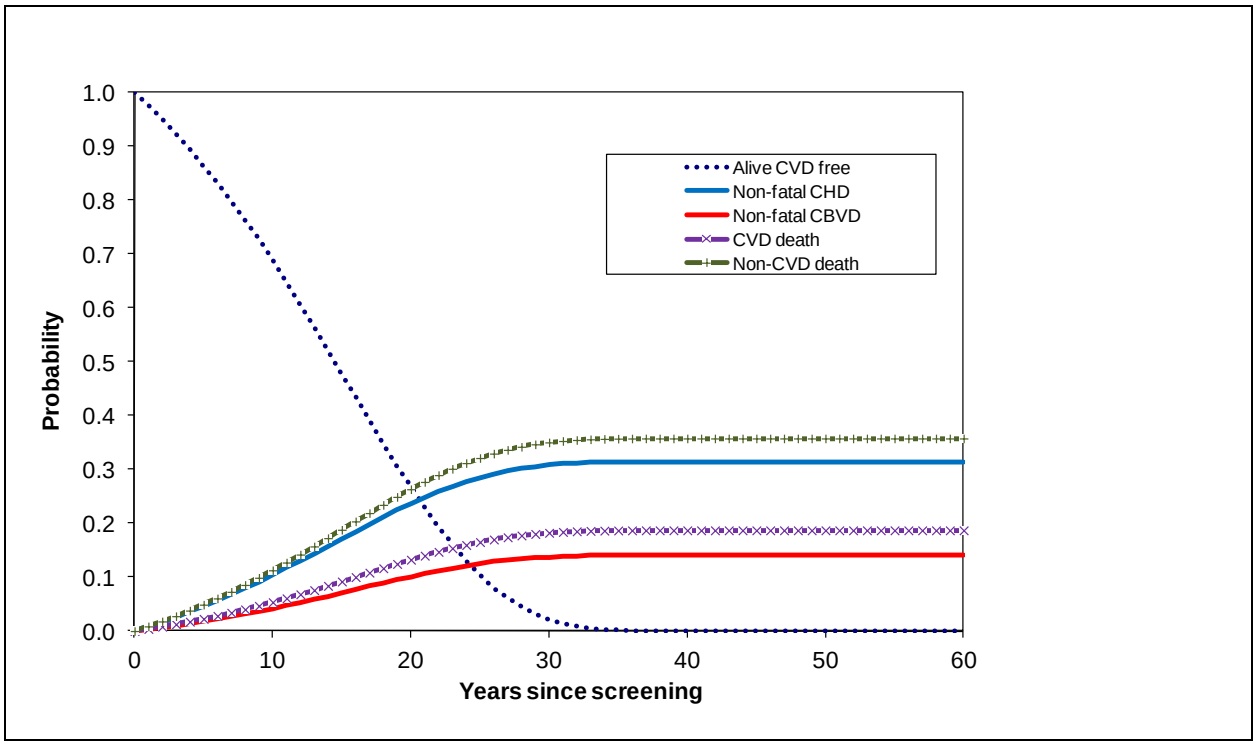
Figures 4-4 and 4-5 illustrate the cumulative incidence curves for women using the same covariate profile as for men, and for the least and most deprived quintiles. Again the deprivation

Figure 4-4: Cumulative incidence of first events – female, least deprived fifth



gradient is apparent with the least deprived remaining free of CVD for longer. Also, and in contrast to men, the order of events in terms of probability is consistent, with the highest risk of fatal non-CVD death. Further, the risk of CVD death is lower in the most deprived over time. In comparing men and women, the probability of remaining alive and CVD free in women in the most deprived quintile is similar to men in the most affluent.

Figure 4-5: Cumulative incidence of first events – female, most deprived fifth



4.3.5 Data modelling II – estimating survival following non-fatal CHD and CBVD events

If the first event incurred was a non-fatal CHD or CVD event, then survival from death was estimated from the following Gompertz regression:

$$S(t) = \exp(-\exp(xb)\gamma^{-1}(\exp(\gamma t) - 1))$$

where xb is the linear predictor from the regression and γ is the ancillary parameter estimated from the data. The non-modifiable risk factors were used in the model with age at event replacing age at SHHEC (used in equation 1). The expert panel advising on the model approach suggested that survival would be more influenced by age at event rather than the age at which individuals entered the baseline survey. To reiterate, SHHEC did not rescreen

individuals to track modifiable risk factors over time post-screening. Therefore, to estimate survival post first event only the non-modifiable risk factors were used.

Table 4-6 Modelling the hazard of death post non-fatal event

a) Men - survival following non-fatal first event

Covariate	After non-fatal CHD		After non-fatal CBVD	
	HRs	p value	HRs	p value
Age at event	1.08 (1.07, 1.09)	<0.001	1.07 (1.05, 1.09)	<0.001
SIMD sc.	1.14 (1.09, 1.19)	<0.001	1.09 (1.03, 1.16)	0.004
Fam. his.	0.97 (0.79, 1.18)	0.7	1.06 (0.77, 1.47)	0.7
c-statistic	0.68 (0.65, 0.71)		0.65 (0.61, 0.69)	

b) Women - survival following non-fatal first event

Covariate	After non-fatal CHD		After non-fatal CBVD	
	HRs	p value	HRs	p value
Age at event	1.08 (1.06, 1.09)	<0.001	1.07 (1.05, 1.09)	<0.001
SIMD sc.	1.08 (1.03, 1.13)	0.003	1.00 (0.93, 1.08)	0.9
Fam. his.	0.75 (0.60, 0.95)	0.02	1.20 (0.86, 1.67)	0.3
c-statistic	0.67 (0.63, 0.70)		0.66 (0.61, 0.71)	

Notes: 95% confidence intervals in brackets; HRs for continuous covariates are for 0.5 unit increases (HDL), 1 unit increases (age, TC), 10 unit increases (SIMD, SBP), and 20 unit increases (CPD)

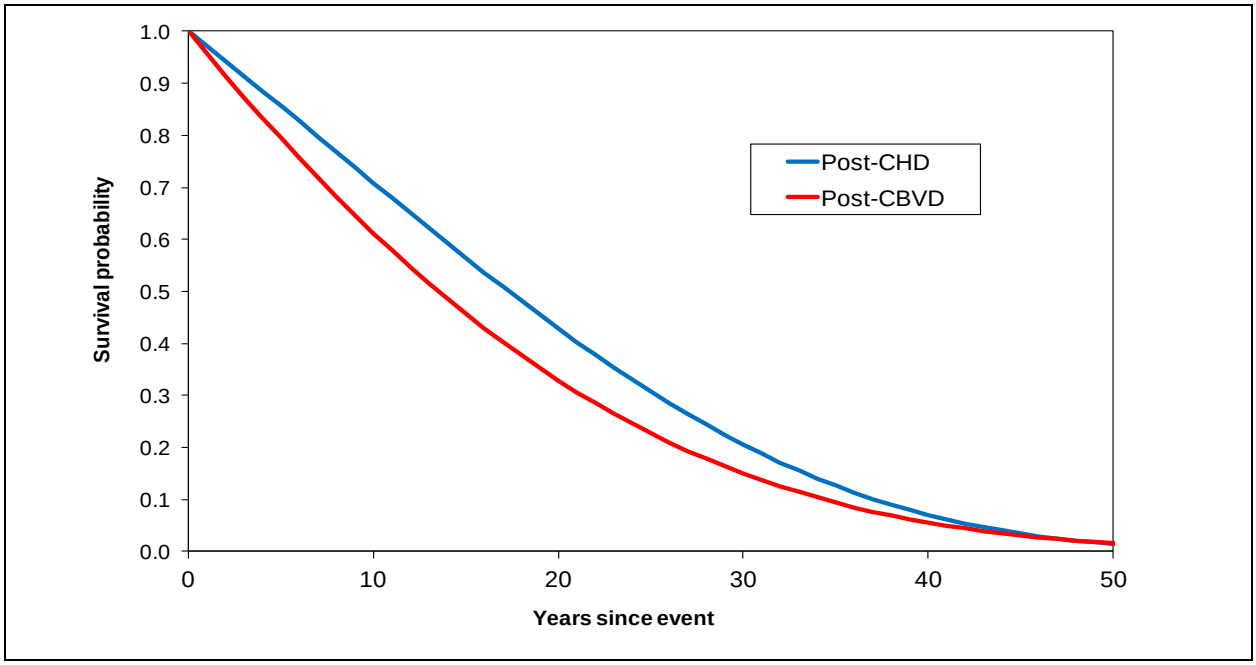
The hazards do vary between men and women, with the exception of age. Noticeably, the estimate for family history is not significant; nonetheless all estimates are used in the modelling. Appendix 3 provides the associated Cholesky decomposition for 2nd events.

The model generates survival curves for each individual covariate profile and conditional upon the age at which a particular non-fatal event occurs.

Illustrating the model - Survival conditional upon first event

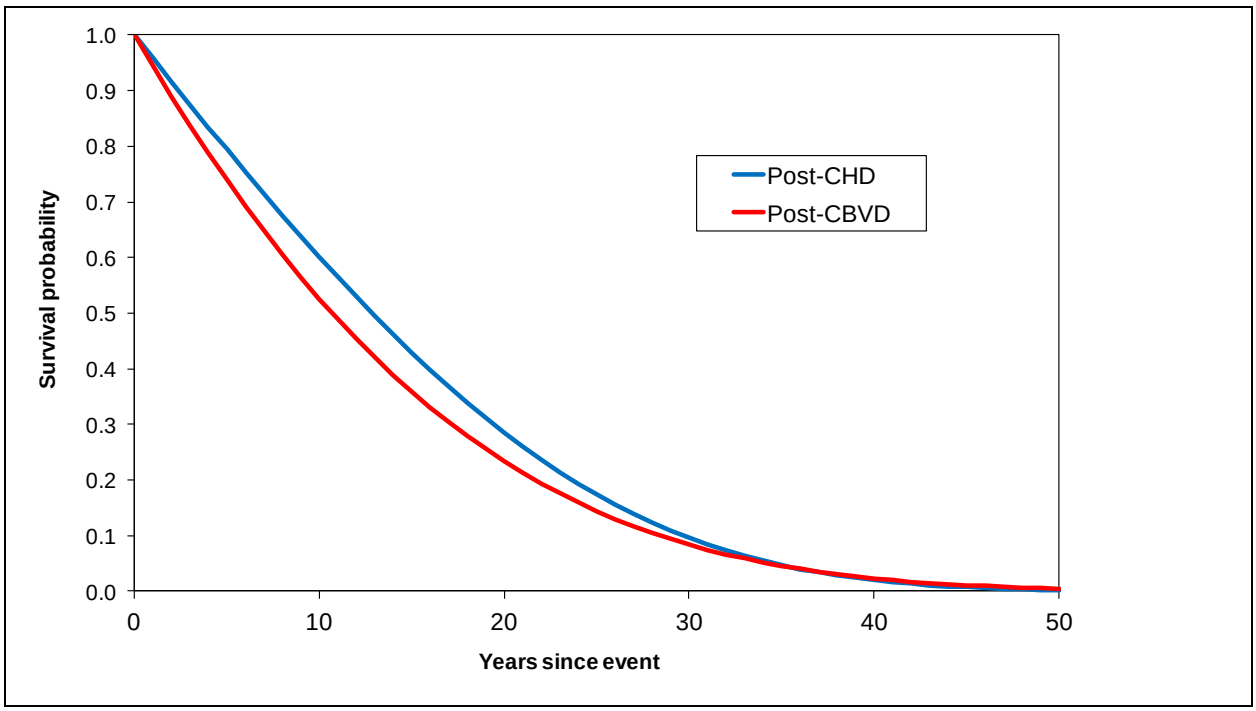
Figure 4-6 and 4-7 illustrates the survival curves that the model can generate. For consistency, of exposition the same covariate profiles as for first events are used.

Figure 4-6: Survival post nonfatal event – men, least deprived fifth



In comparing the figures, survival is higher for post-CHD than post-CBVD and also across the most and least and most deprived fifth. For the least deprived fifth survival post-CHD is higher

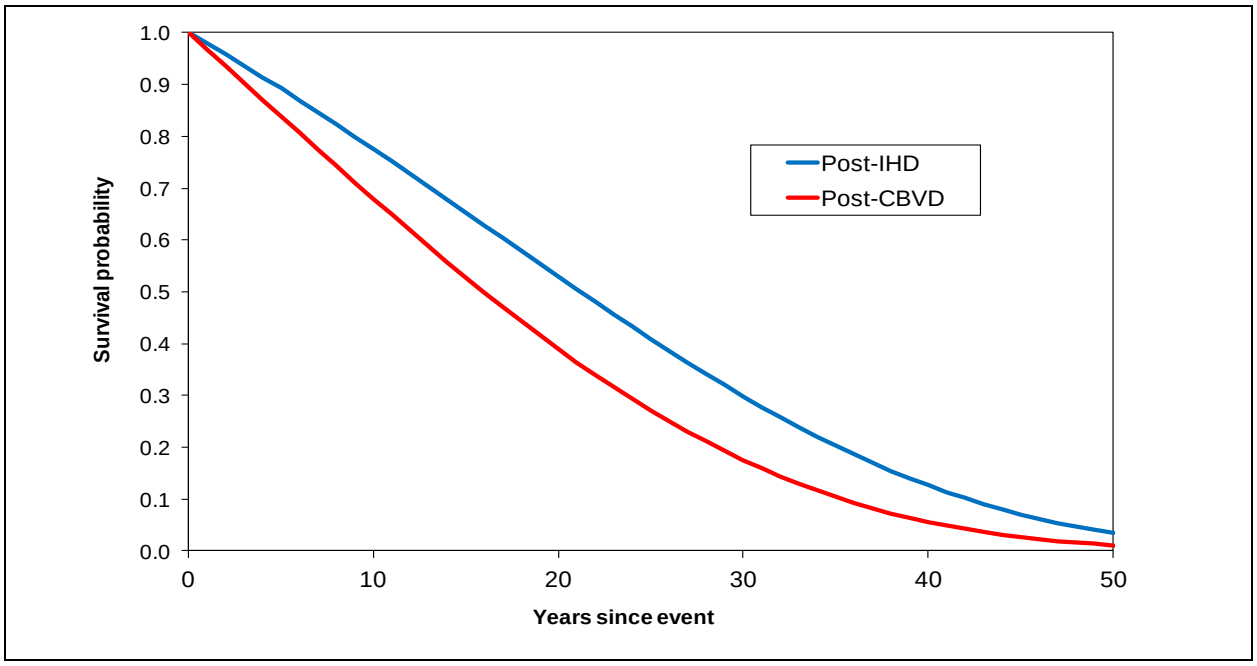
Figure 4-7: Survival post nonfatal event – men, most deprived fifth



compared to survival post CHD. These patterns are also observed for men in the most deprived fifth. Further, the deprivation gradient is evident with the most deprived lower survival across following both CHD and CBVD non-fatal events.

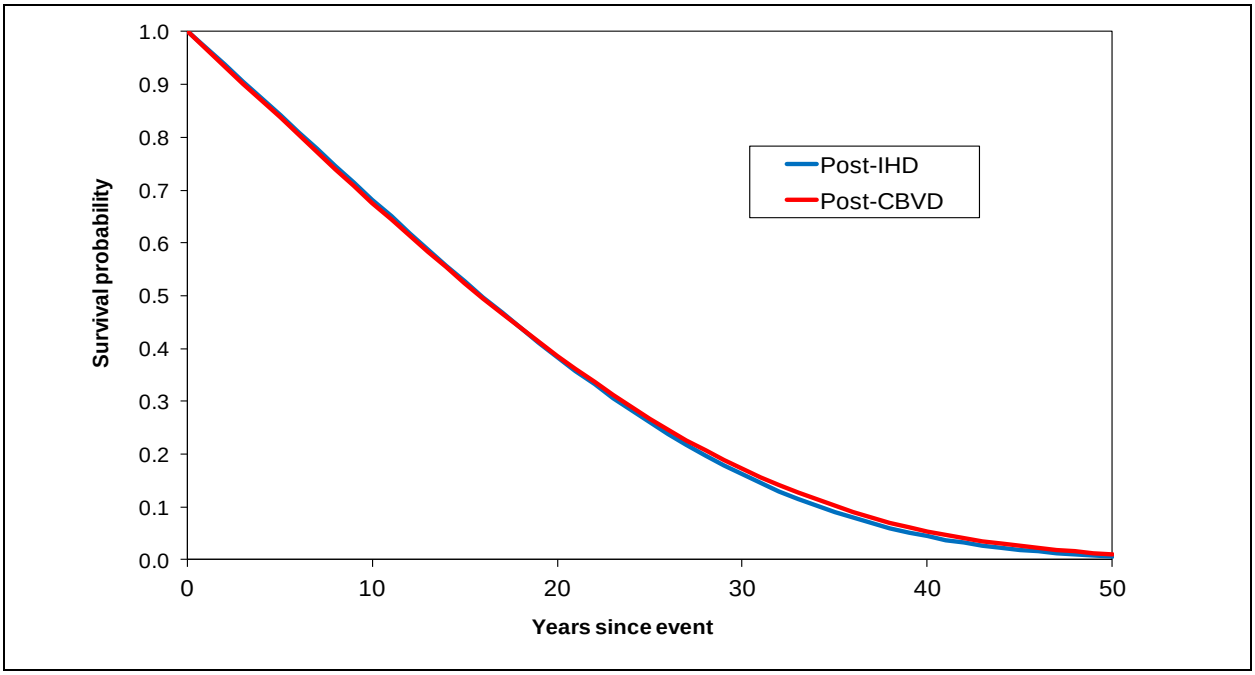
Figure 4-8 and 4-9 shows survival estimates for women, again using the same covariate profiles as for first events and for men. A similar results pattern is also obtained, with survival post-CHD higher and the appearance of the deprivation gradient. In addition, survival for women is higher than for men, in both events and within the deprivation fifths also.

Figure 4-8: Survival post nonfatal event – women, least deprived fifth



Overall, the gender and deprivation gradient is driven by incidence of the first events, rather than risk of death post first event.

Figure 4-9: Survival post nonfatal event – women, most deprived fifth



4.3.4 Data modelling III: estimating average life expectancy

The next stage in the modelling is to estimate average life expectancy. The illustrations above estimated the risk of first events over a lifetime, but and the survival curves if either a non-fatal CHD or non-fatal CVBD event occurred in the first year post screening. However, individuals are at risk of any of the first four events at anytime post screening, and survival is conditional upon which first event occurs and when. Therefore, there is a need to model all possible scenarios an individual faces and weight these possibilities to generate average life expectancy.

Four stage process

There are four stages involved to estimate the average life expectancy of an individual as they enter the model free of CVD. First, the model conduct a "what-if analysis" to estimate the additional life years that can be expected if a particular event was incurred at a particular time. The time (in years) that elapsed before the first event is counted and if the first event is non-fatal this is added to the area under the predicted survival curve to estimate remaining life years. To estimate this area under the survival curve, the area is divided into a series of horizontal segments defined by the annual cycles of the model. The area under each segment is estimated by using the trapezoid method (essentially divided each segment into a

rectangle and triangles. The sum across each segment then gives an estimate under the survival curve.

Overall, this process is repeated for an exhaustive set of scenarios. Given one of four first events can occur in any of 100 annual cycles of the model this generates a total of 400 scenarios an individual faces upon entering the model. Table 4-7 a-c illustrates this process for the 60 year male living in the most deprived fifth that was introduced earlier. 4.7a shows the life years remaining for an individual upon entering the model at time 0 up to incurring one of the first four events. For instance, if the male profile incurred a non-fatal CHD event in the first year post screening then the life years remaining would be 15.7. This is one year being CVD free before the first event, and 14.7 years survival from the first event. If a non-fatal CBVD event were to occur in year 22 post screening, then the life years remaining are 25.8. This is the 22 years CVD free prior to the first event, and 3.8 years survival post first event. On the other hand, if the first event is fatal, then the life years remaining in the model is the time before the event. For instance, if a CVD death occurs in year 24, then life years remaining from entering the model is 24 years.

Table 4-7 a) Life years remaining upon entering model [for non-fatal outcomes = time before event + time after event]

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	CVD death	nonCVD death
1	15.7	14.0	1.0	1.0
2	15.9	14.3	2.0	2.0
3	16.2	14.7	3.0	3.0
.				
.				
22	25.8	25.8	22	22
23	26.6	26.6	23	23
24	27.3	27.4	24	24
.				
.				
100	100.5	100.5	100.0	100.0

The second stage estimates the probability of actually incurring a particular event within a particular cycle. This probability is then derived from the cause specific hazards and is the per cycle addition to the cumulative incidence estimates (i.e. the difference between the cumulative estimates of adjacent cycles) that were illustrated previously.

b) Probability of event occuring [event type and timing]

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	CVD death	nonCVD death
1	0.026	0.006	0.014	0.013
2	0.026	0.006	0.014	0.013
3	0.026	0.007	0.015	0.013
.				
.				
22	0.004	0.002	0.003	0.003
23	0.003	0.002	0.003	0.003
24	0.002	0.001	0.002	0.002
.				
.				
100	0.000	0.000	0.000	0.000

Note, that the sum of the probability of events across all model cycles is always equal to 1. This provides an internal verification check when running the model and denotes that an individual must experience one of the four first events over the course of a lifetime.

The third stage is to then create an overall estimate of life years remaining by weighting stage 1 (all 400 scenarios) by stage 2 (probability of scenarios). This process gives an overall expectation of the additional life expectancy that an individual can expect.

c) Weighted remaining life years [estimates from a) multiplied by estimates from b)]

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	CVD death	nonCVD death	*Sum*
1	0.407	0.087	0.014	0.013	*0.521*
2	0.411	0.092	0.029	0.026	*0.558*
3	0.414	0.097	0.044	0.040	*0.595*
.					
.					
22	0.103	0.050	0.076	0.072	*0.301*
23	0.081	0.041	0.062	0.059	*0.244*
24	0.062	0.033	0.050	0.047	*0.192*
.					
.					
100	0.000	0.000	0.000	0.000	*0.000*

Total life years remaining (Cumulative sum over each model cycle) =	*14.42*
Overall life expectancy (age upon entering model plus remaining life years) =	*74.42*

Fourth, to calculate the overall life expectancy of an individual as they entered the model CVD free, we take the sum of the expected additional life years (calculated above) and add this to the age of the person as they entered the model. Continuing with the example of the

60 year deprived male, he can expect to live an additional 14.42 years, giving him a life expectancy of 74.42 years.

4.4 Modelling Stage 4: Uncertainty analysis

As discussed in chapter 3 under best practice guidelines, there are four main aspects to uncertainty, namely, (i) stochastic, (ii) parameter; (iii) heterogeneity; and (iv) structural. The estimates of the event hazards given previously provide an illustration of (i) and (ii). No structural uncertainty was undertaken such as reformulating the model structure. The focus in the exposition of uncertainty analysis in this thesis is heterogeneity. That is, to illustrate how the model can discriminate between individuals in terms of risk of CVD using the ASSIGN risk factors. The intention is to illustrate that the policy model may be thought of as a natural extension to 10-year risk scores but rather than discriminate individuals on the basis of 10 year risk, the policy model can discriminate on the basis of lifetime risk (including 10-year risk if desired) and life expectancy.

Standard 10-year risk tables as used by JBS2(120) was used to define a set of individual risk factor profiles. These were then fed into the Scottish CVD Policy Model individually and life expectancies were estimated. Smokers were assumed to smoke 20 cigarettes per day. For exposition purposes, all risk profiles were attributed a family history of 0.26 and diabetes of 0.15 - the average proportions found within the SHHEC baseline screening survey. Estimates of risk and life expectancy were made for men and women and for the highest and lowest quintiles of SIMD (SIMD score of 4 and 60 respectively). Separate tables were also estimated conditional upon smoking status.

Figure 4-10 illustrates the life expectancy estimates for men residing in the least deprived fifth (SIMD 1) and the most deprived fifth (SIMD 5). Overall, the model shows an ability to discriminate between risk profiles resulting in different life expectancies. First, we see an age gradient for equivalent risk factors profiles, in that conditional upon reaching a certain age life expectancy improves. Secondly, life expectancy improves (in general) as risk factors are reduced. The risk profile resulting in the highest life expectancy estimate is a non-smoker accompanied with the lowest systolic blood pressure and cholesterol ratio. This profile is consistent with recommendations in clinical guidelines.

Figure 4-10 Life expectancies for multiple risk profiles – men

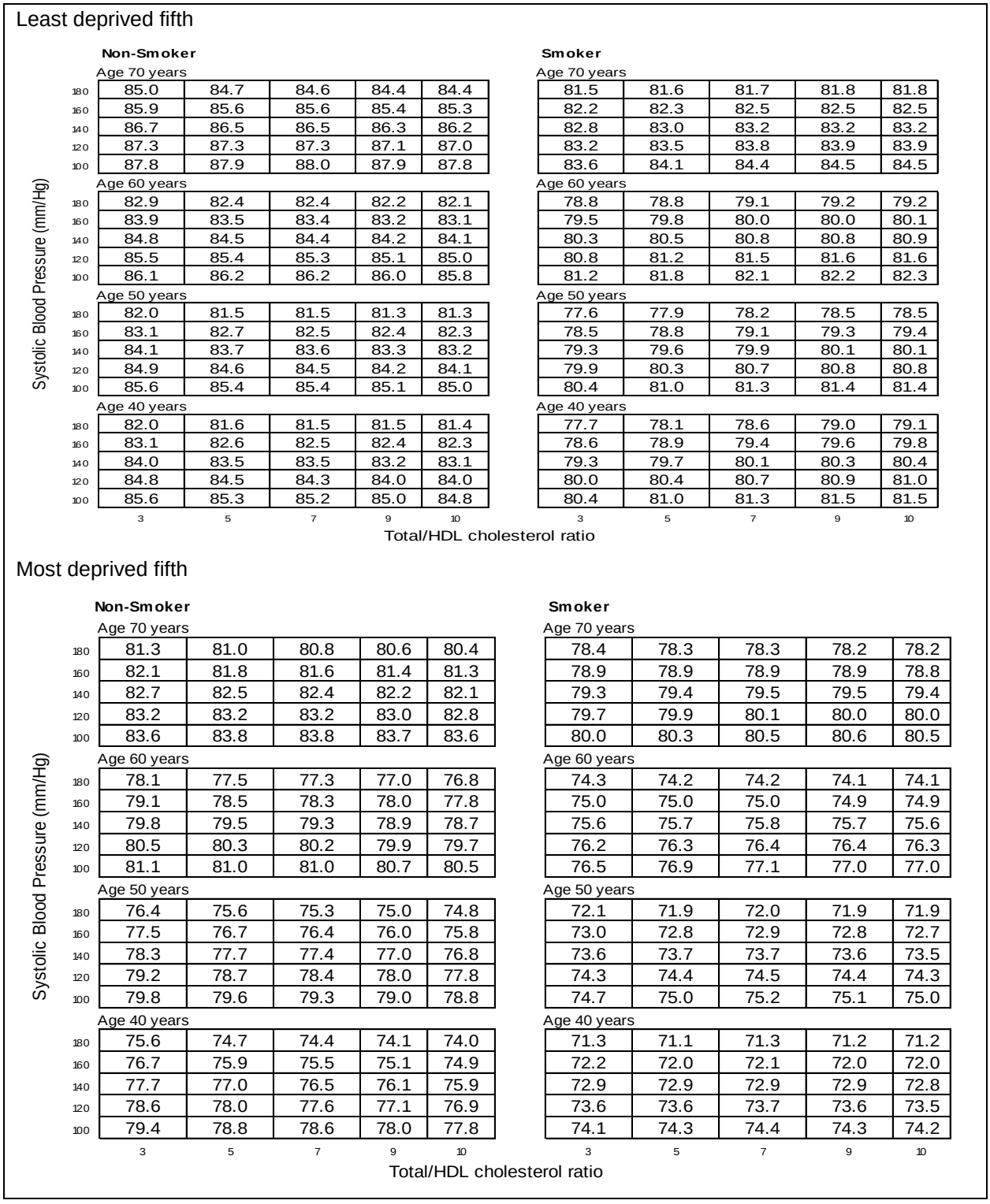
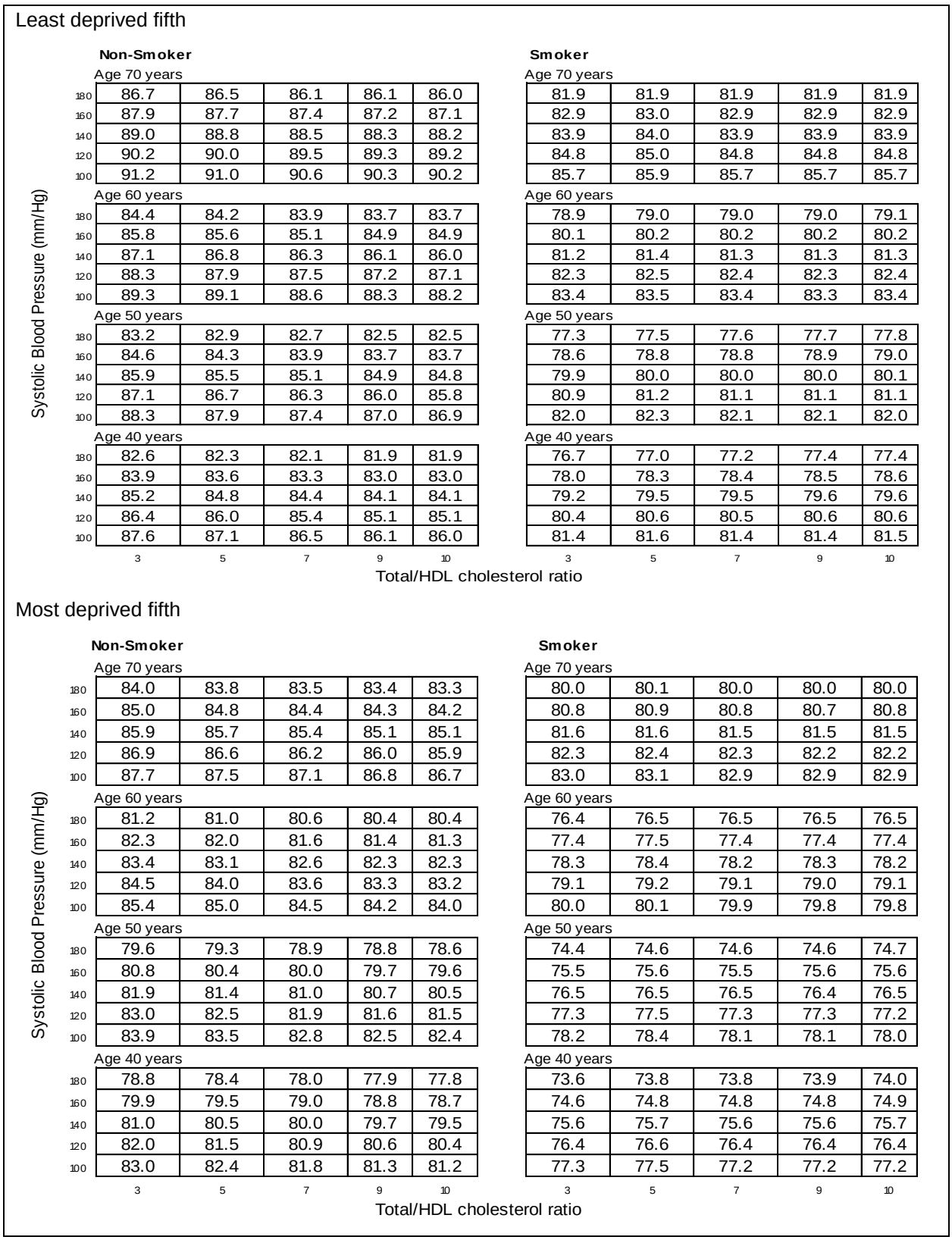


Figure 4-11 Life expectancies for multiple risk profiles - women



More specifically, smoking is the single most important risk factor. For instance, the difference in life expectancies between smokers and non-smokers with an otherwise identical risk factor

profile is as much as 5.3 years – comparing life expectancies for 40 year old men with risk profiles consisting of the highest SBP and total-to-HDL cholesterol reading.

The model can also sensitise life expectancy predictions. This can take the form of univariate, analysis of extremes, or multi-variate sensitivity. In particular, using the Cholesky decomposition matrixes the model can perform probabilistic sensitivity analysis in estimating life expectancy. When running the model, it is straightforward to switch from a deterministic analysis (using mean hazards rates) to a probabilistic analysis, where an individual profile is run through the model multiple times in a series of loops and coefficients are randomly selected using the Cholesky decomposition. That is, to select a coefficient random draws are made from the Cholesky decomposition where all parameters are allowed to vary simultaneously. This process generates a confidence interval for the resultant life expectancy estimate.

For example, using the male profile in the most deprived fifth that was introduced earlier, the average life expectancy was estimated to be 74.42 within a deterministic analysis (using means). After 10,000 loops of the model the life expectancy prediction had a 95% confidence interval that ranged from 73.12-75.78.

4.5. Modelling stage 5: Validating and reporting

4.5.1 Face validity

Face validity of the model was achieved by drawing upon the expert panel of advisors. The model objective, structure and functioning were corroborated as valid representations of the problem of primary prevention and the process of estimating life expectancy using the methods described.

4.5.2 Internal Validity

Discrimination

The discrimination of all statistical models was good with c-statistics in the range 0.65-0.80, for models predicting first and second events. Discrimination was better for the first event models than the models following a first non-fatal event, better for the fatal CVD outcome compared to the other competing first events, and generally better for the model developed for women.

Calibration

The observed number of events in the SHHEC-SMR dataset was compared to model predictions, both for modelling stages 1 and 2. This was done for all individuals at SHHEC baseline, and separately for men and women. Observations and predictions were compared for first and second events (death following a non-fatal CVD event), and across fifths of linear predictors. The latter then tests the model across predicted levels of risk (e.g. the highest fifth of linear predictors are those individuals at higher predicted risk) to provide a more rigorous test of goodness of fit rather than overall event rates. Tables 4-8 to 4-11 provide the results for men and women, for first events and death post non-fatal event.

In comparing the observed and predicted values a p-value in excess of 0.05 means that the null hypothesis that the model is not a good fit can be rejected. Overall, the model fits the data well with p-values generally in excess of 0.05. The exception is for non-fatal CHD events in the lowest fifth of linear predictors. The model tends to over predict the number of events at the lower end of risk, with evidence of lack of fit also seen in the fourth quintile of the linear predictor.

Table 4-8 Comparison of observed first events against predicted events - men

a) non-fatal CHD

		Observed		Predicted		P-value	
Quintile - lowest fifth of linear predictors	1	73	(70, 76)	109	(107, 111)	0.001	(0, 0.002)
	2	196	(188, 204)	194	(191, 195)	0.797	(0.338, 0.932)
	3	277	(267, 289)	258	(256, 261)	0.270	(0.052, 0.555)
	4	382	(370, 394)	326	(322, 328)	0.004	(0, 0.022)
Quintile - highest fifth of linear predictors	5	426	(419, 434)	468	(462, 472)	0.055	(0.016, 0.086)

b) Non-fatal CBVD

		Observed		Predicted		P-value	
Quintile - lowest fifth of linear predictors	1	32	(31, 34)	34	(33, 34)	0.782	(0.658, 0.974)
	2	48	(47, 51)	63	(62, 64)	0.070	(0.036, 0.148)
	3	90	(84, 95)	88	(88, 89)	0.703	(0.448, 0.902)
	4	130	(125, 138)	113	(112, 114)	0.160	(0.023, 0.291)
Quintile - highest fifth of linear predictors	5	163	(160, 165)	165	(163, 166)	0.882	(0.694, 0.989)

c) fatal CVD

		Observed		Predicted		P-value	
Quintile - lowest fifth of linear predictors	1	20	(18, 22)	29	(29, 30)	0.093	(0.044, 0.21)
	2	62	(57, 64)	70	(69, 71)	0.338	(0.134, 0.477)
	3	124	(120, 127)	116	(115, 116)	0.445	(0.245, 0.732)
	4	186	(183, 191)	171	(170, 173)	0.266	(0.1, 0.398)
Quintile - highest fifth of linear predictors	5	305	(302, 308)	310	(308, 312)	0.735	(0.599, 0.834)

d) Non-fatal CVD

		Observed		Predicted		P-value	
Quintile - lowest fifth of linear predictors	1	45	(43, 46)	52	(51, 52)	0.333	(0.223, 0.432)
	2	120	(116, 127)	112	(111, 112)	0.443	(0.158, 0.701)
	3	161	(158, 163)	174	(173, 176)	0.318	(0.178, 0.418)
	4	247	(243, 250)	247	(245, 248)	0.882	(0.779, 0.98)
Quintile - highest fifth of linear predictors	5	413	(408, 417)	402	(398, 403)	0.565	(0.454, 0.699)

Table 4-9 Comparison of observed first events against predicted events - women

a) Non-fatal CHD

		Observed		Predicted		P-value	
Quintile - lowest fifth of linear predictors	1	39	(36, 43)	55	(53, 55)	0.052	(0.01, 0.128)
	2	98	(94, 102)	112	(110, 113)	0.193	(0.084, 0.354)
	3	184	(173, 195)	169	(167, 171)	0.290	(0.056, 0.787)
	4	281	(269, 288)	249	(248, 251)	0.074	(0.013, 0.226)
Quintile - highest fifth of linear predictors	5	383	(375, 397)	400	(396, 402)	0.422	(0.237, 0.818)

b) Non-fatal CBVD

		Observed		Predicted		P-value	
Quintile - lowest fifth of linear predictors	1	15	(14, 17)	18	(17, 18)	0.545	(0.358, 0.878)
	2	39	(36, 42)	39	(39, 40)	0.783	(0.612, 0.985)
	3	62	(58, 66)	62	(62, 63)	0.831	(0.612, 0.991)
	4	98	(93, 101)	93	(92, 93)	0.583	(0.38, 0.952)
Quintile - highest fifth of linear predictors	5	168	(164, 170)	170	(169, 172)	0.865	(0.639, 0.991)

c) Fatal CVD

		Observed		Predicted		P-value	
Quintile - lowest fifth of linear predictors	1	9	(8, 10)	12	(12, 12)	0.442	(0.268, 0.627)
	2	27	(24, 28)	34	(34, 35)	0.198	(0.087, 0.29)
	3	71	(66, 75)	65	(65, 66)	0.527	(0.208, 0.931)
	4	119	(113, 124)	113	(112, 113)	0.567	(0.269, 0.991)
Quintile - highest fifth of linear predictors	5	244	(239, 247)	245	(244, 246)	0.892	(0.727, 0.961)

d) Non-fatal CVD

		Observed		Predicted		P-value	
Quintile - lowest fifth of linear predictors	1	52	(49, 54)	45	(45, 46)	0.350	(0.208, 0.567)
	2	95	(91, 97)	98	(97, 98)	0.760	(0.508, 0.963)
	3	136	(133, 140)	150	(149, 151)	0.264	(0.135, 0.387)
	4	210	(204, 215)	215	(215, 216)	0.741	(0.429, 0.994)
Quintile - highest fifth of linear predictors	5	347	(344, 349)	331	(330, 333)	0.393	(0.318, 0.529)

Table 4-10 Comparison of observed fatal event against predicted events - men

a) From non-fatal CHD

		Observed	Expected	P-value
Quintile - lowest fifth of linear predictors	1	66	65	0.868
	2	90	85	0.603
	3	86	95	0.350
	4	104	103	0.883
Quintile - highest fifth of linear predictors	5	109	108	0.887

b) From non-fatal CBVD

		Observed	Expected	P-value
Quintile - lowest fifth of linear predictors	1	28	29	0.844
	2	44	37	0.277
	3	39	46	0.332
	4	48	46	0.821
Quintile - highest fifth of linear predictors	5	41	42	0.928

Table 4-11 Comparison of observed fatal event against predicted events - women

a) From non-fatal CHD

		Observed	Expected	P-value
Quintile - lowest fifth of linear predictors	1	40	45	0.471
	2	55	58	0.718
	3	68	57	0.157
	4	65	62	0.663
Quintile - highest fifth of linear predictors	5	65	72	0.438

b) From non-fatal CBVD

		Observed	Expected	P-value
Quintile - lowest fifth of linear predictors	1	21	21	0.967
	2	28	31	0.560
	3	37	30	0.207
	4	33	34	0.826
Quintile - highest fifth of linear predictors	5	28	31	0.642

4.5.3 External validation – predicting results from a clinical trial

Access was granted to the West of Scotland Coronary Prevention Study (WOSCOPS) study, through a colleague on the expert panel, Professor Ian Ford who leads the Robertson Centre at the University of Glasgow which holds the dataset. WOSCOPS was a randomised, doubled-blinded, 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. Risk profiles for individuals recruited to WOSCOPS were run through the model and predictions were compared against observations. This was done for both the placebo and intervention groups separately.

For the placebo group baseline risk factors were inputted into the model, and the model's ability was assessed by checking whether the predicted cumulative incidence curves fell within the 95% confidence interval limits of the observed cumulative incidence curves. The predicted line falls well within the confidence interval limits for non-fatal CBVD and fatal CVD events. However, the model under-predicts for non-fatal CHD and over-predicts for fatal non-CVD. The latter may be explained by the fact that WOSCOPS is a clinical trial and that stringent exclusion criteria often result in a lower other cause mortality due to the exclusion of prevalent terminal disease (e.g. cancer).

For the intervention group, validation proceeded through the effect of treatment on total cholesterol in order to mimic the intended use of the model. WOSCOPS reported that pravastatin reduced total cholesterol by 20% and increased HDL by 5% on average. These changes were used to change individual risk profiles. In running the augmented risk profiles through the model to predict event rates, the impact of total cholesterol on non-CVD death was held constant. To reiterate, a protective association was found in the SHHEC-SMR data; however on the advice of the expert panel this was not considered to be a causal relationship.

For the intervention group, the model also performs quite well, with cumulative incidence predictions within the confidence intervals of CHD, stroke and CVD death. For non-CVD death the model systematically under-predicts. Perhaps, this can also be explained by the exclusion criteria employed by WOSCOPS. The insertion of an intercept (negative) would then lead to accurate predictions.

Figure 4-12 Predicting outcomes in the placebo group

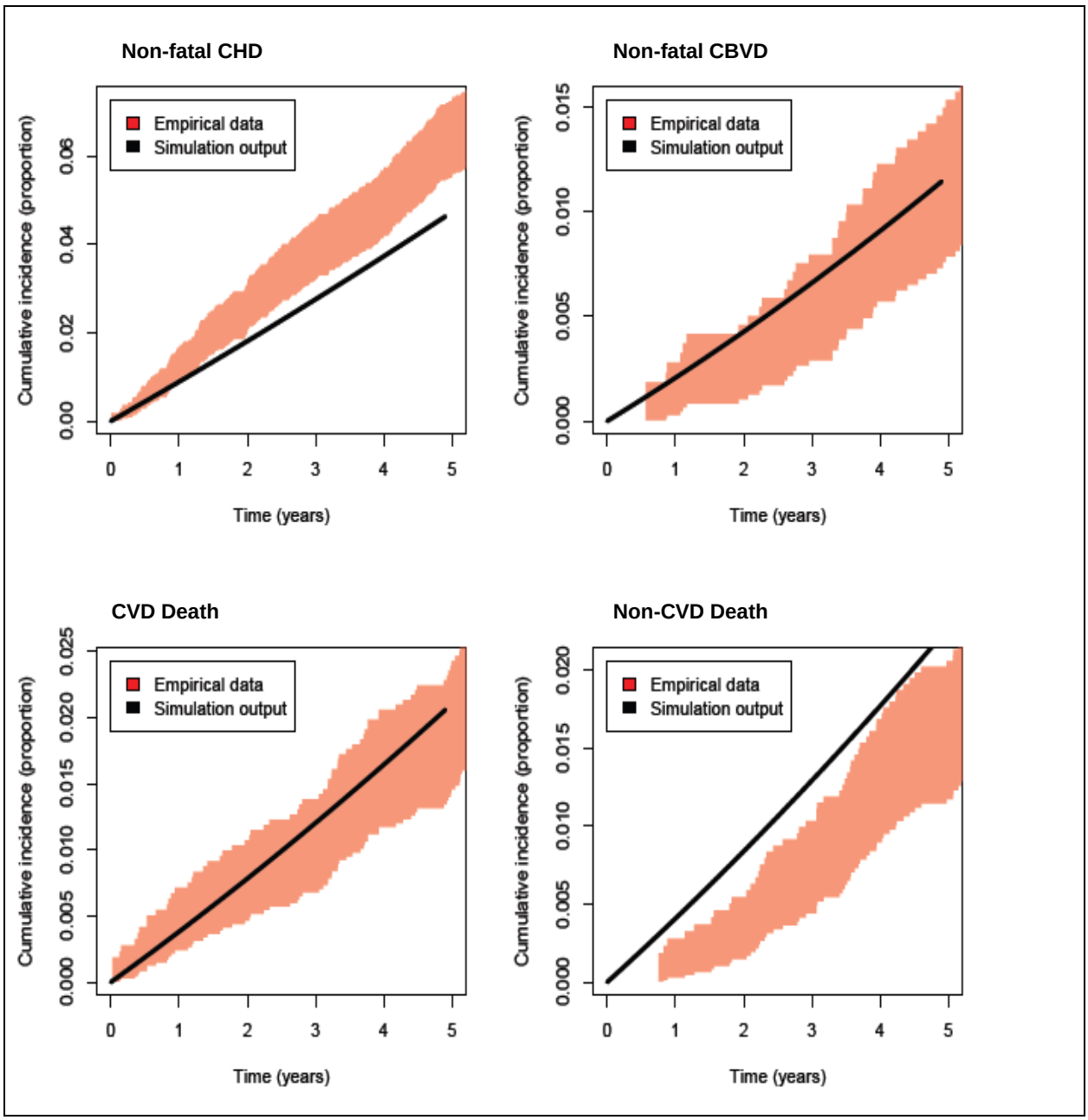
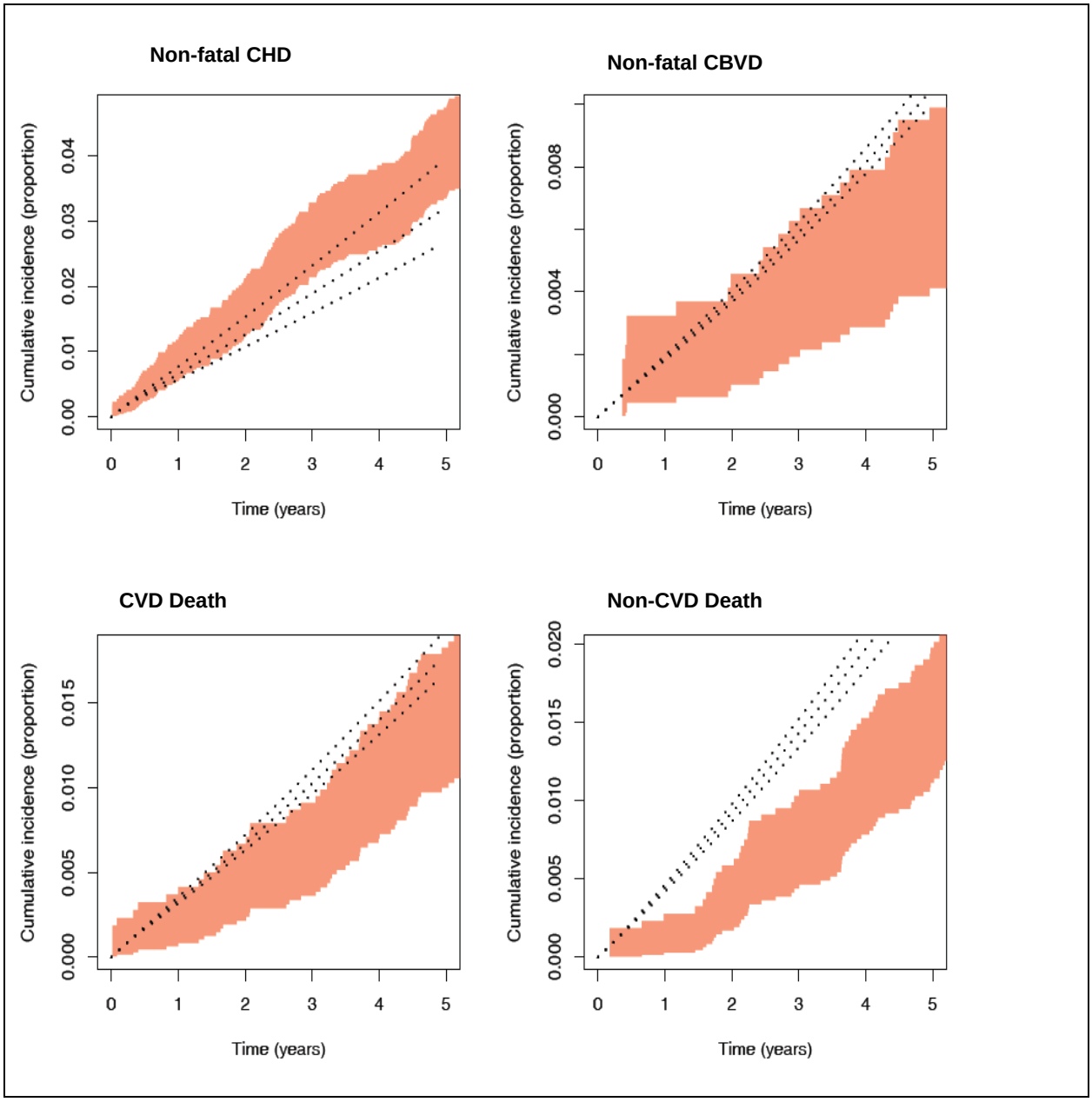


Figure 4-13 Predicting outcomes in the intervention group



4.5.4 Recalibrating model predictions to contemporary Scottish life expectancy estimates

The model performed reasonably well regarding internal validation predicting first and second events of the SHHEC and WOSCOPS populations (1980s). However, the model performed less well in predicting life expectancy in more contemporary populations. Table 4-12 illustrates life expectancy predictions for 40, 60 and 80 year old men and women using average risk factor profiles taken from the Scottish Health Survey (SHeS) 2009. These are compared with 2009 lifetables from General Registrar's Office for Scotland(283). The original model predictions are denoted with a linear predictor multiplication factor of 1.

A judgement was made to keep the calibration exercise as simple and parsimonious as possible. The aim was to develop a single calibration factor (one for men, and one for women) that can be applied across all profiles, rather than a range of calibration factors for different age and socioeconomic deprivation profiles. The consequent assumption is that while the age and socioeconomic gradients have remained unchanged in contemporary Scottish populations, compared to the original SHHEC population (from the mid-1980s).

Further, a pragmatic approach was taken to recalibration, where the linear predictor was adjusted for the first four events. An algorithm was created to run through different linear predictor multiplication factors using the three different age profiles. This started with 0.99 and worked down to 0.90. This process was done separately for men and women. A Root Mean Square Error (RMSE) was to estimate the difference in life expectancy between predictions and observations across all three ages. The algorithm stopped when a multiplicative factor resulted in a fit of less than one year across all profiles. Multiplying the linear predictor by 0.96 produced a RMSE of 0.26 and 0.89 years for men and women, respectively. All model estimates after this calibration factor had been applied were within half a year of the life table estimates with the exception of 80 year old women.

Table 4-12 Recalibrating life expectancy predictions to Scottish Lifetables 2009

a) Men

Linear predictor multiplication factor		Age (years)			RMSE
		40	60	80	
1	Model life expectancy	80.31	81.82	88.38	
	Life table life expectancy	78.01	80.66	87.66	
	Difference	2.30	1.16	0.72	1.54 years
0.96	Model life expectancy	78.21	80.26	87.76	
	Life table life expectancy	78.01	80.66	87.66	
	Difference	0.20	−0.40	0.10	0.26 years

b) Women

Linear predictor multiplication factor		Age (years)			RMSE
		40	60	80	
1	Model life expectancy	83.49	85.62	91.33	
	Life table life expectancy	81.73	83.57	89.02	
	Difference	1.76	2.05	2.31	2.05 years
0.96	Model life expectancy	81.20	83.90	90.42	
	Life table life expectancy	81.73	83.57	89.02	
	Difference	−0.53	0.33	1.40	0.89 years

Re-estimating average life expectancy

Following recalibration of the model, the following illustrates how this affects the life expectancy estimate of the 60 year old male introduced earlier. To reiterate, the estimation of average life expectancy is undertaken in four steps, as follows. First, the remaining life expectancy is estimated from an individual entering a particular first event state in every cycle of the model (Table 4-13). The estimate is the sum of event free years until the first event and cumulative survival if the first event was non-fatal.

Table 4-13 a) Life years remaining upon entering model [for non-fatal outcomes = time before event + time after event]

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	CVD death	nonCVD death
1	15.7	14.0	1.0	1.0
2	15.9	14.3	2.0	2.0
3	16.2	14.7	3.0	3.0
.				
.				
22	25.8	25.8	22	22
23	26.6	26.6	23	23
24	27.3	27.4	24	24
.				
.				
100	100.5	100.5	100.0	100.0

Second, the probability of the first event (table 2) is taken, which the period addition to the cumulative incidence estimates.

b) Probability of event occuring [event type and timing]

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	CVD death	nonCVD death
1	0.026	0.008	0.017	0.013
2	0.026	0.008	0.017	0.013
3	0.025	0.008	0.017	0.013
.				
.				
22	0.003	0.002	0.003	0.002
23	0.002	0.001	0.002	0.002
24	0.002	0.001	0.002	0.001
.				
.				
100	0.000	0.000	0.000	0.000

Third, the product of Table 4-13 a and b then generates weighted remaining life expectancy Table 4-13 c.

c) Weighted remaining life years [estimates from a) multiplied by estimates from b)]

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	CVD death	nonCVD death	*Sum*
1	0.407	0.107	0.017	0.013	*0.544*
2	0.409	0.113	0.034	0.026	*0.582*
3	0.410	0.118	0.051	0.040	*0.620*
.					
.					
22	0.078	0.047	0.068	0.055	*0.249*
23	0.060	0.037	0.054	0.044	*0.195*
24	0.044	0.029	0.042	0.034	*0.148*
.					
.					
100	0.000	0.000	0.000	0.000	*0.000*

Total life years remaining (Cumulative sum over each model cycle) = *13.98*

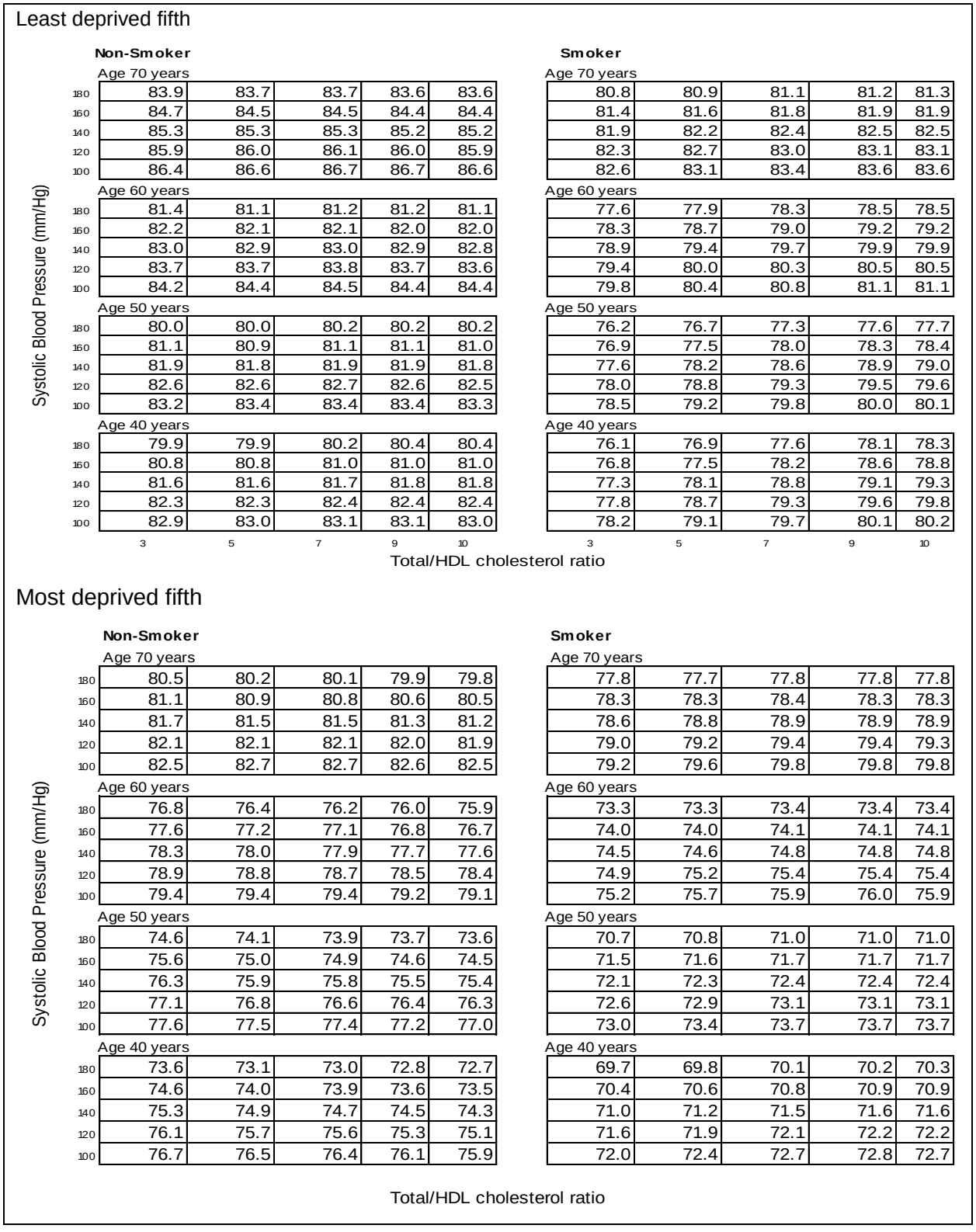
Overall life expectancy (age upon entering model plus remaining life years) = *73.98*

Fourth, age at screening is then added to remaining life expectancy. The estimate of overall life expectancy in the recalibrate model is 73.98 years, compared to 74.42 in the original model.

Note that in comparing Tables 4-13 with Tables 4-7 it is the difference in the probabilities of the first event rather than the consequences for life expectancy which is reason for the reduction in life expectancy in the recalibrated model. This is consistent with the approach to recalibration which was to adjust the linear predictors of the first event risk.

For consistency in exposition, figures 4-14 and 4-15 illustrate the impact of recalibration across a variety of risk profiles by revising the estimates made previously using the format of the 10-year risk tables. Life expectancies across all risk profiles are reduced following recalibration.

Figure 4-14 Recalibrated life expectancies for multiple risk profiles – men



Least deprived fifth

Non-Smoker

Systolic Blood Pressure (mm/Hg)	Total/HDL cholesterol ratio 3	5	7	9	10
Age 70 years					
180	83.9	83.7	83.7	83.6	83.6
160	84.7	84.5	84.5	84.4	84.4
140	85.3	85.3	85.3	85.2	85.2
120	85.9	86.0	86.1	86.0	85.9
100	86.4	86.6	86.7	86.7	86.6
Age 60 years					
180	81.4	81.1	81.2	81.2	81.1
160	82.2	82.1	82.1	82.0	82.0
140	83.0	82.9	83.0	82.9	82.8
120	83.7	83.7	83.8	83.7	83.6
100	84.2	84.4	84.5	84.4	84.4
Age 50 years					
180	80.0	80.0	80.2	80.2	80.2
160	81.1	80.9	81.1	81.1	81.0
140	81.9	81.8	81.9	81.9	81.8
120	82.6	82.6	82.7	82.6	82.5
100	83.2	83.4	83.4	83.4	83.3
Age 40 years					
180	79.9	79.9	80.2	80.4	80.4
160	80.8	80.8	81.0	81.0	81.0
140	81.6	81.6	81.7	81.8	81.8
120	82.3	82.3	82.4	82.4	82.4
100	82.9	83.0	83.1	83.1	83.0

Smoker

Systolic Blood Pressure (mm/Hg)	Total/HDL cholesterol ratio 3	5	7	9	10
Age 70 years					
180	80.8	80.9	81.1	81.2	81.3
160	81.4	81.6	81.8	81.9	81.9
140	81.9	82.2	82.4	82.5	82.5
120	82.3	82.7	83.0	83.1	83.1
100	82.6	83.1	83.4	83.6	83.6
Age 60 years					
180	77.6	77.9	78.3	78.5	78.5
160	78.3	78.7	79.0	79.2	79.2
140	78.9	79.4	79.7	79.9	79.9
120	79.4	80.0	80.3	80.5	80.5
100	79.8	80.4	80.8	81.1	81.1
Age 50 years					
180	76.2	76.7	77.3	77.6	77.7
160	76.9	77.5	78.0	78.3	78.4
140	77.6	78.2	78.6	78.9	79.0
120	78.0	78.8	79.3	79.5	79.6
100	78.5	79.2	79.8	80.0	80.1
Age 40 years					
180	76.1	76.9	77.6	78.1	78.3
160	76.8	77.5	78.2	78.6	78.8
140	77.3	78.1	78.8	79.1	79.3
120	77.8	78.7	79.3	79.6	79.8
100	78.2	79.1	79.7	80.1	80.2

Total/HDL cholesterol ratio

Most deprived fifth

Non-Smoker

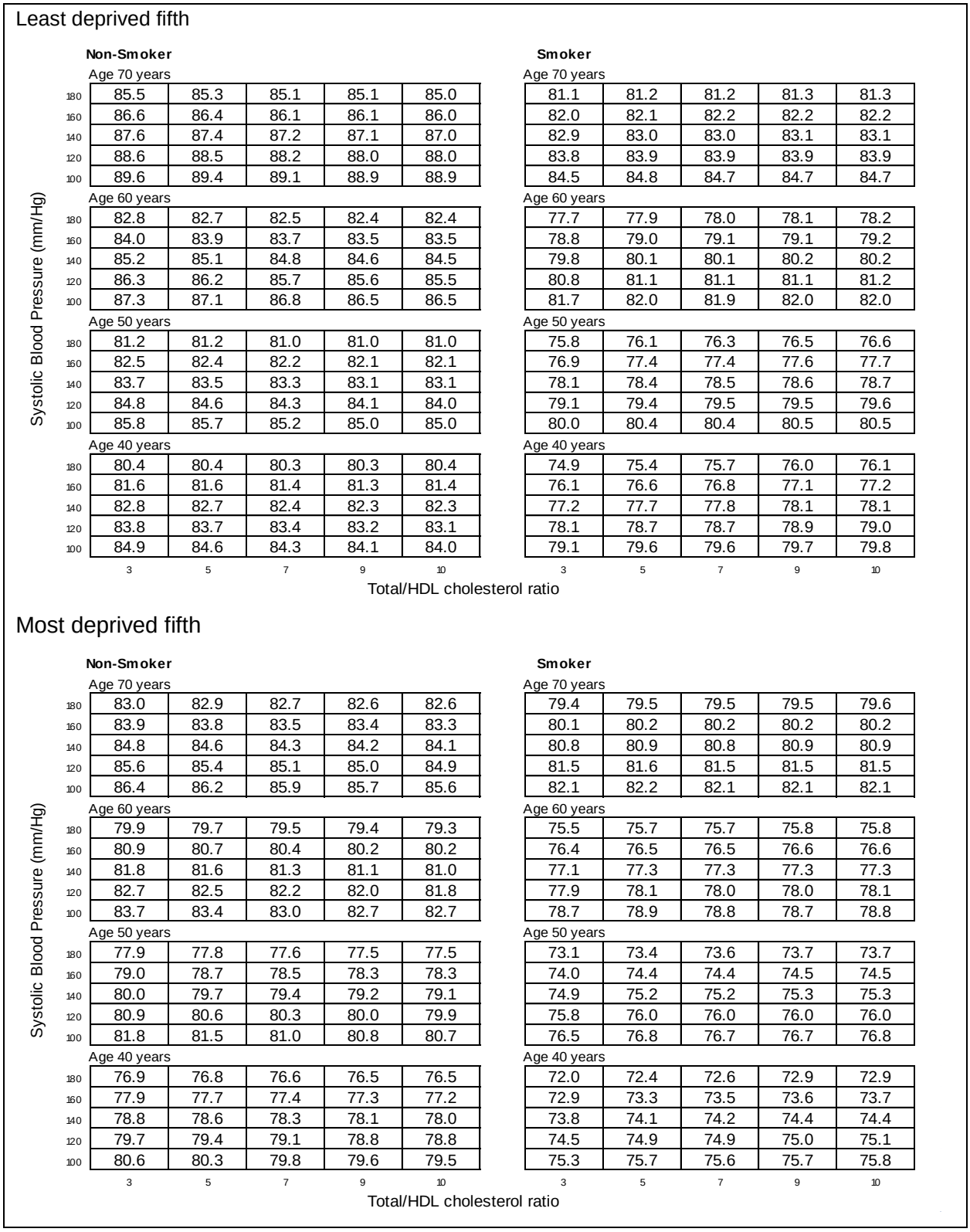
Systolic Blood Pressure (mm/Hg)	Total/HDL cholesterol ratio 3	5	7	9	10
Age 70 years					
180	80.5	80.2	80.1	79.9	79.8
160	81.1	80.9	80.8	80.6	80.5
140	81.7	81.5	81.5	81.3	81.2
120	82.1	82.1	82.1	82.0	81.9
100	82.5	82.7	82.7	82.6	82.5
Age 60 years					
180	76.8	76.4	76.2	76.0	75.9
160	77.6	77.2	77.1	76.8	76.7
140	78.3	78.0	77.9	77.7	77.6
120	78.9	78.8	78.7	78.5	78.4
100	79.4	79.4	79.4	79.2	79.1
Age 50 years					
180	74.6	74.1	73.9	73.7	73.6
160	75.6	75.0	74.9	74.6	74.5
140	76.3	75.9	75.8	75.5	75.4
120	77.1	76.8	76.6	76.4	76.3
100	77.6	77.5	77.4	77.2	77.0
Age 40 years					
180	73.6	73.1	73.0	72.8	72.7
160	74.6	74.0	73.9	73.6	73.5
140	75.3	74.9	74.7	74.5	74.3
120	76.1	75.7	75.6	75.3	75.1
100	76.7	76.5	76.4	76.1	75.9

Smoker

Systolic Blood Pressure (mm/Hg)	Total/HDL cholesterol ratio 3	5	7	9	10
Age 70 years					
180	77.8	77.7	77.8	77.8	77.8
160	78.3	78.3	78.4	78.3	78.3
140	78.6	78.8	78.9	78.9	78.9
120	79.0	79.2	79.4	79.4	79.3
100	79.2	79.6	79.8	79.8	79.8
Age 60 years					
180	73.3	73.3	73.4	73.4	73.4
160	74.0	74.0	74.1	74.1	74.1
140	74.5	74.6	74.8	74.8	74.8
120	74.9	75.2	75.4	75.4	75.4
100	75.2	75.7	75.9	76.0	75.9
Age 50 years					
180	70.7	70.8	71.0	71.0	71.0
160	71.5	71.6	71.7	71.7	71.7
140	72.1	72.3	72.4	72.4	72.4
120	72.6	72.9	73.1	73.1	73.1
100	73.0	73.4	73.7	73.7	73.7
Age 40 years					
180	69.7	69.8	70.1	70.2	70.3
160	70.4	70.6	70.8	70.9	70.9
140	71.0	71.2	71.5	71.6	71.6
120	71.6	71.9	72.1	72.2	72.2
100	72.0	72.4	72.7	72.8	72.7

Total/HDL cholesterol ratio

Figure 4-15 Recalibrated life expectancies for multiple risk profiles - women



Least deprived fifth

Systolic BP (mm/Hg)	Non-Smoker, Age 70 years					Smoker, 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

Systolic BP (mm/Hg)	Non-Smoker, Age 60 years					Smoker, Age 60 years				
	3	5	7	9	10	3	5	7	9	10
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

Systolic BP (mm/Hg)	Non-Smoker, Age 50 years					Smoker, Age 50 years				
	3	5	7	9	10	3	5	7	9	10
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

Systolic BP (mm/Hg)	Non-Smoker, Age 40 years					Smoker, Age 40 years				
	3	5	7	9	10	3	5	7	9	10
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

Total/HDL cholesterol ratio

Most deprived fifth

Systolic BP (mm/Hg)	Non-Smoker, Age 70 years					Smoker, 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

Systolic BP (mm/Hg)	Non-Smoker, Age 60 years					Smoker, Age 60 years				
	3	5	7	9	10	3	5	7	9	10
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

Systolic BP (mm/Hg)	Non-Smoker, Age 50 years					Smoker, Age 50 years				
	3	5	7	9	10	3	5	7	9	10
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

Systolic BP (mm/Hg)	Non-Smoker, Age 40 years					Smoker, Age 40 years				
	3	5	7	9	10	3	5	7	9	10
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

Total/HDL cholesterol ratio

4.6 Summary and discussion

Summary

The aim of the chapter was to describe the first part in building the Scottish CVD Policy Model. The focus was to build a model that could take individuals defined by the ASSIGN risk factors to predict the risk of CVD events and life expectancy. The intention is that the model is a natural extension of the ASSIGN score, so that there is consistency between the clinical tool that is currently used to screen and prioritise individuals for intervention and the policy model that is intended to be used to evaluate the impact of changes to modifiable risk factors. This chapter focused on the statistical approach to estimating lifetime risk and life expectancy. The next chapter will then detail how economic outcomes are generated and how the model is prepared for use in evaluation of interventions aimed at changing modifiable risk factors.

Strengths

Source data: To develop the Scottish CVD Policy Model we had access to the linked SHHEC-SMR dataset used to create the ASSIGN score. This allowed direct estimation of the lifetime risks of CVD events and life expectancy for individuals. In contrast, most policy models have been built using multiple cross-sectional data sources (Chapter 3) which can lead to models being complex, lacking transparency, and where the statistical estimation of event risks can be opaque. In contrast, having access to SHHEC-SMR offered the opportunity for a simple model to be developed, using a single longitudinal dataset and where the statistical methods are straightforward.

Consistency with clinical practice: By choosing to build the Scottish CVD Policy Model using the variables of the ASSIGN score the intention is to provide a degree of continuity between the clinical practice of prioritising individuals using the ASSIGN 10-year score. This is intended to help in the encouraging the future use of the policy model.

Modelling approach: A state transition model was developed, where individuals entering the model are simulated in discrete time steps, defined by annual cycles of the model with half-cycle correction. However, it is not a Markov model. The literature tends to use the term state transition and Markov models interchangeably. However, the modelling approach combines positive features of several modelling types which are often treated as mutually exclusive in

the literature. In contrasting the features of the model with more standard Markov models, the novelties and advantages of the approach taken may be become clearer.

First, the estimates of transition risks are estimated using modifiable risk factors (systolic blood pressure, total cholesterol, smoking, HDL-cholesterol) that are continuous, rather than discrete. Therefore, the model can estimate transition risks tailored to individuals risk profiles. This enhances the discriminatory power of the model. Often Markov models rely on data that are categorical and so individuals are assigned to a subgroup, and consequently discrimination becomes limited. In this sense, perhaps the policy model can be described as an individual state transition model.

Second, the approach of estimating cause specific hazards (within a competing risk analysis) means that the probability of incurring a particular event at a particular time is estimated directly and can simply be read into the model. Further, the cumulative incidence of all events must always sum to 1, providing an automatic check that the model is functioning properly. This hasn't been done before for economic models, to the best of my knowledge. In application, this enables a more elegant approach that is common for state transition models which rely on multiple data sources for different events. Consequently, a "fix" is normally applied in the model were a manual adjustment reduces the size of the event free population in each cycle by accounting for the hazards in the previous period. This is a straightforward but crude adjustment.

Third, the model has the simplifying feature of modelling death directly from the first non-fatal CVD event. This enabled the model to avoid the need to model recurrent events, and individuals moving between non-fatal states; both of which can complicate the structure with the loss of transparency. This enabled the model to maintain a simple structure, and still enable accurate prediction to be made.

Fourth, risk was estimated in continuous time and time to event was modelled. This means that the model can track patient history with life expectancy estimates conditional on an individual profile and event history. Consequently, this avoids the "memoryless" feature common in Markov models. This feature of time to event is normally associated with discrete event simulation.

Fifth, while risk is modelled continuously the model takes an approach where events take place within time steps of one year. In effect, the model could run continuously or for any size

of time step. However, the key modelling decision regarding how the choice of time step was pragmatic, and as a balance between keeping the modelling simple to aid transparency and generating accurate predictions. Crucially, the model performed well under validation tests and was recalibrated to a contemporary population.

Sixth, the model has been extensively validated and, in particular, accurately predicted outcomes from an intervention trial. This form of external validation is unusual for economic models, with only the Archimedes model providing very extensive external validation tests for diabetes predictions and the model performing well(270).

Limitations

There were several weaknesses. First, over half of the SHHEC cohort were still alive and CVD-free and yet to experience one of the four first events. Also of those who experience a non-fatal event over 66% were still alive. There was still sufficient power to undertake the parametric analysis. These two limitations represent an opportunity to make updates to the SHHEC-SMR data to re-estimate life expectancy predictions.

Second, the linked data is only to hospitalised events. This is likely to underestimate the risks of non-fatal events, as we do not detect endpoints that occur in primary care settings. This is especially relevant to stroke patients who are increasing treated in community settings.

Third, the SHHEC study over-represents deprived patients. However, this is not a problem as such. While this means that the study population is not representative of Scotland, the sample size was large (over 16,000 people) and the analysis has adjusted for deprivation status. Therefore, the estimates remain unbiased.

Fourth, it was not asked with SHHEC whether participating individuals were taking relevant medications. For instance, anti-hypertensives were commonly prescribed at the time of the survey (from 1980s), though statins were not routinely used for primary prevention at the time.

Fifth, SHHEC did not report physical activity behaviour in the screening of individuals. This is potentially a limitation as physical activity has been found to be an independent risk factor. While there are diminishing returns in including additional risk factors to predict events(81), this may be a limitation in estimating the impact of physical activity on reducing the risk of

CVD and related conditions. A potential area for future research is to look for a dataset that includes physical activity and all of the other ASSIGN risk factors, link this to hospital records and re-estimate model to test whether the inclusion of physical activity (and other variables) improve the model. This could be done for both the ASSIGN score and the Scottish CVD Policy Model. A good candidate as a dataset would be the Scottish Health Survey, a cross-sectional survey of the Scottish population that dates from 1995. Survey respondents all give permission for hospital records to be accessed and the maximum record linkage at present would extend to 2010, giving 15 years of follow-up.

Fifth, survival post event was calculated by estimating the area under the survival curve, using the trapezoid method that is recommended by NICE. Regardless of how small the time steps taken the state transition the use of trapezoid will always leave an area between the curve and the hypotenuse of the triangle. An alternative approach would have been to estimate the integral, which is possible given that survival was modelled in continuous time. However, model predictions can simply be recalibrated, although this is a less elegant solution.

Finally, the model is limited to a focus on primary prevention. The SHHEC-SMR dataset did not include rescreening of risk factors and so we do not know how risk factors changed once an SHHEC individual experienced a first event. Opportunities for expanding the scope of the model to make it a secondary prevention model will be discussed further in the concluding chapter, when considering a future research agenda.

The model is calibrated to be used specifically in Scotland. It is expected to have high internal validity, but low external validity. In particular, a key strength of the policy model in a Scottish context is that it uses the ASSIGN risk factors and a measure of socioeconomic deprivation, this measure is not applicable outside of Scotland. In principle, however, the model could be recalibrated, as for instance the use of Framingham in the UK is recommended with associated calibration factors(120). Further, SIMD as a variable could be removed and the model equations re-estimated.

Appendix 1 – Cause specific hazards: comparing imputed results to a complete case analysis

In comparing the CSH for the imputed and complete case analysis it is evident that imputation changes the coefficients, but marginally.

Imputed results (in logs) - Males

Risk of non-fatal CHD

Risk factor	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
Age at SHHEC	0.045	0.004	12.620	0.000	0.038	0.052
SIMD	0.004	0.001	3.090	0.002	0.001	0.007
Diabetes	0.653	0.184	3.560	0.000	0.292	1.014
Family history	0.408	0.058	7.050	0.000	0.295	0.522
Cigarettes per day	0.018	0.002	8.070	0.000	0.013	0.022
Systolic blood pressure	0.008	0.001	5.580	0.000	0.005	0.011
Total cholesterol	0.255	0.024	10.630	0.000	0.208	0.302
HDL cholesterol	-0.760	0.094	-8.080	0.000	-0.947	-0.574
Constant	-9.539	0.293	-32.500	0.000	-10.115	-8.963
Gamma	0.057	0.004	13.580	0.000	0.049	0.065

Male - Risk of non-fatal CVD

Risk factor	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
Age at SHHEC	0.066	0.006	10.680	0.000	0.054	0.078
SIMD	0.009	0.002	4.460	0.000	0.005	0.014
Diabetes	1.168	0.257	4.550	0.000	0.664	1.673
Family history	-0.021	0.109	-0.190	0.847	-0.235	0.193
Cigarettes per day	0.024	0.004	6.570	0.000	0.017	0.031
Systolic blood pressure	0.012	0.002	5.250	0.000	0.007	0.016
Total cholesterol	0.083	0.043	1.920	0.056	-0.002	0.168
HDL cholesterol	-0.125	0.137	-0.910	0.362	-0.394	0.144
Constant	-12.505	0.491	-25.460	0.000	-13.469	-11.541
Gamma	0.091	0.007	12.390	0.000	0.076	0.105

Male – Risk of fatal CVD

Risk factor	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
Age at SHHEC	0.093	0.005	17.450	0.000	0.082	0.103
SIMD	0.006	0.002	3.730	0.000	0.003	0.010
Diabetes	0.863	0.240	3.590	0.000	0.389	1.337
Family history	0.165	0.085	1.930	0.054	-0.003	0.332
Cigarettes per day	0.031	0.003	10.880	0.000	0.026	0.037
Systolic blood pressure	0.015	0.002	9.070	0.000	0.012	0.019
Total cholesterol	0.120	0.035	3.380	0.001	0.050	0.189
HDL cholesterol	-0.143	0.115	-1.240	0.218	-0.370	0.085
Constant	-14.128	0.407	-34.750	0.000	-14.926	-13.330
Gamma	0.079	0.006	13.280	0.000	0.068	0.091

Male – Risk of fatal non CVD

Risk factor	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
Age at SHHEC	0.094	0.004	21.940	0.000	0.085	0.102
SIMD	0.009	0.001	6.500	0.000	0.007	0.012
Diabetes	0.335	0.257	1.310	0.192	-0.169	0.839
Family history	-0.015	0.075	-0.200	0.845	-0.162	0.133
Cigarettes per day	0.031	0.002	12.710	0.000	0.026	0.035
Systolic blood pressure	-0.001	0.002	-0.860	0.391	-0.005	0.002
Total cholesterol	-0.051	0.030	-1.690	0.092	-0.111	0.008
HDL cholesterol	0.384	0.086	4.450	0.000	0.214	0.554
Constant	-11.217	0.352	-31.910	0.000	-11.907	-10.527
Gamma	0.081	0.005	16.170	0.000	0.071	0.091

Imputed results (in logs) - females

Female – Risk of non fatal CHD

Risk factor	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
Age at SHHEC	0.058	0.005	12.380	0.000	0.049	0.067
SIMD	0.009	0.002	5.810	0.000	0.006	0.012
Diabetes	0.725	0.195	3.720	0.000	0.343	1.108
Family history	0.516	0.065	7.980	0.000	0.389	0.643
Cigarettes per day	0.021	0.003	6.560	0.000	0.014	0.027
Systolic blood pressure	0.006	0.002	3.910	0.000	0.003	0.009
Total cholesterol	0.188	0.026	7.140	0.000	0.136	0.240
HDL cholesterol	-0.746	0.097	-7.720	0.000	-0.937	-0.555
Constant	-10.516	0.317	-33.200	0.000	-11.138	-9.894
Gamma	0.083	0.005	16.410	0.000	0.073	0.093

Female – Risk of non fatal CVD

Risk factor	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
Age at SHHEC	0.080	0.008	10.570	0.000	0.065	0.095
SIMD	0.013	0.002	5.620	0.000	0.009	0.018
Diabetes	1.101	0.258	4.270	0.000	0.595	1.607
Family history	0.356	0.105	3.380	0.001	0.150	0.562
Cigarettes per day	0.027	0.005	5.410	0.000	0.017	0.037
Systolic blood pressure	0.014	0.002	5.720	0.000	0.009	0.018
Total cholesterol	-0.051	0.050	-1.020	0.308	-0.150	0.048
HDL cholesterol	-0.346	0.147	-2.360	0.020	-0.636	-0.056
Constant	-13.010	0.514	-25.300	0.000	-14.020	-12.000
Gamma	0.096	0.008	11.590	0.000	0.080	0.112

Female – Risk of fatal CVD

Risk factor	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
Age at SHHEC	0.102	0.007	14.060	0.000	0.087	0.116
SIMD	0.004	0.002	1.930	0.054	0.000	0.009
Diabetes	1.144	0.237	4.830	0.000	0.680	1.609
FH	0.239	0.096	2.490	0.013	0.050	0.428
CPD	0.048	0.004	12.490	0.000	0.040	0.056
SBP	0.018	0.002	8.450	0.000	0.013	0.022
TC	0.057	0.040	1.410	0.159	-0.022	0.136
HDL	-0.174	0.125	-1.390	0.166	-0.420	0.073
Constant	-15.424	0.491	-31.390	0.000	-16.388	-14.459
Gamma	0.099	0.007	13.250	0.000	0.084	0.114

Female – Risk of fatal non CVD

Risk factor	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
Age at SHHEC	0.091	0.005	17.770	0.000	0.081	0.101
SIMD	0.007	0.002	4.530	0.000	0.004	0.010
Diabetes	-0.037	0.322	-0.120	0.908	-0.668	0.594
FH	-0.018	0.075	-0.240	0.814	-0.165	0.129
CPD	0.038	0.003	12.720	0.000	0.032	0.044
SBP	0.003	0.002	1.590	0.112	-0.001	0.006
TC	-0.076	0.032	-2.380	0.018	-0.140	-0.013
HDL	-0.045	0.093	-0.490	0.626	-0.229	0.138
Constant	-11.257	0.344	-32.710	0.000	-11.932	-10.581
Gamma	0.089	0.006	16.100	0.000	0.078	0.099

Complete case analysis results (in logs) - Males

Risk of non-fatal CHD

Risk Factor	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age_shhec	.0447733	.0038734	11.56	0.000	.0371815	.0523651
simd04	.0032335	.0014153	2.28	0.022	.0004596	.0060075
diab_sr	.6633511	.1959497	3.39	0.001	.2792968	1.047405
famhis	.3382739	.0628869	5.38	0.000	.2150178	.46153
cpd	.0182862	.0023263	7.86	0.000	.0137268	.0228456
sbp	.0078895	.0015213	5.19	0.000	.0049079	.0108711
chol_c	.2660048	.0252047	10.55	0.000	.2166046	.315405
hdl_c	-.784403	.0882417	-8.89	0.000	-.9573536	-.6114524
_cons	-9.584036	.3155063	-30.38	0.000	-10.20242	-8.965655
/gamma	.0593799	.0045252	13.12	0.000	.0505108	.0682491

Risk of non-fatal CBVD

Risk Factor	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age_shhec	.0649273	.006741	9.63	0.000	.0517151	.0781395
simd04	.0086602	.0023125	3.75	0.000	.0041279	.0131925
diab_sr	1.146499	.2747514	4.17	0.000	.6079959	1.685002
famhis	-.0811428	.119133	-0.68	0.496	-.3146392	.1523536
cpd	.0242973	.0039145	6.21	0.000	.0166249	.0319696
sbp	.0110776	.0024625	4.50	0.000	.0062511	.015904
chol_c	.0809856	.0461376	1.76	0.079	-.0094424	.1714137
hdl_c	-.1691968	.1392056	-1.22	0.224	-.4420348	.1036412
_cons	-12.24458	.5365432	-22.82	0.000	-13.29619	-11.19297
/gamma	.0883115	.0079447	11.12	0.000	.0727401	.1038829

Risk of CVD death

Risk Factor	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age_shhec	.1000427	.0060285	16.59	0.000	.0882271	.1118584
simd04	.0063982	.0019421	3.29	0.001	.0025918	.0102047
diab_sr	.9782542	.2364766	4.14	0.000	.5147686	1.44174
famhis	.1630035	.0941893	1.73	0.084	-.0216041	.3476111
cpd	.0324238	.0031917	10.16	0.000	.0261682	.0386795
sbp	.0148519	.0018566	8.00	0.000	.011213	.0184908
chol_c	.1317112	.038514	3.42	0.001	.0562251	.2071972
hdl_c	-.1505994	.1135343	-1.33	0.185	-.3731225	.0719237
_cons	-14.62659	.4567759	-32.02	0.000	-15.52185	-13.73132
/gamma	.0816066	.0066497	12.27	0.000	.0685734	.0946398

Risk of fatal non-CVD death

Risk Factor	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age_shhec	.0959212	.0046444	20.65	0.000	.0868184	.105024
simd04	.008862	.0015587	5.69	0.000	.005807	.0119169
diab_sr	.4073542	.2705641	1.51	0.132	-.1229416	.93765
famhis	-.0231099	.0800474	-0.29	0.773	-.1799999	.13378
cpd	.0309909	.0025609	12.10	0.000	.0259716	.0360102
sbp	-.0015506	.0017711	-0.88	0.381	-.0050218	.0019206
chol_c	-.0525316	.0325887	-1.61	0.107	-.1164043	.0113411
hdl_c	.3606832	.0887723	4.06	0.000	.1866927	.5346738
_cons	-11.27387	.3781938	-29.81	0.000	-12.01511	-10.53262
/gamma	.0824772	.0053709	15.36	0.000	.0719505	.093004

Complete case analysis results (in logs) - Women

Risk of non-fatal CHD

Risk Factor	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age_shhec	.0601541	.005201	11.57	0.000	.0499604	.0703478
simd04	.0096483	.0016647	5.80	0.000	.0063854	.0129111
diab_sr	.7650296	.2230639	3.43	0.001	.3278324	1.202227
famhis	.5382325	.0721364	7.46	0.000	.3968478	.6796172
cpd	.0216402	.0034463	6.28	0.000	.0148855	.0283949
sbp	.0056178	.0017798	3.16	0.002	.0021294	.0091061
chol_c	.1873546	.027795	6.74	0.000	.1328775	.2418318
hdl_c	-.7009756	.0940833	-7.45	0.000	-.8853755	-.5165757
_cons	-10.72338	.3489158	-30.73	0.000	-11.40725	-10.03952

Risk of non-fatal CBVD

Risk Factor	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age_shhec	.0829577	.008351	9.93	0.000	.06659	.0993254
simd04	.0117021	.0026174	4.47	0.000	.006572	.0168322
diab_sr	1.143402	.2989557	3.82	0.000	.5574594	1.729344
famhis	.342425	.1181066	2.90	0.004	.1109403	.5739097
cpd	.0285492	.0053795	5.31	0.000	.0180056	.0390928
sbp	.0132375	.0026913	4.92	0.000	.0079626	.0185124
chol_c	-.0641339	.0489562	-1.31	0.190	-.1600863	.0318184
hdl_c	-.3396796	.1481795	-2.29	0.022	-.6301061	-.0492531
_cons	-13.04117	.5618587	-23.21	0.000	-14.1424	-11.93995

Risk of CVD death

Risk Factor	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age_shhec	.1083116	.0080751	13.41	0.000	.0924847	.1241386
simd04	.0034479	.0025059	1.38	0.169	-.0014636	.0083595
diab_sr	1.151733	.2765128	4.17	0.000	.6097776	1.693688
famhis	.2094482	.1086949	1.93	0.054	-.0035898	.4224863
cpd	.0452936	.0043783	10.35	0.000	.0367123	.0538749
sbp	.0178031	.0023242	7.66	0.000	.0132478	.0223585
chol_c	.0600561	.0421366	1.43	0.154	-.0225301	.1426422
hdl_c	-.0645549	.1266885	-0.51	0.610	-.3128598	.1837499
_cons	-16.03345	.5518618	-29.05	0.000	-17.11508	-14.95182
/gamma	.1016689	.0084041	12.10	0.000	.0851973	.1181406

Risk of fatal non-CVD death

Risk Factor	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age_shhec	.0944633	.0057592	16.40	0.000	.0831755	.1057511
simd04	.0064458	.0018588	3.47	0.001	.0028028	.0100889
diab_sr	.2125953	.3373178	0.63	0.529	-.4485354	.873726
famhis	.0263424	.0846597	0.31	0.756	-.1395876	.1922724
cpd	.0365315	.0034034	10.73	0.000	.029861	.043202
sbp	.0021377	.0019835	1.08	0.281	-.0017499	.0060253
chol_c	-.0721331	.0336588	-2.14	0.032	-.1381031	-.0061631
hdl_c	-.0553507	.0972073	-0.57	0.569	-.2458736	.1351721
_cons	-11.41056	.3873402	-29.46	0.000	-12.16973	-10.65138
/gamma	.0882224	.0062412	14.14	0.000	.0759898	.100455

Appendix 2 - Cholesky decompositions: 1st events

Men

Non-fatal CHD

	age	SIMD	Diabetes	FH	CPD	SBP	TC	HDL	constant	gamma
age	0.0035									
SIMD	-1.59E-05	0.0013								
Diabetes	-5.43E-03	-0.0076	0.1835							
FH	3.71E-03	-0.0012	0.0008	0.0579						
CPD	2.50E-04	-0.0003	0.0001	0.0000	0.0021					
SBP	-3.82E-04	-0.0001	-0.0001	0.0000	0.0001	0.0013				
TC	-5.13E-04	0.0023	-0.0013	-0.0010	0.0296	-0.0037	-0.0180			
HDL	-5.46E-03	0.0030	0.0011	0.0005	0.0091	-0.0034	0.0281	0.0891		
Constant	-1.26E-01	-0.0472	0.0073	-0.0111	-0.0418	-0.1689	0.1339	-0.1482	-0.0480	
Gamma	4.35E-04	0.0005	0.0003	0.0000	0.0003	0.0003	0.0002	-0.0003	0.0057	0.0042

Non-fatal CBVD

	age	SIMD	Diabetes	FH	CPD	SBP	TC	HDL	constant	gamma
age	0.0062									
SIMD	-1.65E-04	0.0021								
Diabetes	-9.07E-03	-0.0164	0.2559							
FH	6.08E-03	-0.0018	0.0018	0.1089						
CPD	5.33E-04	-0.0005	0.0003	-0.0001	0.0035					
SBP	-6.41E-04	-0.0002	-0.0001	-0.0001	0.0001	0.0021				
TC	-1.20E-03	0.0044	-0.0007	-0.0014	0.0476	-0.0056	-0.0213			
HDL	-4.83E-03	0.0011	0.0115	-0.0026	0.0068	-0.0095	0.0513	0.1255		
Constant	-2.33E-01	-0.0728	-0.0208	-0.0027	-0.0681	-0.2697	0.3691	-0.3070	-0.3557	
Gamma	9.51E-04	0.0010	0.0006	0.0000	0.0005	0.0008	0.0008	-0.0006	0.0032	0.0064

Fatal CVD

	age	SIMD	Diabetes	FH	CPD	SBP	TC	HDL	constant	gamma
age	0.0053									
SIMD	-2.64E-04	0.0017								
Diabetes	-5.40E-03	-0.0134	0.2398							
FH	5.42E-03	-0.0017	0.0012	0.0852						
CPD	5.44E-04	-0.0004	0.0001	-0.0001	0.0028					
SBP	-5.04E-04	-0.0002	0.0000	-0.0001	0.0000	0.0016				
TC	6.02E-04	0.0040	-0.0013	-0.0009	0.0294	-0.0018	0.0192			
HDL	-5.68E-03	-0.0010	-0.0009	-0.0033	0.0035	-0.0181	-0.0382	0.1071		
Constant	-2.23E-01	-0.0526	0.0004	0.0018	-0.0559	-0.2014	-0.2899	-0.2281	-0.2583	
Gamma	8.85E-04	0.0008	0.0005	0.0000	0.0004	0.0007	-0.0005	-0.0004	0.0023	0.0053

Non-fatal CVD

	age	SIMD	Diabetes	FH	CPD	SBP	TC	HDL	constant	gamma
age	0.0043									
SIMD	-1.84E-04	0.0014								
Diabetes	-3.87E-03	-0.0096	0.2566							
FH	4.05E-03	-0.0013	0.0018	0.0752						
CPD	4.02E-04	-0.0004	0.0001	-0.0001	0.0023					
SBP	-3.82E-04	-0.0002	0.0000	0.0000	0.0001	0.0016				
TC	-5.79E-04	0.0032	-0.0004	-0.0010	0.0348	-0.0041	-0.0179			
HDL	-3.81E-03	0.0005	0.0042	0.0000	0.0039	-0.0068	0.0229	0.0827		
Constant	-1.77E-01	-0.0491	-0.0077	-0.0041	-0.0528	-0.1950	0.2073	-0.1626	-0.1434	
Gamma	7.66E-04	0.0007	0.0002	0.0000	0.0003	0.0005	0.0006	-0.0003	0.0031	0.0037

Women

Non-fatal CHD

	age	SIMD	Diabetes	FH	CPD	SBP	TC	HDL	constant	gamma
age	0.0047									
SIMD	-1.71E-04	0.0015								
Diabetes	-6.11E-03	-0.0071	0.1947							
FH	3.86E-03	-0.0010	0.0005	0.0646						
CPD	5.69E-04	-0.0005	0.0001	-0.0001	0.0030					
SBP	-5.26E-04	-0.0001	0.0000	0.0000	0.0002	0.0015				
TC	-7.86E-03	0.0025	-0.0015	-0.0015	0.0380	-0.0089	0.0300			
HDL	-7.95E-03	0.0191	0.0114	0.0000	0.0158	0.0003	-0.0303	0.0872		
Constant	-1.16E-01	-0.0795	-0.0125	-0.0144	-0.0601	-0.1738	-0.0674	-0.1443	0.1447	
Gamma	6.15E-04	0.0006	0.0002	0.0001	0.0002	0.0004	-0.0002	-0.0006	-0.0026	0.0042

Non-fatal CBVD

	age	SIMD	Diabetes	FH	CPD	SBP	TC	HDL	constant	gamma
age	0.0075									
SIMD	-3.99E-04	0.0023								
Diabetes	-1.15E-02	-0.0149	0.2572							
FH	7.10E-03	-0.0004	0.0036	0.1051						
CPD	1.01E-03	-0.0007	0.0002	-0.0001	0.0048					
SBP	-7.81E-04	-0.0003	-0.0001	0.0000	0.0002	0.0022				
TC	-1.54E-02	0.0041	-0.0016	-0.0031	0.0863	-0.0194	-0.0748			
HDL	-1.23E-02	0.0263	0.0140	0.0025	0.0244	-0.0011	0.0380	0.1360		
Constant	-1.89E-01	-0.1194	-0.0187	-0.0276	-0.1015	-0.2529	0.0837	-0.2100	-0.2966	
Gamma	1.27E-03	0.0012	0.0005	0.0001	0.0003	0.0008	0.0001	-0.0008	0.0032	0.0074

Fatal CVD

	age	SIMD	Diabetes	FH	CPD	SBP	TC	HDL	constant	gamma
age	0.0053									
SIMD	-2.64E-04	0.0017								
Diabetes	-5.40E-03	-0.0134	0.2398							
FH	5.42E-03	-0.0017	0.0012	0.0852						
CPD	5.44E-04	-0.0004	0.0001	-0.0001	0.0028					
SBP	-5.04E-04	-0.0002	0.0000	-0.0001	0.0000	0.0016				
TC	6.02E-04	0.0040	-0.0013	-0.0009	0.0294	-0.0018	0.0192			
HDL	-5.68E-03	-0.0010	-0.0009	-0.0033	0.0035	-0.0181	-0.0382	0.1071		
Constant	-2.23E-01	-0.0526	0.0004	0.0018	-0.0559	-0.2014	-0.2899	-0.2281	-0.2583	
Gamma	8.85E-04	0.0008	0.0005	0.0000	0.0004	0.0007	-0.0005	-0.0004	0.0023	0.0053

Non-fatal CVD

	age	SIMD	Diabetes	FH	CPD	SBP	TC	HDL	constant	gamma
age	0.0051									
SIMD	-2.40E-04	0.0016								
Diabetes	-1.06E-02	-0.0095	0.3212							
FH	3.68E-03	-0.0003	0.0005	0.0749						
CPD	6.30E-04	-0.0006	0.0000	0.0000	0.0029					
SBP	-5.62E-04	-0.0002	-0.0001	0.0000	0.0002	0.0016				
TC	-9.55E-03	0.0019	0.0002	-0.0016	0.0505	-0.0111	-0.0418			
HDL	-4.06E-03	0.0144	0.0026	0.0026	0.0145	-0.0007	0.0291	0.0860		
Constant	-1.37E-01	-0.0689	-0.0053	-0.0151	-0.0616	-0.1853	0.0696	-0.1398	0.1791	
Gamma	7.81E-04	0.0008	0.0002	0.0001	0.0002	0.0005	0.0001	-0.0004	-0.0024	0.0048

Appendix 3 – Cholesky decompositions: 2nd events

Men

Survival post-CHD

	age	SIMD	FH	constant	gamma
age	0.0063				
SIMD	2.06E-04	0.0021			
FH	9.24E-03	-0.0060	0.1001		
constant	-4.37E-01	-0.0681	-0.0313	0.4437	
gamma	4.16E-03	0.0006	0.0007	-0.0013	0.0098

Survival post-CBVD

	age	SIMD	FH	constant	gamma
age	0.0098				
SIMD	2.76E-04	0.0031			
FH	1.26E-02	-0.0009	0.1647		
constant	-6.99E-01	-0.1055	-0.0355	0.7079	
gamma	7.41E-03	0.0007	0.0048	-0.0019	0.0173

Women

Survival post-CHD

	age	SIMD	FH	constant	gamma
age	0.0078				
SIMD	1.03E-04	0.0025			
FH	6.45E-03	-0.0023	0.1192		
constant	-5.60E-01	-0.0843	-0.0437	0.5677	
gamma	5.77E-03	-0.0001	0.0023	-0.0014	0.0125

Survival post-CBVD

	age	SIMD	FH	constant	gamma
age	0.0103				
SIMD	-2.52E-04	0.0037			
FH	2.35E-02	-0.0052	0.1680		
constant	-7.53E-01	-0.1337	-0.0643	0.7632	
gamma	9.51E-03	0.0008	0.0023	-0.0023	0.0200

Chapter 5: Generating economic outcomes and preparing the model for evaluation

5.1 Introduction

Chapter 5 details the second part in the development of the Scottish CVD Policy Model. The previous chapter developed the model structure and statistical approach to estimating the lifetime risk of CVD and life expectancy. However, it is not only longevity that is of concern to individuals but also quality of life. Consequently, it is important to weight length of life by the expected health related quality of life (HRQoL). Further, as life expectancy of individuals and populations increase it is expected there will implications for health service costs, given comorbidities tend to cluster in older age groups(46).

The aim of the chapter is to detail how the model uses the survival estimates generated from Chapter 4 to then quality adjust survival and attach health service costs. With reference to the best practice guidelines in building an economic model, the empirical work of the chapter essentially falls under "Modelling stage 3: data identification and incorporation". In effect, economic information is layered on top of survival estimates. This then enables the outcomes of the policy model outputs to be broadened from the risk of CVD and life expectancy to quality adjusted life expectancy (QALE) and cumulative lifetime health service costs.

To set the chapter in context, Section 5.2 provides a brief overview of the approach taken to generate QALE and costs, and how the model is populated with this information. All estimates were derived using routine Scottish data sources, rather than populating the model using secondary literature. Section 5.3 to section 5.6 details the approach to estimating HRQoL and illustrates how survival in the model is quality adjusted to generate QALE. This process of quality adjustment consists of background morbidity and the impact of experiencing non-fatal CVD events. Discounting is also introduced to the model and the chapter illustrates how the model can produce discounted QALE and specific to individual risk profiles. Section 5.7 details how total health service costs (accounting for all CVD and non-CVD events) are estimated as a function of individual risk profiles. Further, in a similar process to quality adjustment, section 5.8 shows how survival in the model is used to generate expected (discounted and undiscounted) lifetime health service costs. The penultimate section 5.9 then illustrates how the model can be used to evaluate the impact of interventions aimed at changing modifiable risk factors to estimate impacts on life expectancy

and lifetime health service costs. Section 5.10 then provides a summary and discussion of the chapter as a whole.

5.2 Overview: Generating economic outcomes

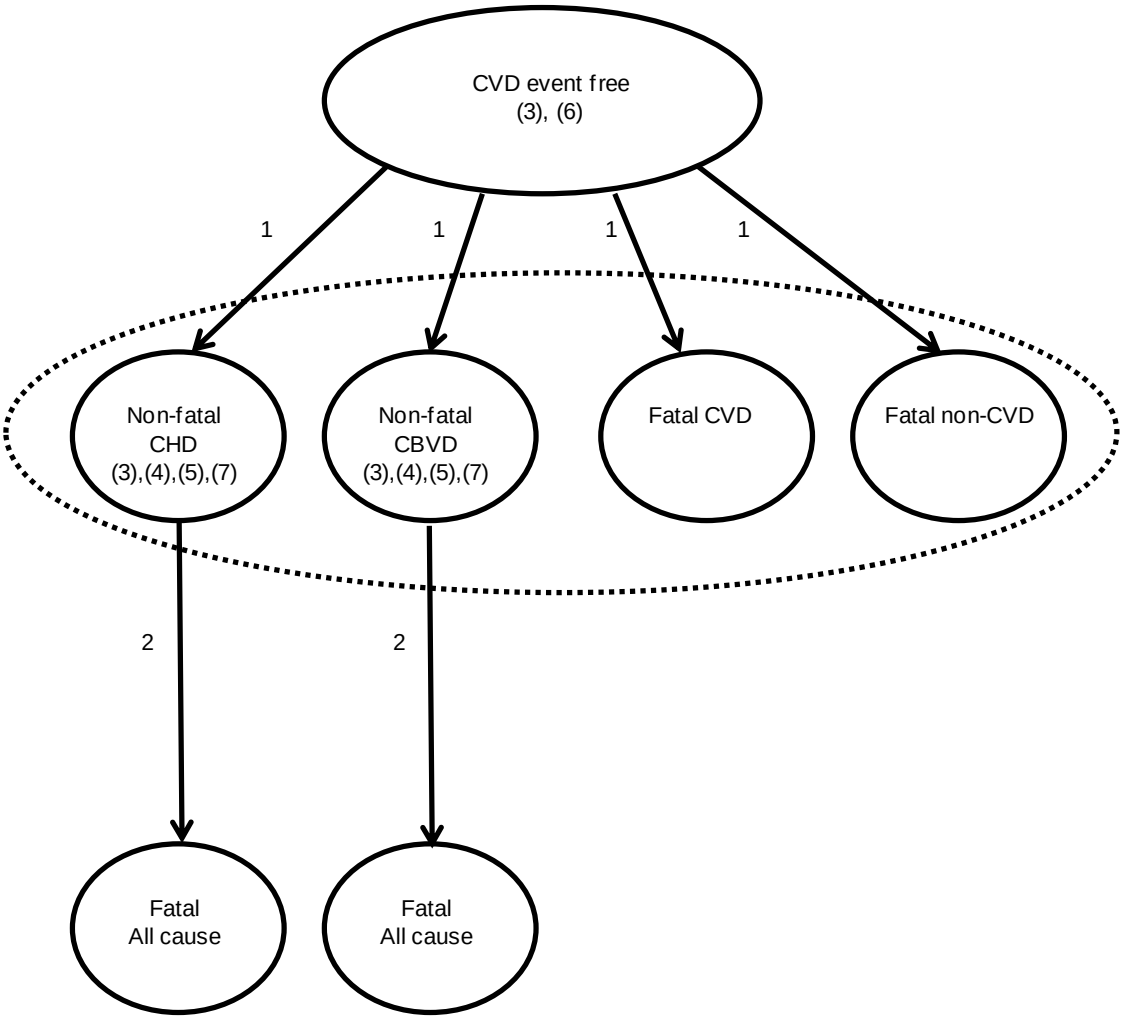
Figure 5-1 illustrates the structure the policy model. Chapter 4 detailed how equation 1 was derived to estimate the risk of first events, and also how equation 2 was derived to estimate survival from a first non-fatal CVD event. Chapter 5 estimates how individual survival in the model states are quality adjusted and how individuals accumulate hospital costs. As the chapter progresses the text refers back to this figure to fully describe the process of generating QALE and the estimation of lifetime health service costs.

Quality adjustment consists of three elements. First, it is important to account for the background morbidity of individuals as they enter and age within the model. The vast majority of individuals do not exist in perfect health prior to death. Individuals suffer from a range of co-morbidities which accumulate with age. Second, it is important to account for morbidity impacts of incurring a first non-fatal CVD event, and not only the consequence for an individual's length of life. Third, it is then necessary to predict the risk of incurring further non-fatal CVD event post a first non-fatal event, and further quality adjust survival.

In reference to figure 5.1, quality adjustment is applied as follows. As individuals remain in a CVD free state the only quality adjustment required is to account for background morbidity (equation 3). As individuals move from a CVD event free state and enter states that denote a first non-fatal CVD event then quality adjustment is comprised of both background morbidity and the impacts of incurring the first event, either CHD or CVBD (equation 3 + 4). Further, individuals who survive a first event are at risk of subsequent non-fatal CVD events prior to death. Therefore, it is also important to also estimate the risk of events and account for the HRQoL impact (equations 3 + 4 + 5).

Regarding the cost side, individuals are also expected to accumulate health service costs over their lifetime. On average, costs will increase with life expectancy as a result of increasing co-morbidities associated with longevity. Costs are estimating separately for those who are within a CVD event free state (equation 6), and those who have experienced a first non-fatal event (equation 7).

Figure 5-1 CVD model: quality adjusting life expectancy and estimating lifetime health service costs



Equation 3: Background morbidity = Function (age, deprivation)

Equation 4: Morbidity impact of non-fatal CVD events = Function (age, CVD events, SIMD)

Equation 5: Risk of subsequent CVD events = Function (age, family history, SIMD)

Equation 6: Costs prior to 1st event = Function (age, family history, SIMD)

Equation 7: Costs post 1st event = Function (age, family history, SIMD)

NB Equation 1 and 2 estimate transition between model states, and were described in Chapter 4.

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5.3 Health related quality of life: background

5.3.1 Measuring health related of life

(i) Generic measures versus disease specific measures:

Quality of life is the perceived quality of an individual's daily life, or well-being. This concept includes all emotional, social, and physical aspects of an individual's life(284). However, operationalising this concept to measure quality of life is a contested area within and between disciplines(284-288). Although there is no consensus on the definition of the concept of health related quality of life (HRQL)(66), definitions usually refer to physical, emotional and social well-being. HRQL is a distinct construct which refers to the impact that health conditions and their symptoms have on an individual's quality of life.

HRQL instruments have evolved in order to measure and assess the impact of disease, the effect of treatment, and other variables that impact upon individual lives(289). These instruments can provide an assessment of the patient's experience of his or her health problems in areas such as physical, emotional or social function, role performance, pain and fatigue; the functional effect of an illness and its consequent therapy upon a patient, as perceived by the individual(286).

There are two types of HRQL instrument: 'generic' and 'disease-specific'. Disease-specific instruments measure the multiple aspects of HRQL relevant to a specific disease group and are more clinically sensitive and potentially more responsive in detecting change. Generic instruments are designed to address multiple aspects of HRQL across a range of different patient or disease groups. Thus, they focus on general issues of health (or ill health), such as functional capacity, disability and distress, rather than specific features of a particular disease Economists prefer the use of generic measures to allow for direct comparability of HRQoL across different diseases. The use of generic measures of HRQoL will be further discussed below; first, it is discussed what the desirable features of any HRQoL measure are.

(ii) Desirable features of health related quality of life measures

It is desired that health related quality of life measures have both reliability and validity. Reliability of an instrument is normally assessed in two ways: internal consistency and test-retest(284). Internal consistency is an estimate of the homogeneity of the items measuring a specific health concept or domain and is the extent to which individual items are inter-correlated with each other. The former is an estimate of the homogeneity of items measuring

a specific health domain and is normally measured using Cronbach's alpha coefficient. The closer the coefficient is to 1, the greater the homogeneity between the items and, therefore, the greater the confidence that can be attributed that items relate to the domain under investigation. However, caution should be noted as alpha coefficients of >0.95 can mean that several of the items are in fact measuring the same thing(290).

Test-retest reliability is a measure of an instrument's ability to produce data that are consistent or stable over time when there is no change in the measured variable or health state. It is normally determined using Cohen's Kappa or Pearson's or Spearman's correlation coefficient. Normally, levels in excess of 0.6 indicate an adequate test-retest reliability(290).

Validity refers to the ability of a measure to quantify the item or dimension it is supposed to measure(284). The three most important aspects of validity are content validity, criterion validity and construct validity(66). Content validity relates to the choice, appropriateness, importance and representativeness of the instrument's content. However, as there is no universal agreement on the defined content of quality of life instruments, validity is largely based on how well and broadly the content has been sampled and derived. Construct validity is supported when expected patterns of relationships are identified between the measured construct (such as physical functioning) and other variables (such as disease severity). Discriminative validity is the instrument's ability to detect changes in the observed variable without provoking a 'floor' or 'ceiling' effect that reflects an inability to detect clinically significant changes at the lower or higher spectrum of quality of life(66).

(iii) Commonly used health related quality of life measures in cardiovascular research

There are a variety of possible measuring tools available. In terms of disease specific tools, a review(290) found that a very wide range have been used, including Seattle Angina Questionnaire (SAQ), Quality of Life after Myocardial Infarction (QLMI) questionnaire, Minnesota Living with Heart Failure (MHFQ) Questionnaire, Myocardial Infarction Dimensional Scale (MIDAS), and the Cardiovascular Limitations and Symptoms Profile (CLASP). All have been used widely and have performed with mixed success relative to the criterion described above.

The most commonly used generic tools used in cardiovascular disease research are the EuroQol EQ-5D index(138) and the Short Form 36 or 12 (SF-36 or SF-12(137, 238). Other measures using in CVD research, but less widely applied as the Quality and Well-Being

(QWB) scale, and the health utilities index (HIU)(65). The consequent discussion is constrained to SF-3612 and EQ-5D.

The EQ-5D is consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with three levels of response or severity (no problems, some problems, or extreme problems). There are two possible questionnaire options: the EQ-5D-3L refers to there being 5 health dimensions (5D) and three possible responses, or levels (3L). A recently developed measure is the EQ-5D-5L, which has the same five health dimensions but with 5 levels (5L) of possible responses. This can produce 243 different health states i.e. different combinations of responses to the question.

The SF-36 consists of 36 questions covering eight domains, including physical functioning (PF), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). The SF-12 is a more parsimonious version consisting of 12 questions to measure the same eight health domains.

(iv) Potential limitations of generic health related quality of life measures

It is important that HRQoL are tested for the above attributes of reliability, validity and responsiveness. Measures which do not perform well are necessarily limited. In general, disease specific measures should be expected to perform better, as they have been developed with the specific condition in mind. However, the key limitation of using disease specific measures is the difficulty of directly comparing the HRQoL impact from different conditions. Generic measures are designed to allow for direct comparisons in HRQoL across disease areas, but may come at the cost of less reliability and validity, as described above.

Encouragingly, both the EQ-5D and the SF-36/12 have been found to perform well in CVD research. However, the mean HRQoL between studies differ(65). The key issue is whether the magnitude of change in HRQoL is adequately measured, rather than baseline HRQoL. In this regard, the used of a generic score seems to adequately evidenced. A review of the use of EQ-5D supports the reliability and validity of the instrument in (291). Further, it has been found that the SF-36 may perform relatively better than the EQ-5D, with better internal consistency and a higher test-retest reliability(66). Importantly, it has been shown that the SF-12 has a similar responsiveness to change as the SF-36 in patients with CHD(292). Therefore, in choosing the SF-36 or SF-12, the latter may be the preferred measure given parsimony.

The debate between generic and disease specific tools is likely to be continuous. The next section will discuss the potential of using both types of measures, and/or mapping between one measure and another.

5.3.2 The process of estimating health utility from health related quality of life measures

(i) Two-stages: From an economics perspective generic HRQoL measures are the preferred measure. Economics is concerned the allocation of scarce resources amongst alternative uses, and a generic measure is intended to enable comparisons of between different interventions and disease areas. However, using a generic questionnaire itself is not sufficient, as a very wide of possible states can result. These states need to be rank ordered in terms of the desirability of one state over another.

So the first stage is to administer a generic health questionnaire and the second stage is to convert responses into a single score summarising overall HRQoL. Economists call this score a health utility score. The process of ranking different HRQoL states involves either direct elicitation methods, or generic preference-based methods(293). The former is applied bespoke to each study and includes the methods of time-trade off and standard gamble where individuals trade-off health state scenarios. The latter simply takes 'off-the-shelf' preference weights from previous studies. Both the EQ-5D and the SF-12 can be converted into utilities using 'off-the-shelf' preference-weights(294). The latter is converted to the utilities using the SF-6D algorithm. The EQ-5D can produce 243 states and the SF-6D can produce 18,000 states.

(ii) Comparison of health utility measures and limitations: The existing literature is in agreement that there is reasonable correlation between EQ-5D and SF-6D ranking of health states on average(239, 295-296). However, neither the EQ-5D not the SF-6D is ideal: neither score measures all possible health states. The EQ-5D has been shown to suffer from 'ceiling effects' as the score ranges from -0.54 (worst that a death state of 0) to 0.88(best health). As such, it has difficulty discriminating between healthier states. The SF-6D suffers from 'floor effects' as the score measures health state utilities from 0.29 (worst health) to 1 (perfect health). As such, it has difficulty discriminating between states of poorer health. It has been argued that the EQ-5D is more appropriate in 'sicker' populations, and the SF-6D better in 'healthier' populations (200, 248,249).

Overall, while mean EQ-5D and SF-6D scores are often similar, depending on the patient group there can be wide variation in estimates depending on the degree of health of the individuals. In CVD patients, the SF-36/12 has been shown to have less ceiling and floor effects that other generic measures, including the EQ-5D(292).

A key issue is whose preferences should be used to rank health states, with the choice between the general population, or the patients affected by the condition under consideration. NICE recommends that preference weights be derived from general population preferences(37). This reflects the fact that the ultimate purpose of economic evaluation of health sector interventions in the UK is to influence how public funds are spent. However, this can raise objections, with respect to whether the healthy general public can properly empathise with the health states of different conditions(66).

On the other hand, directly asking patients may not be ideal either, as individuals may have adapted to their condition which could also be influence by peer group, and social context. Therefore, there may be an apparent inconsistency between so called subjective and objective measures of well-being. This phenomenon has been described as 'adaptive expectations' (Sen, 1999 pg 62)(297) and is often cited in the context of developing countries, where groups may not necessarily 'feel' disadvantaged even though the absolute level of health and poverty for instance may be low(298).

(ii) Estimating utility in practice: Overall, there is not a perfect measure of HRQoL. As discussed, there is disagreement over the concept, its operationalisation, whether to use generic or disease specific measures, and whether patients and/or the general population should be canvassed.

Practical ways forward in the debate whether to use disease specific or generic measures of HRQoL is to either map between one and the other, or to include both in a study. 'Mapping' is the development and use of an algorithm (or algorithms) to predict health-state utility values using data on other indicators or measures of health. The algorithm can be applied to data from clinical trials, other studies or economic models containing the source predictive measure(s) to predict utility values even though the target preference-based measure was not included in the original source study of effectiveness(299).

This mapping exercise may be important to convert past study findings that are for disease specific findings to utility values. For new studies, however, it practical solution is to include

both disease specific and generic measures in so-called pragmatic trial designs(38), as discussed in Chapter 3. This would then test for the agreement between disease and generic measures, and validate wider mapping exercises.

It is contended here that perhaps the key issue is not necessarily for one measure (e.g. disease specific versus generic) to assert dominance, but to recognise they have different immediate purposes. This would be more in keeping with a multi-disciplinary approach to evaluation, and may help further encourage clinicians and health professionals to engage with economists more routinely.

5.4 Estimating background morbidity and the impact of experiencing CVD events

5.4.1 Limited existing research

To reiterate, background morbidity is a term used to describe the average HRQoL in a population. This can also be termed populations. Kind et al(300) conducted a representative survey of the UK general population using 3,395 households to estimate background morbidity. Respondents completed both the EQ-5D questionnaire and also the Visual Analogue Scale, which asked individuals to rate their health from 0 (worst imaginable) to 100 (best imaginable). The creators of the EQ-5D recommend that when conducting economic evaluation and undertaking cost utility analysis, the VAS estimates should not be used to refer to population norms(138). Rather, the EQ-5D should be used and responses preference weighted, as described above.

However, it is important to note that while the generic EQ-5D questionnaire was applied, responses were not preference weighted. Rather, Kind's analysis reports on the VAS responses, which were weighted using a survey of patient preferences, not the general population. Consequently, the estimates produce by Kind are not strictly economic measure of background morbidity (or norms / utilities). Nonetheless, there is an absence of alternative estimates of health status in the general population. Recently, a demonstration of how to generate norms using the SF-6D was published(301), and norms have been derived in Australia using the SF-6D(302). Therefore, there is a need to estimate population norms using preference-weighted HRQoL, and the SF-6D may be the most appropriate measure.

The impact of experiencing CVD events on reducing HRQOL is called utility decrements. There are few studies estimating decrements for specific CVD events and no studies, that we are aware of, drawing upon the general population or using the SF-6D. The main study is Clarke et al (2002) where utilities were derived from the EQ-5D in a population with diabetes. Therefore, is also need to estimate the impact of CVD events in a general population.

The following details how background morbidity and event utility decrements were estimated in a Scottish population and compares results to the studies highlighted above.

5.4.2 An opportunity to estimate health related quality of life in a Scottish Population: the Scottish Health Survey

There was an opportunity to generate background morbidity(population norms) and estimate utility decrements directly for the Scottish general population. The Scottish Health Survey (SHeS) is a periodic cross sectional survey of the Scottish population, and has cardiovascular disease as its principle focus. SHeS uses multi-stage, stratified sampling to provide a representative sample of the Scottish population, and includes face-to-face interviews and physical measurements.

The SHeS 2003 is the only version of the SHeS that included the SF-12 (or any generic) HRQoL questionnaire that can be used to generate health state utilities. The SHeS 2003 had 11,472 respondents, with 7,780 over 20 years and asked for SF-12 responses. There were 7,054 individuals with sufficient SF-12 responses (the 6 question used by the SF-6D) to generate utilities. This represented 91% of eligible respondents. There were no systematic differences between respondents with and without missing data, by age, sex and fifths of SIMD. Given missing data was relatively minor and there was a large sample size, the analysis proceeded with a complete case analysis.

Using the same dataset, there was also an opportunity to estimate the HRQoL impact of experiencing events, or utility decrements. The SHeS 2003 collected information on six CVD events: angina, myocardial infarction, irregular heartbeat, other heart conditions, stroke and intermittent claudication. Events were self-reported with respondents asked, for each event in turn, whether a doctor had made a positive diagnosis and, if so, whether it was in the previous 12 months of the interview date. The exception was intermittent claudication where there was no survey question regarding time from doctor diagnosis.

5.4.3 Estimating background morbidity / population norms

Table 5-1 outlines the final dataset used in the analysis, with 44% males and 56% females. There was a slight under-representation of the more deprived groups (SIMD 4 and 5), although the sample size remained large.

Table 5-1 Scottish Health Survey 2003 - Population characteristics

	All	%	Male	%	Female	%
Total	7054	100%	3,105	100%	0	100%
Less deprived fifth - SIMD 1	1418	20%	634	20.4%	784	19.9%
	1574	22%	701	22.6%	873	22.1%
	1549	22%	691	22.3%	858	21.7%
	1346	19%	597	19.2%	749	19.0%
Most deprived fifth - SIMD 5	1167	17%	482	15.5%	685	17.3%

The SF-6D is used to convert SF-12 responses into utilities. First, the algorithm chooses 6 questions: (i) physical functioning; (ii) role limitation; (iii) social functioning; (iv) bodily pain; (v) vitality; and (vi) mental health. The percentage of respondents experiencing a 'problem' is shown in table 5.2 and was defined here as where the respondent provided a score less than the mode (e.g. ticking boxes 1 or 2 on a 5 point Likert scale). Average responses are shown with respect to the whole sample and across seven age groups used by Kind, to provide a degree of consistently.

Across all age groups, approximately a third of respondents suffered physical symptoms and felt limited in social functioning. Notably, two thirds of respondents had a mental health problem, with almost everyone limited in terms of vitality.

Table 5-2 Summary of SF6D dimensions – percentage experiencing problem

Age band	Physical functioning	Role limitation	Social functioning	Bodily pain	Mental health	Vitality
Total	27%	30%	34%	37%	66%	94%
Male	26%	27%	31%	36%	61%	93%
Female	29%	31%	37%	38%	69%	96%
<25						
Total	15%	20%	35%	22%	74%	93%
Male	15%	14%	30%	17%	71%	95%
Female	16%	20%	39%	26%	76%	92%
25-34						
Total	12%	23%	32%	26%	71%	94%
Male	11%	19%	27%	29%	66%	95%
Female	12%	23%	35%	23%	75%	94%
35-44						
Total	14%	23%	33%	30%	70%	95%
Male	11%	21%	29%	30%	66%	93%
Female	14%	23%	35%	30%	74%	97%
45-54						
Total	21%	31%	34%	36%	72%	95%
Male	20%	24%	30%	36%	68%	92%
Female	22%	31%	37%	37%	76%	97%
55-64						
Total	34%	31%	32%	43%	62%	94%
Male	31%	31%	30%	40%	58%	92%
Female	36%	31%	34%	45%	65%	96%
65-74						
Total	45%	40%	35%	50%	57%	94%
Male	46%	40%	35%	49%	52%	93%
Female	45%	40%	34%	51%	61%	95%
> 74						
Total	63%	59%	45%	53%	53%	94%
Male	54%	46%	39%	44%	48%	93%
Female	68%	59%	49%	59%	56%	95%

Across most categories there is an age gradient, where the percentage reporting a problem increased with respondent age. The notable exception is mental health where the percentage experiencing a problem declines with age.

The SF-6D algorithm was then applied to the SHeS population. Estimates of background morbidity were stratified by sex, age groups and SIMD quintiles. This was a descriptive analysis, reporting on mean scores and confidence intervals. Modelling made very minor differences to mean utility scores.

Table 5-3 reports on mean scores for the population split by age group and sex, 95% confidence intervals and the sample size. Average scores, across age groups, were 0.795 (0.791-0.80) for the population and 0.807 (0.802-0.811) for males, and 0.787 (0.787-0.791) for females. There is an expected, though gradual, age gradient in the population with the greatest step change in the over 74 year olds, where utilities are 0.74. Males consistently report higher health status, though the difference varies across age groups.

Table 5-3: Background morbidity in the general population

Age band	All	Male	Female
All	0.795 (0.791, 0.8) 7054	0.807 (0.802, 0.811) 3105	0.787 (0.782, 0.791) 3949
<25	0.818 (0.806, 0.829) 350	0.831 (0.814, 0.847) 140	0.809 (0.794, 0.824) 210
25-34	0.816 (0.809, 0.823) 998	0.823 (0.812, 0.834) 425	0.811 (0.801, 0.82) 573
35-44	0.81 (0.804, 0.817) 1525	0.82 (0.811, 0.83) 687	0.802 (0.793, 0.811) 838
45-54	0.794 (0.787, 0.802) 1319	0.806 (0.795, 0.818) 571	0.785 (0.776, 0.795) 748
55-64	0.794 (0.786, 0.802) 1270	0.801 (0.789, 0.813) 577	0.787 (0.777, 0.798) 693
65-74	0.782 (0.773, 0.792) 935	0.788 (0.774, 0.802) 446	0.777 (0.763, 0.79) 489
> 74	0.742 (0.73, 0.754) 657	0.774 (0.757, 0.792) 259	0.721 (0.704, 0.737) 398

There is a clear deprivation gradient in scores all age groups and for males and females, with the latter affected to a greater extent (Tables 5-4 and 5-5). On average, the health status of men falls from 0.831 in the lowest deprived fifth (SIMD1) to 0.754 in the highest deprived fifth (SIMD5) a drop of 9%. For females, the difference in health status moves from 0.826 to 0.737 – a fall of 11%. For both sexes, the impact of deprivation status is lowest in the youngest age group, increases approximately fourfold until 55-64 years and falls thereafter. In general, males tend to self-report higher health status than women across all age groups and SIMD status, with the exception of SIMD1 where women tend to self-report higher health status (excluding the over 74). This corroborates a recent study in Australia where norms fell the more poorly educated individuals were(302).

Table 5-4 Background morbidity across fifths of deprivation - men

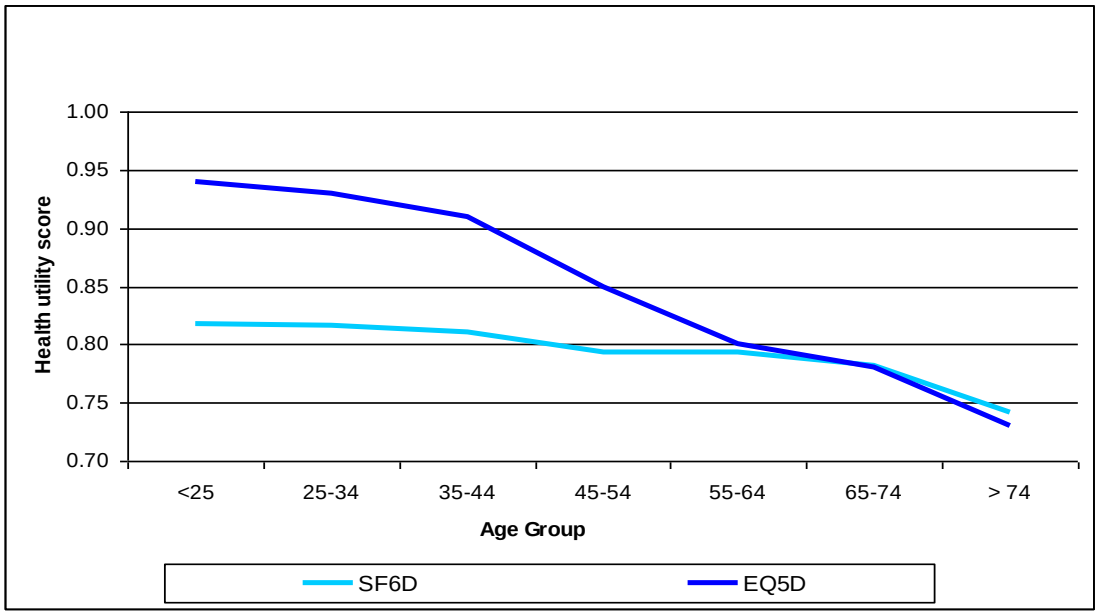
	Male				
Age band	SIMD 1	SIMD 2	SIMD 3	SIMD 4	SIMD 5
All	0.831 (0.808, 0.854)	0.826 (0.803, 0.849)	0.81 (0.785, 0.836)	0.795 (0.766, 0.825)	0.754 (0.719, 0.79)
	634	701	691	597	482
<25	0.822 (0.787, 0.857)	0.853 (0.824, 0.881)	0.834 (0.795, 0.873)	0.857 (0.828, 0.887)	0.787 (0.745, 0.83)
	23	27	27	32	31
25-34	0.848 (0.826, 0.871)	0.849 (0.83, 0.867)	0.823 (0.796, 0.85)	0.816 (0.794, 0.839)	0.774 (0.741, 0.807)
	75	88	88	104	70
35-44	0.834 (0.816, 0.852)	0.838 (0.82, 0.855)	0.823 (0.805, 0.841)	0.811 (0.787, 0.835)	0.777 (0.744, 0.81)
	146	164	155	125	97
45-54	0.825 (0.805, 0.845)	0.827 (0.806, 0.849)	0.808 (0.783, 0.833)	0.791 (0.756, 0.826)	0.762 (0.729, 0.794)
	128	139	126	82	96
55-64	0.845 (0.826, 0.865)	0.803 (0.78, 0.826)	0.82 (0.796, 0.843)	0.782 (0.751, 0.813)	0.718 (0.68, 0.757)
	138	127	121	111	80
65-74	0.813 (0.784, 0.841)	0.822 (0.791, 0.853)	0.802 (0.775, 0.83)	0.761 (0.729, 0.792)	0.732 (0.697, 0.768)
	86	89	107	92	72
> 74	0.797 (0.75, 0.843)	0.802 (0.77, 0.835)	0.756 (0.722, 0.791)	0.775 (0.731, 0.818)	0.732 (0.685, 0.779)
	38	67	67	51	36

Table 5-5 Background morbidity across fifths of deprivation - women

	Female				
Age band	SIMD 1	SIMD 2	SIMD 3	SIMD 4	SIMD 5
All	0.826 (0.806, 0.846)	0.807 (0.786, 0.828)	0.785 (0.761, 0.809)	0.769 (0.743, 0.795)	0.737 (0.707, 0.766)
	784	873	858	749	685
<25	0.846 (0.813, 0.88)	0.81 (0.779, 0.842)	0.78 (0.739, 0.821)	0.799 (0.765, 0.832)	0.816 (0.787, 0.845)
	30	37	36	48	59
25-34	0.839 (0.822, 0.856)	0.816 (0.795, 0.836)	0.822 (0.803, 0.841)	0.803 (0.78, 0.825)	0.775 (0.749, 0.8)
	105	122	114	128	104
35-44	0.837 (0.823, 0.852)	0.827 (0.812, 0.841)	0.794 (0.773, 0.815)	0.788 (0.769, 0.808)	0.748 (0.722, 0.774)
	176	198	172	150	142
45-54	0.827 (0.812, 0.843)	0.793 (0.773, 0.812)	0.78 (0.758, 0.802)	0.769 (0.745, 0.792)	0.736 (0.708, 0.764)
	180	166	157	128	117
55-64	0.835 (0.816, 0.854)	0.815 (0.798, 0.832)	0.791 (0.768, 0.814)	0.769 (0.742, 0.796)	0.701 (0.67, 0.732)
	133	162	167	126	105
65-74	0.827 (0.803, 0.851)	0.803 (0.776, 0.83)	0.792 (0.766, 0.818)	0.742 (0.709, 0.776)	0.702 (0.668, 0.736)
	96	102	118	86	87
> 74	0.741 (0.702, 0.779)	0.765 (0.732, 0.798)	0.715 (0.681, 0.748)	0.693 (0.655, 0.731)	0.689 (0.652, 0.726)
	64	86	94	83	71

The background morbidity scores derived in this study using the SF-6D are notably different from Kind's analysis which was based upon the Euro-Qol Visual Analogue Scale (VAS) – figure 5-2.

Figure 5-2: Comparison of background morbidity scores: SF-6D and EQ-5D



The scores generated by SF-6D tend to be lower and have a shallower age gradient than responses derived from the EQ-5D VAS. Average scores using the SF-6D were 0.80 compared to 0.86 in Kind. Differences were most pronounced in the youngest age groups. However, as age increases the scores converge and by 65 years estimates between studies were virtually identical. A similar set of findings were evident in a study conducted in Greece, where both the EQ-5D VAS and the SF-6D was administered to a representative sample (1,005) of the general population(303). This analysis suggests that in older and sicker age groups using either SF-6D or EQ-5D VAS may provide consistent results. However, it is important to reiterate that creators of the EQ-5D VAS have stated it should not be used in economic evaluation.

More generally, despite close correlation between the EQ-5D and the SF-6D across most values, it is contended here that perhaps the SF-6D may be more appropriate to estimate background morbidity in the general population. It has been shown that the EQ-5D (preference-weighted scores) suffers from ceiling effects, and may not adequately discriminate between states were individuals are in relatively good health. The SF-6D in contrast suffers from floor effects, being bound by 0.29, and so cannot adequately discriminate between poorer health states. However, given the general population is in relatively good health on average perhaps the SF-6D is a more discriminatory measure to estimate background morbidity scores.

5.4.4 Estimating the impact of experiencing non-fatal CVD events: utility decrements

An average utility score is called background morbidity or population norms, and the difference between a utility score and perfect health (a score of 1) is called an overall utility decrement. The impact of an experiencing a specific CVD is called an event utility decrement, as this contributes to the overall utility decrement. This section details how utility decrements were estimated.

Table 5-6 outlines event history with the SHeS 2003. Average age was 50.4 years (s.e. 16.6), with males composing 44% of total respondents and females 56%. In total, there were 1,068 survey respondents with a CVD event history, 15% of the eligible sample population, with approximately one third having incurred multiple events.

Table 5-6: Summary of Scottish Health Survey 2003

	Total/Average	Male (proportion)	Female (proportion)
Sample population	7054	3105 (44%)	3949 (55%)
Age (SD)	50.4 (16.6)	50.5 (16.3)	50.3 (16.8)
Respondents with CVD			
Single event	703	307 (44%)	396 (56%)
Multiple events	365	206 (56%)	159 (44%)
Total	1068	513 (48%)	555 (52%)
Event types			
Angina	451	243 (54%)	208 (46%)
Myocardial infraction	252	156 (62%)	96 (38%)
Irregular heart beat	393	173 (44%)	220 (56%)
Other heart condition	134	74 (55%)	60 (45%)
Stroke	155	75 (48%)	80 (48%)
Intermittent claudication	182	76 (42%)	106 (58%)
Total	1567	797 (51%)	770 (49%)

Overall, there were 1567 separate events balanced evenly between males (51%) and females (49%). Angina was the most frequent event (451 cases) followed by irregular heartbeat (393 cases) and myocardial infarction (252 cases), together accounting for 70% of all 1,567 events. Males had the greatest share of total angina and myocardial infarctions, with females relatively more dominant in those incurring strokes and having an irregular heartbeat.

Time from event: Table 5-6 illustrates the number and proportion of events that occurred within and over 12 months, for both the sample as a whole and separately for males and females. For total events, angina was the only condition where most events (59%) were within one year of the interview date. Respondents incurring myocardial infarction and strokes overwhelmingly reported these as occurring over one year from the interview date (88% for MI and 79% for strokes). The pattern regarding the incidence of events was very similar between males and females.

Table 5-7 CVD events within and over 12 months of interview

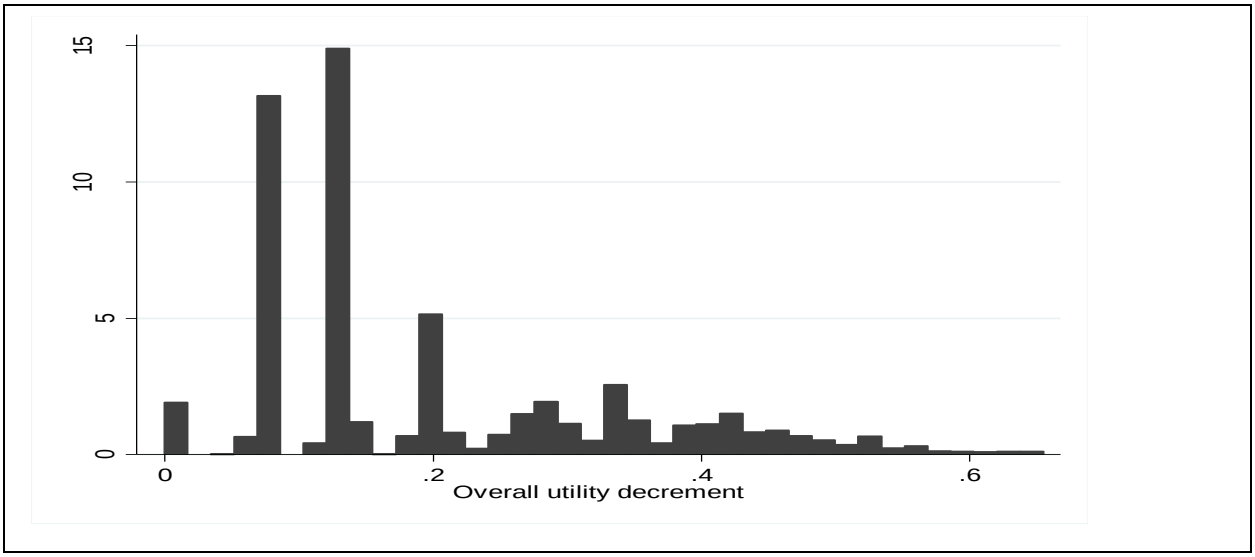
CVD Event	Breakdown per event		Breakdown per event by gender			
	Total	%	Male	%	Female	%
Angina						
Within 12 months	268	59%	134	55%	134	64%
Over 12 months	183	41%	109	45%	74	36%
Total	451	100%	243	100%	208	100%
Myocardial infraction						
Within 12 months	30	12%	16	10%	14	15%
Over 12 months	222	88%	140	90%	82	85%
Total	252	100%	156	100%	96	100%
Irregular heart beat						
Within 12 months	206	52%	96	55%	110	50%
Over 12 months	187	48%	77	45%	110	50%
Total	393	100%	173	100%	220	100%
Other heart condition						
Within 12 months	70	52%	39	53%	31	52%
Over 12 months	64	48%	35	47%	29	48%
Total	134	100%	74	100%	60	100%
Stroke						
Within 12 months	33	21%	13	17%	20	25%
Over 12 months	122	79%	62	83%	60	75%
Total	155	100%	75	100%	80	100%

To estimate the utility decrements of experiencing CVD events explore an appropriate modelling approach, Generalized Linear Modelling (GLM) was used(304). GLMs encompass the general linear model and also enlarge the class of linear least-squares models considered. In choosing a model type there are two key decisions to make. First, an appropriate "family" is required to be selected and secondly an appropriate "link function". The family refers to the distributional assumptions regarding the variance around mean coefficients and the error term. The distribution of Y for fixed x is assumed to be from the exponential family of distributions, which includes important distributions such as the binomial, Poisson, exponential, and gamma distributions, in addition to the normal distribution. The link function defines the linear predictor and the power terms are required (if

any) to achieve best fit with the dependent variable. The only restrictions are that the functions are required to be monotonic and differentiable.

To use GLM a positive scale is required for the dependent variable. However, the overall utility decrement is by definition on a negative scale. Therefore, a positive right skew was created by subtracting the overall utility decrement for each responded from (essentially the distribution is flipped over). Figure 5-3 illustrates the overall utility decrements (i.e. 1 - utility score) in the 7,054 respondents. The left skew reflects the frequency of respondents in very good health, and the long right tail is limited at 0.71. This reflects that the SF-6D has a floor effect of 0.29, and so when scores from 1 there is now a ceiling of 0.71.

Figure 5-3 Distribution of overall utility decrements



The next step is to choose the form of the regression model, where the dependent variable is the overall utility decrement and the independent variables were the six events, with sex and also age included, with the latter defined as a continuous variable.

A series of “families” were tested and the Modified-Park’s test was used to suggest the most appropriate family that the most robust model specification was defined by a Gaussian family. Next, to choose the power function for the linear predictor, the iterative procedure suggested by Glick was undertaken to manually test different powers and the choice was guided by using the three diagnostic tests (Pearson, Pregibon and modified Hosmer-Lemeshow)(305). A link function was the most appropriate choice.

A Gaussian with a link function, is equivalent to Ordinary Least Square (OLS). Despite the skewed data, this appeared to be an appropriate choice given the purpose of the analysis was to estimate mean event decrements and normality can be assumed in large samples such as the SHeS 2003 (7,054 individuals)(306).

Using the Gaussian with a link function the six CVD events were regressed on the overall utility decrement to estimate the contribution by experiencing CVD events (i.e. event utility decrements). A separate model was run to investigate whether event utility decrements within and over 12 months were significantly different. Next, the presence of interactions between all possible event combinations was tested, and also the interaction of event type with age as a continuous variable. Significance tests for time from event and interactions were conducted using the log-rank test. Finally, it was investigated whether event utility decrements are specific to sex, age group and also fifths of SIMD.

Table 5-8 provides estimated event decrements, all of which were significant at the 1% level. Mean decrements were: angina 0.089, myocardial infarction 0.040, irregular heartbeat 0.050, other heart conditions 0.034, stroke 0.094 and intermittent claudication 0.020. When considering the impact of multiple events on an overall utility decrement there was an additive relationship. For instance, intermittent claudication followed by stoke would result in a combined decrement of 0.098 (0.02 plus 0.096). The only interaction found to be significant was the combination of angina and myocardial infarction which results in a decrement of 0.037 ($p = 0.05$) – which is less that either angina or myocardial infarction separately. This may be explained by the fact that a non-fatal heart attack may remove the dead heart tissue that causes angina pain.

Table 5-8 The impact of experiencing CVD - event utility decrements

	Overall	Within 12 months	Over 12 months
Age	0.0005 (0.0001)	0.0005 (0.0001)	0.0005 (0.0001)
Male	-0.024 (0.003)	-0.024 (0.003)	-0.024 (0.003)
Angina	0.089 (0.007)	0.113 (0.009)	0.058 (0.011)
Myocardial infraction	0.04 (0.01)	0.014 (0.025)	0.04 (0.01)
Irregular heart beat	0.05 (0.007)	0.067 (0.01)	0.028 (0.067)
Other heart condition	0.034 (0.012)	0.071 (0.016)	-0.002 (0.017)
Stroke	0.094 (0.011)	0.128 (0.023)	0.077 (0.012)
Intermittent claudication	0.02 (0.01)	-	-
Constant	0.177 (0.005)	0.177 (0.005)	0.177 (0.005)

* Estimates were all significant at 1% level, with exception of MI within 1 year, and other heart condition over 1 year

In terms of the other estimates, the constant refers to the overall impact of other co-morbidities, age has a positive but minor impact, and males tend to experience lower event utility decrements (-0.024) on average than females. The latter is consistent with findings from the previous section where males report higher health utility than females, on average.

Time from event is generally important, with event utility decrements substantially and significantly higher if the event occurred within 12 months of the interview date. For instance, the impact of angina is almost double (0.113 versus 0.058). Time from event was not significant for myocardial infarction within 12 months and other heart conditions over 12 months. This is likely to be the result of a lower number of events

There were no significant results when the analysis was repeated for men and women separately, across different age groups and for different levels of socioeconomic status.

There are few studies estimating decrements for specific CVD events and no studies, that we are aware of, drawing upon the general population or using the SF-6D. The main study is Clarke et al (2002) where utilities were derived from the EQ-5D in a population with diabetes. The modelling approach was to use a Tobit model and where event decrements were: MI 0.055, CHD 0.090 and stroke 0.164. These estimates are reasonably similar to those estimated in the thesis, though stroke is substantially higher. This may be because the SHeS as a general population survey relies on individuals to self-report and those with more severe strokes perhaps could not participate.

The finding that the impacts of events are greater within the first year, with the exception of myocardial infarction, likely reflects the initial shock post event followed by consequent adaptation by healthy survivors(307). A similar trend was also found by Clarke et al.

5.5 Estimating the risk of subsequent non-fatal CVD events

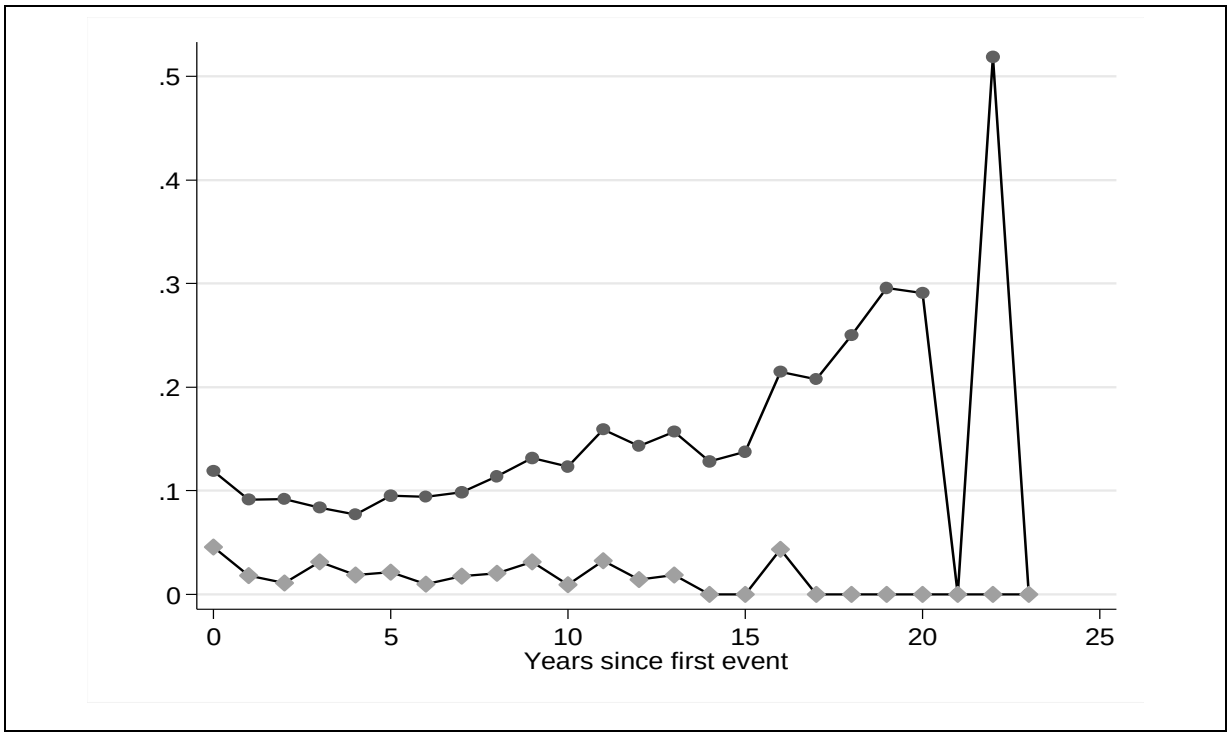
5.5.1 Source data

Following a non-fatal first event the model predicts survival and consequent life expectancy, as detailed in Chapter 4. However, individuals who survive a first event are at risk of further non-fatal events as they transit in the model towards death. Using the Scottish Morbidity Records (SMR) there was the opportunity to estimate the probability of subsequent CVD events following a first non-fatal event. Within the SMR data each hospital admission has diagnostic points: principal diagnosis (the primary reason for hospitalisation) and five secondary diagnoses. An individual was identified as having an experiencing a new CVD event if it was recorded in any diagnostic position for the first time. Therefore, this includes hospitalisation for a CVD event, events incurred while in-stay, and events that may have been recorded outside of secondary care.

The events considered were CHD, stroke, intermittent claudication, heart failure and other heart events. Following the structure of the model, separate datasets were created that followed patients who had experienced either CHD or CBVD as the first non-fatal event. Further, this was repeated men and women separately. Therefore, four different datasets were created. Within each of the dataset, the average event count per annual cycle of the model was estimated, by dividing the number of individuals experiencing an event by the total number of SHHEC participants still alive. This is termed the observed proportions. The following figures show the observed proportions of events following a CHD and CBVD events: Figures 5-4 to 5-8 for men and Figures 5-9 to 5-13 for women.

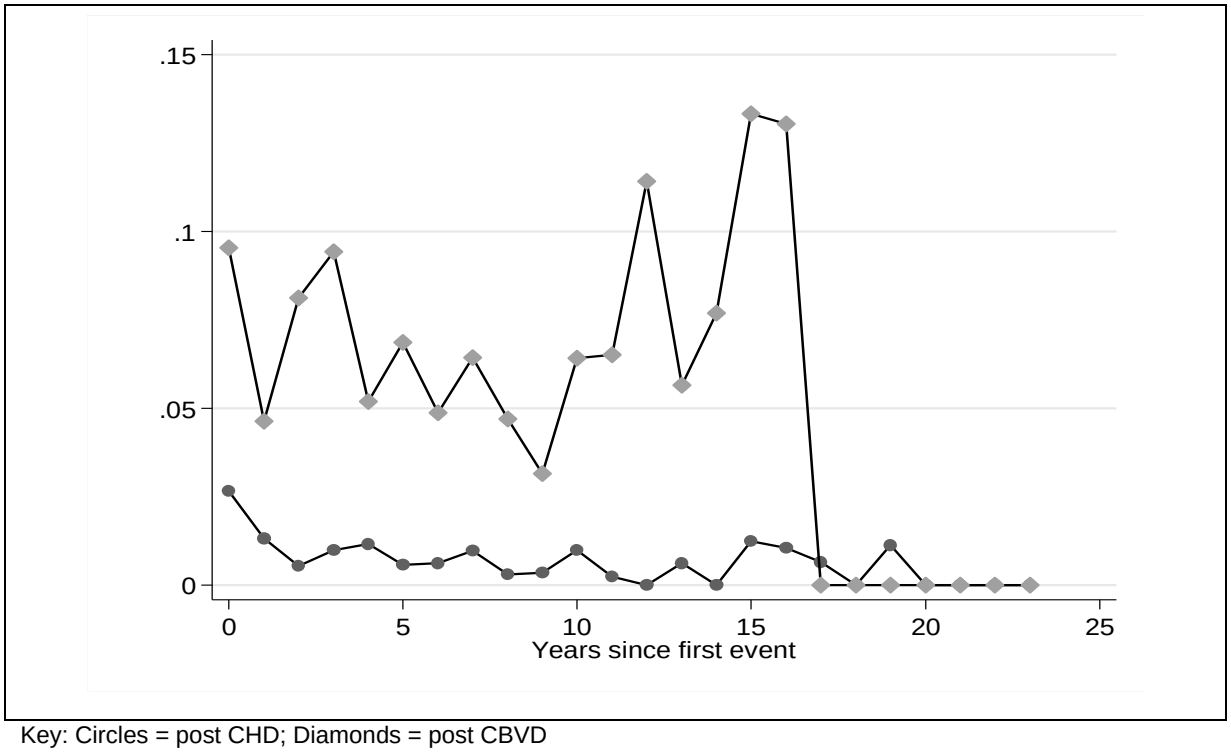
The observed proportions of events are erratic, particularly as years since first event increase, where the observed follow-up of SHHEC participants falls. Overall, the most common subsequent events are CHD for men and women

Figure 5-4 Observed proportions of CHD hospitalisations since first event - men



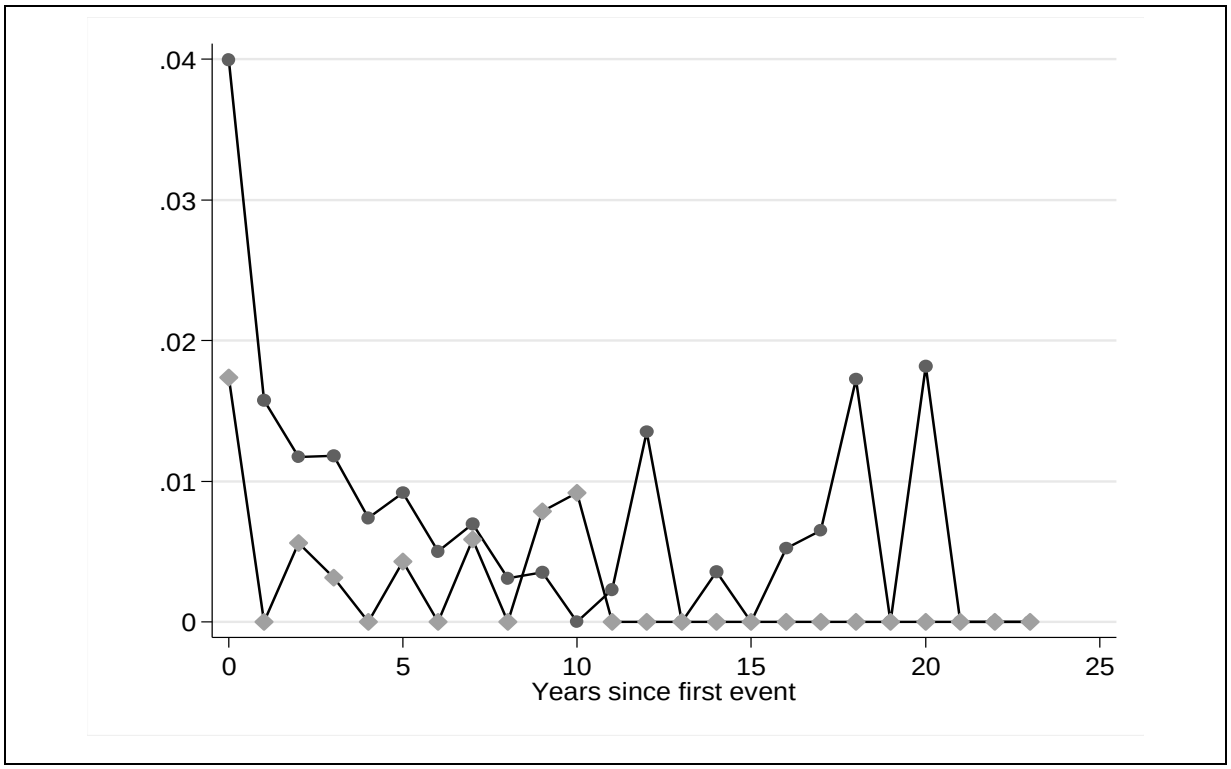
Key: Circles = post CHD; Diamonds = post CBVD

Figure 5-5 Observed proportions of CBVD hospitalisations since first event - men



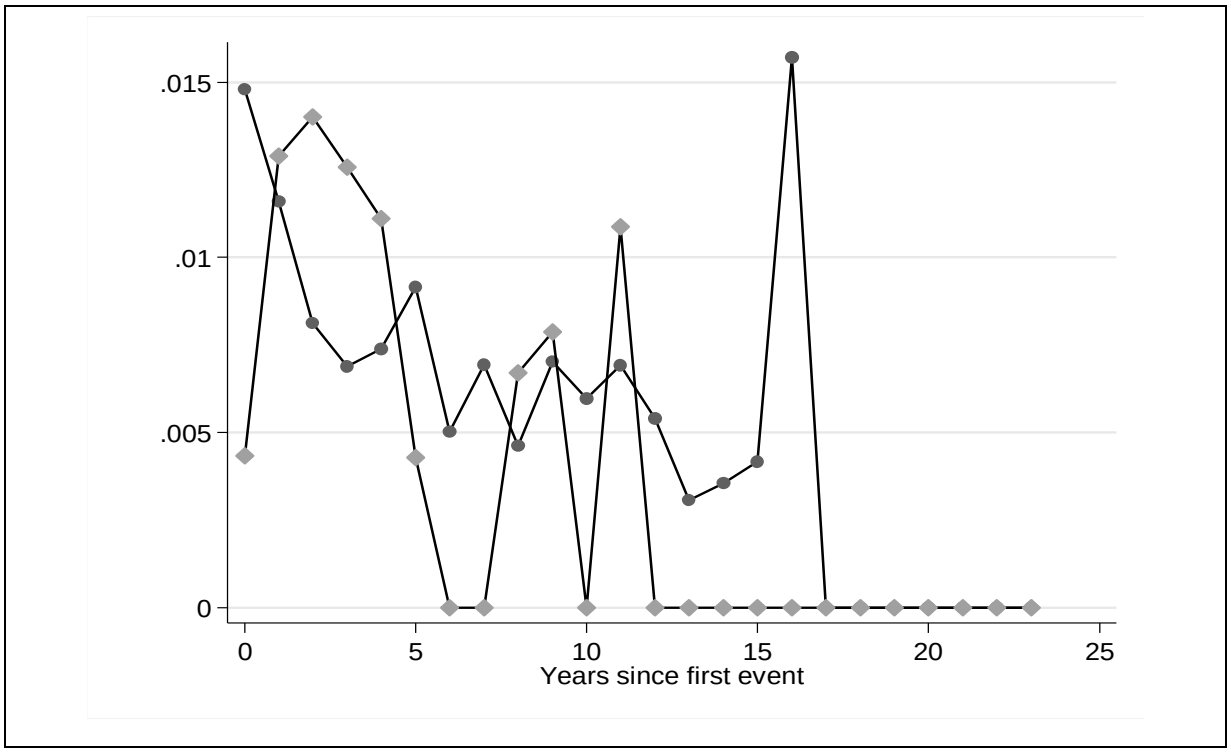
Key: Circles = post CHD; Diamonds = post CBVD

Figure 5-6 Observed proportions of heart failure hospitalisations since first event - men



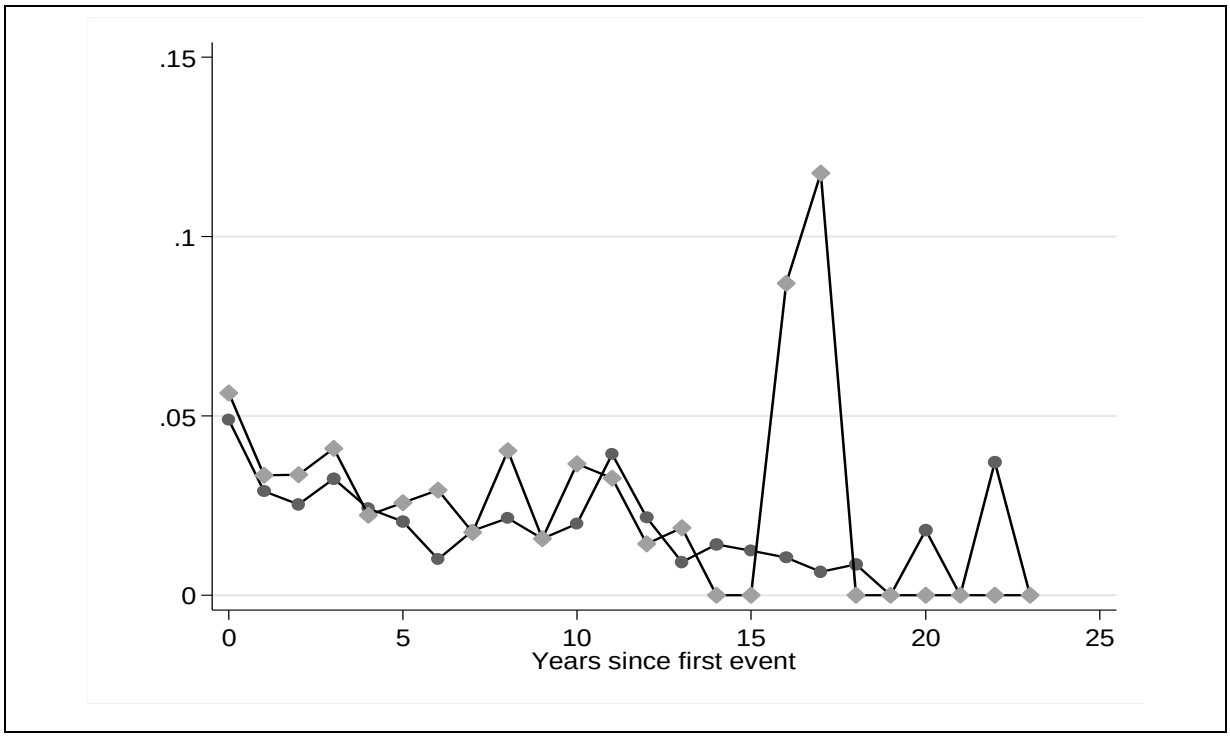
Key: Circles = post CHD; Diamonds = post CBVD

Figure 5-7 Observed proportions of PAD hospitalisations since first event - men



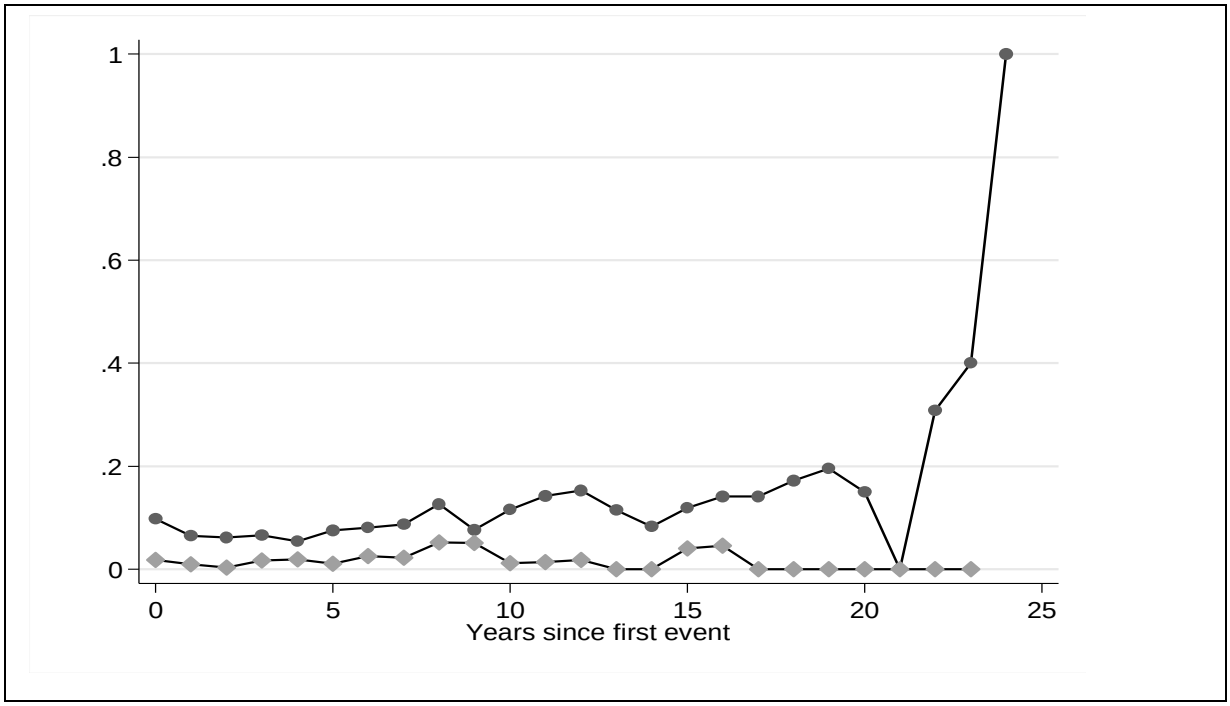
Key: Circles = post CHD; Diamonds = post CBVD

Figure 5-8 Observed proportions of other heart event hospitalisations since first event -men



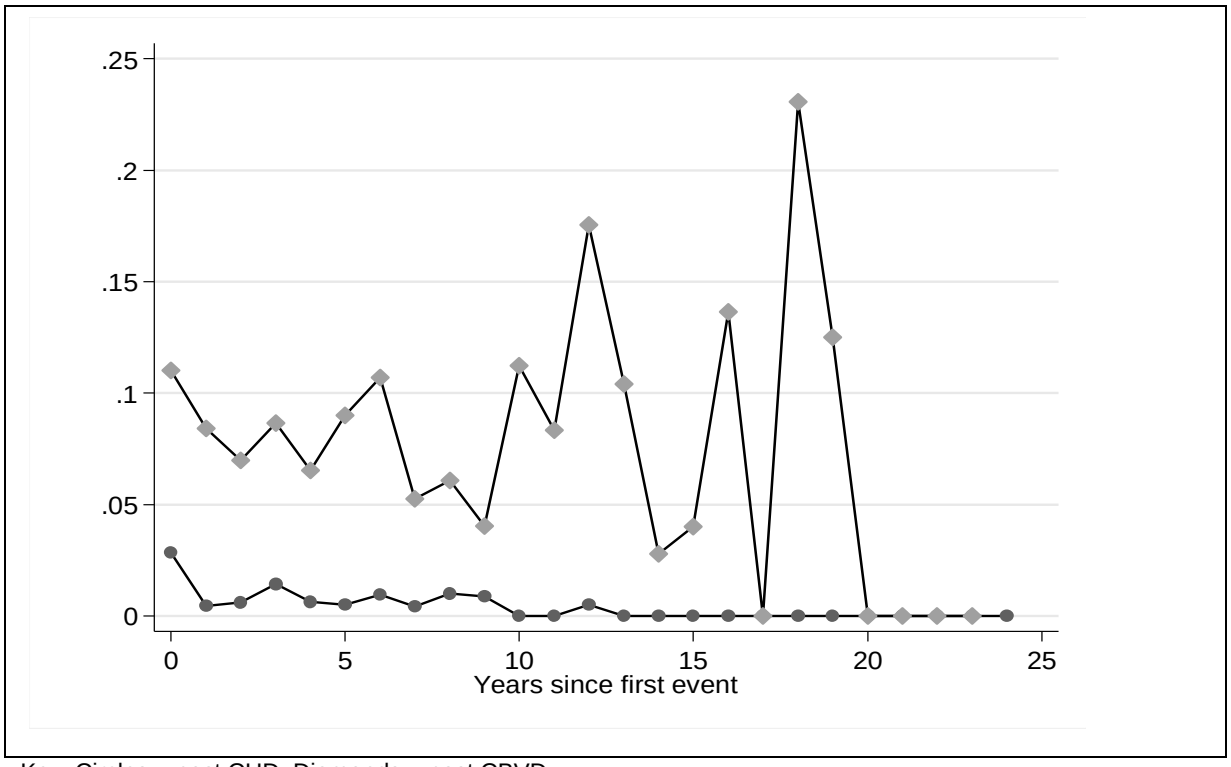
Key: Circles = post CHD; Diamonds = post CBVD

Figure 5-9 Observed proportions of CHD hospitalisations since first event - women



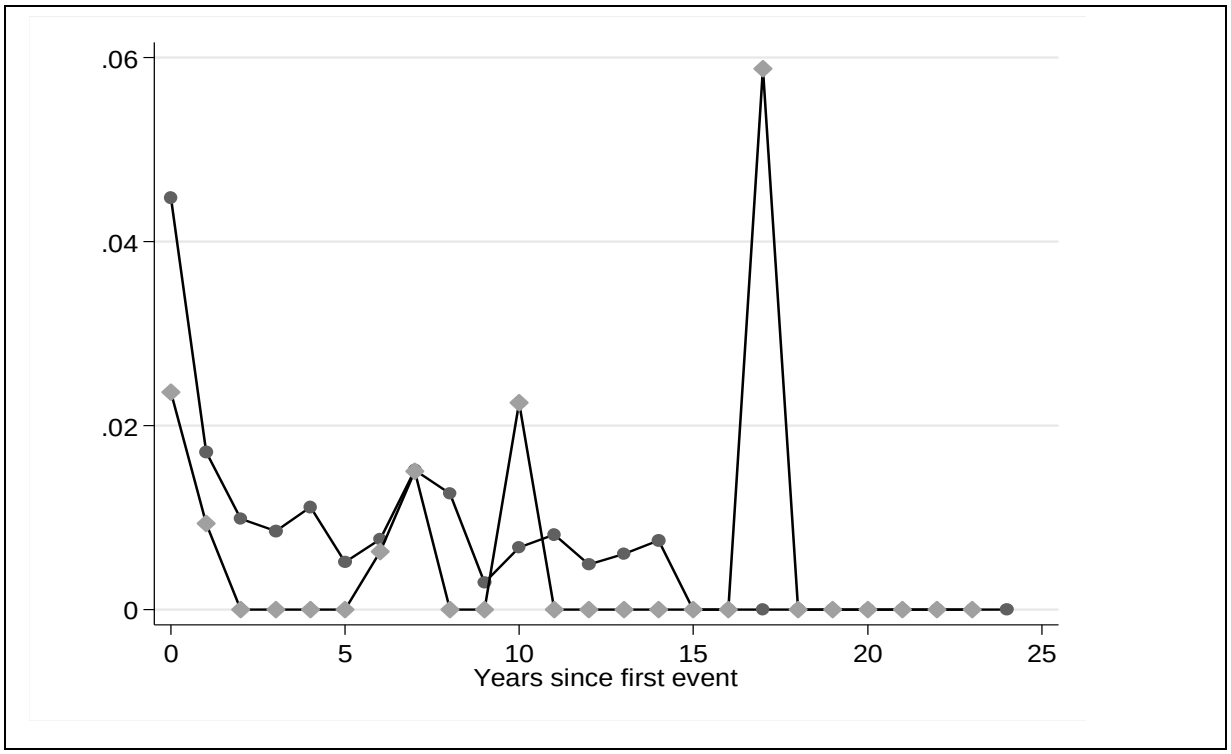
Key: Circles = post CHD; Diamonds = post CBVD

Figure 5-10 Observed proportions of CBVD hospitalisations since first event - women



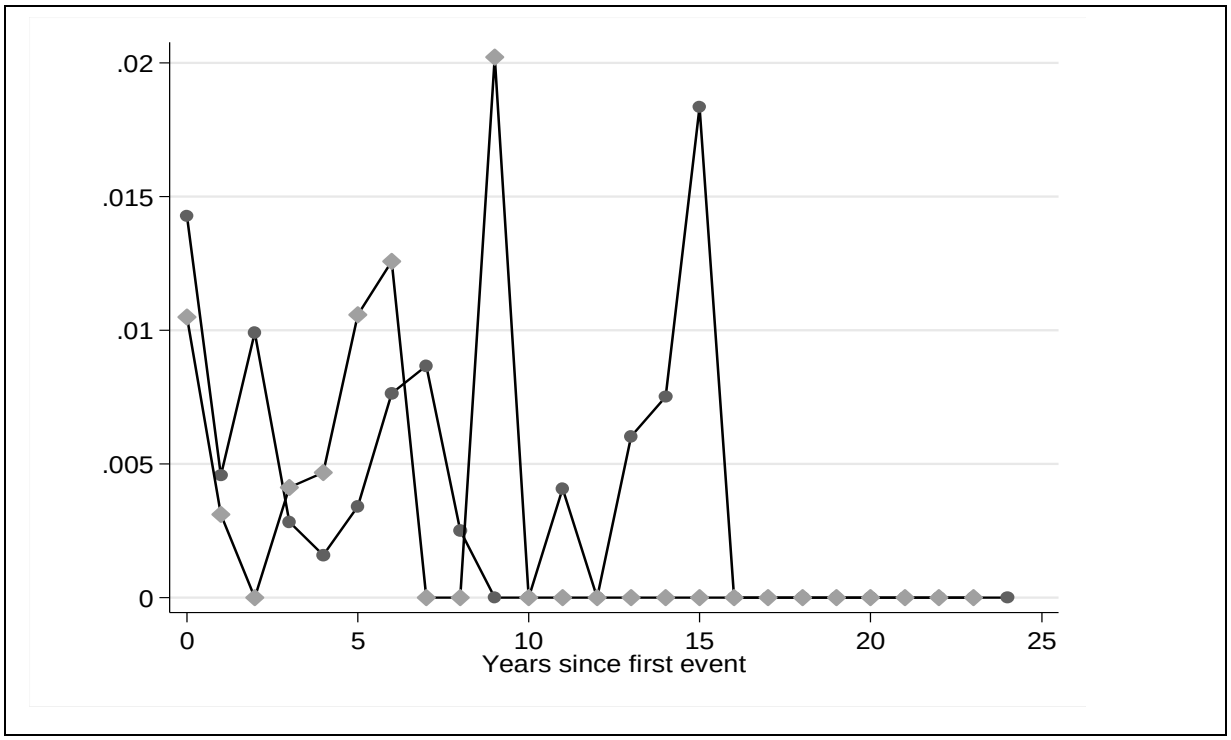
Key: Circles = post CHD; Diamonds = post CBVD

Figure 5-11 Observed proportions of heart failure hospitalisations since first event - women



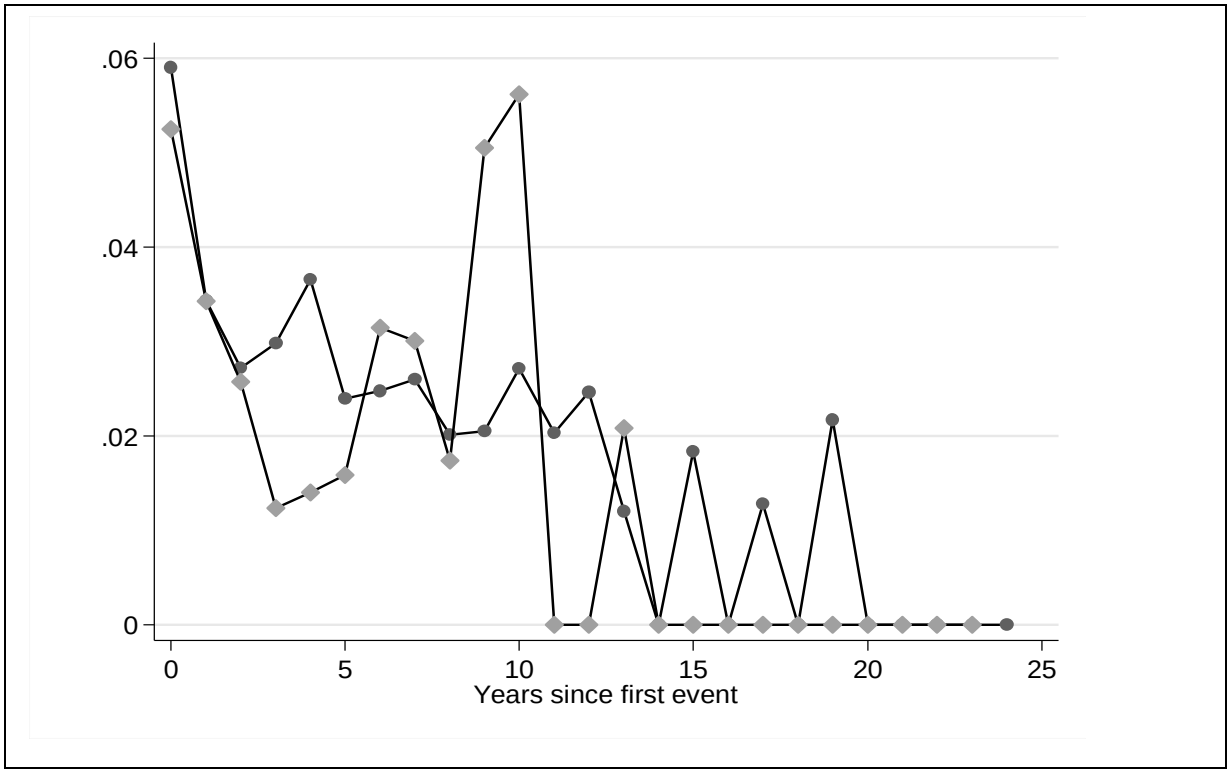
Key: Circles = post CHD; Diamonds = post CBVD

Figure 5-12 Observed proportions of PAD hospitalisations since first event - women



Key: Circles = post CHD; Diamonds = post CBVD

Figure 5-13 Observed proportions of other heart event hospitalisations since first event - women



Key: Circles = post CHD; Diamonds = post CBVD

5.5.2 Modelling to estimate subsequent non-fatal CVD events

The aim of the modelling was to predict the probability that an individual who has experienced a first non-fatal event would incur any of the five non-fatal CVD events - conditional upon being alive at a point in time. Invoking the assumption of non-informative censoring (i.e. that there is no systematic differences between individuals still alive and those who have died) the modelled average observed event count is assumed representative of all individuals that have the same risk profile defined by the ASSIGN risk factors.

The ultimate aim of the analysis was to model lifetime risk of subsequent non-fatal CVD events for patient profiles. Given the maximum follow-up in the SHHEC-SMR data was 25 years. Before developing a regression approach the observed data was first extrapolated to allow regression across 100 years that the model runs for.

In choosing an extrapolation approach, a key observation is that observed event proportions were highly erratic. For the purpose of prediction it is common to take an extrapolation approach that both smoothes predictions, and fits to the underlying 'curvature' of the data. This was the rationale for taking the parametric approach of restricted cubic splines (RCS) to extrapolate observations. First, the observed time period was divided into equally space percentiles and within each percentile the frequency of first event rates was estimated. The next stage is to choose a set of knots which groups the data into segments. Following Harrell's guidance(308) three knots were chosen to generate three segments. This then allows piecewise regression between adjacent knots. When using restricted cubic splines one obtains a continuous smooth function that is linear before the first knot, a piecewise cubic polynomial between adjacent knots, and linear again after the last knot. The RCS function in STATA selects the knots automatically based on the events frequencies across percentiles. The empirical approach is intended to enable smoothing across the whole predicted function, rather than simply extrapolating from the end of the observations.

The advantage of the restricted cubic method is that the shape of the function is less influenced at the edges of the data than a fractional polynomial approach, which can be a popular alternative. This is particularly important in this setting where events at the end of the observed period are few and the observations are erratic.

A probit model was then chosen to regress the average event count per period on the four non-modifiable CVD risk factors of age, sex, family history and SIMD. Further, the time splines were used in the modelling to then project how risk is related to time.

The probit model was chosen because the model assumes that the event proportions are continuous, ranging from 0 to 1 and following a standard normal distribution. In this way the model generates probabilities of CVD events that can be used directly to estimate risk of subsequent events.

Overall this modelling approach generates the following generic expression:

Expected proportion = $F(xb(t))$

where F is the cumulative standard Normal distribution and $xb(t)$ is the linear predictor from the probit regression at time period t.

To reiterate, the modelling to predict the 5 events post CHD and post CBVD was done separately for each event and also for men and women. The resultant coefficients and associated time splines are shown on Tables 5-9 to 5-16.

The estimated coefficients regarding the risk of subsequent events following a first non-fatal event provide some justification for having separate models that estimated event coefficients separately with respect to the 5 events and with different models for men and women. Note, that the time splines are similar, or identical, across events and between men and women. This is simply a function of the frequency of the observed counts and the approach of RCS.

Intuitively, the modelling results suggest that individual event history matters, and the risk of future events is conditional not only upon the ASSIGN risk factors but also with respect to which event occurred first and at what time.

Table 5-9 Modelling the probability of non-fatal CVD events: men post CHD event

Covariate	CHD		Stroke		Inter. claudication		Other heart condition	
	coeff. (95% CI)	p value	coeff. (95% CI)	p value	coeff. (95% CI)	p value	coeff. (95% CI)	p value
ti1	-0.019 (-0.040, 0.002)	0.073	-0.101 (-0.147, -0.055)	<0.001	-0.049 (-0.104, 0.006)	0.080	-0.060 (-0.091, -0.028)	<0.001
ti2	0.071 (0.045, 0.098)	<0.001	0.098 (0.035, 0.161)	0.002	0.034 (-0.039, 0.107)	0.363	0.050 (0.008, 0.092)	0.019
Age	0.010 (0.005, 0.016)	<0.001	0.001 (-0.007, 0.009)	0.821	-0.001 (-0.012, 0.010)	0.888	0.005 (-0.002, 0.013)	0.150
SIMD sc.	0.003 (0.001, 0.005)	0.004	0.003 (0.000, 0.007)	0.051	0.002 (-0.003, 0.006)	0.444	0.003 (0.001, 0.006)	0.012
Fam. his.	0.106 (0.019, 0.193)	0.016	-0.011 (-0.168, 0.145)	0.886	-0.136 (-0.350, 0.077)	0.211	0.174 (0.051, 0.297)	0.006
Constant	-2.012 (-2.420, -1.605)	<0.001	-2.085 (-2.640, -1.530)	<0.001	-2.137 (-2.903, -1.371)	<0.001	-2.187 (-2.680, -1.693)	<0.001

Covariate	HF	
	coeff. (95% CI)	p value
ti1	-0.152 (-0.195, -0.110)	<0.001
ti2	0.160 (0.098, 0.223)	<0.001
Age	0.014 (0.004, 0.023)	0.004
SIMD sc.	0.002 (-0.002, 0.006)	0.297
Fam. his.	0.044 (-0.121, 0.210)	0.599
Constant	-2.626 (-3.260, -1.992)	<0.001

Note: ‘Age’ is age at first event; ‘ti1’ and ‘ti2’ are time spline function variables

Table 5-10 Time spline variables: Men post-CHD

Cycle (year)	ti1	ti2	Cycle (year)	ti1	ti2	Cycle (year)	ti1	ti2
1	1	0	35	35	32.30769	68	68	70.38461
2	2	0.0059172	36	36	33.46154	69	69	71.53846
3	3	0.0473373	37	37	34.61538	70	70	72.69231
4	4	0.1597633	38	38	35.76923	71	71	73.84615
5	5	0.3786982	39	39	36.92308	72	72	75
6	6	0.7396449	40	40	38.07692	73	73	76.15385
7	7	1.268491	41	41	39.23077	74	74	77.30769
8	8	1.952663	42	42	40.38462	75	75	78.46154
9	9	2.76997	43	43	41.53846	76	76	79.61539
10	10	3.698225	44	44	42.69231	77	77	80.76923
11	11	4.715237	45	45	43.84615	78	78	81.92308
12	12	5.798817	46	46	45	79	79	83.07692
13	13	6.926775	47	47	46.15385	80	80	84.23077
14	14	8.076923	48	48	47.30769	81	81	85.38461
15	15	9.230769	49	49	48.46154	82	82	86.53846
16	16	10.38461	50	50	49.61538	83	83	87.69231
17	17	11.53846	51	51	50.76923	84	84	88.84615
18	18	12.69231	52	52	51.92308	85	85	90
19	19	13.84615	53	53	53.07692	86	86	91.15385
20	20	15	54	54	54.23077	87	87	92.30769
21	21	16.15385	55	55	55.38462	88	88	93.46154
22	22	17.30769	56	56	56.53846	89	89	94.61539
23	23	18.46154	57	57	57.69231	90	90	95.76923
24	24	19.61539	58	58	58.84615	91	91	96.92308
25	25	20.76923	59	59	60	92	92	98.07692
26	26	21.92308	60	60	61.15385	93	93	99.23077
27	27	23.07692	61	61	62.30769	94	94	100.3846
28	28	24.23077	62	62	63.46154	95	95	101.5385
29	29	25.38461	63	63	64.61539	96	96	102.6923
30	30	26.53846	64	64	65.76923	97	97	103.8462
31	31	27.69231	65	65	66.92308	98	98	105
32	32	28.84615	66	66	68.07692	99	99	106.1538
33	33	30	67	67	69.23077	100	100	107.3077
34	34	31.15385						

Table 5-11 Modelling the probability of non-fatal CVD events: men post CBVD event

Covariate	CHD		Stroke		Inter. claudication		Other heart condition	
	coeff. (95% CI)	p value	coeff. (95% CI)	p value	coeff. (95% CI)	p value	coeff. (95% CI)	p value
ti1	-0.069 (-0.150, 0.012)	0.095	-0.035 (-0.087, 0.017)	0.183	0.020 (-0.085, 0.125)	0.712	-0.070 (-0.134, -0.006)	0.032
ti2	0.063 (-0.049, 0.174)	0.270	0.046 (-0.030, 0.123)	0.235	-0.108 (-0.305, 0.090)	0.285	0.077 (-0.016, 0.170)	0.103
Age	-0.003 (-0.016, 0.010)	0.613	0.010 (-0.001, 0.021)	0.075	0.001 (-0.016, 0.019)	0.873	0.004 (-0.009, 0.017)	0.537
SIMD sc.	-0.002 (-0.008, 0.004)	0.455	0.003 (-0.000, 0.006)	0.073	0.007 (0.001, 0.014)	0.030	0.002 (-0.002, 0.007)	0.315
Fam. his.	0.144 (-0.085, 0.373)	0.218	0.019 (-0.154, 0.191)	0.833	0.024 (-0.340, 0.389)	0.895	0.053 (0.169, 0.275)	0.641
Constant	-1.506 (-2.420, -1.605)	0.001	-2.109 (-2.891, -1.327)	<0.001	-2.744 (-4.034, -1.454)	<0.001	-1.923 (-2.789, -1.058)	<0.001

Covariate	HF	
	coeff. (95% CI)	p value
ti1	-0.129 (-0.275, 0.017)	0.083
ti2	0.159 (-0.021, 0.340)	0.084
Age	0.039 (0.009, 0.070)	0.012
SIMD sc.	-0.010 (-0.021, 0.001)	0.079
Fam. his.	0.353 (-0.063, 0.770)	0.097
Constant	-4.697 (-6.983, -2.410)	<0.001

Note: ‘Age’ is age at first event; ‘ti1’ and ‘ti2’ are time spline function variables

Table 5-12 Time spline variables: Men post-CBVD

Cycle (year)	ti1	ti2	Cycle (year)	ti1	ti2	Cycle (year)	ti1	ti2
1	1	0	35	35	31.63636	68	68	67.63636
2	2	0.0082645	36	36	32.72727	69	69	68.72727
3	3	0.0661157	37	37	33.81818	70	70	69.81818
4	4	0.2231405	38	38	34.90909	71	71	70.90909
5	5	0.5289256	39	39	36	72	72	72
6	6	1.020071	40	40	37.09091	73	73	73.09091
7	7	1.681228	41	41	38.18182	74	74	74.18182
8	8	2.484061	42	42	39.27273	75	75	75.27273
9	9	3.400236	43	43	40.36364	76	76	76.36364
10	10	4.401417	44	44	41.45454	77	77	77.45454
11	11	5.459268	45	45	42.54546	78	78	78.54546
12	12	6.545455	46	46	43.63636	79	79	79.63636
13	13	7.636364	47	47	44.72727	80	80	80.72727
14	14	8.727273	48	48	45.81818	81	81	81.81818
15	15	9.818182	49	49	46.90909	82	82	82.90909
16	16	10.90909	50	50	48	83	83	84
17	17	12	51	51	49.09091	84	84	85.09091
18	18	13.09091	52	52	50.18182	85	85	86.18182
19	19	14.18182	53	53	51.27273	86	86	87.27273
20	20	15.27273	54	54	52.36364	87	87	88.36364
21	21	16.36364	55	55	53.45454	88	88	89.45454
22	22	17.45455	56	56	54.54546	89	89	90.54546
23	23	18.54545	57	57	55.63636	90	90	91.63636
24	24	19.63636	58	58	56.72727	91	91	92.72727
25	25	20.72727	59	59	57.81818	92	92	93.81818
26	26	21.81818	60	60	58.90909	93	93	94.90909
27	27	22.90909	61	61	60	94	94	96
28	28	24	62	62	61.09091	95	95	97.09091
29	29	25.09091	63	63	62.18182	96	96	98.18182
30	30	26.18182	64	64	63.27273	97	97	99.27273
31	31	27.27273	65	65	64.36364	98	98	100.3636
32	32	28.36364	66	66	65.45454	99	99	101.4545
33	33	29.45455	67	67	66.54546	100	100	102.5455
34	34	30.54545						

Table 5-13 Modelling the probability of non-fatal CVD events: women post CHD event

Covariate	CHD		Stroke		Inter. claudication		Other heart condition	
	coeff. (95% CI)	p value	coeff. (95% CI)	p value	coeff. (95% CI)	p value	coeff. (95% CI)	p value
ti1	-0.003 (-0.033, 0.027)	0.823	-0.072 (-0.144, 0.000)	0.051	-0.078 (-0.152, -0.004)	0.040	-0.045 (-0.087, -0.003)	0.037
ti2	0.057 (0.011, 0.103)	0.016	0.026 (-0.102, 0.155)	0.688	0.106 (-0.015, 0.228)	0.086	0.026 (-0.045, 0.096)	0.477
Age	0.010 (0.004, 0.016)	0.002	0.007 (-0.006, 0.019)	0.281	0.016 (-0.001, 0.033)	0.061	0.012 (0.003, 0.021)	0.009
SIMD sc.	0.001 (-0.001, 0.004)	0.198	0.005 (0.001, 0.009)	0.014	0.001 (-0.005, 0.008)	0.705	0.001 (-0.002, 0.004)	0.484
Fam. his.	0.056 (-0.046, 0.158)	0.279	-0.014 (-0.221, 0.194)	0.898	-0.129 (-0.379, 0.122)	0.314	-0.138 (-0.270, -0.005)	0.041
Constant	-2.137 (-2.580, -1.694)	<0.001	-2.638 (-3.492, -1.783)	<0.001	-3.274 (-4.558, -1.990)	<0.001	-2.407 (-3.00, -1.810)	<0.001

Covariate	HF	
	coeff. (95% CI)	p value
ti1	-0.119 (-0.176, -0.061)	<0.001
ti2	0.133 (0.039, 0.227)	0.005
Age	0.018 (0.00, 0.029)	0.003
SIMD sc.	0.004 (-0.000, 0.009)	0.077
Fam. his.	-0.038 (-0.246, 0.170)	0.721
Constant	-3.017 (-3.857, -2.177)	<0.001

Note: ‘Age’ is age at first event; ‘ti1’ and ‘ti2’ are time spline function variables

Table 5-14 Time spline variables: Women post-CHD

year	ti1	ti2	year	ti1	ti2	year	ti1	ti2
1	1	0	35	35	26.15385	68	68	56.61538
2	2	0.005917	36	36	27.07692	69	69	57.53846
3	3	0.047337	37	37	28	70	70	58.46154
4	4	0.159763	38	38	28.92308	71	71	59.38462
5	5	0.378698	39	39	29.84615	72	72	60.30769
6	6	0.731098	40	40	30.76923	73	73	61.23077
7	7	1.20973	41	41	31.69231	74	74	62.15385
8	8	1.798817	42	42	32.61538	75	75	63.07692
9	9	2.482577	43	43	33.53846	76	76	64
10	10	3.245233	44	44	34.46154	77	77	64.92308
11	11	4.071006	45	45	35.38462	78	78	65.84615
12	12	4.944116	46	46	36.30769	79	79	66.76923
13	13	5.848783	47	47	37.23077	80	80	67.69231
14	14	6.769231	48	48	38.15385	81	81	68.61539
15	15	7.692307	49	49	39.07692	82	82	69.53846
16	16	8.615385	50	50	40	83	83	70.46154
17	17	9.538462	51	51	40.92308	84	84	71.38461
18	18	10.46154	52	52	41.84615	85	85	72.30769
19	19	11.38461	53	53	42.76923	86	86	73.23077
20	20	12.30769	54	54	43.69231	87	87	74.15385
21	21	13.23077	55	55	44.61538	88	88	75.07692
22	22	14.15385	56	56	45.53846	89	89	76
23	23	15.07692	57	57	46.46154	90	90	76.92308
24	24	16	58	58	47.38462	91	91	77.84615
25	25	16.92308	59	59	48.30769	92	92	78.76923
26	26	17.84615	60	60	49.23077	93	93	79.69231
27	27	18.76923	61	61	50.15385	94	94	80.61539
28	28	19.69231	62	62	51.07692	95	95	81.53846
29	29	20.61539	63	63	52	96	96	82.46154
30	30	21.53846	64	64	52.92308	97	97	83.38461
31	31	22.46154	65	65	53.84615	98	98	84.30769
32	32	23.38461	66	66	54.76923	99	99	85.23077
33	33	24.30769	67	67	55.69231	100	100	86.15385
34	34	25.23077						

Table 5-15 Modelling the probability of non-fatal CVD events: women post CBVD event

Covariate	CHD		Stroke		Inter. claudication		Other heart condition	
	coeff. (95% CI)	p value	coeff. (95% CI)	p value	coeff. (95% CI)	p value	coeff. (95% CI)	p value
ti1	0.078 (-0.028, 0.183)	0.150	-0.023 (-0.077, 0.030)	0.392	0.008 (-0.137, 0.152)	0.916	-0.053 (-0.138, 0.032)	0.222
ti2	-0.088 (-0.225, 0.049)	0.209	0.056 (-0.020, 0.132)	0.150	-0.069 (-0.275, 0.137)	0.513	0.034 (-0.071, 0.140)	0.524
Age	-0.0004 (-0.014, 0.013)	0.951	0.022 (0.013, 0.030)	<0.001	-0.011 (-0.031, 0.009)	0.279	0.006 (-0.005, 0.017)	0.302
SIMD sc.	0.004 (-0.003, 0.011)	0.304	0.001 (-0.002, 0.004)	0.525	0.0004 (-0.013, 0.014)	0.955	-0.001 (-0.006, 0.004)	0.749
Fam. his.	0.068 (-0.222, 0.359)	0.644	0.042 (-0.192, 0.108)	0.582	-0.303 (-0.798, 0.192)	0.230	0.281 (0.044, 0.517)	0.020
Constant	-2.531 (-3.653, -1.409)	<0.001	-2.777 (-3.424, -2.130)	<0.001	-1.714 (-3.543, 0.115)	0.066	-2.178 (-2.983, -1.373)	<0.001

Covariate	HF	
	coeff. (95% CI)	p value
ti1	-0.186 (-0.319, -0.054)	0.006
ti2	0.227 (0.069, 0.386)	0.005
Age	-0.002 (-0.017, 0.014)	0.839
SIMD sc.	0.001 (-0.007, 0.010)	0.757
Fam. his.	0.036 (-0.360, 0.432)	0.859
Constant	-1.881 (-3.219, -0.542)	0.006

Note: ‘Age’ is age at first event; ‘ti1’ and ‘ti2’ are time spline function variables

Table 5-16 Time spline variables: Women post-CBVD

Cycle (year)	ti1	ti2	Cycle (year)	ti1	ti2	Cycle (year)	ti1	ti2
1	1	0	35	35	31.63636	68	68	67.63636
2	2	0.0082645	36	36	32.72727	69	69	68.72727
3	3	0.0661157	37	37	33.81818	70	70	69.81818
4	4	0.2231405	38	38	34.90909	71	71	70.90909
5	5	0.5289256	39	39	36	72	72	72
6	6	1.020071	40	40	37.09091	73	73	73.09091
7	7	1.681228	41	41	38.18182	74	74	74.18182
8	8	2.484061	42	42	39.27273	75	75	75.27273
9	9	3.400236	43	43	40.36364	76	76	76.36364
10	10	4.401417	44	44	41.45454	77	77	77.45454
11	11	5.459268	45	45	42.54546	78	78	78.54546
12	12	6.545455	46	46	43.63636	79	79	79.63636
13	13	7.636364	47	47	44.72727	80	80	80.72727
14	14	8.727273	48	48	45.81818	81	81	81.81818
15	15	9.818182	49	49	46.90909	82	82	82.90909
16	16	10.90909	50	50	48	83	83	84
17	17	12	51	51	49.09091	84	84	85.09091
18	18	13.09091	52	52	50.18182	85	85	86.18182
19	19	14.18182	53	53	51.27273	86	86	87.27273
20	20	15.27273	54	54	52.36364	87	87	88.36364
21	21	16.36364	55	55	53.45454	88	88	89.45454
22	22	17.45455	56	56	54.54546	89	89	90.54546
23	23	18.54545	57	57	55.63636	90	90	91.63636
24	24	19.63636	58	58	56.72727	91	91	92.72727
25	25	20.72727	59	59	57.81818	92	92	93.81818
26	26	21.81818	60	60	58.90909	93	93	94.90909
27	27	22.90909	61	61	60	94	94	96
28	28	24	62	62	61.09091	95	95	97.09091
29	29	25.09091	63	63	62.18182	96	96	98.18182
30	30	26.18182	64	64	63.27273	97	97	99.27273
31	31	27.27273	65	65	64.36364	98	98	100.3636
32	32	28.36364	66	66	65.45454	99	99	101.4545
33	33	29.45455	67	67	66.54546	100	100	102.5455
34	34	30.54545						

5.5.3 Using the model to predict subsequent non-fatal CVD events

To illustrate the ability of model to predict subsequent non-fatal CVD events, a risk profile of a 60 year man living in the most deprived fifth (SIMD 60) is used where it is also assumed that he has with no family history, no diabetes, a smoker of 20 cigarettes per day, total cholesterol of 7 and HDL Cholesterol of 1.2. It is assumed that a non-fatal CHD event occurred in the first year upon entering the model. This was the same risk profile selected in Chapter 4 to illustrate how the model predicts life expectancy.

Figures 5-14 to 5-18 show the probability of incurring one of the five non-fatal events, where the x-axis of time from non-fatal event is denominated in years. Overall, the process of using RCS now results in smoothed predictions compared to observed proportions as witnessed earlier. In terms of event predictions, the scale and shape of the curves are quite different across the five events of CHD, CBVD, heart failure, intermittent claudication and other heart events. Following a first CHD event, the probability of incurring CHD events is the highest of all the events, with a steady increase over time. The probability of stroke remains quite low and is highest in the years immediately following a non-fatal event. The probability of heart failure falls and then increases sharply after 25 years. The probability of intermittent claudication and other heart events follow similar trends, although the risk of the former is higher.

Figure 5-14 Probability of CHD post-CHD hospitalisation

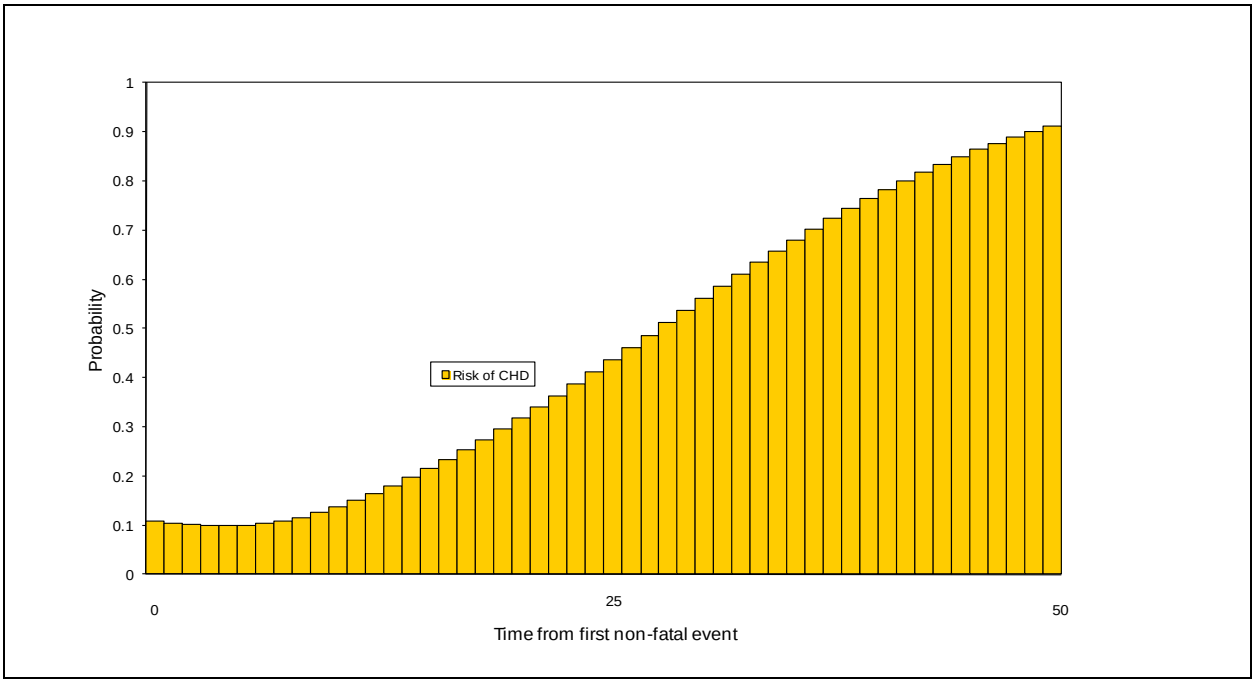


Figure 5-15 Probability of CBVD post CHD hospitalisation

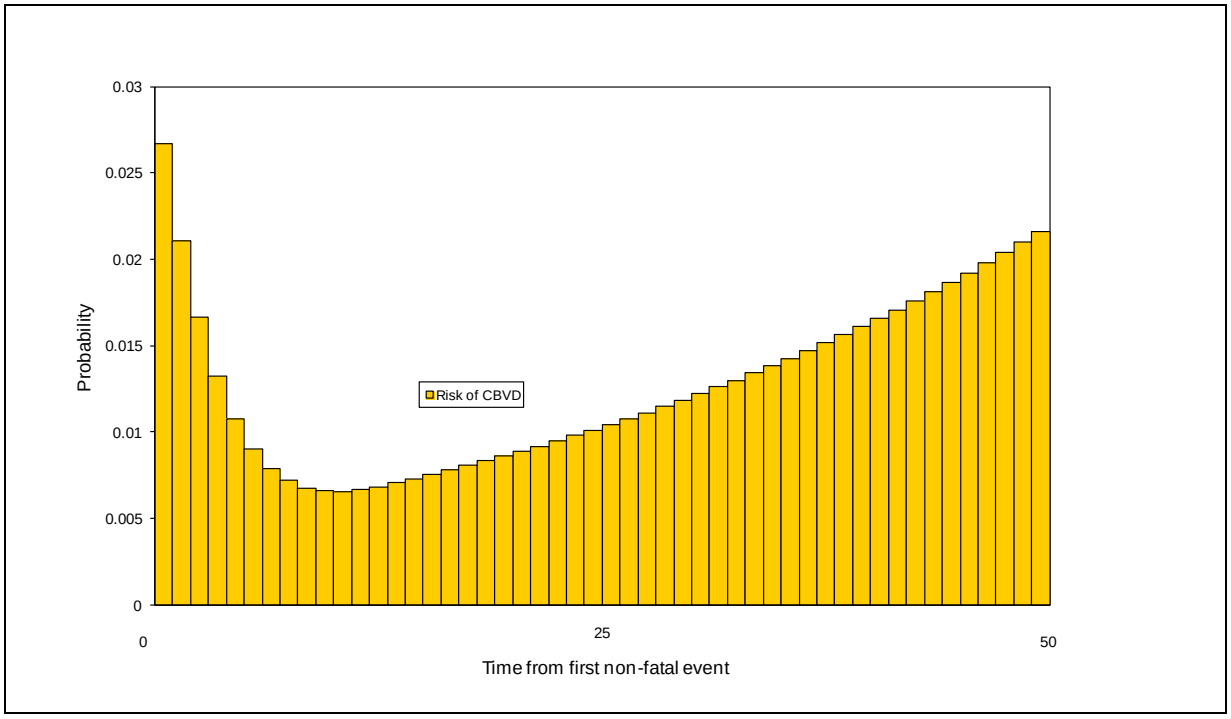


Figure 5-16 Probability of heart failure post-CHD hospitalisation

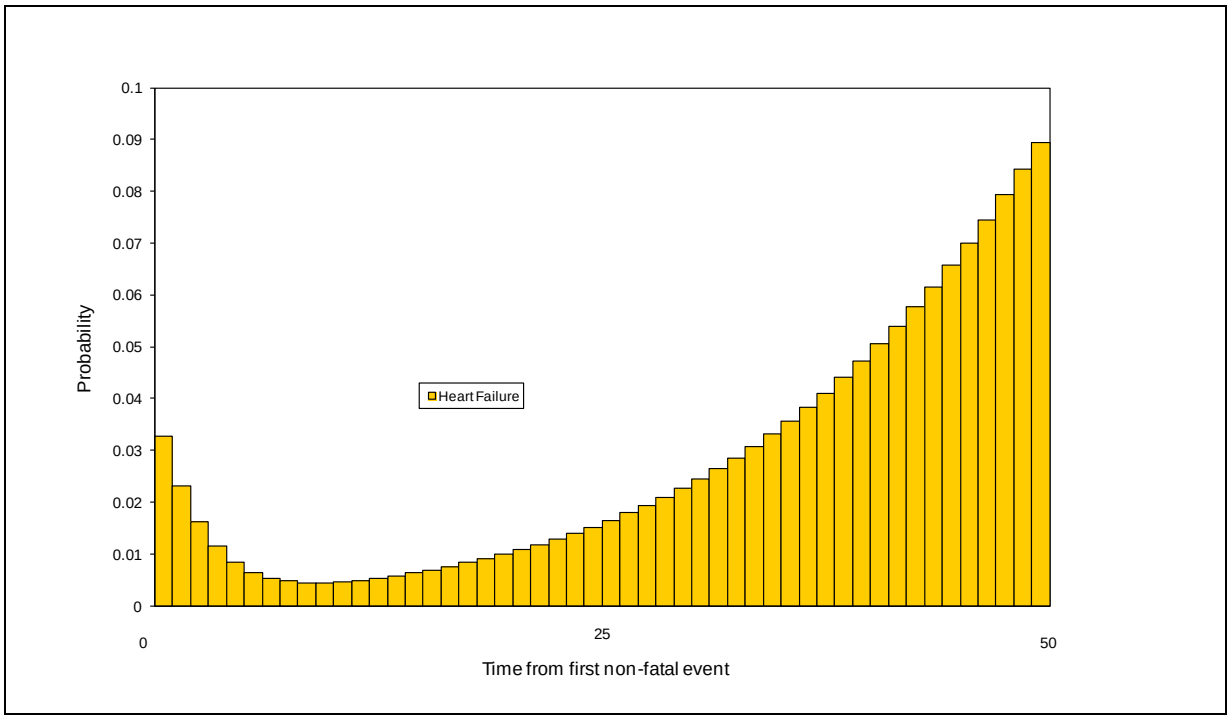


Figure 5-17 Probability of intermittent claudication post CHD hospitalisation

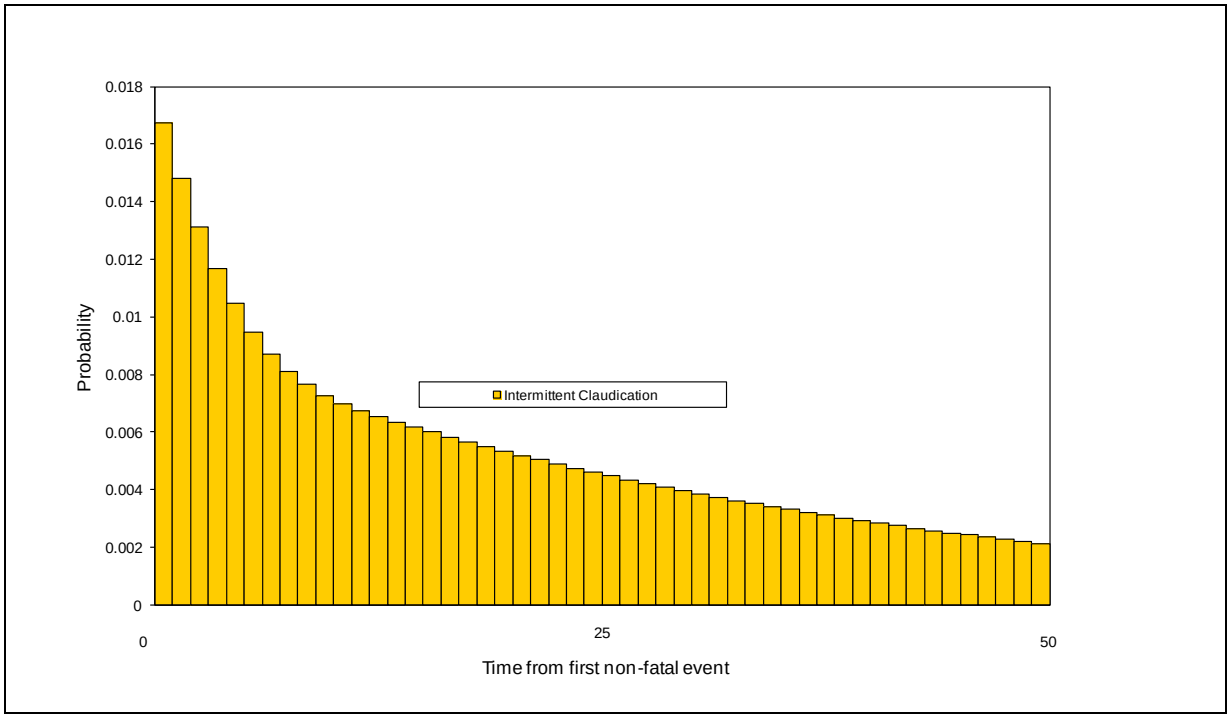
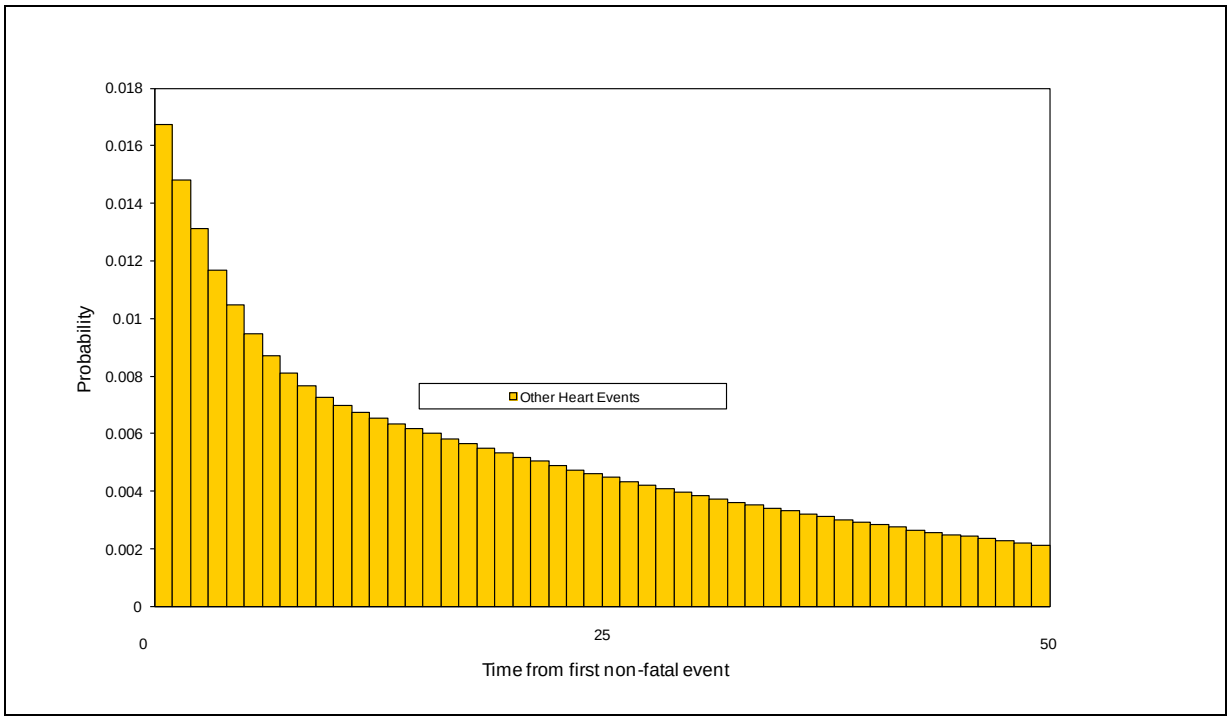


Figure 5-18 Probability of other heart events post CHD hospitalisation



It is interesting to reflect on a plausible rationale for such event patterns. From first principles, increasing age is associated with a deterioration in the CVD system in general. This may first result in more minor (yet still potentially serious) conditions of irregular heartbeat and intermittent claudication, for instance. Major events such as CHD and stroke may follow as

the system weakens. However, if the first event experienced is an initial CHD event for instance, then perhaps the system is so damaged that it is more likely that other associated and major CHD and stroke events are more likely to occur than the relatively less serious events. This may explain the relative magnitude of the risks of different events at each point in time. Further, what is also interesting to explore is how the risk of events change in time. Risks are relatively higher in the immediate aftermath of a first event, leading to a fall and then a steady increase. The initial decline may reflect a healthy survivor effect, where patients with a weaker constitution have died early post-event. The subsequent increase in event risk may then reflect the effect of age given the independent relationship of age with events and inevitable breakdown of the CVD system and mortality. Note, that a very similar pattern was found for patient post-CBVD, with the exception that following a first CBVD event, the main risk was further CBVD, followed by CHD and then the other more minor events.

5.6 Generating quality adjusted life expectancy

5.6.1 Approach to quality adjustment

Now that we have estimated background morbidity/population norms, utility decrements for CVD events, and the risk of incurring first and subsequent CVD events, this section details how these estimates are incorporated into the model to quality adjust the life expectancy predictions that were made in Chapter 4.

Figure 5-1 shows that quality adjustment is made in three states of the policy model. Within a CVD free state survival is adjusted for background morbidity only. In contrast, within a non-fatal CHD and a non-fatal CBVD state quality adjustment accounts for background morbidity, the impact of experiencing a first non-fatal event and the impact of experiencing further non-fatal CVD events.

A Kaplan-Meier Sample Average (KMSA) estimator(309) approach is used, where the survival probability of the individual within a model state over time is multiplied by the associated quality of life from existing in that state. Summing across time generates quality adjusted life expectancy (QALE). This is summarised, as follows:

$$QALE = \sum[S(t) * Ut]$$

Where S(t) is the survival probability in period t and Ut is the associated health state utility, which in turn is a function of background morbidity, and the impact of experiencing first and subsequent events. This process of quality adjusting a survival is described, as below.

(i) Adjusting for background morbidity: Estimates of background morbidity were made specific to the age, sex and fifths of SIMD. These estimates are used weight the time spent in a CVD free state. With reference to the KMSA estimator, the assumption is that St = 1 before a first event. Note, that as the person ages in the model, a different norm may be selected given norms were estimated across seven age groups.

(ii) Adjusting for first non-fatal CVD event: The impact of experiencing a first non-fatal event is subtracted from background morbidity. If the first event was non-fatal CHD then the utility decrement of myocardial infarction was used. For a first event that was CBVD then the utility decrement of stroke was used. This is simply subtracted from background morbidity / health utility.

(iii) Adjusting for subsequent non-fatal events: The previous section estimated the probability of incurring five non-fatal events in each cycle of the model post-first event. These probabilities are then weighted (multiplied) by the associated event decrement. For heart failure the estimate from Clarke(310) of -0.108 was used. This process creates five weighted utility decrements.

The following illustrates a model scenario where the 60 year old male profile introduced previously incurred a non-fatal CHD event upon entering the model. Figures 5-19 to 5-23 illustrates that the expected utility impact (probability of event weighted by associated utility decrement). The curves retain the same shape as the event predictions made earlier, but are essentially rescaled**.**

Figure 5-19 Utility impact (decrement) of incurring a CHD event – post non-fatal CHD

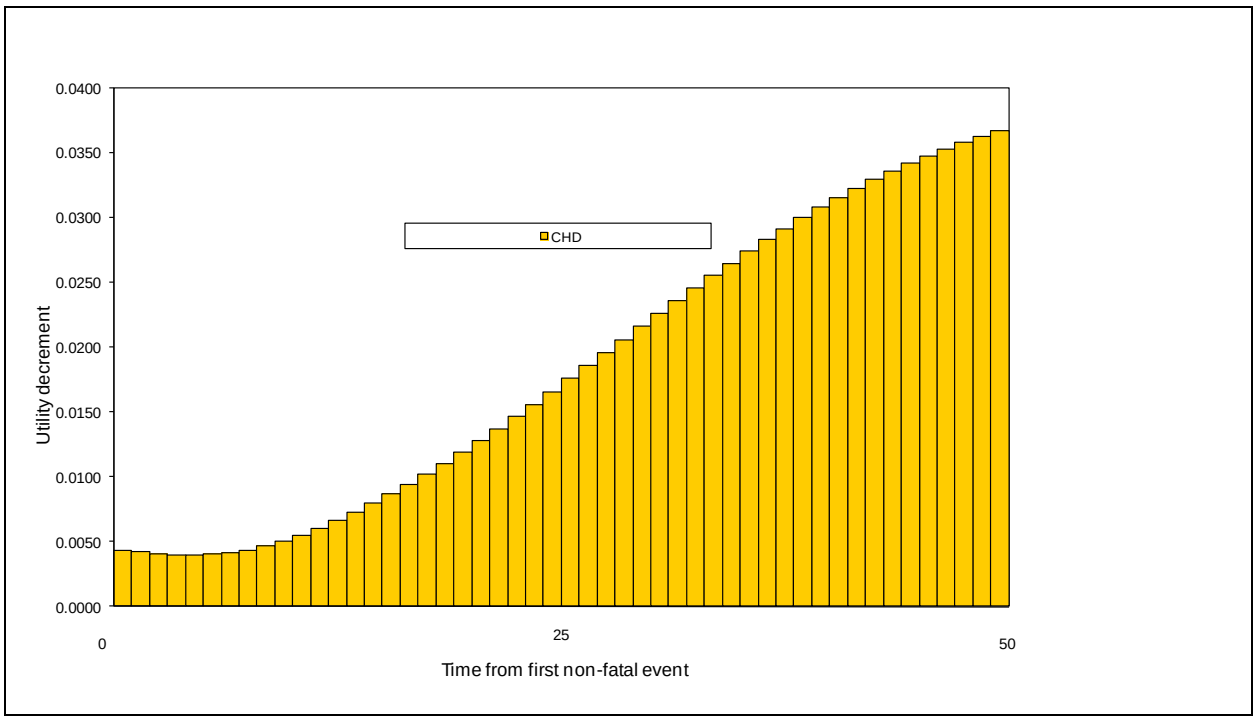


Figure 5-20 Utility impact (decrement) of incurring a CBVD event – post non-fatal CHD

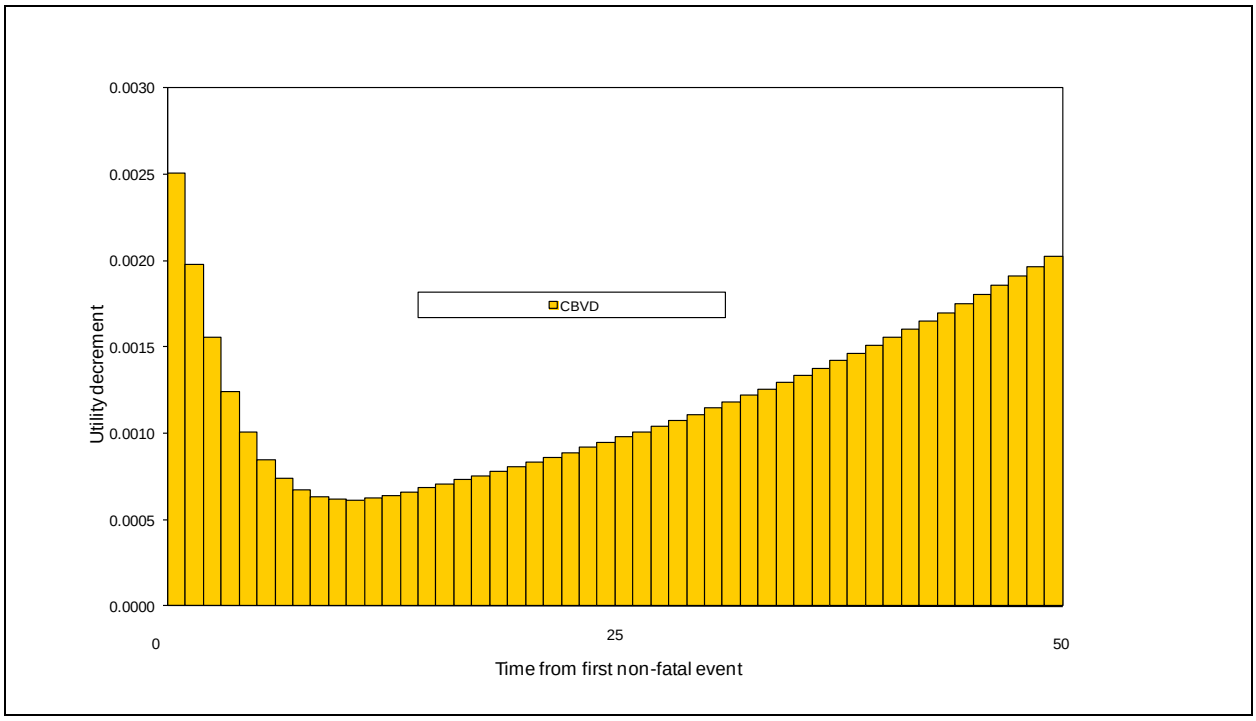


Figure 5-21 Utility impact (decrement) of incurring a heart failure – post non-fatal CHD

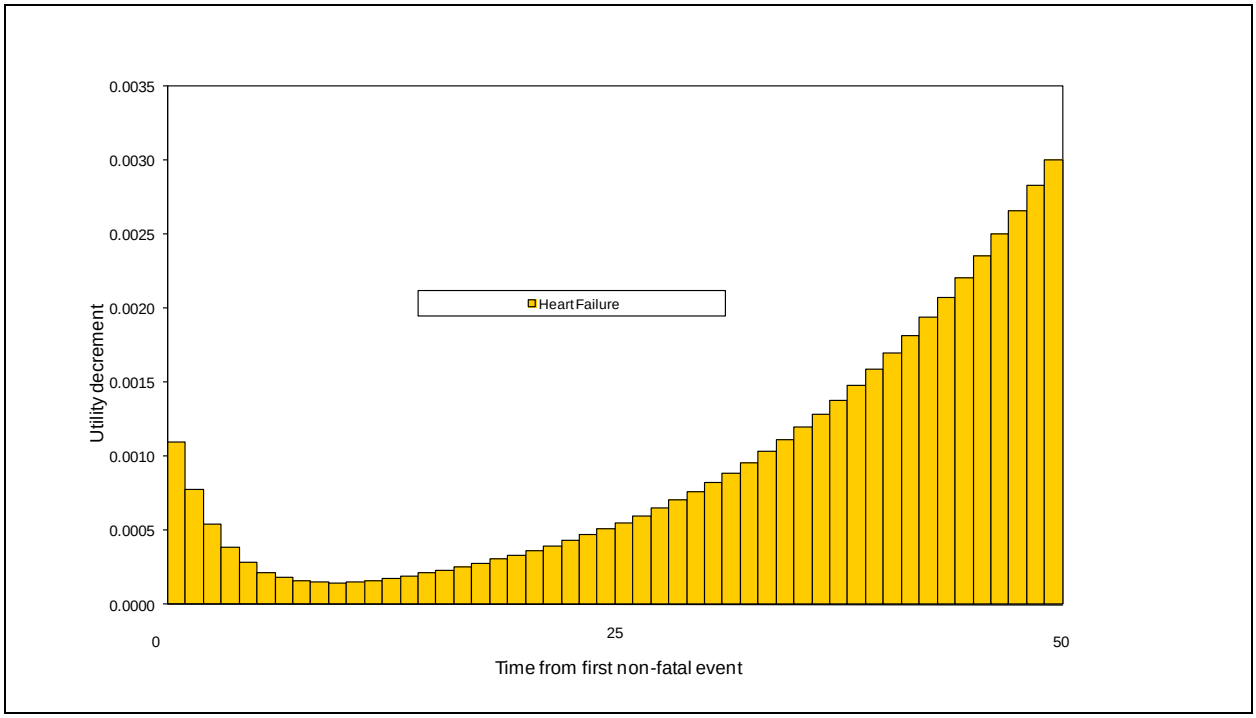


Figure 5-22 Utility impact (decrement) of incurring other-heat event – post non-fatal CHD

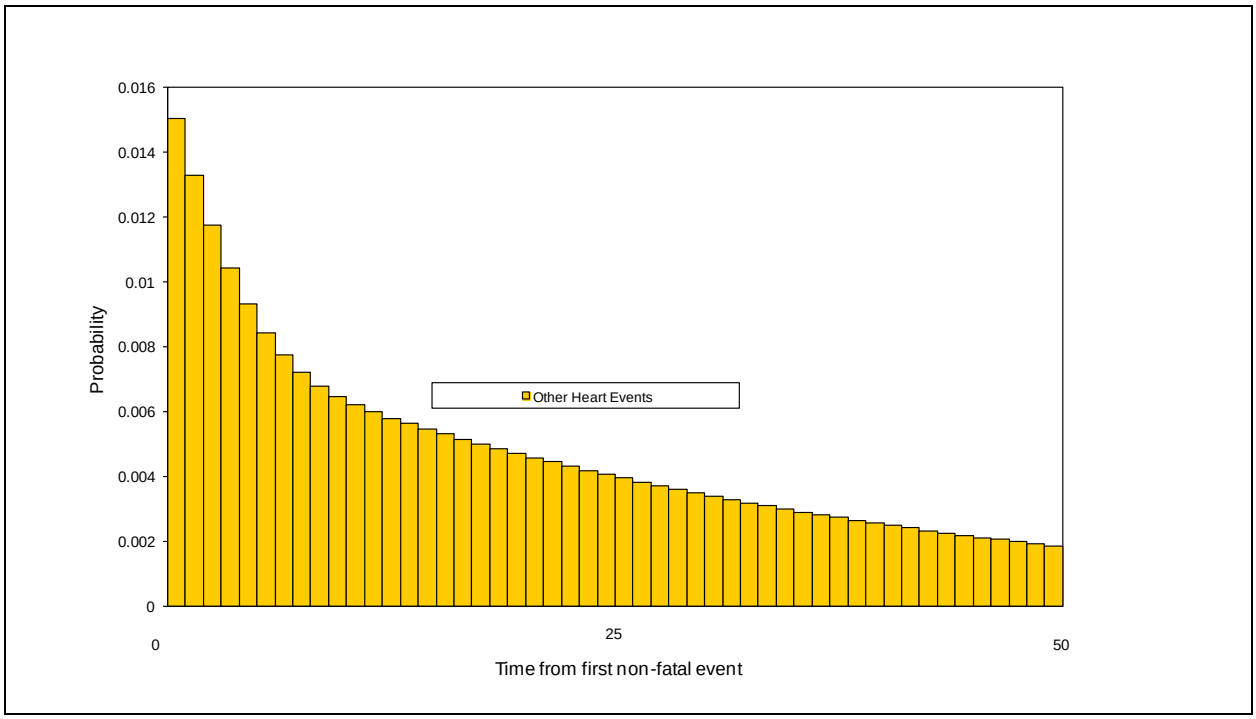
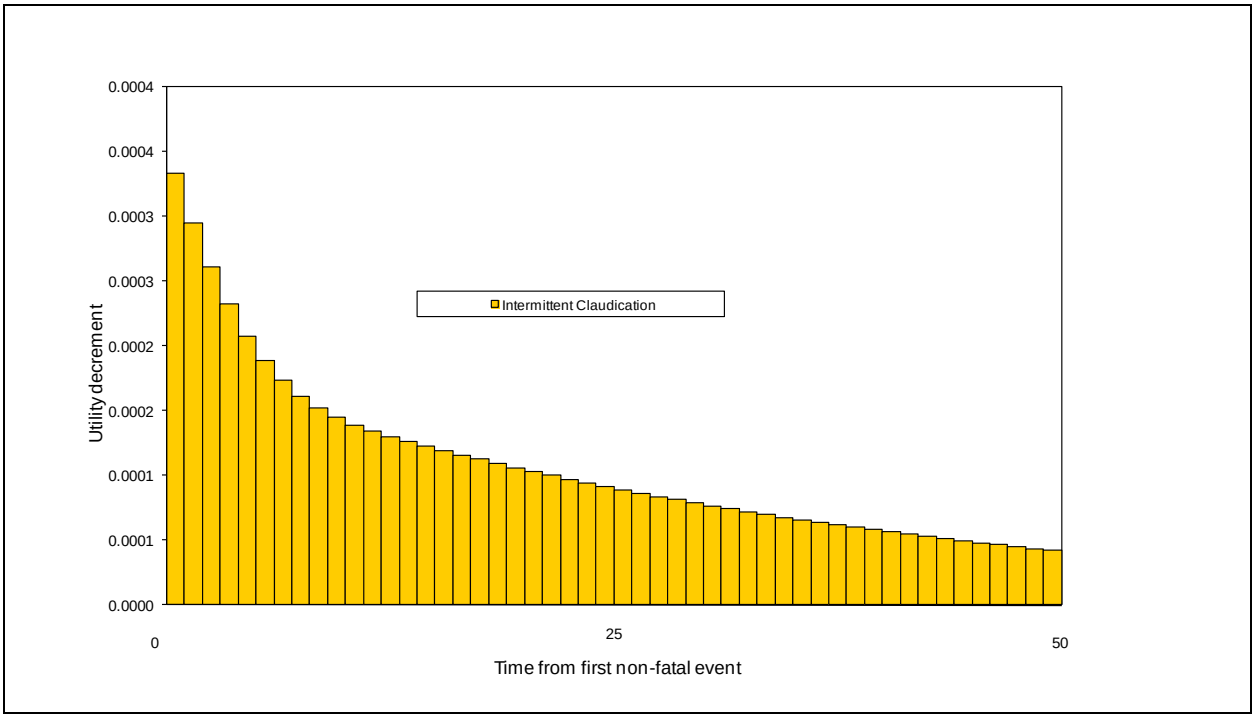
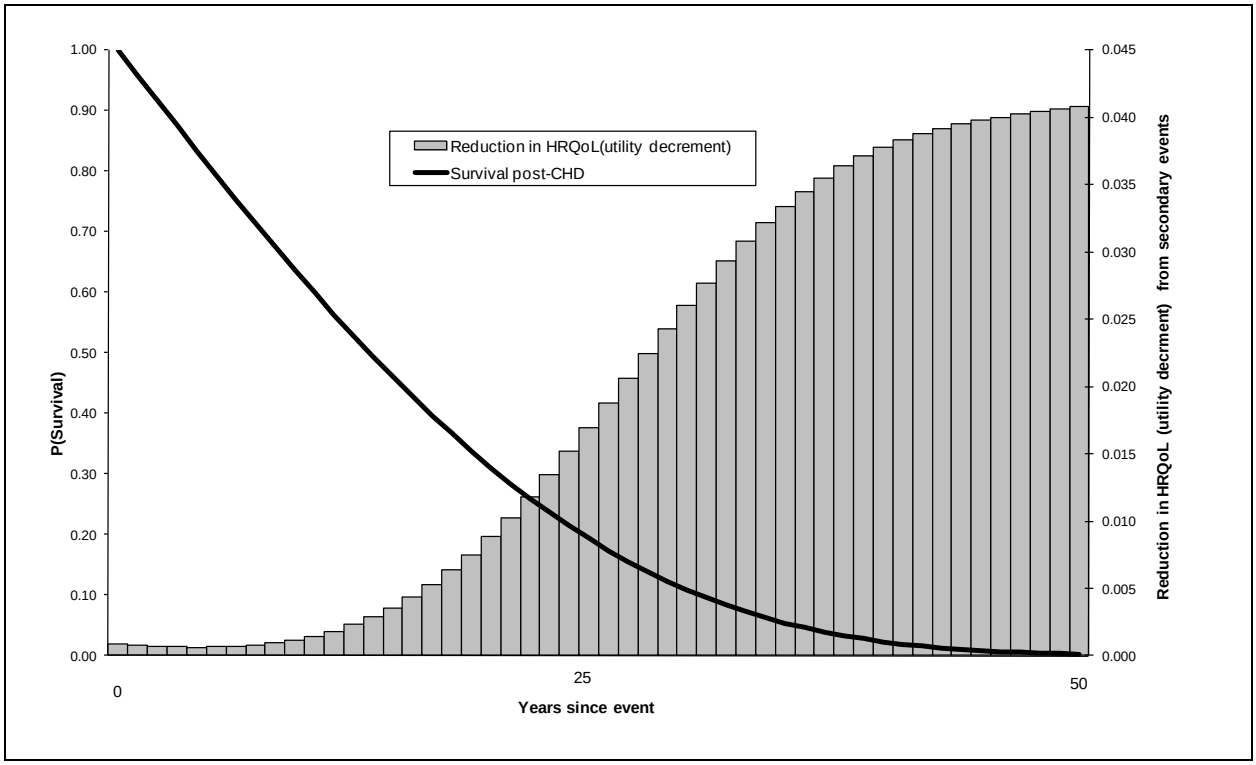


Figure 5-23 Utility impact (decrement) of incurring intermittent claudication – post non-fatal CHD



To use these estimates to quality adjust survival within a non-fatal CVD state three steps are taken consistent with a KMSA estimator approach. First, the sum of the five utility decrements is taken in each year of the model. This creates an overall composite decrement. Second, this composite decrement is weighted by the probability that the individual is actually alive to experience events. This probability is read off an individual's survival curve, which was estimated in Chapter 4, and laid-on top of the composite decrement (Figure 5-24). Third, with the survival curve not quality adjusted, the area under the curve is estimated and summed to give remaining QALE.

Figure 5-24 Composite with survival curve – post first CHD



5.6.2 Estimating expected quality adjusted life expectancy

Having illustrated how quality adjustment is undertaken in a CVD free state (background morbidity), and a non-fatal CVD state (event decrement plus the weighted decrement of further events), it is now possible to generate overall expected QALE.

A similar process is adopted as shown in Chapter 4 when estimating average life expectancy. To reiterate as an individual enters the model CVD free they are at risk of incurring one the competing first four events. This risk is estimated over 100 cycles. Life expectancy is conditional on the type and timing of the first event. Therefore, in total, an individual faces 400 possible scenarios (i.e. four events multiplied by 100 cycles).

To generate average QALE, these scenarios are re-run but this time with quality adjustment, and consequently each particular scenario leads to a different estimate of QALE. The following three tables follow exactly the same logic as outlined in Chapter 4. That is, for each annual cycle of the model we estimate the QALE that can be expected from incurring one the first four events (Table 8). All estimates are discounted at 3.5% in line with guidance from NICE(37).

For consistency of exposition, this process uses the same 60 year old male profile as before. First, table 5-17a estimates the remaining QALE across each model scenario. Survival before and after the first event (if non-fatal) has been quality adjusted.

Table 5-17 a) Remaining discounted quality adjusted life expectancy upon entering model [time before event + plus time after event]

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	CVD death	nonCVD death
1	7.8	6.1	0.8	0.8
2	8.0	6.7	1.5	1.5
3	8.9	7.6	2.2	2.2
.				
.				
22	15.4	14.7	11.7	11.7
23	16.0	15.2	12.1	12.1
24	15.9	15.2	12.4	12.4
.				
.				
100	21.0	21.4	21.0	21.0

Second, the probability that a particular event occurs at a particular time is estimated table 5-17b. These are the same probabilities as illustrated in Chapter 4. The probabilities are not affected by quality adjustment.

b) Probability of event occurring [event type and timing]

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	CVD death	nonCVD death
1	0.026	0.008	0.017	0.013
2	0.026	0.008	0.017	0.013
3	0.025	0.008	0.017	0.013
.				
.				
22	0.003	0.002	0.003	0.002
23	0.002	0.001	0.002	0.002
24	0.002	0.001	0.002	0.001
.				
.				
100	0	0	0	0

Third, the product of Tables 5-17 a and 5-17 b then generates a weighted discounted QALE estimate for each scenario in the model Table 5-17 c.

c) Weighted remaining discounted quality adjusted life expectancy [estimates from table a) multiplied by estimated from table b)]

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	CVD death	nonCVD death	*Sum*
1	0.202	0.047	0.013	0.010	0.272
2	0.205	0.053	0.026	0.020	0.303
3	0.226	0.061	0.038	0.030	0.355
.					
.					
22	0.047	0.027	0.037	0.029	0.139
23	0.036	0.021	0.029	0.023	0.109
24	0.026	0.016	0.022	0.017	0.081
.					
.					
100	0.000	0.000	0.000	0.000	

Total life years remaining (Cumulative sum over each model cycle) =	8.46
Overall life expectancy (age upon entering model plus remaining life years) =	68.46

Fourth, by summing across all possible realisations of the model we find that the 60 year man is now expected to have an additional 8.46 discounted QALEs remaining upon entering the model. By added the initial age of the man upon entering the model an overall discounted QALE of 68.46 is generated. This is contrasted with an undiscounted life expectancy estimate of 73.98 years that was made in Chapter 4 in the recalibrated model.

Figures 5-25 and 5-26 illustrates the model estimates of discounted QALEs across individual risk profiles for men and women. Most notably, the age gradient is increased sharply reflecting discounting, and quality adjustment; given younger individuals have greater remaining life expectancy so have a longer time period over which to experience events.

Figure 5-25 Discounted quality adjusted life expectancy - men

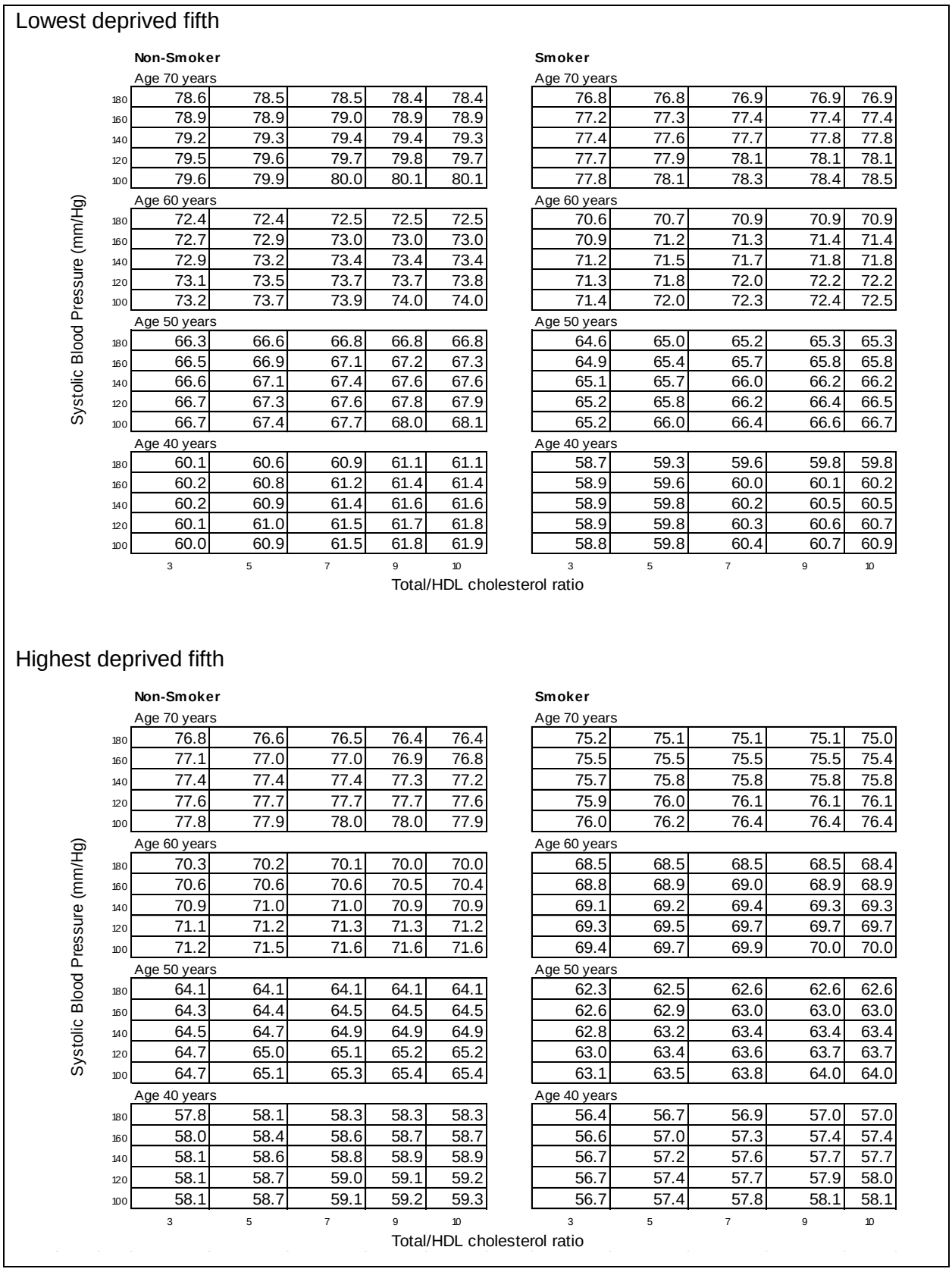
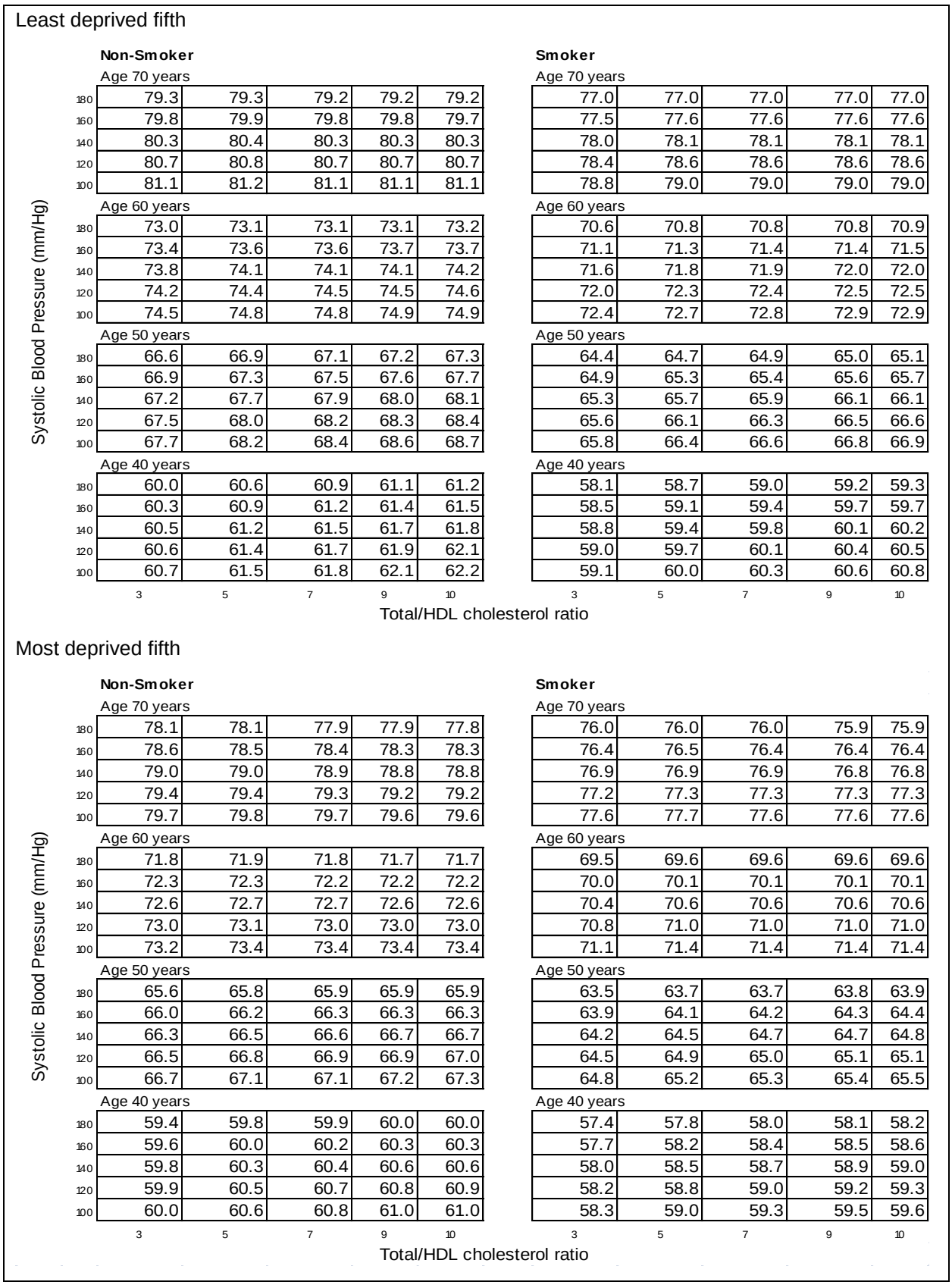


Figure 5-26 Discounted quality adjusted life expectancy - women



5.7 Estimating lifetime hospitalisation costs

5.7.1 Source data – identifying hospitalisations

There was the opportunity to further utilise the linked dataset of the Scottish Heart Health Extended Cohort and the Scottish Morbidity Records (SHHEC-SMR). To reiterate, SHHEC defined individuals by the nine ASSIGN risk factors and the SMR records all hospitalisations (up to 6 diagnostic positions) and death events using ICD codes. The datasets were linked by a unique patient identifier through CHI numbers.

Both datasets were detailed in Chapter 4. To reiterate, the hospitalisations that were recorded in the linked dataset included were all outpatient stays, general/acute (inpatient/day case), maternity, mental health (inpatient/day case), geriatric, cancer and neonatal. All events were recorded using the International Classification of Diseases. For each admission, the dataset records the dominant cause of admission and up to a further 5 events incurred within an inpatient stay, if relevant. This provided a detailed dataset from which to then estimate costs.

5.7.2 Costing hospital episodes

The overall objective was to use the SHHEC-SMR dataset to predict an individual's annual hospital costs conditional upon the individual's risk profile, as defined by the ASSIGN risk factors, and to project total future hospitalisation costs over the course of an entire lifetime.

A cost function is driven by events incurred, their associated costs and the overall length of stay (LOS) of the entire visit. Taken together, these elements comprise a Continuous Inpatient Stay (CIS). A costing method detailed by Geue (method 1)(277, 311) was employed estimate the costs of CIS and applied to the SHHEC-SMR dataset. For each individual in the dataset, and up to a maximum of 24 years of follow-up, every hospital admission was recorded and the associated costs of the CIS were estimated.

The estimation approach consists of two stages. First, the HRGv3.5 Grouper software (where HRG denotes Hospital Related Group) was used to assign an HRG code to every episode within patient record. This software was available from the Health and Social Care Information Centre in England(312). This assigns an HRG code to each hospital admission based on principle diagnosis, procedure(s) performed, gender, age, LOS and the discharge method.

Healthcare resource groups (HRGs) are similar to Diagnostic Related Groups, which were first developed in the USA in the early 1980s for Medicare to use as a prospective payment system for hospitals. Since the 1990s, HRGs have routinely been used to cost hospital activities in England(313). HRGs are a measure of case mix presenting standard groupings for clinically similar treatments, which consume a common set of health care resources. Based on procedure, diagnosis, LOS, complications, co-morbidity, discharge method, age and gender, each patient record is grouped in an HRG and reflects one finished consultant episode (FCE).

Second, the costs associated with each episode are taken from the English tariff which provides cost data for elective and non-elective hospital episodes. Within these estimate LOS is a key driver of costs and for each episode an average LOS is estimate, called the 'trim-point'. In addition, if LOS for a particular episode exceeds the trim-point additional per diem cost are also available and can be applied. Estimated costs are reported as a national schedule of reference costs. Tariffs are estimated for individual episodes, as if they occur independently(313).

Third, having information on all admission, episodes and episode costs it was then necessary to estimate the overall costs of each CIS that may involved multiple episodes. Simply summing over the cost of each episode incurred would likely overestimate the cost of a CIS. The tariff costs are estimated 'as if' the episodes occur in isolation; however in a CIS episodes occur together. While total the length of a CIS is likely to increase with multiple episodes, this is unlikely to be the linear sum of average LOS of independent episodes(277, 311).

To estimate costs of a CIS a dominant HRG is selected by simultaneously taking into account any other 'non-dominant' episodes within this CIS, again using the method 1 in Geue(277, 311). This was done using the 'Spell Converter' software which utilises information on the date of admission for the first episode of a CIS, the date of discharge of the last episode within that CIS, the episode order, episode LOS and the HRG and so selects the dominant episode within each CIS. A relevant tariff was then assigned to each CIS.

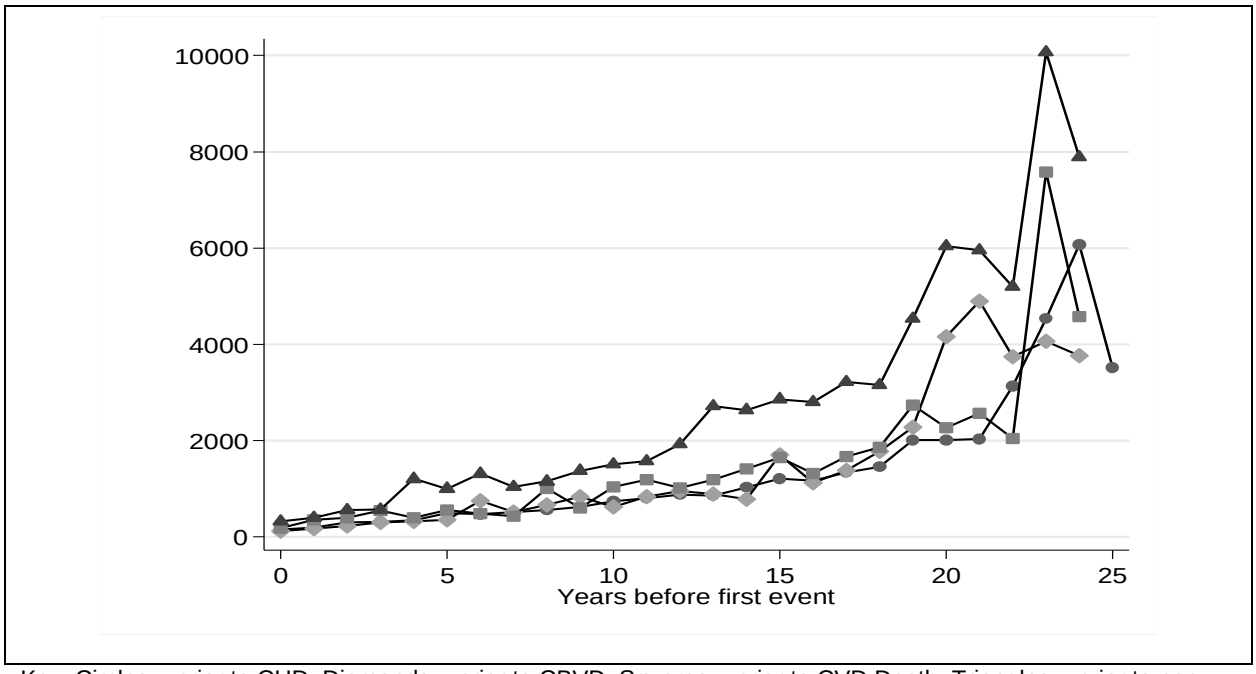
5.7.3 Estimating mean hospital costs before and after a first event

Having costed all hospital admissions for all individuals in the SHHEC-SMR database, the next stage was to manipulate the dataset to match the structure of the policy model (see page 186). Consequently, the SHHEC-SMR dataset was stratified into separate datasets to match patient pathways in the policy model. First, all individuals were divided into four datasets from the SHHEC baseline to one of the first four hospitalised events represented in the model (i.e. CHD hospitalisation, CBVD hospitalisation, fatal CVD and fatal non-CVD). Second, for those individuals who incurred a non-fatal event, two datasets were generated that followed individuals from a non-fatal CHD or CVBD event to eventual death.

Given all hospital admissions were costed, this allowed mean costs across all individuals to be calculated for every year since SHHEC screening. If an individual in SHHEC was alive in a given year but had no hospitalisations then a zero cost was included in the calculation.

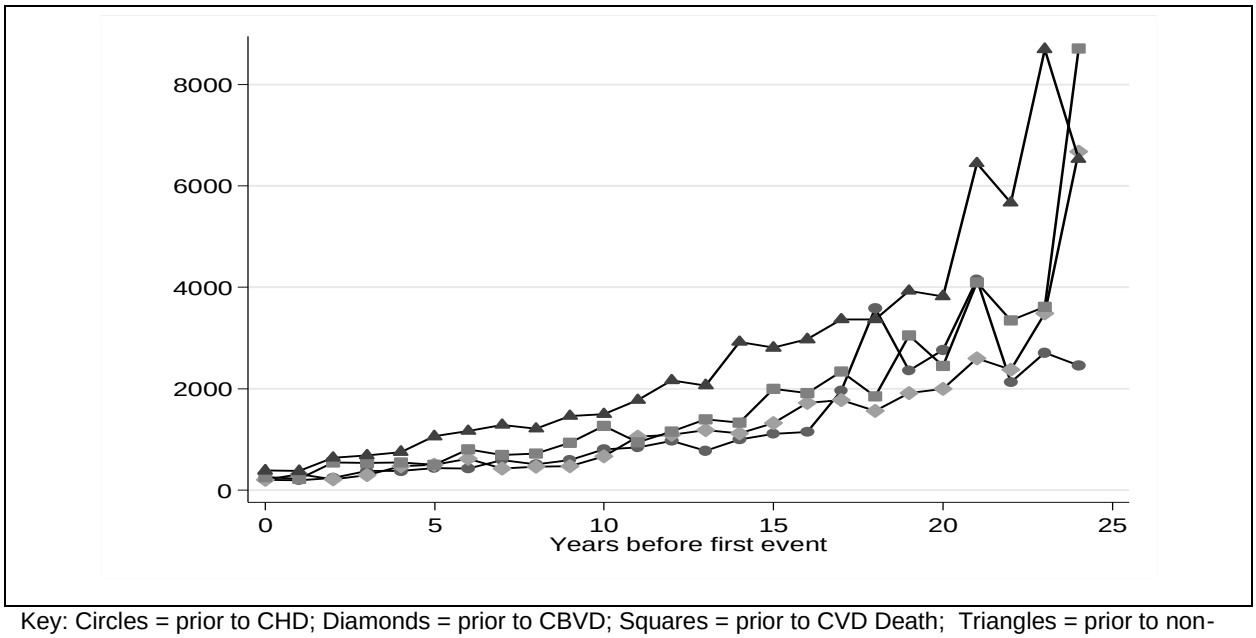
Figures 5-27 and 5-28 illustrates these “observed” mean costs for all men and women before each of the first four events. Costs increase with time (as the SHHEC sample ages), and as we approach the 25 year maximum follow-up the data become more erratic reflecting fewer patent numbers. Patients who eventually go onto experience a fatal non-CVD event incur the greatest expense, with similar pre-event costs of other events.

Figure 5-27 Observed mean costs over time since screening before each of the first events - men



Key: Circles = prior to CHD; Diamonds = prior to CBVD; Squares = prior to CVD Death; Triangles = prior to non-CVD death

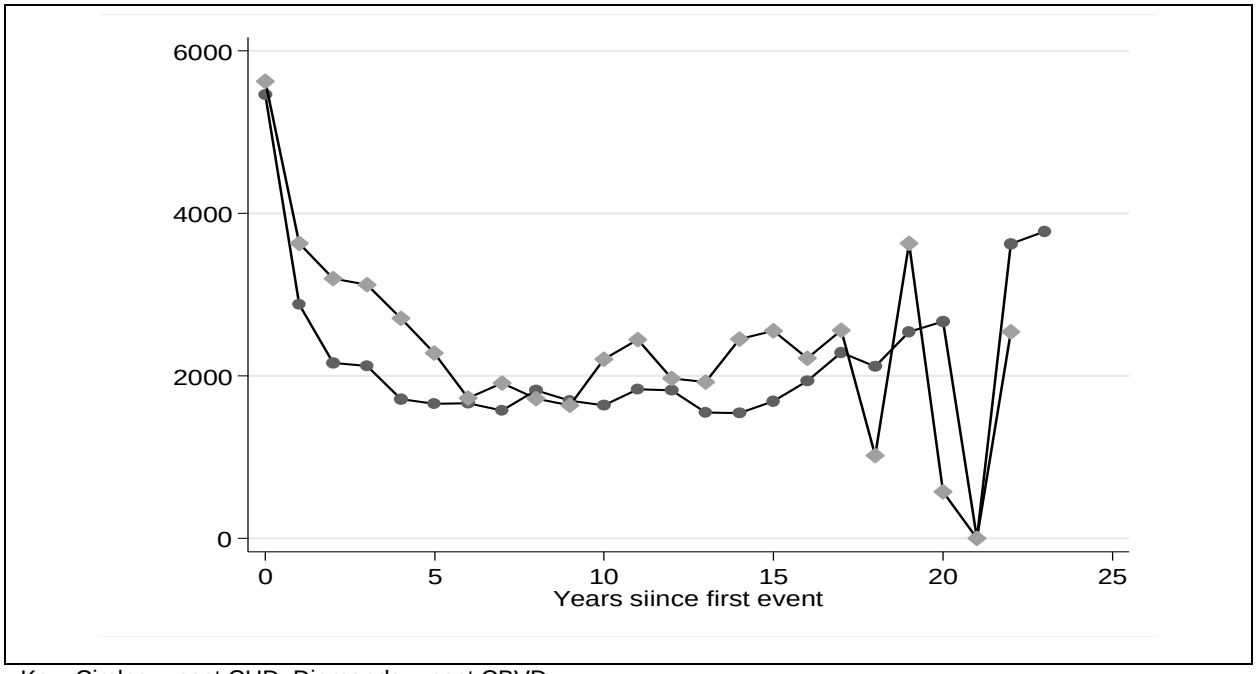
Figure 5-28 Observed mean costs over time since screening before each of the first events - women



Key: Circles = prior to CHD; Diamonds = prior to CBVD; Squares = prior to CVD Death; Triangles = prior to non-CVD death

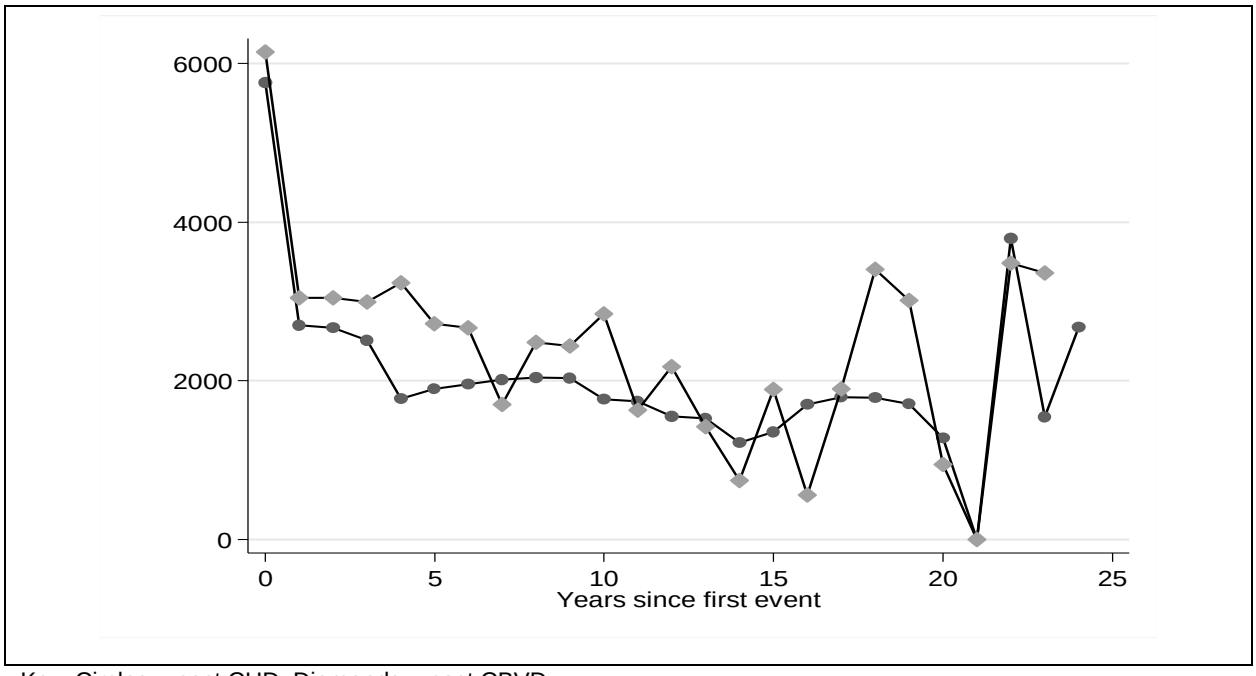
Figure 5-29 and 5-30 illustrates “observed” mean costs for men and women post non-fatal CHD and non-fatal CBVD. Costs are higher it the immediate few years post events, fall and then tend

Figure 5-29 Observed mean costs over time since first non-fatal CVD event - men



Key: Circles = post CHD; Diamonds = post CBVD

Figure 5-30 Observed mean costs over time since first non-fatal CVD event - women



Key: Circles = post CHD; Diamonds = post CBVD

to rise thereafter. Again the data is quite erratic as we approach the maximum follow up period in the SHHEC-SMR of 25 years.

5.7.4 Discussion of the costing methods

A key strength of the costing analysis is that there was a comprehensive longitudinal dataset (SHHEC-SMR) that followed over 16,000 individuals for a maximum follow-up of 24 years, and recorded each hospitalisation incurred. For each hospitalisation up to 6 diagnoses were made and recorded using ICD codes. Further, records are routinely validated by the Information Services Division (ISD) finding over 99% accuracy in correct identification of diagnosis and linkage from SHHEC to SMR(277, 311), as discussed in Chapter 4. The costing method employed, as described previously, which was based on research by Geue(311) takes into account a patients continuous inpatient stay (CIS), including principle diagnosis, entire length of stay (LOS), and additional per diem costs to account for additional diagnoses.

However, it is important to discuss the potential limitations of the costing methods employed. First, the historical nature of the SHHEC-SMR dataset, which dates from the 1980s, was necessary to follow patients over time but it may be that this introduces bias in inferring similar episode patterns in contemporary patients. Given care is likely to have improved over time and perhaps the incidence of multiple episodes is less likely. If so, this may mean that overall LOS of a CIS may be overestimated. It is difficult to verify or quantify this. Again the key issue is that, in using the costing methods described previously, the tariffs values should be continually updated which would then account for such changes.

Second, the HRG codes and tariffs represent average costs for English hospitals. Equivalent data for Scotland is not available. It is quite possible that average hospital costs in Scotland differ from England; however the direction and magnitude of any estimation bias is difficult to estimate.

Third, the English tariff values used in the model date from 2010. This is relatively recent; however, the important point is that over time the model will need to update tariff values to maintain contemporary relevance. In particular, there is an historical trend that LOS falls over time, and LOS plays a key role in tariff values. If tariffs are not updated then this may result in bias where perhaps costs are overestimated. On the other hand, unit costs may increase due to improved technology for instance, implying that the using historical tariffs may

underestimate costs. Nonetheless, the key issue is that the tariffs values in the model should be continually updated.

Fourth, a potential limitation in the SHHEC-SMR dataset is whether the multiple diagnoses actually represent incident cases, and rather than simply historical records. It is not expected that this itself has introduced systematic bias into the costing analysis, however. The method chosen is driven by the dominant HRG code which is typically the primary diagnostic position which would most likely be an incident case.

Fifth, a potential weakness in the approach is that the principal diagnosis drives costs and if the overall length of a CIS was greater than the average LOS of the principal diagnosis then it would be sufficient to cost 'extra' days in hospital at a per diem rates that are intended to approximate hotelier costs. This may have underestimated costs if event episodes were incurred, than cost more than simply extra bed days. The practical issue though is that there is not a perfect costing method to cost CIS. Further, in using the model to under cost effectiveness analysis the key issue is the difference in costs between intervention options.

Sixth, the main weakness in the approach to cost the impact of CVD on lifetime patient costs is that it is limited to hospitalisation costs. What is omitted is primary care and community care costs. This may be particularly important for costing the impact of stroke, which is increasing treated at the community level.

5.7.5 Modelling to estimate hospitalisation costs pre and post event

To model costs, a similar approach was taken as when predicting non-fatal CVD events following a first event. That is, there was a need to extrapolate beyond the observed follow-up period. Restricted cubic splines, with 3 knots, were used again. Linear regression was used to predict mean hospital costs using the non-modifiable risk factors of age at SHHEC, family history, and socioeconomic status. Separate models were generated for men and women, and before each of the first four events and after the two non-fatal events. So, in total, 12 models were generated.

Figure 5-31 to 5-38 provide the results of the modelling which estimated the costs pre and post first event, and separately for men and women. The results show the coefficients and 95% confidence intervals. Further, the time splines that were generated are also shown.

In summary, the strength of the relationship between the coefficients and mean costs varies pre and post event, is specific to the event type experienced and is different for men and women. This provides further justification for splitting events and running separate models for men and women. Estimates are often not significant though these were still incorporated into the model.

Table 5-18 a) Costs pre-event - 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
ti1	18.6 (-2.0, 39.2)	0.077	5.5 (-38.0, 49.0)	0.804	26.1 (-7.1, 59.3)	0.123	42.1 (-4.5, 88.7)	0.076
ti2	115.0 (70.3, 159.8)	<0.001	156.6 (72.0, 241.2)	<0.001	114.6 (56.8, 172.5)	<0.001	237.2 (157.1, 317.4)	<0.001
Age	22.7 (16.4, 29.0)	<0.001	17.3 (5.8, 28.9)	0.003	27.7 (16.5, 38.89)	<0.001	24.7 (9.0, 40.5)	0.002
SIMD sc.	5.2 (3.0, 7.4)	<0.001	6.6 (2.9, 10.3)	<0.001	3.8 (-0.1, 7.8)	0.059	4.7 (-0.5, 10.0)	0.078
Fam. his.	93.8 (1.5, 186.1)	0.046	-161.9 (-328.5, 4.8)	0.057	67.4 (-120.9, 255.7)	0.483	116.9 (-198.7, 432.6)	0.468
Constant	-1121 (-1446, -795)	<0.001	-832.8 (-1483, -182.4)	0.012	-1345 (-1981, -709.2)	<0.001	-1029 (-1890, -169.2)	0.019

b) Costs pre-first event - 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
ti1	-7.3 (-94.3, 79.8)	0.870	14.2 (-23.3, 51.6)	0.458	23.9 (-18.4, 66.2)	0.269	59.0 (11.5, 106.4)	0.015
ti2	172.2 (-64.6, 408.9)	0.154	121.8 (57.7, 185.8)	<0.001	144.7 (72.2, 217.3)	<0.001	202.6 (125.8, 279.4)	<0.001
Age	0.5 (-25.1, 26.2)	0.967	26.3 (15.0, 37.6)	<0.001	33.7 (18.4, 49.0)	<0.001	16.0 (-3.5, 35.4)	0.107
SIMD sc.	10.6 (2.3, 19.0)	0.013	8.4 (2.4, 14.4)	0.006	5.5 (0.8, 10.2)	0.022	11.9 (5.6, 18.3)	<0.001
Fam. his.	337.8 (-235.7, 911.4)	0.248	22.7 (-176.6, 222.0)	0.823	105.5 (-125.0, 336.0)	0.370	47.7 (-229.7, 325.2)	0.736
Constant	-214.2 (-1359, 930.8)	0.714	-1462 (-2123, -800.5)	<0.001	-1727 (-2643, -809.9)	<0.001	-832.0 (-1894, 230.1)	0.125

Table 5-19 Time spline variables: men pre-first event

year	ti1	ti2	year	ti1	ti2	year	ti1	ti2
1	1	0	35	35	31.2	68	68	70.8
2	2	0	36	36	32.4	69	69	72
3	3	0.004444	37	37	33.6	70	70	73.2
4	4	0.035556	38	38	34.8	71	71	74.4
5	5	0.12	39	39	36	72	72	75.6
6	6	0.284445	40	40	37.2	73	73	76.8
7	7	0.555556	41	41	38.4	74	74	78
8	8	0.96	42	42	39.6	75	75	79.2
9	9	1.517037	43	43	40.8	76	76	80.4
10	10	2.216296	44	44	42	77	77	81.6
11	11	3.04	45	45	43.2	78	78	82.8
12	12	3.97037	46	46	44.4	79	79	84
13	13	4.98963	47	47	45.6	80	80	85.2
14	14	6.08	48	48	46.8	81	81	86.4
15	15	7.223704	49	49	48	82	82	87.6
16	16	8.402963	50	50	49.2	83	83	88.8
17	17	9.6	51	51	50.4	84	84	90
18	18	10.8	52	52	51.6	85	85	91.2
19	19	12	53	53	52.8	86	86	92.4
20	20	13.2	54	54	54	87	87	93.6
21	21	14.4	55	55	55.2	88	88	94.8
22	22	15.6	56	56	56.4	89	89	96
23	23	16.8	57	57	57.6	90	90	97.2
24	24	18	58	58	58.8	91	91	98.4
25	25	19.2	59	59	60	92	92	99.6
26	26	20.4	60	60	61.2	93	93	100.8
27	27	21.6	61	61	62.4	94	94	102
28	28	22.8	62	62	63.6	95	95	103.2
29	29	24	63	63	64.8	96	96	104.4
30	30	25.2	64	64	66	97	97	105.6
31	31	26.4	65	65	67.2	98	98	106.8
32	32	27.6	66	66	68.4	99	99	108
33	33	28.8	67	67	69.6	100	100	109.2
34	34	30						

Table 5-20 Time spline variables: women pre-first event

year	ti1	ti2	year	ti1	ti2	year	ti1	ti2
1	1	0	35	35	31.2	68	68	70.8
2	2	0	36	36	32.4	69	69	72
3	3	0.004444	37	37	33.6	70	70	73.2
4	4	0.035556	38	38	34.8	71	71	74.4
5	5	0.12	39	39	36	72	72	75.6
6	6	0.284445	40	40	37.2	73	73	76.8
7	7	0.555556	41	41	38.4	74	74	78
8	8	0.96	42	42	39.6	75	75	79.2
9	9	1.517037	43	43	40.8	76	76	80.4
10	10	2.216296	44	44	42	77	77	81.6
11	11	3.04	45	45	43.2	78	78	82.8
12	12	3.97037	46	46	44.4	79	79	84
13	13	4.98963	47	47	45.6	80	80	85.2
14	14	6.08	48	48	46.8	81	81	86.4
15	15	7.223704	49	49	48	82	82	87.6
16	16	8.402963	50	50	49.2	83	83	88.8
17	17	9.6	51	51	50.4	84	84	90
18	18	10.8	52	52	51.6	85	85	91.2
19	19	12	53	53	52.8	86	86	92.4
20	20	13.2	54	54	54	87	87	93.6
21	21	14.4	55	55	55.2	88	88	94.8
22	22	15.6	56	56	56.4	89	89	96
23	23	16.8	57	57	57.6	90	90	97.2
24	24	18	58	58	58.8	91	91	98.4
25	25	19.2	59	59	60	92	92	99.6
26	26	20.4	60	60	61.2	93	93	100.8
27	27	21.6	61	61	62.4	94	94	102
28	28	22.8	62	62	63.6	95	95	103.2
29	29	24	63	63	64.8	96	96	104.4
30	30	25.2	64	64	66	97	97	105.6
31	31	26.4	65	65	67.2	98	98	106.8
32	32	27.6	66	66	68.4	99	99	108
33	33	28.8	67	67	69.6	100	100	109.2
34	34	30						

Table 5-21 a) Cost post non-fatal CHD event - men

Covariate	coeff. (95% CI)	p value
ti1	-552.6 (-638.7, -466.6)	<0.001
ti2	654.9 (554.5, 755.3)	<0.001
Age at event	84.6 (66.9, 102.4)	<0.001
SIMD score	14.2 (7.6, 20.8)	<0.001
Family history	239.8 (-80.4, 560.0)	0.142
Constant	-1024 (-2107, 59.0)	<0.001

b) Costs post non-fatal CBVD event - men

Covariate	coeff. (95% CI)	p value
ti1	-680.0 (-854.7, -505.2)	<0.001
ti2	787.7 (555.7, 1020)	<0.001
Age at event	112.6 (81.2, 144.0)	<0.001
SIMD score	6.8 (-4.5, 18.1)	0.236
Family history	-102.2 (-717.2, 512.9)	0.745
Constant	-1836 (-4010, 338.3)	0.098

c) Costs post non-fatal CHD event - women

Covariate	coeff. (95% CI)	p value
ti1	-548.6 (-652.4, -444.8)	<0.001
ti2	745.4 (600.4, 890.3)	<0.001
Age at event	90.7 (68.5, 112.9)	<0.001
SIMD score	13.6 (6.0, 21.3)	<0.001
Family history	-227.9 (-596.5, 140.7)	0.226
Constant	-1321 (-2900, 257.1)	<0.001

d) Costs post non-fatal CBVD event - women

Covariate	coeff. (95% CI)	p value
ti1	-542.3 (-744.1, -340.4)	<0.001
ti2	595.6 (357.4, 833.9)	<0.001
Age at event	97.1 (67.0, 127.2)	<0.001
SIMD score	7.7 (-4.7, 20.0)	0.223
Family history	-93.9 (-656.1, 468.4)	0.743
Constant	-1251 (-3593, 1092)	0.295

Table 5-22 Time spline variables: Men post-CHD

Cycle (year)	ti1	ti2	Cycle (year)	ti1	ti2	Cycle (year)	ti1	ti2
1	1	0	35	35	32.30769	68	68	70.38461
2	2	0.0059172	36	36	33.46154	69	69	71.53846
3	3	0.0473373	37	37	34.61538	70	70	72.69231
4	4	0.1597633	38	38	35.76923	71	71	73.84615
5	5	0.3786982	39	39	36.92308	72	72	75
6	6	0.7396449	40	40	38.07692	73	73	76.15385
7	7	1.268491	41	41	39.23077	74	74	77.30769
8	8	1.952663	42	42	40.38462	75	75	78.46154
9	9	2.76997	43	43	41.53846	76	76	79.61539
10	10	3.698225	44	44	42.69231	77	77	80.76923
11	11	4.715237	45	45	43.84615	78	78	81.92308
12	12	5.798817	46	46	45	79	79	83.07692
13	13	6.926775	47	47	46.15385	80	80	84.23077
14	14	8.076923	48	48	47.30769	81	81	85.38461
15	15	9.230769	49	49	48.46154	82	82	86.53846
16	16	10.38461	50	50	49.61538	83	83	87.69231
17	17	11.53846	51	51	50.76923	84	84	88.84615
18	18	12.69231	52	52	51.92308	85	85	90
19	19	13.84615	53	53	53.07692	86	86	91.15385
20	20	15	54	54	54.23077	87	87	92.30769
21	21	16.15385	55	55	55.38462	88	88	93.46154
22	22	17.30769	56	56	56.53846	89	89	94.61539
23	23	18.46154	57	57	57.69231	90	90	95.76923
24	24	19.61539	58	58	58.84615	91	91	96.92308
25	25	20.76923	59	59	60	92	92	98.07692
26	26	21.92308	60	60	61.15385	93	93	99.23077
27	27	23.07692	61	61	62.30769	94	94	100.3846
28	28	24.23077	62	62	63.46154	95	95	101.5385
29	29	25.38461	63	63	64.61539	96	96	102.6923
30	30	26.53846	64	64	65.76923	97	97	103.8462
31	31	27.69231	65	65	66.92308	98	98	105
32	32	28.84615	66	66	68.07692	99	99	106.1538
33	33	30	67	67	69.23077	100	100	107.3077
34	34	31.15385						

Table 5-23 Time spline variables: Men post-CBVD

Cycle (year)	ti1	ti2	Cycle (year)	ti1	ti2	Cycle (year)	ti1	ti2
1	1	0	35	35	31.63636	68	68	67.63636
2	2	0.0082645	36	36	32.72727	69	69	68.72727
3	3	0.0661157	37	37	33.81818	70	70	69.81818
4	4	0.2231405	38	38	34.90909	71	71	70.90909
5	5	0.5289256	39	39	36	72	72	72
6	6	1.020071	40	40	37.09091	73	73	73.09091
7	7	1.681228	41	41	38.18182	74	74	74.18182
8	8	2.484061	42	42	39.27273	75	75	75.27273
9	9	3.400236	43	43	40.36364	76	76	76.36364
10	10	4.401417	44	44	41.45454	77	77	77.45454
11	11	5.459268	45	45	42.54546	78	78	78.54546
12	12	6.545455	46	46	43.63636	79	79	79.63636
13	13	7.636364	47	47	44.72727	80	80	80.72727
14	14	8.727273	48	48	45.81818	81	81	81.81818
15	15	9.818182	49	49	46.90909	82	82	82.90909
16	16	10.90909	50	50	48	83	83	84
17	17	12	51	51	49.09091	84	84	85.09091
18	18	13.09091	52	52	50.18182	85	85	86.18182
19	19	14.18182	53	53	51.27273	86	86	87.27273
20	20	15.27273	54	54	52.36364	87	87	88.36364
21	21	16.36364	55	55	53.45454	88	88	89.45454
22	22	17.45455	56	56	54.54546	89	89	90.54546
23	23	18.54545	57	57	55.63636	90	90	91.63636
24	24	19.63636	58	58	56.72727	91	91	92.72727
25	25	20.72727	59	59	57.81818	92	92	93.81818
26	26	21.81818	60	60	58.90909	93	93	94.90909
27	27	22.90909	61	61	60	94	94	96
28	28	24	62	62	61.09091	95	95	97.09091
29	29	25.09091	63	63	62.18182	96	96	98.18182
30	30	26.18182	64	64	63.27273	97	97	99.27273
31	31	27.27273	65	65	64.36364	98	98	100.3636
32	32	28.36364	66	66	65.45454	99	99	101.4545
33	33	29.45455	67	67	66.54546	100	100	102.5455
34	34	30.54545						

Table 5-24 Time spline variables: Women post-CHD

year	ti1	ti2	year	ti1	ti2	year	ti1	ti2
1	1	0	35	35	26.15385	68	68	56.61538
2	2	0.005917	36	36	27.07692	69	69	57.53846
3	3	0.047337	37	37	28	70	70	58.46154
4	4	0.159763	38	38	28.92308	71	71	59.38462
5	5	0.378698	39	39	29.84615	72	72	60.30769
6	6	0.731098	40	40	30.76923	73	73	61.23077
7	7	1.20973	41	41	31.69231	74	74	62.15385
8	8	1.798817	42	42	32.61538	75	75	63.07692
9	9	2.482577	43	43	33.53846	76	76	64
10	10	3.245233	44	44	34.46154	77	77	64.92308
11	11	4.071006	45	45	35.38462	78	78	65.84615
12	12	4.944116	46	46	36.30769	79	79	66.76923
13	13	5.848783	47	47	37.23077	80	80	67.69231
14	14	6.769231	48	48	38.15385	81	81	68.61539
15	15	7.692307	49	49	39.07692	82	82	69.53846
16	16	8.615385	50	50	40	83	83	70.46154
17	17	9.538462	51	51	40.92308	84	84	71.38461
18	18	10.46154	52	52	41.84615	85	85	72.30769
19	19	11.38461	53	53	42.76923	86	86	73.23077
20	20	12.30769	54	54	43.69231	87	87	74.15385
21	21	13.23077	55	55	44.61538	88	88	75.07692
22	22	14.15385	56	56	45.53846	89	89	76
23	23	15.07692	57	57	46.46154	90	90	76.92308
24	24	16	58	58	47.38462	91	91	77.84615
25	25	16.92308	59	59	48.30769	92	92	78.76923
26	26	17.84615	60	60	49.23077	93	93	79.69231
27	27	18.76923	61	61	50.15385	94	94	80.61539
28	28	19.69231	62	62	51.07692	95	95	81.53846
29	29	20.61539	63	63	52	96	96	82.46154
30	30	21.53846	64	64	52.92308	97	97	83.38461
31	31	22.46154	65	65	53.84615	98	98	84.30769
32	32	23.38461	66	66	54.76923	99	99	85.23077
33	33	24.30769	67	67	55.69231	100	100	86.15385
34	34	25.23077						

Table 5-25 Time spline variables: Women post-CBVD

Cycle (year)	ti1	ti2	Cycle (year)	ti1	ti2	Cycle (year)	ti1	ti2
1	1	0	35	35	31.63636	68	68	67.63636
2	2	0.0082645	36	36	32.72727	69	69	68.72727
3	3	0.0661157	37	37	33.81818	70	70	69.81818
4	4	0.2231405	38	38	34.90909	71	71	70.90909
5	5	0.5289256	39	39	36	72	72	72
6	6	1.020071	40	40	37.09091	73	73	73.09091
7	7	1.681228	41	41	38.18182	74	74	74.18182
8	8	2.484061	42	42	39.27273	75	75	75.27273
9	9	3.400236	43	43	40.36364	76	76	76.36364
10	10	4.401417	44	44	41.45454	77	77	77.45454
11	11	5.459268	45	45	42.54546	78	78	78.54546
12	12	6.545455	46	46	43.63636	79	79	79.63636
13	13	7.636364	47	47	44.72727	80	80	80.72727
14	14	8.727273	48	48	45.81818	81	81	81.81818
15	15	9.818182	49	49	46.90909	82	82	82.90909
16	16	10.90909	50	50	48	83	83	84
17	17	12	51	51	49.09091	84	84	85.09091
18	18	13.09091	52	52	50.18182	85	85	86.18182
19	19	14.18182	53	53	51.27273	86	86	87.27273
20	20	15.27273	54	54	52.36364	87	87	88.36364
21	21	16.36364	55	55	53.45454	88	88	89.45454
22	22	17.45455	56	56	54.54546	89	89	90.54546
23	23	18.54545	57	57	55.63636	90	90	91.63636
24	24	19.63636	58	58	56.72727	91	91	92.72727
25	25	20.72727	59	59	57.81818	92	92	93.81818
26	26	21.81818	60	60	58.90909	93	93	94.90909
27	27	22.90909	61	61	60	94	94	96
28	28	24	62	62	61.09091	95	95	97.09091
29	29	25.09091	63	63	62.18182	96	96	98.18182
30	30	26.18182	64	64	63.27273	97	97	99.27273
31	31	27.27273	65	65	64.36364	98	98	100.3636
32	32	28.36364	66	66	65.45454	99	99	101.4545
33	33	29.45455	67	67	66.54546	100	100	102.5455
34	34	30.54545						

5.7.6 Using the model to predict hospitalisation costs

To estimate cumulative lifetime costs a Kaplain-Meier Sample Average (KMSA) estimator was used again, similar to the process of quality adjustment. This gives the generic expression:

$$\text{Expected cost} = \sum S(t)xb(t))$$

where xb(t) is the linear predictor from the linear regression at time period t, and S(t) is the survival probability.

Prior to the first event, the survival probability is 1. Post first event, the probability of survival declines with time, as estimated in Chapter 4. Costs in each time period is weighted by survival to the end of that time period. To estimate cumulative costs the KMSA estimator simply sums expected costs across time periods. The following four figures 5-31 to 5-34 illustrates how the model estimates costs for the same 60 year male profiles as introduced previously.

(i) Cost pre-event: In summary, the figures show that the model smoothes the observed data which was erratic.

Figure 5-31 Predicted costs pre-nonfatal CHD

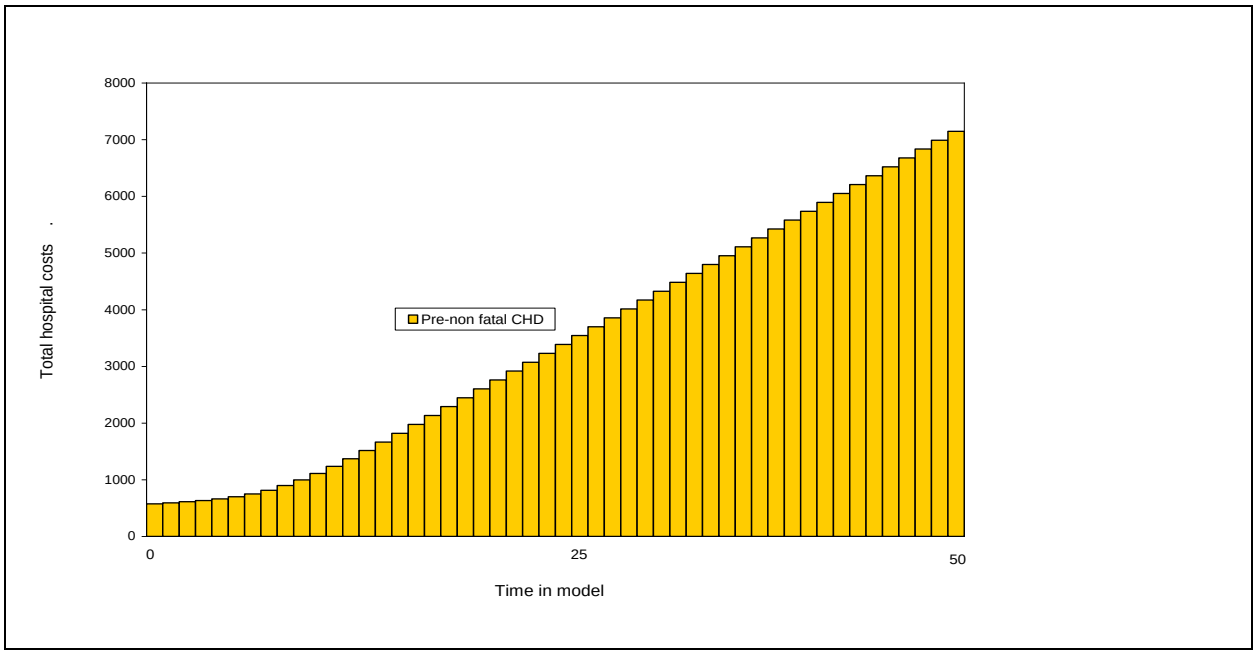


Figure 5-32 Predicted costs pre-nonfatal CVBD

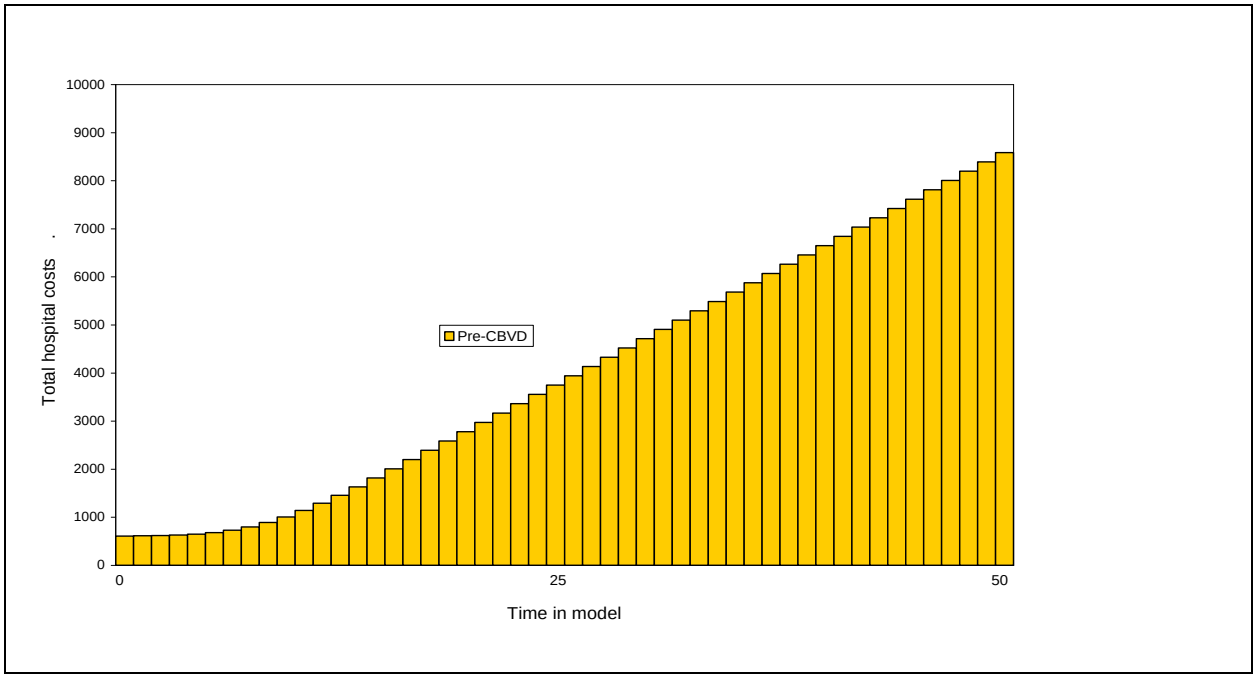


Figure 5-33 Predicted costs pre-fatal CVD

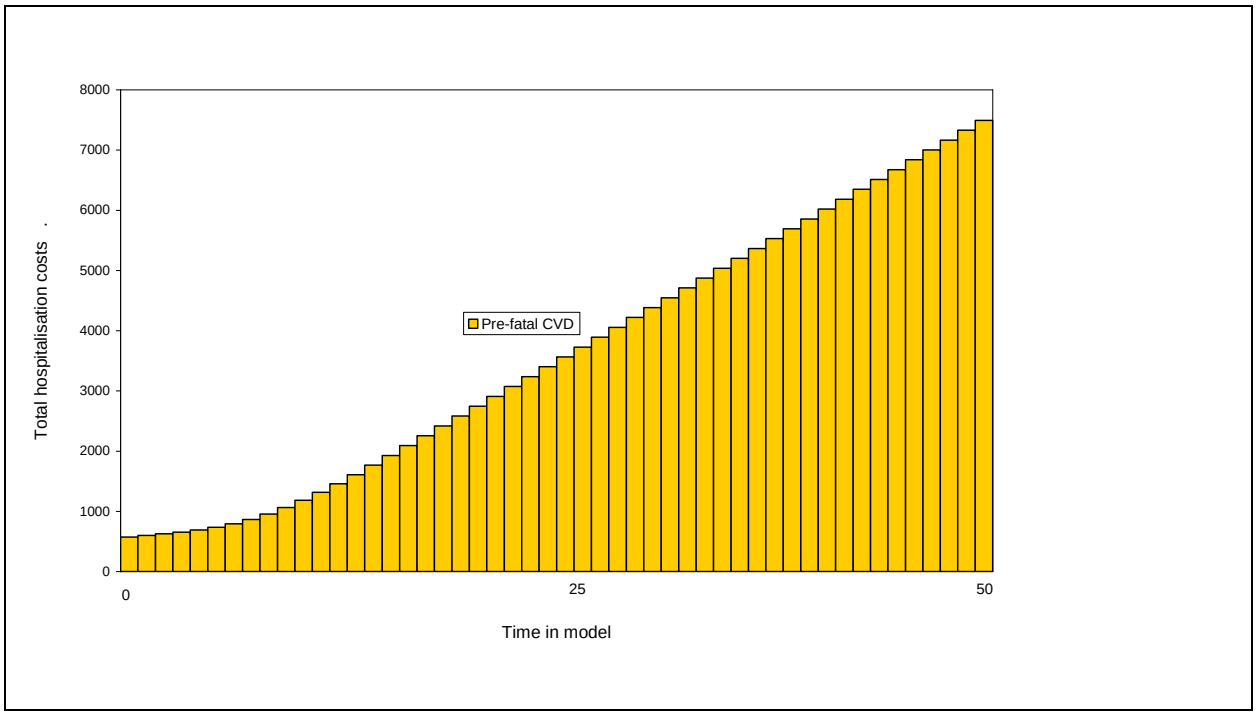
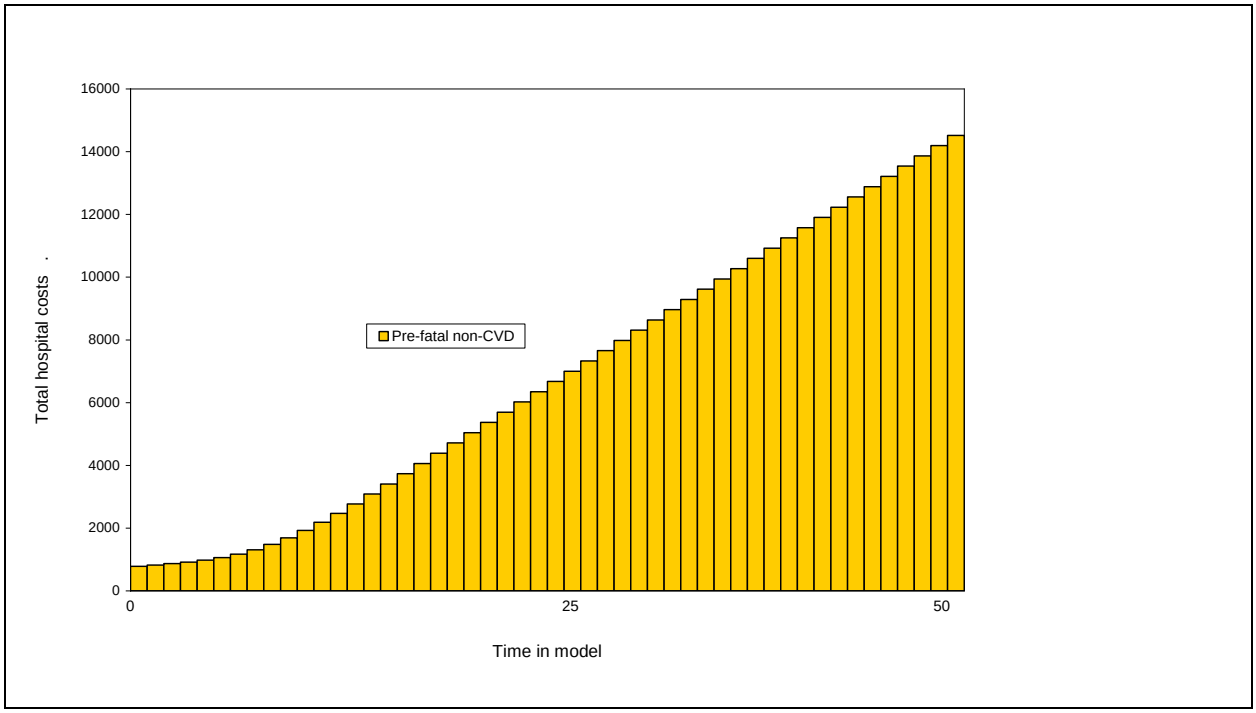


Figure 5-34 Predicted costs pre-fatal non CVD



To incorporate the annual costs estimates before the first four events, then are summed across to the period when a particular first event occurs. That is, the survival probability is assumed to be 1 up until the period in which an event occurs.

(ii) Costs post event**:** Figures 5-35 and 5-36 illustrate modelled lifetime costs for the 60 male we have used throughout the thesis so far. The assumption is that a CHD or CBVD event occurs in year 1 upon entering the model. Similar to the process of quality adjustment, a KMSA estimator approach is adopted whereby the estimates in each year of the model are weighted by the probability of actually being alive and then summed. This provides an estimate of cumulative costs over a remaining lifetime.

Figure 5-35 Predicted costs post non-fatal CHD hospitalisation

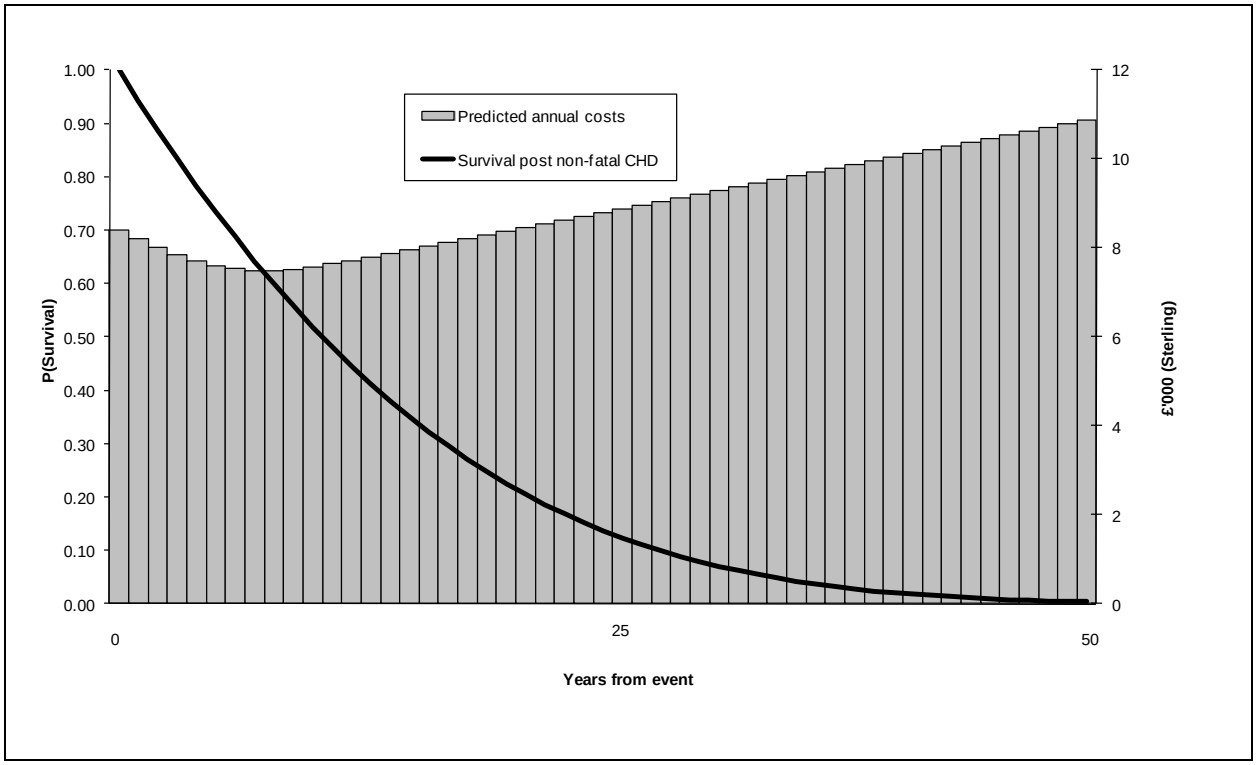
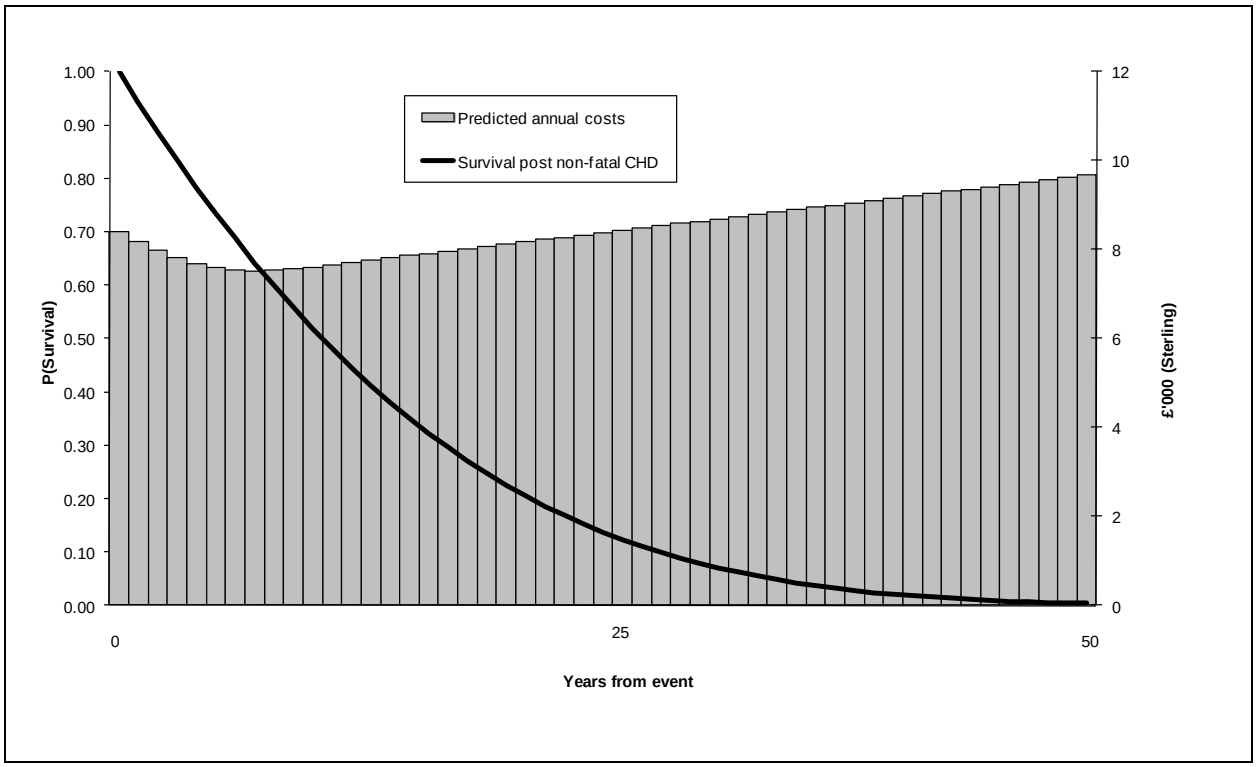


Figure 5-36 Predicted costs post non-fatal CBVD hospitalisation



The next section provides an illustration how these cost predictions are combined to estimate expected cumulative lifetime hospitalisation costs.

5.8 Generating expected cumulative lifetime hospitalisation costs

To then estimate average expected lifetime costs, all event scenarios need to be run and weighted in a similar process to quality adjusting life expectancy. First, an estimate of the lifetime costs are made for each model scenario defined by type and timing of the first event – table 5-26a. Each of the 400 scenarios (4 first events multiple by 100 cycles) has its own cost estimate.

Table 5-26 a) Remaining discounted lifetime costs upon entering model [pre-first event + post first event]

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	CVD death	nonCVD death
1	87	78	6	6
2	88	78	12	13
3	88	79	17	18
.				
.				
22	91	84	32	35
23	93	86	37	39
24	95	88	41	44
.				
.				
100	249	263	39	40

b) Probability of first event

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	CVD death	nonCVD death
1	0.026	0.008	0.017	0.013
2	0.026	0.008	0.017	0.013
3	0.025	0.008	0.017	0.013
.				
.				
22	0.003	0.002	0.003	0.002
23	0.002	0.001	0.002	0.002
24	0.002	0.001	0.002	0.001
.				
.				
100	0	0	0	0

Table 5-26b give the probability of each event scenario, and table 5.26c provides weighted costs by multiply tables a and b together. All estimates are discounted at 3.5%.

c) Weighted discounted lifetime costs [estimates from table a) multiplied by estimated from table b)]

Cycle (time in years)	Non-fatal CHD	Non-fatal CBVD	CVD death	nonCVD death	*Sum*
1	1.082	0.238	0.032	0.075	1.426
2	1.111	0.254	0.066	0.154	1.585
3	1.143	0.272	0.101	0.237	1.752
.					
.					
22	0.722	0.333	0.175	0.427	1.659
23	0.658	0.316	0.183	0.447	1.604
24	0.591	0.296	0.184	0.452	1.523
.					
.					
100	0.000	0.000	0.000	0.000	0.000
			Total lifetime costs (pre and post event) =		45.8

For the 60 year old male, life time discounted hospital costs was estimated to be a discounted £45,800.

Figures 5-37 to 5-38 illustrate the model's ability to estimate lifetime costs specific to individual risk profiles as defined by the ASSIGN risk factors. The standard format of 10-year risk tables is again used. For consistency, this is also shown for men and women and for the highest and lowest fifths of SIMD. These are shown in discounted terms. In general, for a given age band healthier profiles (lower modifiable risk factors) are associated with higher costs given longer life expectancies. Costs also rise with age groups. While younger age groups have a longer to live and absolute costs are higher, discounting results in distant costs valued much less is present day terms. This will be further illustrated shortly.

Figure 5-37 Discounted lifetime hospital costs - men

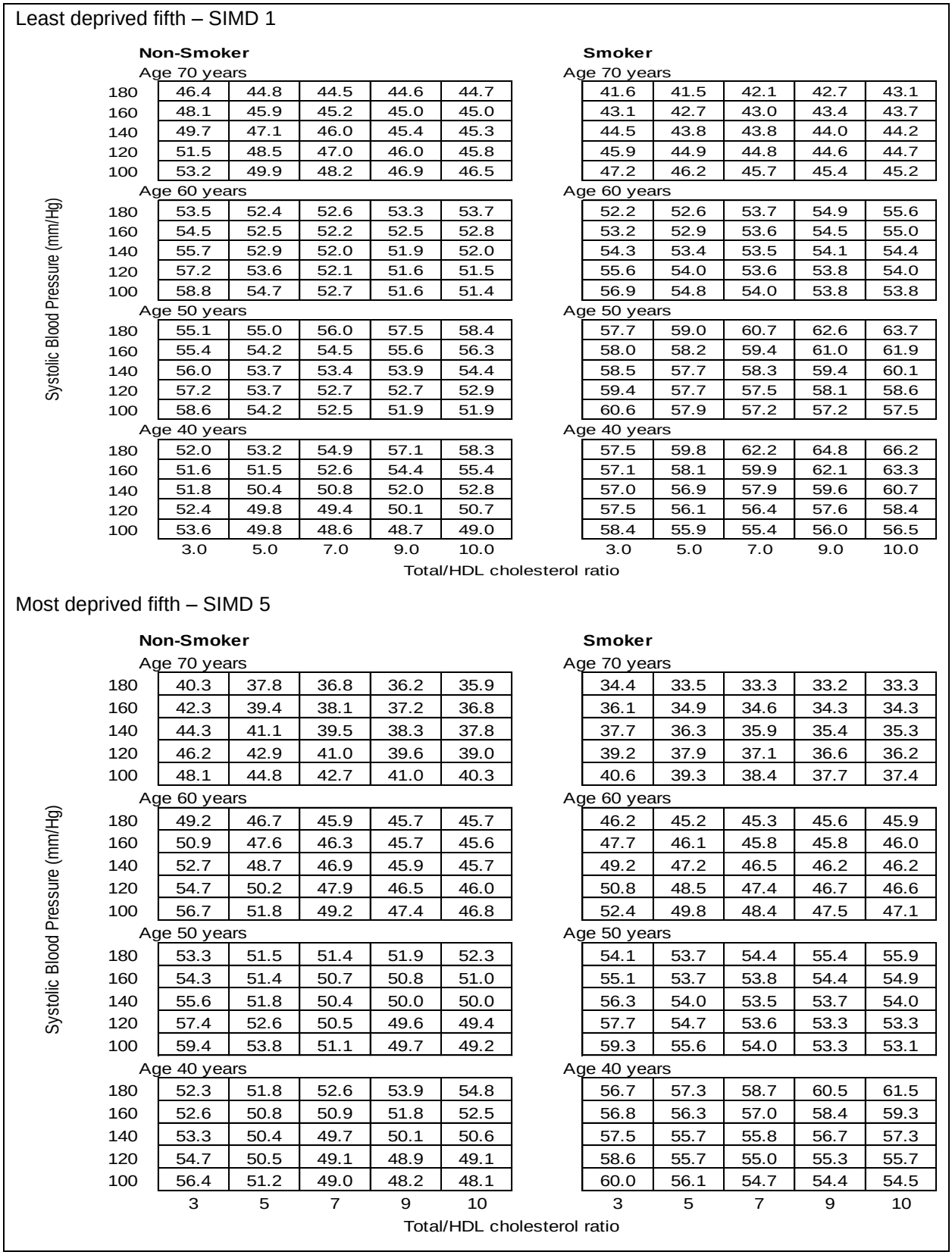
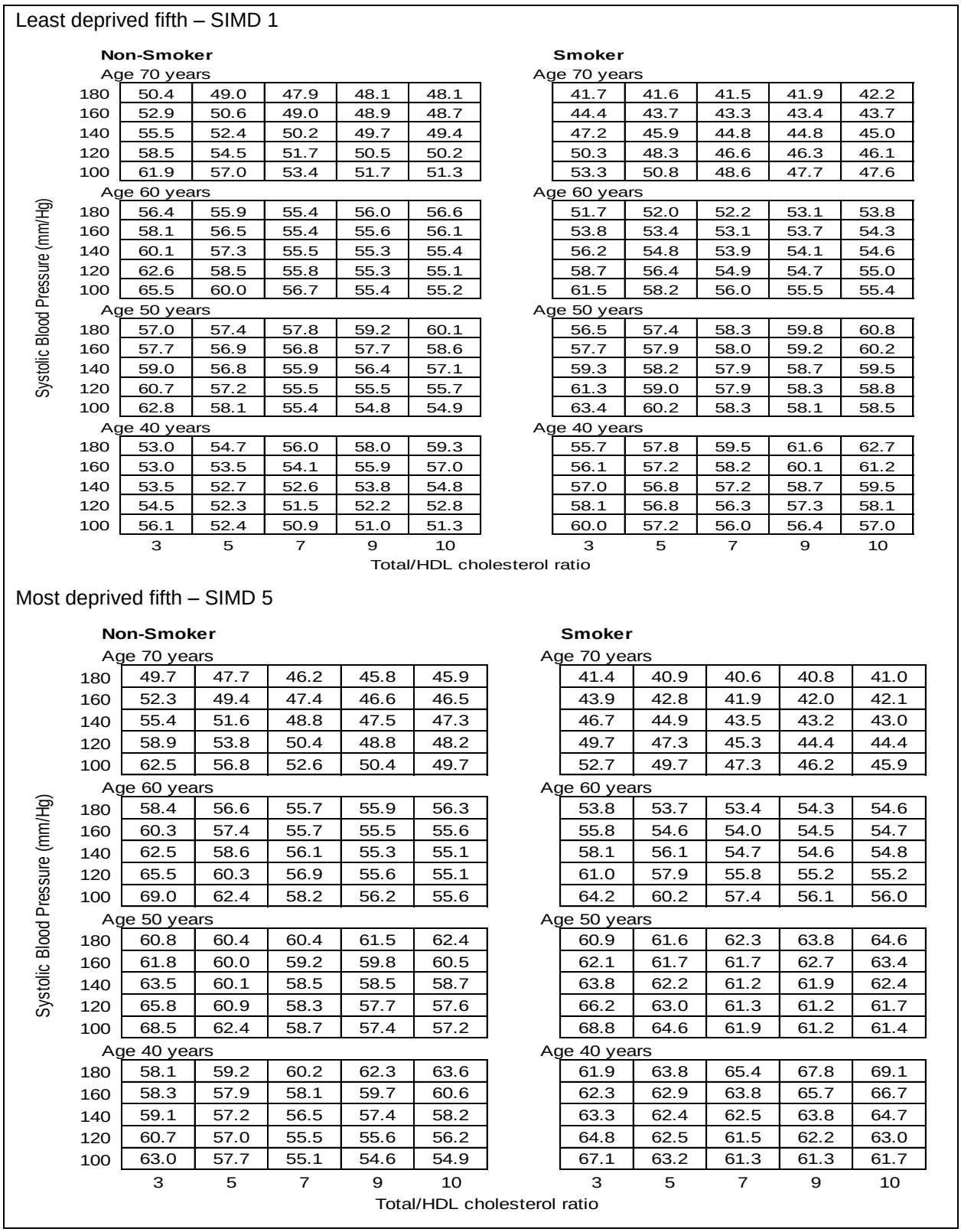


Figure 5-38 Discounted lifetime hospital costs - women



5.9 Preparing the model for economic evaluation

In taking stock of the modelling so far in Part 2 of thesis, the model has the ability to estimate the lifetime risk CVD, life expectancy, QALE and lifetime hospitalisation costs. The next step is to prepare the model to be ready for economic evaluation. This is the purpose of this section.

5.9.1 Inputs to the model

The purpose of the evaluation module is to estimate the lifetime impact of changes to modifiable risk factors on life expectancy, QALE and costs. The model can be used either to conduct "what-if" analysis to simulate the potential impact of modifying risk factor(s), or alongside trial evidence of intervention(s) to project the expected lifetime impacts from evidenced changes to risk factors.

Three main inputs are used in the model: (i) the intervention(s), (ii) associated evidence regarding the interventions impact on reducing risk factors, and (iii) intervention costs. The model can include any primary interventions, including pharmaceuticals, behavioural change interventions and legislative changes. Evidence can either relate to efficacy or effectiveness. Further, the model can be used flexibly to manually include relevant compliance assumptions which may be important when making long term predictions. Compliance assumptions can be tailored to particular individual risk profiles where relevant, such as age, sex and socioeconomic deprivation. Intervention costs may include one-off costs (e.g. legislation) or periodic costs (e.g. pharmaceuticals) where the model includes / estimates annual costs for each year that an individual is alive in the model.

The model can also incorporate evidence relating to the impact of intervention(s) on event rates (e.g. CHD). To do this, the model estimates the necessary changes to relevant ASSIGN risk factors to observe reported event rates. This can be done on a case-by-case basis using appropriate literature and expert opinion regarding how particular risk factor(s) may be affected by an intervention. In converting observed event rates into assumed risk factor reductions the model is able to estimate the impact of interventions on all four first events of the model (non-fatal CHD, non-fatal CBVD, fatal CVD and fatal non-CVD) rather than a single event.

5.9.2 Illustrating the model: simulate the potential impacts of risk factor modification

To estimate the impact of interventions two scenarios are run for each individual risk profile. First, baseline risk profiles are run through the model to estimate life expectancy, QALE and costs. Second, risk profiles are adjusted (using evidence or conducting a what-if analysis), and re-run through the model. The difference in life expectancy, QALE and costs (net of intervention costs) are then calculated. This prepared the model to be used to assess the cost-effectiveness of interventions as recommended by health technology agencies (such as NICE). All estimates can be discounted and undiscounted.

To illustrate this process, the Scottish Health Survey (SHeS) 2009 was used to estimate average risk profiles for 60 year old men and women across fifths of socioeconomic deprivation. This served as baseline risk profiles and entered into the model. The model is used to first produce both undiscounted life expectancy and discounted QALE. This is shown in Figure 5-46 as the dark columns, denoted as “before” risk factor modification.

To then demonstrate the capability of the evaluation module, all profiles were switched to a “perfect” risk factor profile defined with reference to standard 10-year risk tables, where individuals are non-smoking, have a systolic blood pressure of 100, and a ratio of total cholesterol to HDL cholesterol of 3.

Next, individuals with perfect profiles are run through the module. For illustration purposes, the simplifying assumptions are made that individuals immediately switch risk profiles and acquire the associated life expectancy and QALE.

Figure 5-39 and 5-40 illustrates the potential gains from reducing risk factors for average 60 year men and women across fifths of socioeconomic deprivation. This is shown for both life expectancy and discounted QALE. The gain are shown as extensions to the columns denoted as being “after” risk factor modification, and the figure at the top the columns represents the overall life expectancy and QALE following modification.

Overall, the potential gains in life expectancy are greater for those in lower socioeconomic status and higher for women. The exception is men within the most deprived fifth who gain more than women. Before risk factor modification, men in the least deprived (SIMD1) fifth have a 7% higher life expectancy than the most deprived (SIMD 5) fifth and a 3.5% higher discounted QALE. After risk factor modification the gradient closes to 4.8% and 2.7%

respectively. For women, the least deprived fifth have 5.5% higher life expectancy than the most deprived fifth and 2.3% higher QALE. Following risk factor modification the gradient closes to 2.7% and 1.9% respectively.

Using the same process of running baseline and modified risk factor profiles through the model, estimates of discounted and undiscounted lifetime hospitalisation costs are also made. Cost increase post risk factor modification, consistent with longer life expectancies. Discounting reduces the absolute cost estimate and narrows the gradient between women and men, and by fifth of socioeconomic deprivation.

Figure 5-39 Modifying risk factors for average 60 year old men and women by fifths of socioeconomic deprivation (SIMD) – the potential impact on undiscounted life expectancy and discounted quality adjusted life expectancy

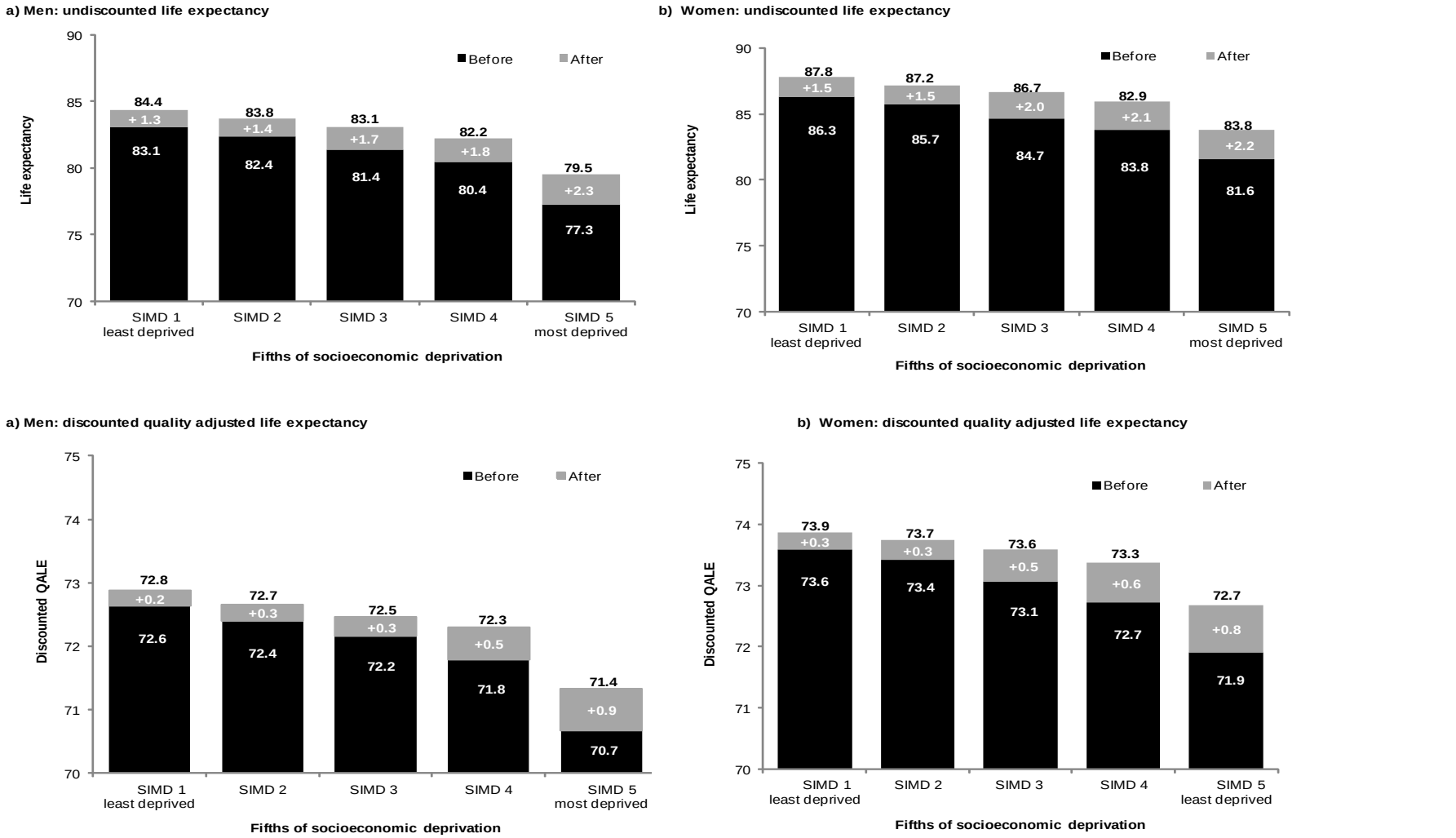
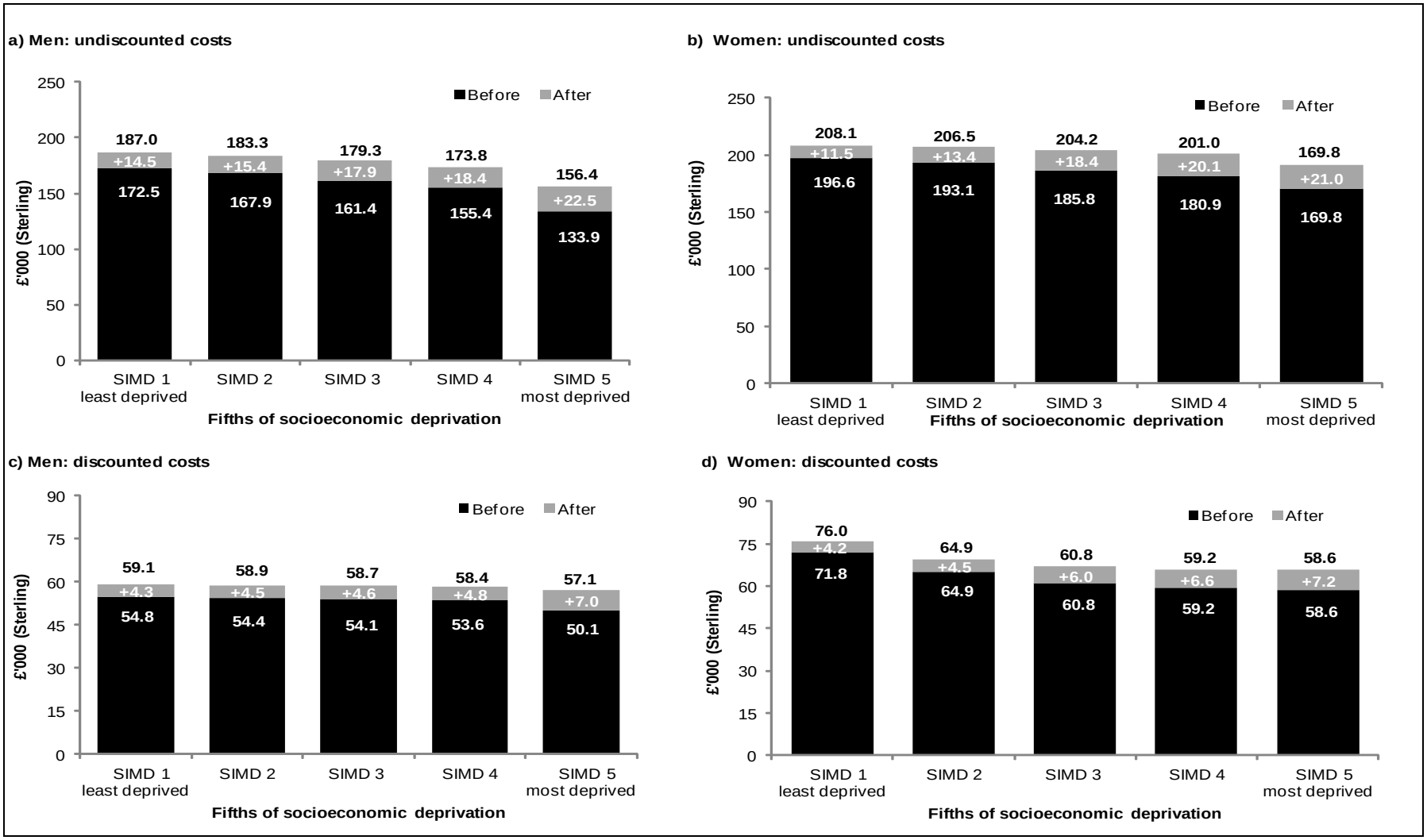


Figure 5-40 Modifying risk factors for average 60 year old men and women by fifths of socioeconomic deprivation (SIMD) – the potential impact on undiscounted lifetime costs and discounted lifetime costs



This short section was intended to provide a brief illustration that the model can be used easily to assess the impact of risk factor modification that may be the result of intervention. The next final part of the thesis provides a fuller demonstration of the model.

5.10 Summary and discussion

The aim of this chapter was to build upon the underlying epidemiology of the policy model to illustrate how we could generate economic outputs. The previous chapter estimated the lifetime risk of CVD and overall life expectancy. We first quality adjusted life expectancy estimates, by accounting for the background health utility, and the utility impact of incurring non-fatal secondary CVD events. The chapter detailed how costs were estimated across an individual's lifetime, and incorporated into the model. Overall, the model can now predict quality adjusted life expectancy, and cumulative lifetime hospital costs; and these estimates can be discounted or undiscounted.

Strengths and limitations

There were several perceived strengths in the analysis. First, to make quality adjustments and estimate hospitalisation costs comprehensive Scottish data sources were used. The SHeS 2003 was used to estimate the background morbidity and the utility impact of incurring 5 CVD events. The SHHEC-SMR dataset was used to estimate the risk of subsequent non-fatal events following a first non-fatal CVD event. Overall, this enabled quality adjustment to be comprehensive. In contrast, most policy models do not undertake the same extent of quality adjustment.

Second, the SHHEC-SMR dataset also enabled modelling of the annual risk and mean cost of all hospitalised events, including CVD and non-CVD events. This then enabled the cumulative lifetime costs to be estimated over an individual's lifetime. The only other model that can estimate how hospitalisation costs vary according to life expectancy is the Archimedes model.

Third, the use Scottish data sources are intended to increase the applicability of the model to a Scottish context.

Third, in general, the modelling is intended to be transparent. This was made possible due to the longitudinal SHHEC-SMR data source. Most other models combine multiple cross-sectional data sources in an effort to estimate event risks, which is perfectly valid but can result in a loss of transparency.

A potential limitation is that the SHeS 2003 relied upon individuals self-reporting CVD conditions. Future research could investigate the accuracy of self-reporting by acquiring linked hospital data to patient ID. This type of linkage is readily available in Scotland for the purposes of research, subject to Government permission. Further, the main event not captured in the SHeS 2003 was heart failure. The decrement associated with heart failure has been estimated by Clarke to be 0.074 within the first year and 0.058 over 12 months.

The main weakness in the approach to cost the impact of CVD on lifetime patient costs is that it is limited to hospitalisation costs. What is omitted is primary care and community care costs. This may be particularly important for costing the impact of stroke, which is increasing treated at the community level.

Overall, Part 2 of the thesis was intended to build the Scottish CVD Policy Model to using the same ASSIGN risk factors as employed in clinical screening to prioritise individuals for targeted interventions, the focus of primary prevention in Scotland. The model estimation is intended to be comprehensive, transparent and as simple as possible. The opportunity to achieve these features was greater enhanced by having access to excellent data sources.

Part 3 - Demonstrating the Scottish CVD Policy Model

Overview

The final part of the thesis builds upon Part 1 and 2 to demonstrate how the policy model can be used to inform the development and evaluation of primary prevention interventions. This overview first takes stock of the thesis so far before describing the approach taken in Part 3.

Part 1 of the thesis described the considerable burden that results from the onset of CVD. While rates have been falling throughout the general population, CVD remains the number one cause of death, has major morbidity impacts and remains a key driver of health inequalities. Further CVD also results in considerable health and wider economic costs. Policymakers are attempting to respond with a focus on primary prevention. However, there is a lack of evidence underpinning approaches and, in particular, there the targeted multi-factorial approaches on individuals deemed to be at high risk.

The thesis has sought to build the Scottish CVD Policy Model for the purpose of helping policymakers develop and evaluate primary prevention interventions. Three key research questions were offered to challenge the application of model: (i) can the model identify optimal screening approaches to identify individuals at high risk of a CVD event; (ii) can the model be used to develop a new targeted approach that prioritises individuals for intervention based upon potential benefit from changes to modifiable risk factors; and (iii) can the model be used consistently to evaluate both targeted and population interventions to inform optimal prevention strategies.

Part 2 developed the Scottish CVD Policy Model with these research questions in mind. A generic modelling approach was adopted where the model takes the nine ASSIGN risk factors currently used in clinical practice to screen and estimate lifetime risk, life expectancy, quality adjusted life expectancy and cumulative lifetime hospital costs. The intention was to then use the policy model to help address each of the current weaknesses in primary prevention that exist at present.

Part 3 of the thesis now attempts to provide a demonstration of how the policy model could be applied to help address the research questions. The questions deal with a particular problem and the model is used in a particular way to address the problem. For the purposes

of exposition, four short chapters follow with each focused on a particular illustration of the model.

Chapter 6 is concerned with identifying efficient screening strategies to identify high risk individuals. Chapter 7 focuses on the developing a new clinical tool that can discriminate between individuals on the basis of the potential benefit from interventions. Chapter 8 demonstrates how the model can be used to evaluate Scotland's flagship primary prevention initiative, which is a multi-factorial programme of interventions. Chapter 9 then illustrates that the model can also be used to evaluate population-wide interventions.

The intention of separate chapters is to reflect the fact that these address different problems, and use the model in different ways. That is, each chapter essentially draws upon a particular element of the discussions in Chapter 2 and 3 that identified a key weakness or uncertainty in current primary prevention approaches. Further, to address the identified weakness the model is used in a particular way, drawing on either Chapter 4 Chapter 5 as appropriate, depending on the outcome required from the model.

Each chapter is structured in a similar fashion consisting of 4 sections, similar in manuscript style. This is intended to help the flow of the chapter and orientate the reader, given that the volume of material covered so far as been quite substantial. Beginning with the background to a particular problem (e.g. sub-optimal screening strategies) a summary of the relevant discussion of Chapter 2 is provided. A methods section then discusses how the policy model is used in a particular way to help address the particular issues under consideration, drawing upon Chapter 4 and/or 5. The results section applies the model and details relevant findings, and the implications for decision making. Finally, a discussion section focuses on the strengths and weaknesses of the policy model regarding the extent to which it can be used to address the identified problem area.

Chapter 6 Identifying efficient screening strategies to target high risk individuals

6.1 Background

Current clinical guidelines advise that primary prevention is most effective if people are selected for intervention on the basis of their overall cardiovascular risk(9). The Scottish Intercollegiate Guidelines Network (SIGN) recommends treatment of anyone with more than 20% risk of a cardiovascular event over the subsequent 10-years. Since 2007 the ASSIGN score has been used in Scotland(124). However, determining which members of the general population have a high cardiovascular risk is problematic.

Mass screening of the whole population is one option. Alternatively, screening could be targeted at sub-groups of the population known to have higher rates of cardiovascular disease. Deprived communities have a higher prevalence of cardiovascular risk factors and a higher incidence of cardiovascular events. Similarly, people with a family history of premature cardiovascular disease have a two-fold risk of developing the condition, due to a combination of shared genetic predisposition and shared lifestyle.

In 2007, Scotland began piloting a screening and intervention programme focusing only in the communities who reside with the most deprived fifth, and aged between 45-64 years. However, Scottish policymakers have been considering widening the programme to the entire population aged between 40-74 years in an attempt capture high risk individuals throughout the entire population. This approach would be consistent with SIGN Guidelines. Further, England began such a national screening programme in 2009 with the intention to screen every 5-years, detecting and referring high risk individuals onto multi-factorial interventions(180).

However, neither Scotland's nor England's programme has been evaluated to date; and, notably, both programmes state the same objective to help reduce health inequalities. This dichotomy of approaches begs the question which approaches may be the most cost effective, and have the most favourable impact on inequalities?

The aim of this short Chapter is to use the Scottish Policy Model to compare the relative strengths and weaknesses of alternative screening approaches in terms of effectiveness, cost effectiveness and coverage.

6.2 Methods

Source data: The Scottish Health Survey (SHeS) 2003 is a periodic cross sectional survey of the Scottish population, and has cardiovascular disease as its principle focus(314). The Survey uses multi-stage, stratified sampling to provide a representative sample of the Scottish population, and includes face to face interviews and physical measurements. This sample was used in the consequent analysis to test different screening strategies. More contemporary SHeS are available, but lack sufficient statistical power with huge amount of missing data on key ASSIGN variables. For instance, as much as 80% of cholesterol readings are missing from 2008 and 2009. Further, the full SHeS 2010 dataset was not available at the time of writing.

Participants within the SHeS 2003 were included if they were between 40 and 74 years. Participants were excluded if they (self-reported) a prior diagnosis of a CVD event. In total, 4,082 individuals were included in the analysis

The SHeS contains information on all of the ASSIGN risk factors. However, in the Scottish Health Survey, a family history of premature cardiovascular disease was defined as death of either natural parent due to cardiovascular disease before the age of 65 years. In the Scottish Heart Health Extended Cohort (SHHEC) used to define the ASSIGN risk factors, family history was a wider definition including the incidence of any CVD event and for parents, siblings and second degree relatives.

Defining screening strategies: The Scottish Health Survey data were used to simulate the impact of five alternative screening strategies to identify those at high risk of cardiovascular events (i) mass screening of the whole population; (ii) screening individuals living in deprived communities; (iii) screening individuals with a family history of premature cardiovascular disease; (iv) screening individuals who either lived in deprived communities or had a family history of premature cardiovascular disease, and finally (v) screening individuals who both lived in deprived communities and had a family history of premature cardiovascular disease.

The SHeS 2003 then stratified into these five groups then ran through the model one individual at a time to assess 10 year CVD risk. The results were then stratified by age group: by ages 40-74 years, and for those at risk of premature cardiovascular disease. The later was defined as men aged 40-54 years and women aged 40-64 years. This follows the definition of

family history of premature CVD used by JBS2 Guidelines(120). The difference in the definition used in the clinical literature reflects shorter background life expectancy of men.

Cost and cost-effectiveness: It was assumed that the screening process would be identical in all of the models studied and therefore that the unit costs would be common to all. Costs included contacting individuals and arranging appointments, a screening appointment undertaken by a practice-based nurse, the laboratory costs of assaying cholesterol and glucose concentrations, and the cost of a follow-up appointment at which the results would be fed back. Screening costs were based on the 2008 prices published by the Department of Health for England and Wales. Subsequent investigation and treatment costs were not included in the models.

First, the absolute costs and effects associated with implementing each of the five screening strategies in isolation referent to no screening were determined. The effectiveness of each strategy was defined as the number needed to screen (NNS) to detect one person at high-risk of cardiovascular disease. The cost of detecting one person was calculated as the unit cost per patient screened multiplied by the NNS for that strategy.

Second, the additional costs and effects of each strategy referent to the other strategies was determined by assuming that more effective strategies were substituted in an incremental fashion, from the lowest population coverage (lowest overall cost) up to mass screening of the whole population (highest overall cost). The cost and NNS of detecting one additional person at high-risk was calculated and associated the incremental cost effectiveness ratio (ICER).

Finally, any strategies that were both more costly and less effective (higher NNS) than the next incremental strategy were then excluded from the calculations as they were ‘dominated’ by the more effective strategy. Further, any strategies that were associated with a higher ICER than more effective (lower NNS) strategies were excluded from the calculations as they were ‘extended dominated.’ Where this occurred, the ICERs were then recalculated following the exclusion of the dominated or extended dominated strategy. The robustness of the results was tested by applying sensitivity analyses to the costs using an analysis of extremes. The ICERs were recalculated using the lower and upper bounds for screening costs quoted by the Department of Health (Table 6-1).

Table 6-1 Unit costs for cardiovascular screening

	Minimum (£)	Maximum (£)	Base case (£)
Administration	1.0	3.5	2.3
Screening and feedback appointments	9.3	23.3	16.3
Laboratory costs	3.0	6.0	4.5
Total	13.3	32.8	23.1

The assumption is that the unit costs of screening are constant regardless of the screening strategy adopted. Further, the simplifying assumption is 100% engagement across all strategies. The main intention of the analysis is to identify efficient strategies; to identify where in the population the high risk are to ultimately challenge a mass screening approach, as recommended in clinical guidelines and being implemented in England (where engagement and costs assumptions were not sensitised for different population subgroups). The final chapter will return the issue of engagement to explore whether mass screening could increase inequalities.

The overall costs at the level of the Scottish population were then estimated for different screening strategies. The analysis above estimates the percentage of the SHeS 2003 that were at high risk in each of the screening strategies. Holding these percentages constant the corresponding number of people in the 2009 Scottish population - the latest available from the General Registrar's Office for Scotland (GROS) – was estimated.

6.3 Results

Source data: There were 4,082 individuals free of CVD and aged between 40 and 74 years, the eligible population for screening according to the SIGN Guidelines(315). A third of cholesterol readings were missing. Mean imputation was used to estimate these missing values conditional on age, sex and social deprivation stratifications.

Screening strategies – all population: Targeting deprived communities would result in 15% of the total population being screened but would identify 25% of the high-risk population (Table 6-2). To identify one high-risk individual would require 3.0 people to be screened at a cost of £69. Targeting relatives of people who die prematurely from cardiovascular disease would result in 28% of the total population being screened but would identify 43% of the high-risk population (Table 6-3). To identify one high-risk individual would require 3.2 people to be screened at a cost of £75. Combining both strategies would enable 57% of the high-risk population to be identified by screening 39% of the general population. Moving directly from no screening to mass screening would identify all high-risk individuals and would require 4.9 people to be screened to identify one high-risk individual at a cost of £113.

Table 6-2 Coverage, effectiveness and cost-effectiveness of alternative screening strategies applied to the population at risk of any cardiovascular disease (40-74 years of age)

	Targeted screening				Mass screening
	Family members living in deprived communities	Deprived communities	Family members	Family members and deprived communities	
Strategies implemented in isolation*					
Coverage of general population	5%	15%	28%	39%	100%
Coverage of high risk population	10%	25%	43%	57%	100%
% of screened population at high-risk	44%	34%	31%	30%	21%
Number needed to screen	2.3	3.0	3.2	3.3	4.9
Mean cost per high-risk case detected (£)	53	69	75	76	113
Strategies implemented incrementally**					
Additional coverage of general population	5%	-	23%	10%	61%
Additional coverage of high risk population	10%	-	32%	15%	43%
% of additional screened population at high-risk	44%	-	28%	26%	12%
Additional number needed to screen	2.3	3.8	3.5	3.9	8.6
Incremental cost-effectiveness ratio	53 (31, 75)	89 (51, 126)	81 (47, 116)	91 (52, 129)	199 (115, 283)
Revised incremental cost-effectiveness ratio***	53 (31, 75)	dominated	80 (46, 114)	91 (52, 129)	199 (115, 283)

*referent to no screening
**referent to screening strategy directly to the left (no screening for strategy 1)
***referent to the next non-dominated screening strategy to the left (no screening for strategy 1)

Table 6-3 Coverage, effectiveness and cost-effectiveness of alternative screening strategies applied to the population at risk of premature cardiovascular disease (men 40-54 years of age; women 40-64 years of age)

	Targeted screening				Mass screening
	Family members living in deprived communities	Deprived communities	Family members	Family members and deprived communities	
Strategies implemented in isolation*					
Coverage of general population	5%	17%	28%	41%	100%
Coverage of high risk population	23%	45%	61%	84%	100%
% of screened population at high-risk	31%	16%	14%	13%	6%
Number needed to screen	3.3	6.1	7.4	7.8	16.0
Mean cost per high-risk case detected (£)	75	141	170	180	370
Strategies implemented incrementally**					
Additional coverage of general population	5%	-	-	36%	59%
Additional coverage of high risk population	23%	-	-	61%	16%
% of additional screened population at high-risk	31%	-	-	12%	2%
Additional number needed to screen	3.3	8.8	-	8.5	58.8
Incremental cost-effectiveness ratio	75 (43, 107)	203 (117, 289)	225 (130, 321)	196 (113, 278)	1,358 (784, 1931)
Revised incremental cost-effectiveness ratio***	75 (43, 107)	extended dominated	extended dominated	215 (124, 306)	1,358 (784,1,931)

*referent to no screening

**referent to screening strategy directly to the left (no screening for strategy 1)

***referent to the next non-dominated screening strategy to the left (no screening for strategy 1)

In the incremental cost-effectiveness analysis, targeting deprived communities was dominated by targeting family members which was a more effective strategy, requiring fewer additional people to be screened to detect one additional high-risk person. Compared with the most effective targeted strategy (combining family members and deprived communities) the additional cost of expanding coverage to mass screening was £199 for every additional high-risk person identified because an additional 8.6 people needed to be screened.

Screening strategies – population at premature risk: Targeting deprived communities would result in 17% of the total population being screened but would identify 45% of the high-risk population (Table 6-3). To identify one high-risk individual would require 6.1 people to be screened at a cost of £141. Targeting relatives of people who die prematurely from cardiovascular disease would result in 28% of the total population being screened but would identify 61% of the high-risk population (Table 64). To identify one high-risk individual would require 7.4 people to be screened at a cost of £170. Combining both strategies would enable 84% of the high-risk population to be identified by screening only 41% of the general population. Compared with no screening to mass screening would identify all high-risk individuals and would require 16.0 people to be screened to identify one high-risk individual at a cost of £370.

In the incremental cost-effectiveness analysis, a combined strategy of targeting both family members and deprived communities extended dominated either strategy in isolation, because this more effective strategy could be secured for a lower cost per additional high-risk person identified. Compared with combined screening of family members and deprived communities, expanding coverage to mass screening would require an additional 58.8 people to be screened to identify each additional high-risk person at a cost of £1,358. In the 2009 Scottish population this would cost the government an additional £12 million just to detect the additional 16% that are still at high risk.

6.4 Discussion

Mass screening is the best method to ensure complete coverage but the absolute cost may be prohibitive. Using the model, the cost of screening all 1.4 million people aged 40-74 in the 2009 Scotland would have been £33 million.

An alternative approach is to target screening at a sub-group of the population in which cardiovascular risk is over-represented and where there is more opportunity that risk can be reversed. For instance, risk measured over 10 year is driven by age.

If the aim of primary prevention is to identify those at high-risk of premature cardiovascular disease, then a combined strategy that targets both family members and deprived communities is more cost-effective model than either strategy in isolation. The cost-effectiveness of targeted screening is not achieved at the expense of coverage since this combined strategy identifies the vast majority of high-risk people in the general population. That is 84% of the high risk are detected by screening just 41% of the population. Relative to mass screening of the entire population this would save over £18 million for each round of screening, which in SIGN Guidelines recommend is every five years.

Limitations: The SHeS only provided information on parental death from cardiovascular disease. It did not provide information on parental premature, non-fatal disease or premature disease in siblings. Therefore, the analysis is likely to have underestimated the potential coverage of a strategy targeting family members. In the Utah family health tree study, families with a positive family history accounted for 48% of all cardiovascular events and 72% of premature events. In our study the figures were only 43% and 61% respectively(316). Use of more complete information on family history would have reduced still further the additional benefits of mass screening.

The analysis assumed identical unit costs for screening. However, in practice, the costs may be higher in deprived than affluent communities because of poorer uptake requiring more stringent efforts to attract participants into screening appointments. This issue will be revisited in Chapter 9.

Guidelines already exist recommending screening of people with a family history, but surveys suggest that only a minority are, in fact, screened. Identifying people with a family history from the general population is difficult. Using hospitalisation of a patient for premature

cardiovascular disease as the trigger to contact family members may be a more feasible mechanism and may improve the motivation of asymptomatic relatives. To date, there has been only one published study of this type of intervention. Further studies are required to devise effective methods of identifying family members and reducing their cardiovascular risk.

Estimating QALEs and impact on health inequalities: The analysis did not consider the impact of different approaches on either QALE or inequalities. To confidently estimate this would require evidence of engagement success and compliance with subsequent interventions (and how this varies across the population), and the impact of multi-factorial interventions on reducing CVD risk factors. At present, robust evidence of this key information is lacking. To provide a more robust analysis, the focus was on cost per case detected. Consequently, this analysis addresses technical efficiency, rather allocative efficiency issues.

Nonetheless, for the purpose of exposition within this thesis, it is important to illustrate how the model can be used in economic evaluation where cost per QALY is the main output and estimated over a lifetime. Chapter 8 illustrates how the model can be used in economic evaluation to assess Scotland's CVD primary prevention initiative which consists of screening and interventions.

Chapter 7 A new approach to prevention: prioritising individuals on the basis of potential benefit

7.1 Background

There appears to be an important contradiction in the current clinical approach to primary prevention. The ultimate aims of prevention are the avoidance of premature morbidity, mortality and the reduction of health inequalities. However, as Chapter 2 discussed, clinical guidelines currently recommend the use of risk scores to screen individuals 40-74 years and prioritise high risk individuals for targeted interventions. SIGN Guidelines identified ASSIGN 10-year score as the most appropriate risk score for use in Scotland(9). ASSIGN was developed in Scotland and includes socioeconomic deprivation as an independent risk factor which then account for the social gradient in the incidence of CVD.

Prioritising individuals on the basis of CVD risk scores is unlikely to result in the greatest treatment benefits. Risk scores are comprised of a mixture of modifiable and non-modifiable factors. For instance, risk scores over a 10-year period are driven by age, such that the elderly with normal risk factors would be automatically classified as high risk and prioritised for treatment. In contrast, relatively younger individuals with inflated risk factors may not be classified as high risk purely because of age – yet such individuals have potentially more to gain from early intervention.

Further, risk factors are generic to an array of conditions beyond CVD, such as cancers and respiratory diseases. Consequently, it is important when estimating the potential benefit of interventions to account for competing risks and to estimate the impact of interventions on life expectancy. At present, concerns remain that interventions may simply change the cause of death especially in the elderly.

Alternative approaches to 10-year risk scores to prioritise individuals for primary prevention are being explored in the literature. First, there has been recent interest in developing 30-year risk scores(117) or lifetime CVD risk scores(317). However, it is unclear how such approaches directly address the aims of targeted prevention. For instance, the entire population has high lifetime risk of CVD and it is difficult to meaningfully discriminate among individuals(25, 318). Second, Norway has recently developed an approach to primary prevention where individuals are prioritised based upon age-defined risk thresholds(319). Underlying the choice of threshold is the evidenced impact of particular interventions on CVD

death. This is a step in the right direction; however, benefits from risk factor interventions extend beyond CVD mortality. Further, if patient prioritisation is to be based upon expected lifetime benefits then perhaps this should be revealed explicitly rather than indirectly through risk thresholds.

Ideally, the evidence base would be complete and be able to discriminate between individuals on the basis of the likely benefits from intervention in terms of effectiveness and cost effectiveness. However, as Chapter 2 discussed the evidence base is incomplete. There is considerable evidence of the impact of single, in particular pharmaceutical, interventions on CVD events. However, while it is postulated that polypill could reduce ischaemic heart disease by over 80%(34), trial evidence is awaited to observe such benefits [13, 14]. Overall, there is very little economic evidence regarding the impact of multi-factorial initiatives which is the focus of primary prevention at present.

An alternative approach to using 10-year risk tools is to develop a modelling tool that can estimate the potential benefit from changes to risk factors. This chapter uses the policy model to develop an approach to patient prioritisation based on the maximum potential benefit that could be achieved if individuals switched to an optimal risk profile as defined by clinical guidelines. This was measured in terms of discounted life expectancy.

From an economic perspective it would be better if individuals could be prioritised on the basis of cost effectiveness. However, in seeking to use the model to influence clinical practice, it is perhaps prudent to proceed incrementally. A switch from discriminating between patients on the basis of 10 year risk to one of cost effectiveness would represent a significant paradigm shift that may likely incur substantial resistance in the clinical community. Perhaps, in the short (to medium term) a move from risk to potential benefit based on life expectancy would be likely to be accepted, rather than cost effectiveness. A potential benefit approach would nonetheless represent a significant shift in practice, commensurate with Kuhn's view of science and applied applications(320).

7.2 Methods

Source data: The same SHeS 2003 dataset was as in the previous section to identify cost effective screening strategies. In total, 4,082 individuals were aged between 40 and 74 years,

and free of CVD and so represented the eligible population for screening accordingly to the SIGN Guidelines.

The ASSIGN variables were classified into modifiable and non-modifiable risk factors. Systolic blood pressure, total cholesterol, HDL cholesterol and cigarettes per day were defined as modifiable risk factors. Age, sex, diabetes, family history and deprivation were defined as non-modifiable risk factors. The latter was estimated by the Scottish Index of Multiple Deprivation (SIMD).

10-year risk tables and life expectancies estimates: Standard 10-year risk tables(120) were used to define a set of patient risk factor profiles; and, using the Scottish CVD Policy Model, both 10-year risk scores and life expectancy were estimated. Smokers were assumed to smoke 20 cigarettes per day. For exposition purposes, all risk profiles were attributed average family history (0.26) and diabetes (0.15) - the proportions found within the SHHEC baseline survey. Estimates of risk and life expectancy were made for males and females and for the lowest and highest fifths of SIMD; separate tables were also estimated conditional upon smoking status.

Discounted maximum potential benefit: Consistent with the intuition of risk tables, the optimal modifiable risk factor profile is defined as the lowest systolic blood pressure, lowest total-to-HDL cholesterol ratio and non-smoking. A theoretical “maximum potential benefit” was defined as the difference in estimated life expectancy between any given risk factor profile and that of the optimal modifiable profile. It was assumed that all individuals would instantly switch to a perfect profile. This assumption is unrealistic. However, at present there is a lack of research regarding the reversibility of risk (e.g. by age group) and compliance behaviour (e.g. by socioeconomic deprivation status). The modelling is flexible such that estimates can be easily updated with real world evidence of intervention efficacy and effectiveness as and when this becomes available.

Maximum potential benefit was calculated in undiscounted and discounted terms at 3.5% in line with guidance from the NICE and SMC(321). Estimates were made for males and females and for the highest and lowest quintiles of SIMD; separate tables were also estimated conditional upon smoking status.

Patient reprioritisation using a maximum potential benefit approach: The Scottish Health Survey (SHeS) 2003 was used to estimate the impact of a potential benefit approach in a

general population. The number and type of people who would be treated using the ASSIGN 10-year risk score was first estimated. Then, holding the number to be treated constant, the extent of reprioritisation between individuals if there was a switch to a maximum potential benefit approach was estimated. The results are scaled up to the total 2003 Scottish population.

7.3 Results

10-year risk scores: Figures 7-1 and 7-2 shows 10-year risk scores for men and woman residing in highest and lowest deprivation quintiles. Cell values represent risk scores over 10 years. Patients are denoted as high risk if the score is 20% or above (red); intermediate risk when the score is between 10-20% (yellow); and low risk with scores below 10% (green). Profiles towards the top right corner denote the highest systolic blood pressure and total to HDL cholesterol values, resulting in the highest risk. Separate tables are presented conditional upon smoking status. For exposition purposes, rather than have separate tables for diabetic patients and those with family history, patients were attributed the same proportion of diabetes (2%) and family history (26%) found within SHHEC.

Both figures illustrate the age gradient that drives short term CVD risk scores, and men tend to have higher risk score than women for an otherwise equivalent risk factor profile. For the same modifiable risk factor profile, patients are only denoted as high risk in older age groups. We also observe the significant impact of smoking status in increasing risk and reclassifying patients.

Life expectancy estimates: Figures 7-4 and 7-5 illustrates life expectancies for individual risk factor profiles defined by standard 10 year risk tables. Smoking is the single most important risk factor. For instance, the difference in life expectancies between smokers and non-smokers with an otherwise identical risk factor profile is as much as 6 years for females, and 5.2 years for males.

Figure 7-1 ASSIGN 10-year risk charts - Men

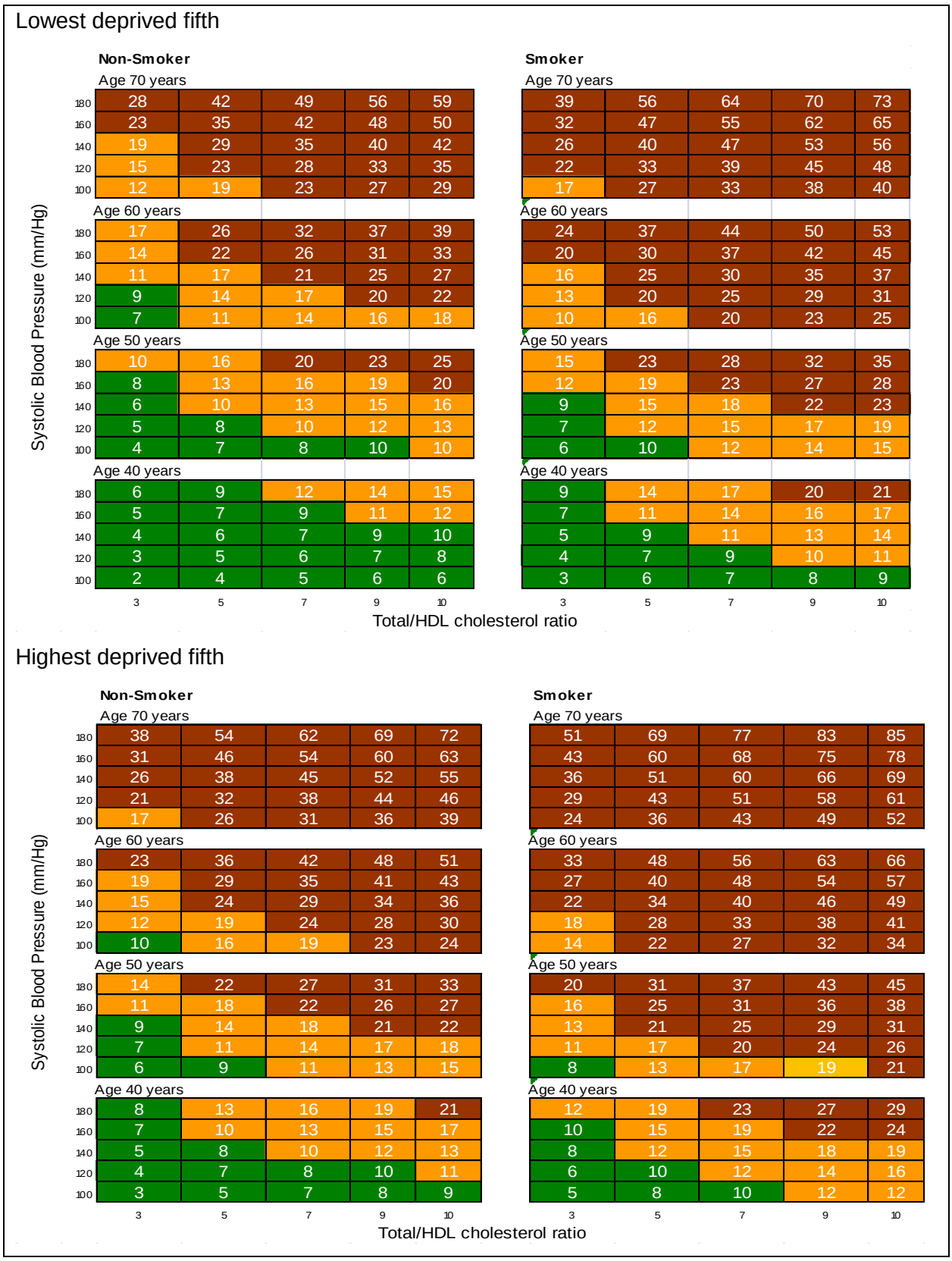


Figure 7-2 ASSIGN 10-year risk charts - women

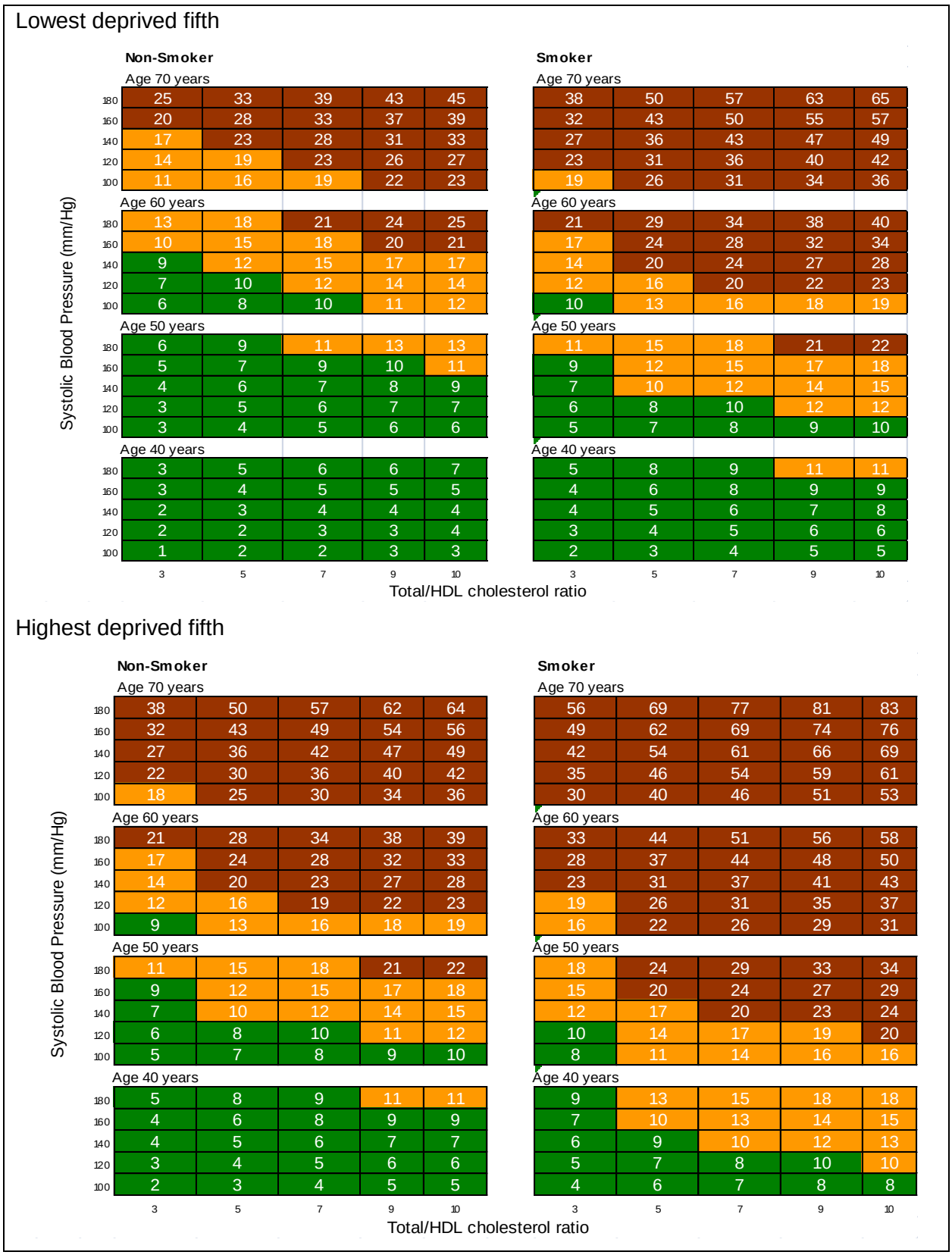
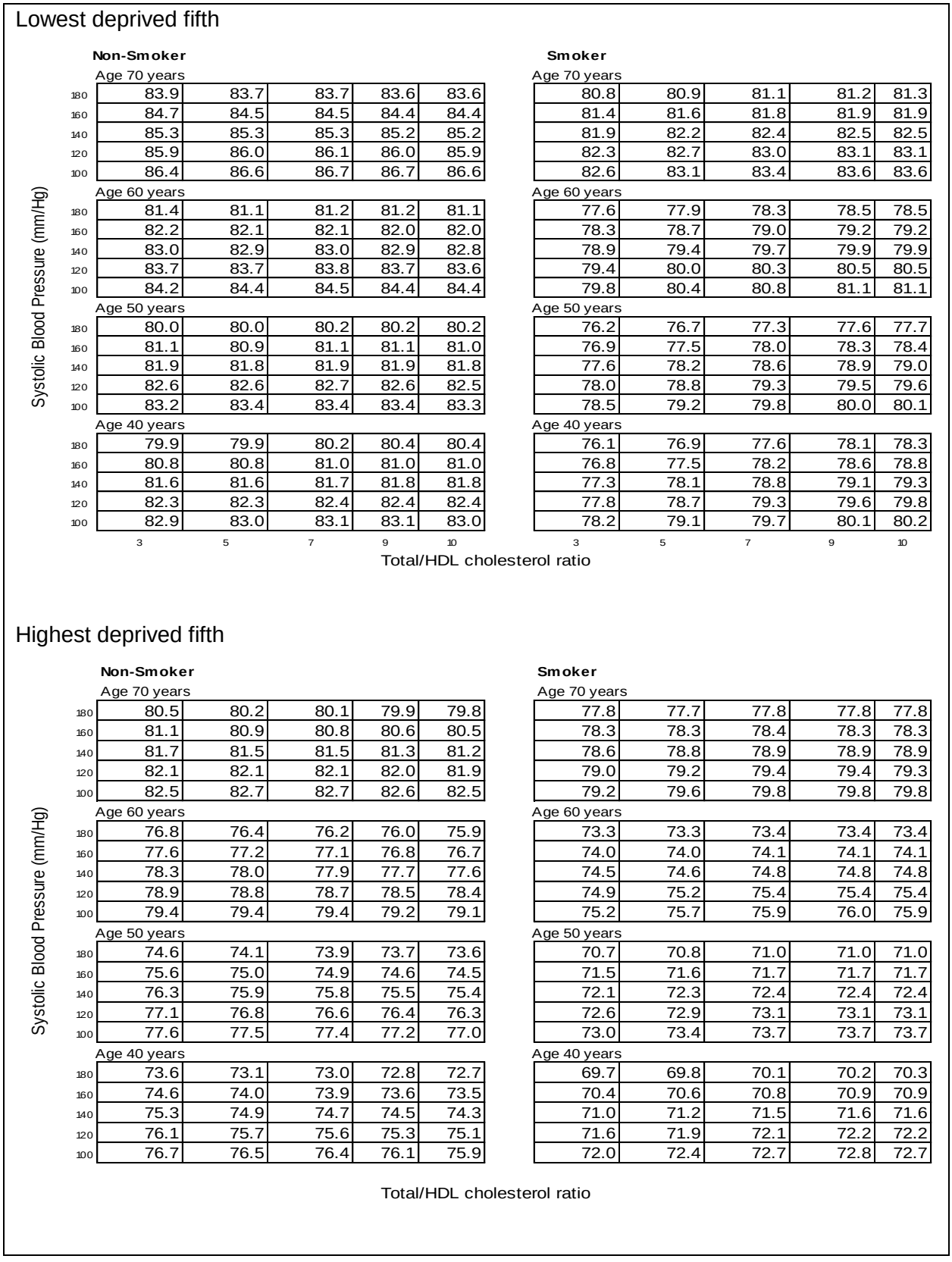


Figure 7-3: Life expectancies - men



Lowest deprived fifth

Non-Smoker

Systolic Blood Pressure (mm/Hg)	3	5	7	9	10
Age 70 years					
180	83.9	83.7	83.7	83.6	83.6
160	84.7	84.5	84.5	84.4	84.4
140	85.3	85.3	85.3	85.2	85.2
120	85.9	86.0	86.1	86.0	85.9
100	86.4	86.6	86.7	86.7	86.6
Age 60 years					
180	81.4	81.1	81.2	81.2	81.1
160	82.2	82.1	82.1	82.0	82.0
140	83.0	82.9	83.0	82.9	82.8
120	83.7	83.7	83.8	83.7	83.6
100	84.2	84.4	84.5	84.4	84.4
Age 50 years					
180	80.0	80.0	80.2	80.2	80.2
160	81.1	80.9	81.1	81.1	81.0
140	81.9	81.8	81.9	81.9	81.8
120	82.6	82.6	82.7	82.6	82.5
100	83.2	83.4	83.4	83.4	83.3
Age 40 years					
180	79.9	79.9	80.2	80.4	80.4
160	80.8	80.8	81.0	81.0	81.0
140	81.6	81.6	81.7	81.8	81.8
120	82.3	82.3	82.4	82.4	82.4
100	82.9	83.0	83.1	83.1	83.0

Smoker

3	5	7	9	10
Age 70 years				
80.8	80.9	81.1	81.2	81.3
81.4	81.6	81.8	81.9	81.9
81.9	82.2	82.4	82.5	82.5
82.3	82.7	83.0	83.1	83.1
82.6	83.1	83.4	83.6	83.6
Age 60 years				
77.6	77.9	78.3	78.5	78.5
78.3	78.7	79.0	79.2	79.2
78.9	79.4	79.7	79.9	79.9
79.4	80.0	80.3	80.5	80.5
79.8	80.4	80.8	81.1	81.1
Age 50 years				
76.2	76.7	77.3	77.6	77.7
76.9	77.5	78.0	78.3	78.4
77.6	78.2	78.6	78.9	79.0
78.0	78.8	79.3	79.5	79.6
78.5	79.2	79.8	80.0	80.1
Age 40 years				
76.1	76.9	77.6	78.1	78.3
76.8	77.5	78.2	78.6	78.8
77.3	78.1	78.8	79.1	79.3
77.8	78.7	79.3	79.6	79.8
78.2	79.1	79.7	80.1	80.2

Total/HDL cholesterol ratio

Highest deprived fifth

Non-Smoker

Systolic Blood Pressure (mm/Hg)	3	5	7	9	10
Age 70 years					
180	80.5	80.2	80.1	79.9	79.8
160	81.1	80.9	80.8	80.6	80.5
140	81.7	81.5	81.5	81.3	81.2
120	82.1	82.1	82.1	82.0	81.9
100	82.5	82.7	82.7	82.6	82.5
Age 60 years					
180	76.8	76.4	76.2	76.0	75.9
160	77.6	77.2	77.1	76.8	76.7
140	78.3	78.0	77.9	77.7	77.6
120	78.9	78.8	78.7	78.5	78.4
100	79.4	79.4	79.4	79.2	79.1
Age 50 years					
180	74.6	74.1	73.9	73.7	73.6
160	75.6	75.0	74.9	74.6	74.5
140	76.3	75.9	75.8	75.5	75.4
120	77.1	76.8	76.6	76.4	76.3
100	77.6	77.5	77.4	77.2	77.0
Age 40 years					
180	73.6	73.1	73.0	72.8	72.7
160	74.6	74.0	73.9	73.6	73.5
140	75.3	74.9	74.7	74.5	74.3
120	76.1	75.7	75.6	75.3	75.1
100	76.7	76.5	76.4	76.1	75.9

Smoker

3	5	7	9	10
Age 70 years				
77.8	77.7	77.8	77.8	77.8
78.3	78.3	78.4	78.3	78.3
78.6	78.8	78.9	78.9	78.9
79.0	79.2	79.4	79.4	79.3
79.2	79.6	79.8	79.8	79.8
Age 60 years				
73.3	73.3	73.4	73.4	73.4
74.0	74.0	74.1	74.1	74.1
74.5	74.6	74.8	74.8	74.8
74.9	75.2	75.4	75.4	75.4
75.2	75.7	75.9	76.0	75.9
Age 50 years				
70.7	70.8	71.0	71.0	71.0
71.5	71.6	71.7	71.7	71.7
72.1	72.3	72.4	72.4	72.4
72.6	72.9	73.1	73.1	73.1
73.0	73.4	73.7	73.7	73.7
Age 40 years				
69.7	69.8	70.1	70.2	70.3
70.4	70.6	70.8	70.9	70.9
71.0	71.2	71.5	71.6	71.6
71.6	71.9	72.1	72.2	72.2
72.0	72.4	72.7	72.8	72.7

Total/HDL cholesterol ratio

Figure 7-4 Life expectancies - Women

Lowest deprived fifth

Non-Smoker

Systolic BP (mm/Hg)	3	5	7	9	10
Age 70 years					
180	85.5	85.3	85.1	85.1	85.0
160	86.6	86.4	86.1	86.1	86.0
140	87.6	87.4	87.2	87.1	87.0
120	88.6	88.5	88.2	88.0	88.0
100	89.6	89.4	89.1	88.9	88.9
Age 60 years					
180	82.8	82.7	82.5	82.4	82.4
160	84.0	83.9	83.7	83.5	83.5
140	85.2	85.1	84.8	84.6	84.5
120	86.3	86.2	85.7	85.6	85.5
100	87.3	87.1	86.8	86.5	86.5
Age 50 years					
180	81.2	81.2	81.0	81.0	81.0
160	82.5	82.4	82.2	82.1	82.1
140	83.7	83.5	83.3	83.1	83.1
120	84.8	84.6	84.3	84.1	84.0
100	85.8	85.7	85.2	85.0	85.0
Age 40 years					
180	80.4	80.4	80.3	80.3	80.4
160	81.6	81.6	81.4	81.3	81.4
140	82.8	82.7	82.4	82.3	82.3
120	83.8	83.7	83.4	83.2	83.1
100	84.9	84.6	84.3	84.1	84.0

Smoker

Systolic BP (mm/Hg)	3	5	7	9	10
Age 70 years					
180	81.1	81.2	81.2	81.3	81.3
160	82.0	82.1	82.2	82.2	82.2
140	82.9	83.0	83.0	83.1	83.1
120	83.8	83.9	83.9	83.9	83.9
100	84.5	84.8	84.7	84.7	84.7
Age 60 years					
180	77.7	77.9	78.0	78.1	78.2
160	78.8	79.0	79.1	79.1	79.2
140	79.8	80.1	80.1	80.2	80.2
120	80.8	81.1	81.1	81.1	81.2
100	81.7	82.0	81.9	82.0	82.0
Age 50 years					
180	75.8	76.1	76.3	76.5	76.6
160	76.9	77.4	77.4	77.6	77.7
140	78.1	78.4	78.5	78.6	78.7
120	79.1	79.4	79.5	79.5	79.6
100	80.0	80.4	80.4	80.5	80.5
Age 40 years					
180	74.9	75.4	75.7	76.0	76.1
160	76.1	76.6	76.8	77.1	77.2
140	77.2	77.7	77.8	78.1	78.1
120	78.1	78.7	78.7	78.9	79.0
100	79.1	79.6	79.6	79.7	79.8

Systolic Blood Pressure (mm/Hg)

Total/HDL cholesterol ratio

Highest deprived fifth

Non-Smoker

Systolic BP (mm/Hg)	3	5	7	9	10
Age 70 years					
180	83.0	82.9	82.7	82.6	82.6
160	83.9	83.8	83.5	83.4	83.3
140	84.8	84.6	84.3	84.2	84.1
120	85.6	85.4	85.1	85.0	84.9
100	86.4	86.2	85.9	85.7	85.6
Age 60 years					
180	79.9	79.7	79.5	79.4	79.3
160	80.9	80.7	80.4	80.2	80.2
140	81.8	81.6	81.3	81.1	81.0
120	82.7	82.5	82.2	82.0	81.8
100	83.7	83.4	83.0	82.7	82.7
Age 50 years					
180	77.9	77.8	77.6	77.5	77.5
160	79.0	78.7	78.5	78.3	78.3
140	80.0	79.7	79.4	79.2	79.1
120	80.9	80.6	80.3	80.0	79.9
100	81.8	81.5	81.0	80.8	80.7
Age 40 years					
180	76.9	76.8	76.6	76.5	76.5
160	77.9	77.7	77.4	77.3	77.2
140	78.8	78.6	78.3	78.1	78.0
120	79.7	79.4	79.1	78.8	78.8
100	80.6	80.3	79.8	79.6	79.5

Smoker

Systolic BP (mm/Hg)	3	5	7	9	10
Age 70 years					
180	79.4	79.5	79.5	79.5	79.6
160	80.1	80.2	80.2	80.2	80.2
140	80.8	80.9	80.8	80.9	80.9
120	81.5	81.6	81.5	81.5	81.5
100	82.1	82.2	82.1	82.1	82.1
Age 60 years					
180	75.5	75.7	75.7	75.8	75.8
160	76.4	76.5	76.5	76.6	76.6
140	77.1	77.3	77.3	77.3	77.3
120	77.9	78.1	78.0	78.0	78.1
100	78.7	78.9	78.8	78.7	78.8
Age 50 years					
180	73.1	73.4	73.6	73.7	73.7
160	74.0	74.4	74.4	74.5	74.5
140	74.9	75.2	75.2	75.3	75.3
120	75.8	76.0	76.0	76.0	76.0
100	76.5	76.8	76.7	76.7	76.8
Age 40 years					
180	72.0	72.4	72.6	72.9	72.9
160	72.9	73.3	73.5	73.6	73.7
140	73.8	74.1	74.2	74.4	74.4
120	74.5	74.9	74.9	75.0	75.1
100	75.3	75.7	75.6	75.7	75.8

Systolic Blood Pressure (mm/Hg)

Total/HDL cholesterol ratio

Discounted maximum potential benefit: Figures 7-5 and 7-6 illustrates the maximum potential benefit from changes to modifiable risk factors. To reiterate, the assumption is to take modifiable risk profiles for individuals (stratified by age) to the bottom left hand corner of the non-smoking tables. Individuals are then assumed to acquire to the life expectancy of that profile. Almost everyone can benefit from primary prevention. Discounting results in benefits to older age groups being valued more highly than otherwise equivalent risk factor profiles in younger groups. Females typically gain the most across all risk factor profiles.

Figure 7-5 Discounted maximum potential benefit - males

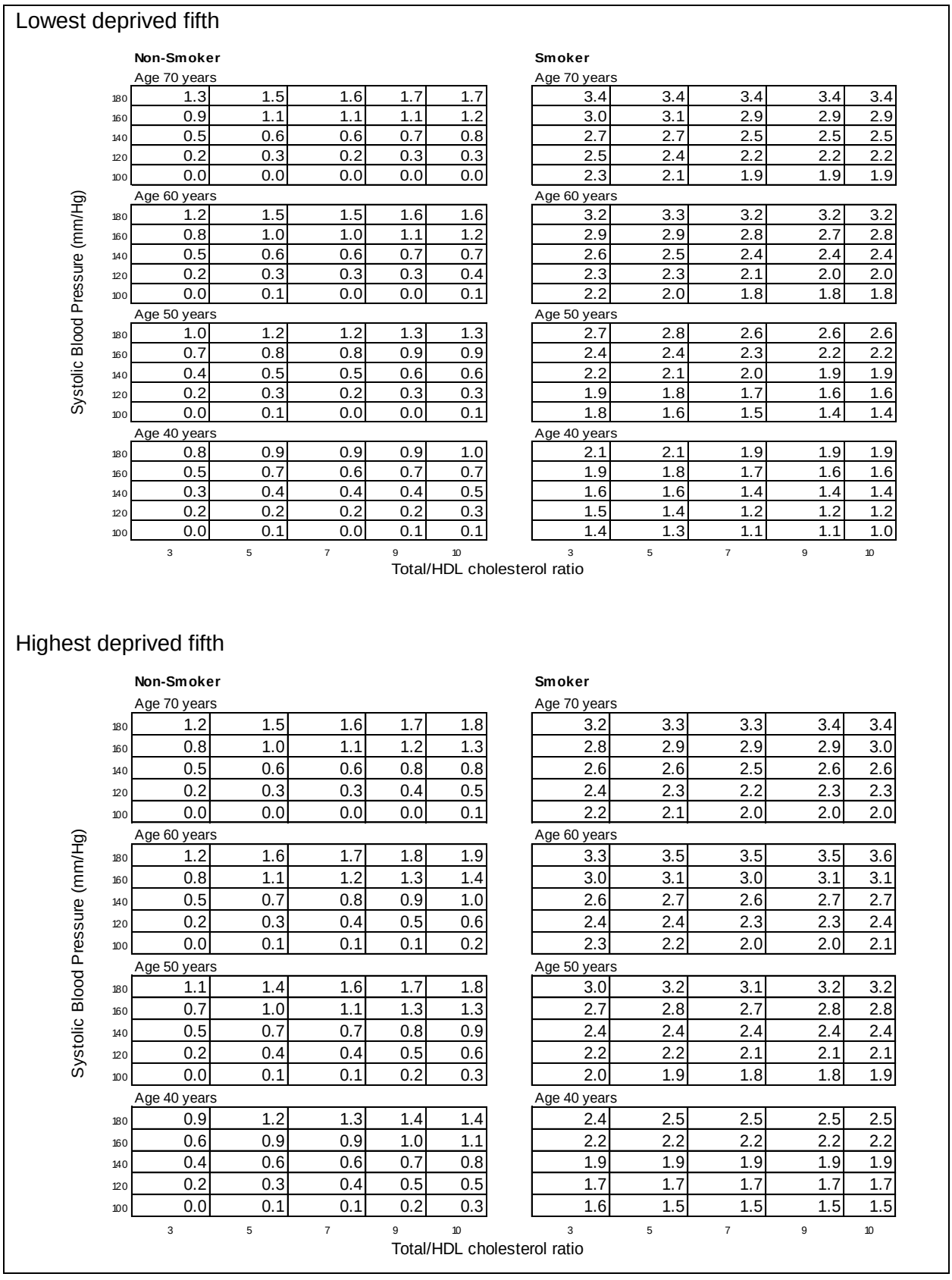
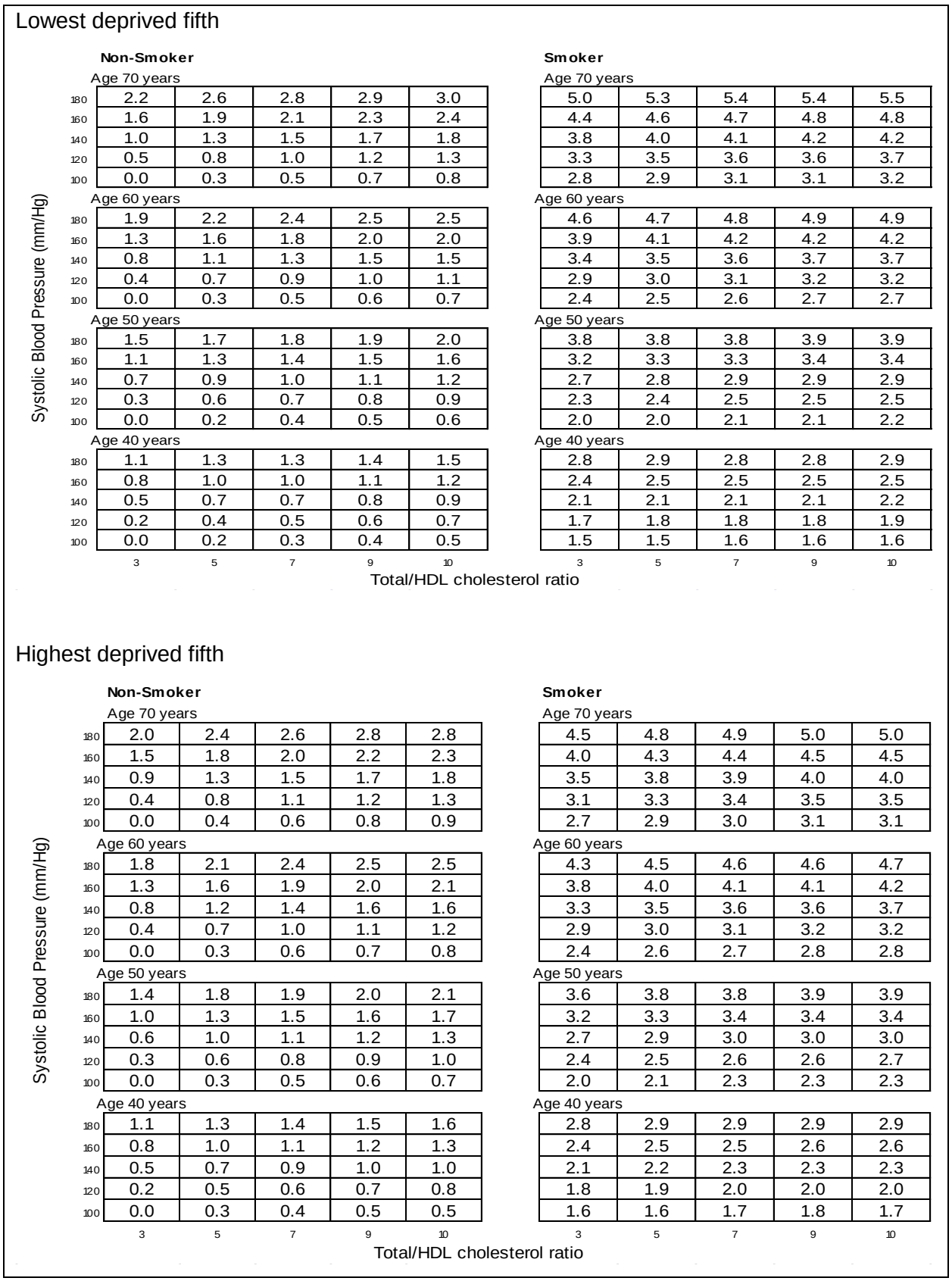


Figure 7-6 Discounted maximum potential benefit - females



Implications for patient reprioritisation using a maximum potential benefit approach: Table 7-1 compares which individuals would be given priority for primary prevention by moving from the ASSIGN 10-year risk score to a maximum potential benefit approach. This is dependent on the distribution of risk in the population. Following reprioritisation there would be a focus on females, younger individuals, more deprived groups and smokers.

The key determinant in prioritising individuals was smoking behaviour. Prevalence is higher in these groups. For instance, the prevalence of smokers in the SHeS 2003 was 31% in 40-49 year olds, compared to 17% in the over 70 year olds; and 14% in the lowest deprivation fifth compared to 45% in the higher deprivation fifth.

Table 7-1 Patient prioritisation: comparing the ASSIGN 10-year risk score with a maximum potential benefit approach

			ASSIGN score	Maximum benefit
Gender	Males		58.7	39.2
	Females		41.3	60.8
Age group	40-49		1.2	29.5
	50-59		17.0	34.0
	60-69		49.0	26.8
	70-74		31.9	9.6
Fifths of population (SHeS 2003)	Least deprived	1	14.0	11.6
		2	17.2	16.3
		3	20.2	19.4
		4	22.2	24.3
	Most deprived	5	26.4	28.4
Smoking status	Smokers		36.3	90.5
	Non-smokers		63.7	9.5

Population impact from re-prioritisation: Table 7-2 illustrates the maximum potential gains and losses in life years resulting from the switch in prioritisation method – from holding the number to be treated constant. Under a maximum potential benefit approach, it is estimated that a net gain of 1.5 million additional life years could have been achieved across the lifetime of the 2009 Scottish population. However, since different groups are reprioritised the gains and losses vary between subgroups. The magnitude of the potential gain in life years increases with deprivation quintile and age. Notably, the potential gains for the 40-59 year olds is 1.7 million years, in contrast to the 60-74 year olds which lose a total of 110,000 years.

Table 7-2 Expected additional life years from a switch to a potential to benefit approach in the Scottish general population

		Expected additional life years (000s)		
		ASSIGN	Potential to benefit	Change
Total Population		65,746	67,296	1,551
Gender	Males	29,926	30,489	562
	Females	35,819	36,808	988
Age Group	40-49	30,337	31,455	1,118
	50-59	19,792	20,335	543
	60-69	12,152	12,127	-26
	70-74	3,464	3,380	-84
SIMD 2004 quintile	1 (least)	12,078	12,213	135
	2	12,840	13,038	198
	3	13,524	13,837	313
	4	14,359	14,740	381
	5 (most)	12,945	13,468	523
Smoking status	Smokers	18,014	19,736	1,722
	Non-smokers	47,731	47,560	-171

7.4 Discussion

A potential benefit approach: The avoidance of premature mortality and the reduction of health inequalities are key aims of primary prevention. Conventional approaches of prioritising individuals solely on the basis of CVD risk scores, which is composed of modifiable and non-modifiable factors, is unlikely to elicit the greatest gains from prevention activities. Rather, prioritisation according to the potential benefit in terms of extended life expectancy may be more aligned with the ultimate aims of prevention.

The policy model was used to describe a modelling approach which can transparently estimate the potential benefits from changes to modifiable risk factors in terms of additional life expectancy. Currently, the evidence base is incomplete regarding the reversibility of risk factors and how this may differ by age, gender and deprivation status. Consequently, a potential benefit approach was illustrated by assuming modifiable risk to be completely reversible, and consequently termed a maximum potential benefit approach.

For equivalent risk profiles, older age groups have potentially the most to gain in discounted life years than younger individuals with equivalent risk factor profiles. This is a similar finding as 10-year risk tables. However, 10-year risk is driven by age, whereas a potential benefit approach is driven by modifiable risk factors. Therefore, the actual population impact if there was a switch from prioritisation based upon 10-year risk to a maximum potential benefit approach would dependent on the distribution of modifiable risk factors across the population.

In the simulated within the SHeS, a switch to a potential benefit approach would result in a focus on younger individuals, females, smokers and deprived groups.

Strengths and weakness: A key strength of the modelling framework is that it makes explicit weaknesses in the evidence base regarding the reversibility of risk and how this may differ between individuals. These potential benefit estimates can be adjusted based upon evidence of intervention efficacy and effectiveness, including intervention engagement and compliance estimates. Further, the model can formalise and make explicit equity judgements by weighting an extra year of life in particular groups, if appropriate.

These results are largely consistent with current health policy aims. In terms of population-wide interventions, for instance, there is a drive towards reducing smoking prevalence (e.g. legislation banning indoor smoking in enclosed public spaces) and general lifestyle advice is increasingly extended to younger age groups14-16). The model predictions have only been validated on individuals 40 year and above. However, the direction of using the model to make the case for prevention in younger age groups is fairly clear.

Further, prevention programmes often have the reduction of health inequalities as a key aim. The value added of formalising a potential benefit approach is the ability to make explicit the additional life expectancy from interventions, permitting more focussed targeting, if required.

Within the analysis socioeconomic deprivation status was defined as a non-modifiable risk factor. This was for exposition purposes, and there is a vibrant policy and research movement regarding the wider determinants of health, such as changing the key variables that defined socioeconomic deprivation status such as income and employment(85). However, at present there is no direct evidence linking such interventions and consequent changes in risk factors. In principle, the model can incorporate such evidence if available.

Further research: If an approach to prevention was to be based upon potential benefit rather than 10-year risk scores then several research areas are required to be addressed. Key among these is the reversibility of risk factors and equity implications regarding whether the additions to life expectancy should be valued more highly for certain groups than others. Indeed these areas are important to address regardless of which approach to primary prevention is adopted. The model makes such research gaps more explicit.

It is important to test whether the associations between risk factors and life expectancies are causal (Chapter 4). Total cholesterol was found to be protective of non-CVD mortality, consistent with findings elsewhere(322-323). However, it was decided to hold constant the impact of changes of total cholesterol constant when estimating non-CVD death, on the assumption that there is no causal relationship. Further research could usefully unpack the non-CVD event category within the model to investigate the impact of risk factor changes on specific conditions.

A multi-factorial approach to treatment is currently recommended by clinical guidelines. If this approach continued under a potential benefit approach then smokers would receive priority, including non-smoking interventions. This may be an emotive issue and is a decision for clinical guidelines. That said, it may be no more controversial that current skew in prioritisation towards the elderly using 10-year scores. Further, the policy model is very flexible and, for instance, can easily remove smoking as a covariate in the prioritisation of non-smoking interventions.

Finally, reimbursement agencies such as NICE, recommend that cost effectiveness evidence is used to evaluate new interventions and to make reimbursement decisions. For primary prevention to be consistent with such policy guidelines, it has been argued that clinical guidelines should recommend that individuals also be prioritised on the basis of cost effectiveness evidence, and not risk thresholds(25).

As was shown in Chapter 5, it is straightforward to extend quality adjusting life expectancy estimates and estimating the impact on lifetime health service costs, net of intervention costs. Therefore, there is a direct link between the flexible model structure presented here and the sort of cost-effectiveness models used by policymakers.

It is important to reiterate that the starting point for the application of the model was the current practice of focussing targeted prevention on those aged 40-74 years. The chapter did not challenge the age at which individuals were to be screened or treated; but rather the basis upon which individuals are subsequently prioritised for intervention. The rationale was to build upon current practice, rather than necessary suggest a full scale ‘paradigm shift’.

However, as discussed in Chapter 2 the onset of risk begins at a far earlier age in Scotland; and in the West of Scotland in particular. It was shown that risk behaviours and elevated risk factors cluster from 16 years or younger(86). This suggests that prevention should be

increasingly widening its focus to primordial prevention, to prevent the onset of risk behaviours. Taking a lifecourse perspective to prevention(324), would necessarily entail focussing on the social drivers of health behaviours, and brining the importance of upstream public health and social interventions into focus(325). To date, the effectiveness and economic evidence of such interventions to prevent early onset of risk behaviours is relatively limited(86, 325-326). Nonetheless, the Scottish government is investing heavily in early years prevention(18) and in an attempt to close health and social inequalities in general(326-327). The implication for the Scottish CVD Policy Model would be to extend the focus to younger individuals. The challenge is that data on the ASSIGN risk factors in young adults is not routinely available to model the relationship between risk factors and event in this group. The SHHEC-SMR dataset used to estimate model equations was a cohort aged 30-74 years. However, assumptions could be made to extend the model to these age groups, although appropriate validation checks would need to be undertaken in bespoke surveys and recalibration undertaken if required. An exercise of this kind has been attempted elsewhere(108).

Summary: Overall, the Chapter has attempted to illustrate that the policy model could be used to develop a new clinical tool to replace 10-year risk scores in screening and prioritising individuals for intervention on the basis of potential gains in life expectancy. The model framework can be updated conditional on evidence of reversibility of risk, effectiveness of treatment (including compliance) and equity judgements. Overall, prioritising individuals on the basis of potential benefit, rather than risk, appear to provide greater congruence with the ultimate aims of primary prevention which is the avoidance of premature mortality, morbidity and the reduction of health inequalities.

Chapter 8 Economic evaluation of Scotland's primary prevention programme

8.1 Background

Keep Well is a CVD primary prevention initiative funded by NHS Scotland(12). The programme is intended to identify asymptomatic individuals at high risk of premature CVD to be prioritised for subsequent intervention. The programme targets 45-64 year olds living in the 15% most deprived communities in Scotland, identified by the Scottish Index of Multiple Deprivation (SIMD) – an area based measure of socioeconomic deprivation.

The programme was launched in 2007 within the Health Board areas of Greater Glasgow and Clyde (GGC) as a pilot. It has been subsequently rolled out nationally, in the absence of evaluative evidence, and its coverage now extends to all eligible areas within Scotland.

The Keep Well programme is comprised of a sequence of stages, including the initial engagement individuals, clinical screening using the ASSIGN risk tool to identify those at high risk of an event over the next 10 years, and the offering of medication and behavioural interventions for those at high risk.

GCC and Scottish Government intend to undertake an economic evaluation of the programme for Glasgow North and East, the first two administrative areas within GGC to begin Keep Well. In principle, this provides an opportunity to use the Scottish CVD Policy Model to estimate the long term cost effectiveness of the programme.

However, there are major constraints. The programme pilot in 2007 was not set up in an experimental manner to test effectiveness or cost effectiveness. In particular, re-screening data for individuals who have completed the programme of intervention have not been made available. Further, there is no control group. This limited the ability to undertake a comprehensive economic evaluation. Rather, the baseline data of individual ASSIGN risk factors is used, and the literature is drawn upon to develop estimates of effectiveness and project the potential cost effectiveness of Keep Well.

Given the severe limitations of the data currently available, key aims of the analysis were to: (i) make clear to policymakers the considerable uncertainty regarding the impact of Keep Well and need to conduct a rigorous evaluation, including following up patients regarding

rescreening and intervention compliance; and (ii) demonstrating the ease at which the policy model can be used to project trial findings if an evaluation was conducted.

The communication of how the policy model works and outputs generated is important. The policy audience that was recipient of the following work was not familiar with methods of health economic evaluation or models of this type. Therefore, a key aim was to communicate the methods used and findings as transparently and simply as possible. This influenced the methods used, especially the sensitivity analysis undertaken. Nonetheless, the analysis is intended to be as rigorous as the data allows.

8.2 Methods

Source data

GGC provided a dataset for the Keep Well programme which was called the Tracking Tool. This covered Glasgow North and Glasgow East. The dataset spanned an 18 month period, beginning in December 2006 and ending in August 2008. The dataset included the eligible asymptomatic population for Keep Well, baseline screening data for individuals who had been successfully contacted, the ASSIGN variables and 10 year risk scores for each individual, and tracked the medications prescribe and referrals to service interventions that were made.

Engagement and screening:

The tracking tool recorded the engagement success of the programme in attracting the eligible population for screening. Engagement was conducted mainly through GP practices contacting individuals between 45 and 64 years through a combination of telephone and letters.

Keep Well programme interventions:

Once high risk individuals are identified they are offered a range of medications and behavioural change interventions. Table 1 lists the interventions that could be offered. Medications included statins and anti-hypertensives. The behavioural interventions were very wide ranging; amongst the most prominent were (i) a health counsellor offering quarterly advice over the period of a year on exercise and diet; (ii) a 12 week group intervention to stop smoking; (iii) a three-month individualised alcohol counselling for heavy drinkers; and (iv), various mental health interventions (including massage), (v) social welfare intervention, such as advice regarding benefit entitlements; and (vi) an intervention to improve literacy levels. Individuals were also tracked to assess whether they completed the behavioural

interventions. It was not known whether individuals collected and/or took medications prescribed.

Absence of follow-up data or a control group:
There was a substantial amount of missing information that inhibited the conduct of a rigorous economic evaluation. This extended to missing data regarding whether individuals completed their referrals to behavioural interventions; the compliance behaviour with medication and re-screening data to detect changes in risk factors.

Further, no control group was to infer a counterfactual (risk factor changes under usual routine care) in order to attribute observed changes in CVD risk to the Keep Well programme. These are serious omissions. Therefore, there was no formal trial or rigorous evaluation. Consequently, it was unknown to what extent ASSIGN risk factors had changed and what could be attributed to the intervention group.

Assumptions of impact:
The impact of Keep Well was estimated by projecting the likely change in ASSIGN CVD risk factors from an individual who received the interventions. First, individuals referred to interventions were identified. For pharmaceuticals there was information regarding prescriptions received over the entire 18 month period. For individuals referred to behavioural interventions, the impact of these referrals was only estimate if individuals completed the entire intervention course (e.g. competed a full counselling programme regarding diet and physical activity). Once individuals were identified, the estimation of impact was developed in three stages:

(i) Efficacy evidence: Efficacy evidence was taken from the national SIGN Guidelines (on CVD), which was the result of various systematic reviews and expert clinical opinion. This evidence was summarised in Chapter 2.

Keep Well interventions were only included in the modelling if there was sufficient evidence of similar interventions as judged by SIGN Guidelines(9). There was strong evidence for pharmaceuticals and to a lesser extent (given absence of RCTs) for lifestyle advice. There was no evidence for the other interventions impact on CVD outcomes, and were consequently excluded.

The impact of alcohol was excluded. While there is evidence of the impact of alcohol consumption on systolic blood pressure, there wasn't adequate information on alcohol consumption in the Keep Well dataset. In any case, the number of individuals referred to this intervention to reduce alcohol consumption was very small (less than 40).

Finally, to adjust for the possible side effects of medications, such as intolerance, quality of life from individuals taking medication by weight survival by 0.9875 is taken, as used in a Dutch economic model(248).

(ii) Adjusted for compliance - effectiveness: To generate estimates of effectiveness, efficacy evidence was weighted by the long term compliance behaviour of individuals. The evidence base regarding compliance is poor, especially regarding the compliance behaviour of individuals from deprived backgrounds. Rather, an assumption of compliance was generated. Access to research conducted by GCC on compliance behaviour by secondary prevention patients was provided. This was a 2-year study that tracked the percentage of patients who regularly collected the prescriptions made by GPs. It was assumed that if prescriptions were pick-up then they were also taken correctly, which is optimistic. To then generate compliance estimates for primary patients, a study which measured the average compliance rates between secondary and primary patients who were prescribed statins was used. This provided a ratio that was applied to the Glasgow study of secondary individuals. All individuals in the Keep Well dataset were assumed to have the same compliance behaviour. With agreement from Keep Well programme management the same compliance estimates were applied to all interventions including behavioural, but with the exception of smoking. To estimate compliance regarding smoking quit rates, a previous study conducted in Glasgow was drawn upon, where the long term rate was estimated to 5.5%(169).

(iii) Multiplicative interactions: It is largely unknown how risk factor interventions combine. The strongest evidence is regards single interventions. It was assumed that interventions combined multiplicatively.

(iv) Adjusting for usual care: Finally, it is vital to estimate a counterfactual so that any changes in risk factors observed in Keep Well patient can be attributed to the programme. However, to reiterate there was no control group. As a consequence, it was estimated what proportion of the Keep Well patients would have received in routine care, in the absence of the programme. Estimates made by England's Department for Health (DoH) Vascular

Screening Checks initiative was used(180). To reiterate, was a document that underpinned the roll-out of a population CVD screening initiative that began in 2009.

Overall, the model was used to estimate the effectiveness of medications, the health counsellor and smoking group therapy on the Keep Well population.

Costs: Unit costs were not available, but rather GGC provided annual budgets that were allocated to each of the key stages of the programme, including engagement, screening, and the interventions. Further, budgets for the management and administration of the programme, and the costs of the IT system used to track individuals through the programme.

Budgets were provided for two years. Given, the evaluation period was over 18 months, monthly costs were estimated on a pro-rata basis provides estimates for the 18 month period. It was assumed that all budgets had been spent.

Finally, a cost per patient was estimated by dividing the total number of patient screened by the total costs of the Keep Programme.

Cost effectiveness: Individual risk profiles were run through the CVD Policy Model to estimate baseline hospital costs and QALYs in the absence of the Keep Well intervention. Using the Tracking Tool (which tracked which interventions were received) the effectiveness estimates were applied to relevant individual and the model re-estimated hospital costs and QALYs. The impact on health service costs is net of the cost of Keep Well. All estimates were discounted at 3.5%. Finally, an incremental cost effectiveness ratio (ICER) was calculated by estimating the differences in costs and dividing this by the differences is QALYs.

Sensitivity analysis: There is clearly considerable uncertainty. The sensitivity analysis adopted an analysis of extremes, where the expected, worst case and best case scenarios were estimated. This approach takes the mean, and upper and lower confidence intervals of the intervention effect and divides each by the costs of the programme.

8.3 Results

Source data: Table 8-1 outlines the screened population for Glasgow North and East. There were 15,258 individuals eligible for the programme, and 8,495 patients screened in the period

between November 2007 and August 2009. This represents engagement success of 56%. The average age was 54 years and there was a higher proportion of woman (55%). Notably, smoking prevalence was very high, and average total cholesterol was in excess of 6 mmHg across both genders.

Table 8-1 Keep Well population

	Men	Women
Cohort size (total / %)	3,835 (45.1%)	4,660 (54.9%)
Age	54.4 (6.0)	54.5 (5.8)
Systolic blood pressure	134.9 (18.1)	130.1 (18.4)
Total cholesterol	6.0 (1.5)	6.1(1.5)
HDL cholesterol	1.3 (0.3)	1.5 (0.6)
Smokers (%)	42.2	40.9
Cigarettes per day	23.2 (9.2)	17.5 (8.7)
Family history (%)	29.5	34.6

Evidence of efficacy: Table 8-2 details the efficacy evidence used and refers to the impact that interventions have on reducing modifiable risk factors if individuals were fully compliant. Obviously, for the smoking intervention the impact was be a 100% quit rate. The mean, minimum and maximum impacts are shown - where taken from the confidence intervals of relevant studies. For statins, SIGN Guidelines reported the percentage change in cholesterol readings; whereas evidence of the impact of other interventions was based on absolute reductions in risk factor levels.

Table 8-2 Intervention efficacy estimates

	Statins	Anti-hypertensives	Health counsellor
Systolic blood pressure			
min	-	-8.3	-2.7
expected	-	-8.8	-3.8
max	-	-9.4	-5
Total cholesterol			
min	-16%	-	-0.49
expected	-20%	-	-0.79
max	-24%	-	-1.09
HDL Cholesterol			
min	4%	-	0.16
expected	5%	-	0.21
max	6%	-	0.25

Evidence of effectiveness: The Glasgow study of secondary prevention patients found that compliance after two years was 30% on average, with a lower estimate of 18% and an upper estimate of 37%. The efficacy estimates were then rescaled by using the ratio of compliance behaviour between primary and secondary patients, which was found to be 0.76. This gave a mean estimate of compliance in primary patients of 18%, with a lower limit of 8% and an upper limit of 37%. Finally, a study in Glasgow estimated that the long term quit rates for those engaging with the smoking intervention was 5.5%(169). An arbitrary lower and upper bound was then given of 4.5 and 6.5% respectively. These estimates were applied the efficacy evidence (Table 8-3).

Table 8-3 Effectiveness estimates - adjusted for compliance

	Statins	Anti-hypertensives	Health counsellor
Systolic blood pressure			
min	-	-0.681	-0.222
expected	-	-1.605	-0.693
max	-	-3.459	-0.912
Total cholesterol			
min	-0.013	-	-0.040
expected	-0.036	-	-0.144
max	-0.088	-	-0.401
HDL Cholesterol			
min	0.003	-	0.013
expected	0.009	-	0.038
max	0.022	-	0.092

Attribution: The effectiveness estimates were adjusted to take into account what was likely to have taken place anyway under routine care (Table 8-4). The DoH estimated that 80% of anti-hypertensives and 50% of statins would have been prescribed in the absence of Keep Well. Further, of those referred to diet and exercise advice, and group smoking therapy for smoking 45% and 50% would have received this under usual care. There was no account made whether individuals would have received these interventions quicker under a screening programme.

Table 8-4 Effectiveness estimates – adjusted for compliance and attribution

	Statins	Anti-hypertensives	Health counsellor
Systolic blood pressure			
min	-	-0.34	-0.11
expected	-	-0.80	-0.35
max	-	-1.73	-0.46
Total cholesterol			
min	-0.01	-	-0.02
expected	-0.04	-	-0.07
max	-0.09	-	-0.20
HDL Cholesterol			
min	0.003	-	0.001
expected	0.01	-	0.02
max	0.02	-	0.05

Costs: Table 8-5 outlines the main costs of Keep Well, which included coordination, screening for CVD risk, lifestyle interventions (e.g. diet and exercise) and IT support. Cost per individuals was estimated by dividing global totals by patient numbers. For instance, the average cost of the intervention, excluding pharmaceutical (considered next) was £349 per person.

Table 8-5 Total intervention costs

Activity	Total costs (21 months)
Management/coordination	£868,125
Screening	£967,500
Practice costs (GP, management,admin)	£1,272,387
Referrals/Signposts	£103,125
Interventions	£1,863,990
Tracking tool	£46,875
Total	*£5,122,002*

Source: John Clyde North Glasgow CHCP

Table 8-6 provides annual medication costs used in the primary prevention of CVD. The recommended prescription dose was given by the SIGN Guidelines and the costs of drugs were taken from the Scottish Drug Tariff. The methods just described and consequent estimates were then validated by the Lead Pharmacist in Glasgow, Richard Lowrie. For consistency with the effectiveness estimates, individual medication costs were weighted by compliance estimates.

Table 8-6 Medication costs

Medication	Annual costs
Aspirin	£13
Simvastatin	£35
Amlodipine	£15
Perindopril	£29
Total	*£92*

Source: Richard Lowrie/Scottish Drug Tariff

Cost effectiveness: Using the analysis of extremes approach, the base case analysis of Keep Well had a cost effectiveness ratio of £58,948. Under a worst scenario, the cost per QALY is estimated to be £120,558. Under a "best case scenario", Keep Well becomes cost effective with a cost per QALY of £12,762. In other words, there is huge uncertainty, and a necessity to conduct a robust evaluation and estimate the cost effectiveness results.

8.4 Discussion

Cost effectiveness of Keep Well: This analysis was illustrative of the Scottish CVD Policy Model's ability to undertake cost effectiveness analysis of a CVD primary prevention programme.

Strengths and limitations: Despite only having baseline information on risk factors and interventions referrals, this provided an opportunity to show how the Scottish CVD Policy Model can be used in the evaluation of Scotland multi-factorial programme.

The fundamental limitation of the analysis is the lack of follow-up data (rescreening) and absence of a control groups. Consequently, a rigorous economic evaluation was not possible. Rather, a modelling exercise was conducted which gave an opportunity to illustrate the functioning of the policy model.

Consequently, there was considerable uncertainty. The decision was made to represent uncertainty as simply as possible given the audience for the outputs was a policymakers who were unfamiliar with such modelling and sensitivity analysis. Nonetheless, this was also an opportunity to demonstrate whether the process of generating outputs was transparent and comprehensible to policymakers, who are intended to be the ultimate end-users.

Regarding sensitivity analysis, an analysis of extremes was felt to be the most effective method. This was a simple approach to communicate to policymakers the wide bounds of the uncertainty concerning the Keep Well programme, the origin of this uncertainty, and the need to undertake a rigorous study before assuming this national multi-factorial programme is a good use of scarce public resources. While a more sophisticated sensitivity analysis would have been probability sensitivity analysis, this requires knowledge of how interventions interact (and the associated statistical covariance); however there is a lack of trial evidence to inform this, as discussed in chapter 2 and chapter 3.

The data constraints are symptomatic of the lack of (rigorous) evaluation culture in local policy circles. A key aim of the analysis was to make clear to policy that appropriate information needs to be collected before a rigorous evaluation can be conducted. Otherwise, there would remain considerable uncertainty regarding the programme effectiveness and cost effectiveness.

The model functioning and outputs can be presented quite clearly. The results of the analysis were presented to Glasgow and the Scottish Government, where the latter has expressed a wish to undertake a national economic evaluation of the Keep well programme in the future.

The Department of Health (DoH) for England conducted a modelling exercise prior to rolling-out the National Vascular Screening Checks interventions in 2009. This is a similar programme to Scotland's Keep Well intervention. They found that the mean cost per QALY was £7,000. This is in stark contrast to the estimates made here. The reasons for such a difference in estimates have been investigated as far as possible. However, the economic model used by the DoH to generate estimates has not been published or made publically available. A report has been published that details the screening approach that the DoH is advocating, and key assumptions used in the modelling have been published(180). Perhaps a key reason why the DoH exercise found the programme will be cost effective result may be due to the compliance assumptions used; which may be considered to be optimistic. For instance, it was assumed that compliance with statins would be 75% and this estimate was

not sensitised. These compliance assumptions are in stark contrast to a 2-year study in Glasgow that found patient compliance in secondary patients was just 30% on average. A threshold sensitivity analysis using the Keep Well data found that compliance levels were the key area of uncertainty. The intervention can become cost effective if average compliance rates are 62% across all individuals (holding efficacy and usual care assumptions constant).

Summary: Overall, this exercise demonstrated how the Scottish CVD Policy Model can be used to evaluate the lifetime impacts of multi-factorial interventions, using the same risk variables as the ASSIGN score which is used to screen and prioritise individuals for interventions. This is the only model of its kind that can do this. The results of the exercise are speculative given the absence of outcome evaluation to date. In a sense the model has been used 'pre-trial' and intended to demonstrate the huge uncertainty regarding the programme. The practical implications for policymakers that while there are good intentions in rolling out primary prevention programmes, it is very important to properly evaluate impacts to ensure that scarce resources are being used cost effectively.

Chapter 9 Estimating the impact of population interventions

9.1 Background

The previous chapter showed how the model can be used to estimate the lifetime impact of targeted interventions. This chapter now demonstrates how the policy model can be used to assess the impact of population interventions.

It has been argued that population interventions may have the potential to elicit the greatest gains in health, due to the intention to impact upon the whole population rather than the high risk, which is the extreme of the population(99-100). Existing policy models such as CHD Policy Model, IMPACT and NICE's Programme Development Group (PDG) have produced convincing modelling exercises which corroborate these claims. However, existing estimates are limited in that the impacts of cumulative health service costs are not estimated, and the impact of extending life expectancy. These models also do not estimate the quality adjusted life years, and the NICE PDG model only estimates impacts over 10 years. Further, the impacts population health interventions on health inequalities have not been estimated by existing models. That is, while the population approach may deliver the greatest gain, the incidence of premature CVD tends to be concentrated in specific groups and Scotland suffers from a pronounced gradient in CVD by socioeconomic deprivation.

There are two main determinants as to whether population interventions will reduce health inequalities. First, to reduce health inequalities a primary prevention intervention would need to impact upon the CVD risk of a higher percentage of asymptomatic individuals in deprived groups. The potential problem for population health approaches to primary prevention is that the more deprived the group the higher percentage who already have CVD. Such individuals will likely be the recipients of intensive secondary prevention interventions.

Secondly, the impact of an intervention on inequalities will likely depend on whether the intervention requires individual engagement with statutory health services and an individual's long term compliance behaviour. Mass campaigns (e.g. screening and public health information) will tend to elicit greatest benefits in more affluent areas, given the greater tendency to engage with statutory services, undertake behaviour change, and affluent area tend to be better resourced than more deprived areas, exhibiting the Inverse Care Law(24). Population wide interventions that rely on patient engagement and/or the ability to local health

systems to respond may actually increase health inequalities(23). Therefore, there may be a trade-off equality of access and equality of outcome. The distinction is important given an explicit policy aim is to reduce health inequalities

This Chapter provides an illustration that the Scottish CVD Policy can be used to generate estimates of the impact of population interventions, and also to assess the impact on health inequalities. For the sake of exposition the approach of cost utility analysis is used, and the discount rate of 3.5% is selected. This is intended to help facilitate comparison of the impact of these public health interventions with interventions that fall under health technology assessment. This approach is also consistent with a similar modelling exercise recently undertaken in the UK(35).

The purpose of this chapter is to use the Scottish CVD Policy Model to run three intervention scenarios, and estimate the impact on population health, health service costs and inequalities. First, screening strategies are revisited and there is an illustration that a mass screening approach could increase health inequalities. Second, the impact of three legal/regulatory changes are simulated, where unlike screening these interventions are essentially paternal; there is no need to model individual engagement or compliance behaviour. Third, an illustration is provided to show how the model can be used strategically to develop optimal combinations of population and targeted approaches, whereas there both approaches can still often be treated as competing in the literature.

9.2 Methods

Mass screening and inequalities:
This simulation extends the analysis in Chapter 7 and is intended to inform whether Scotland should move to population wide screening programme like England. The purpose of this illustration was to illustrate at which point a population wide screening strategy may increase health inequalities. The analysis determines to what extent engagement with screening would need to vary in the population for life expectancy to widen in the population, defined by fifths of socioeconomic deprivation. It is then discussed whether this difference between groups is plausible in reality.

Defining the asymptomatic population: For the purpose of consistency to compare targeted and population approaches the impacts of intervention on 40-74 year olds. This may significantly underestimate the impact of population interventions that impact on all age

groups, and may have intergenerational impacts. Nonetheless, this comparison is still intended to be instructive of the potential for population interventions. Further, the NICE PDG also estimated impacts on the same age groups in England but over 10 years(35).

Legal and regulatory interventions:

Using the SHeS 2003 (the largest and most comprehensive of the surveys) the cost effectiveness of three interventions are estimated. The analysis as limited to primary prevention, and so first the proportion of the Scottish population that were asymptomatic was estimated, including how this varied by fifth of socioeconomic deprivation (SIMD).

First, the impact of a reduction in salt within processed food is estimated, assuming that this will lead to a fall in systolic blood pressure (SBP) of 5% across all individuals.

Secondly, a 5% reduction in total cholesterol was simulated which could be expected from a 0.5% reduction in trans-fats. These reductions in SBP and total cholesterol are consistent with recent findings from prevention programmes administered elsewhere outside Scotland(35).

Third, for exposition, a smoking intervention was simulated to demonstrate the importance of reducing smoking in the population. For exposition, it was speculatively assumed that there was agreement from government and industry to reduce nicotine content of cigarettes leading to reductions of 25%, on average, across all brands. To be clear, nicotine is not itself harmful to health. Rather nicotine is the addictive substance leading to the inhalation of associated carcinogens which driven the harmful biochemical process leading to the associated CVD and non-CVD events(328).

To simulate the impact of reducing nicotine content, and so the addictive nature of cigarettes, this was converted into an equivalent drop in average cigarettes smoked per day. It has been estimated that on cigarettes contain between 1 to 3 grams of nicotine (329). Conservatively, it was assumed that on average the nicotine inhaled by smokers was 1 gram, in a crude attempt to account for differences in filters, length of draws, and so forth. Overall it was assumed that a 25% reduction in nicotine content for cigarettes is equivalent to a 25% reduction in cigarettes smoked per day. So for example, for a smoker of 20 per day this equates to 5 cigarettes per day.

Any knock-on effect as consequence of reducing nicotine is held constant. For instance, individuals may decide to buy more cigarettes or increase the yield from greater inhalation. On the other hand, future smokers may becoming less addicted, and/or enhance quit rates of other interventions (e.g. group therapy NRT treatments).

Combing targeted and population approaches:
The model is also used to illustrate that a combination of targeted and population interventions may an efficient and effective approach to improve population and also reduce health inequalities. This is done by revisiting the finding from Chapter 7 that targeted screening on deprived groups and those with family history could detect the majority of individuals are premature risk and free up resources for population wide interventions.

9.3 Results

Mass screening and inequalities: When investigating efficient screening strategies, we saw 16% of the deprived population is at risk of premature CVD compared to just under 4% in the general population - a ratio of 4:1. Therefore, a mass screening approach may increase health inequalities if engagement and compliance in the deprived was less than a quarter that the rest of the population. This is a realistic scenario, especially if the deprived are further categorised into hard to reach groups(23), and we further consider the inverse care law where there is generally less support for deprived groups(24). Therefore, a population wide intervention that requires GP surgeries to contact everyone is unlikely to engage with such groups.

Asymptomatic population: Table 9-1 estimates the percentage of the Scottish population between the ages of 40 and 74 years who were free of CVD. Just over 36% of the total population is free of CVD. There is a clear SIMD gradient where least deprived (SIMD) have 43% who are asymptomatic falling to 30% in the most deprived (SIMD 5). This is consistent with the findings in Chapter 2 that the prevalence of CVD is higher in more deprived communities.

Table 9-1 Numbers asymptomatic in Scottish population

	Total	SIMD 1	SIMD 2	SIMD 3	SIMD 4	SIMD 5
Population	5,194,000	993,668	1,015,852	1,037,679	1,080,118	1,066,683
Asymptomatic	1,891,571	422,867	403,892	389,468	359,468	315,876
Percentage	36%	43%	40%	38%	33%	30%

The impact of such interventions on QALY, costs and health inequalities will depend on the level and distribution of risk factors in the population. Table 9-2 illustrates that more deprived communities have on average high systolic blood pressure and in particular smoking prevalence, where over twice as many people in SIMD 5 smoked (45%) compared to 22% in SIMD 1. The distribution of cholesterol readings are fairly even across quintiles.

Table 9-2 Average modifiable risk factors by fifths of socioeconomic deprivation (SIMD)

	Average	SIMD 1	SIMD 2	SIMD 3	SIMD 4	SIMD 5
Systolic blood pressure	133.4	131.2	133.4	133.8	134.4	134.5
Smoking %	21.8	14	20	2	34	45
Total cholesterol	6.0	6	5.9	6	6	5.9
HDL Cholesterol	1.5	1.6	1.6	1.5	1.5	1.5

Legal and regulatory interventions: Table 9-3 then illustrates the gains in discounted QALEs at the national level and across fifths of SIMD, which is a function of the numbers of people in each fifth and the risk factors levels. Overall, the potential gains are enormous and especially for the smoking intervention. Further, the impact on inequalities is generally favourable, and again this is especially the case for smoking. A reduction in salt intake would increase inequalities slightly due to the greater numbers of asymptomatic individuals more affluent quintiles. However, this is only with respects to the total (incremental) QALEs each deprivation fifth can achieve. At the level of individual, more deprived people are still expected to benefit more given higher (on average) systolic blood pressure readings.

Table 9-3 Gains in discounted quality adjusted life expectancy (QALE)

	Total		Least deprived fifth SIMD 1		SIMD 2		SIMD 3		SIMD 4		Most deprived fifth SIMD 5	
Salt reduction												
Quality adjusted life years ('000)	369	(341, 402)	69	(61, 74)	65	(59, 73)	87	(83, 94)	80	(76, 86)	68	(63, 76)
Cost reduction (£m)	467	(443, 508)	91	(84, 95)	88	(82, 95)	105	(95, 118)	96	(91, 101)	87	(77, 93)
Trans-fat reduction												
Quality adjusted life years ('000)	140	(116, 156)	20	(14, 23)	32	(26, 37)	32	(27, 37)	29	(26, 34)	27	(23, 34)
Cost reduction (£m)	207	(194, 219)	34	(29, 41)	45	(39, 53)	48	(41, 54)	42	(37, 46)	38	(35, 43)
Nicotine reduction												
Quality adjusted life years ('000)	471	(454, 496)	53	(44, 57)	71	(65, 78)	83	(76, 89)	125	(115, 131)	139	(126, 145)
Cost reduction (£m)	569	-546,581	74	(67, 79)	92	(86, 99)	95	(89, 102)	141	(131, 153)	167	(152, 176)

Further, these interventions are cost saving, in discounted terms. In undiscounted terms, costs actually increase due to greater life expectancies, and the onset of co-morbidities in older age groups.

Combining targeted and population approaches: Chapter 7 showed that a targeted screening approach that focussed on the most deprived fifth and those with family history could detect 84% of the high risk by screening just 41% of the population. At a screening cost of £28 per person, a targeted rather than a mass population wide approach would save £18 million. Further, given clinical guidelines recommend screening every 5 years, this potential saving would be in perpetuity.

The remaining 16% of the population at high risk of premature events over 10 years could be picked up by legal and regulatory changes. This freed resource could either be saved; redirected into better engagement strategies for the deprived or additional interventions, such as to improve adherence levels; or/and used to fund public health interventions such as mass media campaigns. Such population wide interventions would also reinforce the impacts of targeted initiatives.

9.4 Discussion

The impacts of population interventions: Population health interventions can have an enormous impact, and the legal and regulatory interventions would be relatively inexpensive to achieve. While heath service costs will increase (reversing what other research has

concluded); once discounted the intervention are cost effective, given that the immediate cost of CVD events are averted and the costs of living longer lives are deferred to the future.

Strengths and limitations: The policy model can be used to quickly undertake such modelling exercises. It is the only model to use socioeconomic deprivation as a risk factor to assess the impact of interventions on health inequalities. A key strength is the same model can be used to assess the impact of both population and targeted interventions. This consistency then allows all forms of interventions to be assessed and compared using the same model which can produce the outcomes of interest to individuals, clinician and policymakers.

It is difficult to directly compare these results to other authors. For instance, the NICE PDG estimated the impacts on QALYs only over a 10-year period, there was no account taken of the quality of life impacts, and the cost impact was limited to avoidance or postponement of CVD events. Nonetheless, the fundamental issue is that such population health interventions can results in considerable improvements is consistent.

The model can be used in a similar fashion to simulate any population interventions (e.g. mass media campaigns) if consequent changes in risk factors are estimated. The model can be used to convert changes into risk into QALE and costs.

Summary: This Chapter concludes Part 3 of the thesis and demonstrates that the Scottish CVD Policy Model can be used to assess the impact of population interventions and on health inequalities, which can have considerable impacts and be cost saving (in discounted terms).

Overall, the previous four chapters has attempted to address the research questions, and demonstrate that the model can be used flexibly as both a clinical tool to identify individuals at high risk and those who can benefit the most from intervention; and also as an evaluation tool and can inform the development and evaluation of both targeted and population interventions. This range of comprehensive outputs is an advance on existing policy models, and in application could help bring more coherence to the approach of primary prevention in Scottish policy making circles.

Chapter 10: Conclusions and further research

10.1 Introduction

To complete the thesis this final chapter assesses the extent to which the objectives were met. The chapter is structured in three main parts. First a summary of the rationale, function and application of the Scottish CVD Policy Model is provided. This draws upon and summarises each of three parts of the thesis. Second, a discussion of the key strengths and weakness of the research is provided; and third, the chapter ends by describing certain areas for future research.

10.2 Summary of the thesis

The overall purpose of the thesis was to develop a Scottish CVD Policy Model that can be used to assist decision makers develop and evaluate primary prevention interventions. Part 1 of the thesis developed the rationale behind why a Scottish CVD Policy Model is needed, by describing the aims of primary prevention, the need for economic models to help generate the information required by decision makers to inform approaches to primary prevention; but then highlighting the weakness of current models regarding their potential use in Scotland. Part 2 then described in detail how the Scottish CVD Policy Model was developed, and how it functions to generate the information required by both clinicians and policy makers. Part 3 demonstrated how the model can be used to address key research questions to help improve the approach to primary prevention. Each of the three parts of the thesis is summarised in more detail below.

Part 1 – Review of primary prevention

Part one consisted of Chapters 2 and 3. Chapter 2 described how the primary prevention of CVD is a policy priority across the developed world. The general goals of prevention are to avoid premature mortality, morbidity and the consequent health service and wider economic costs. The prevalence of CVD has been falling consistently in recent decades, but the incidence and costs of CVD remain substantial. It is estimated that in 2011, CVD accounted for 30% of all deaths and resulted costs of over to the health sector and £3.4 billion to the health service and wider economy.

The primary prevention of CVD is an increasing policy priority in Scotland. The goals are to avoid premature mortality, morbidity and the associated economic costs. Further, a key policy

aim is to reduce health inequalities. In all countries, the prevalence of premature CVD is generally skewed towards areas of lower socio-economic position. However, this social gradient is particularly apparent in Scotland. Scotland has among the highest concentration of deprived areas in Western Europe, and the incidence of premature CVD is especially high.

There are two main approaches to primary prevention: a targeted approach on individuals screened and identified as being at high risk of CVD events and a population approach intended to impact on everyone in a defined population (e.g. legal and regulatory changes) where interventions do not require the engagement of specific individuals.

The current policy emphasis is on a targeted approach. Following clinical guidelines, individuals are screened using CVD risk scores and those at high risk of an event (estimated to be ≥ 20% over 10 years) are offered a tailored set of pharmaceutical and behavioural interventions. The SIGN 97 clinical guidelines adopted the ASSIGN 10-year risk score as the most appropriate risk tool, which was developed in Scotland and includes a measure of socioeconomic deprivation (the Scottish Index of Multiple Deprivation), as an independent risk factor.

While there is a significant policy effort to reduce CVD and inequalities, the evidence base underpinning current approaches is relatively limited. There is robust cost effectiveness evidence of single drug interventions, and convincing modelling exercises of particular population-wide interventions. However, in particular, there is lack of efficacy, effectiveness and cost effectiveness evidence regarding multi-factorial interventions of the sort being rolled out in Scotland, and elsewhere.

Overall, there are three main strategic weaknesses with current approaches to primary prevention. First, it is unknown what the optimal screening approach is to identify the high risk. Clinical guidelines recommend screening the entire population from 40-74 year old. However, more focussed approaches may be more efficient. Second, it is increasingly questioned whether 10-year risk scores are the most appropriate mechanism to prioritise individuals for intervention. The aims of prevention are to avoid premature CVD; yet 10-year scores are driven by age resulting in the prioritisation of older patients at the expense of younger individuals who may have most to benefit from early prevention. Third, the targeted and population approaches to prevention are still often treated as competing approaches whereas perhaps the key issue is how they might best combine.

An important part of the continued uncertainties is the lack of consistency in the evidence base. The efficacy and effectiveness evidence base consists of studies with different time frames, different end points (e.g. risk factors, CVD events, all cause mortality), and different populations, and often not fully exploring heterogeneity within a population. This is a problem for policy makers who are interested in the extent to which interventions prevent premature mortality, and when cost constrained how to prioritise resources.

The approach of cost effectiveness analysis may provide a consistent framework to enable interventions to be directly compared in terms of quality adjusted life expectancy and health service costs. From an economic perspective these outcomes are necessary given scarce resources, and congruent with how reimbursement agencies, such as health technology agencies, make funding decisions.

Chapter 3 outlined the importance of economic modelling to help generate cost effectiveness evidence. Among the key potential benefits of models are: the ability to project trial results to longer term outcomes, such as changes in risk factors to events rates and life expectancy; the syntheses of evidence from different sources; to enable comparison of interventions that may not have been trialled together; undertake sensitivity analysis; and ultimately to make the best decisions based on the information available. In this sense, economic models can be a useful aid to both develop evidence and also inform decision making.

The chapter described existing models and made the case why building the Scottish CVD Policy Model is necessary. Health economists have tended to concentrate on building bespoke economic models to evaluate the cost effectiveness of single interventions, such as statins. This practice has been entirely appropriate given the trials have focussed on single interventions. However, these models are not best placed to assess the impact of multi-factorial intervention which is now the focus of policymakers. There is a class of models called Policy Models that seek to take a more generic modelling approach. There are two elements to the term generic. First, this is where a model includes multiple risk factors relevant to the disease area of focus. Secondly, that the long term impact of risk factors on a range of conditions, beyond that of principal interest, is included. In this sense, generic models seek to be comprehensive, in both the inputs used and outputs produced. The advantage is to provide a consistent modelling approach to estimate the impact of relevant interventions, as opposed to building multiple bespoke models.

A systematic review illustrated that there are a variety of generic policy models in existence. Modelling experts have developed best practice guidance regarding how to develop, test and disseminate economic models. These guidelines were used to appraise current models. It was shown that all models have considerable merits. Most models are built from synthesising numerous cross-sectional sources which estimate how the change in population prevalence of risk factors is associated with the change in incidence of CVD events over time. These models tend to produce convincing simulations of how falling risk factors levels have contributed to the observed reductions in CVD events in the population historically. These simulations appear to have informed the discourse regarding the role primary prevention appears to have had regarding the observed declines in CVD in the population.

However, there are also common limitations to current policy models. No existing models estimate impacts of risk factor changes on non-CVD events which may be important when generating life expectancy estimates. Further, the increase in health service costs from extending life expectancy (given the accumulation of co-morbidities) is also not considered. Few models account for background morbidity of the population of interest and the impacts of non-fatal events. This may then lead to inaccurate estimates regarding the process of quality adjusted to generate quality adjusted life expectancy (QALE). Of crucial importance is that there has been a lack of consistency in the epidemiological models used to estimate the risk of events and the economic models used to estimate lifetime impacts from changes to risk factors to generate cost effectiveness evidence. Three models use the same set of risk factors as used in 10-year risk scores. However, these models used the Framingham risk score which is inappropriate for use in Scotland, as it does not adjust for social deprivation and may lead to worsening health inequalities if the score is used as a basis for prioritising individuals. Further, the model estimates impacts only over 10 years and only on CVD mortality. Finally, it is rare for policy models to be tested in terms of external validity or the success in predicting outcomes in contemporary populations. The exception to these weaknesses may be the Archimedes model, which was developed in the United States and is extremely comprehensive. Nonetheless, this model is not ideally placed for use in Scotland, as there is a need for a model to use the ASSIGN risk factors, and bring consistency between clinical practice and policy decision making.

The consequence of these weaknesses is that even if trial evidence existed regarding the impact of multi-factorial interventions, there is lack an economic model to project (short term) evaluation findings to lifetime impacts and to discriminate between individuals, in terms of quality adjusted life expectancy and lifetime health service costs.

Overall, the intention was to develop a new and comprehensive Scottish CVD Policy Model to help inform primary prevention and address the key uncertainties as discussed, which were formulated into the following specific research questions:

(i) If the current approach to prioritising individuals for intervention is to use 10-year risk scores, can the model be used to identify optimal screening approaches to identify high-risk individuals?

(ii) Given the weaknesses in 10-year risk scores, can a new approach to prioritising individuals be developed based upon individuals' potential to benefit rather than risk?

(iii) Can the model be used consistently to assess the cost effectiveness of both targeted and population interventions?

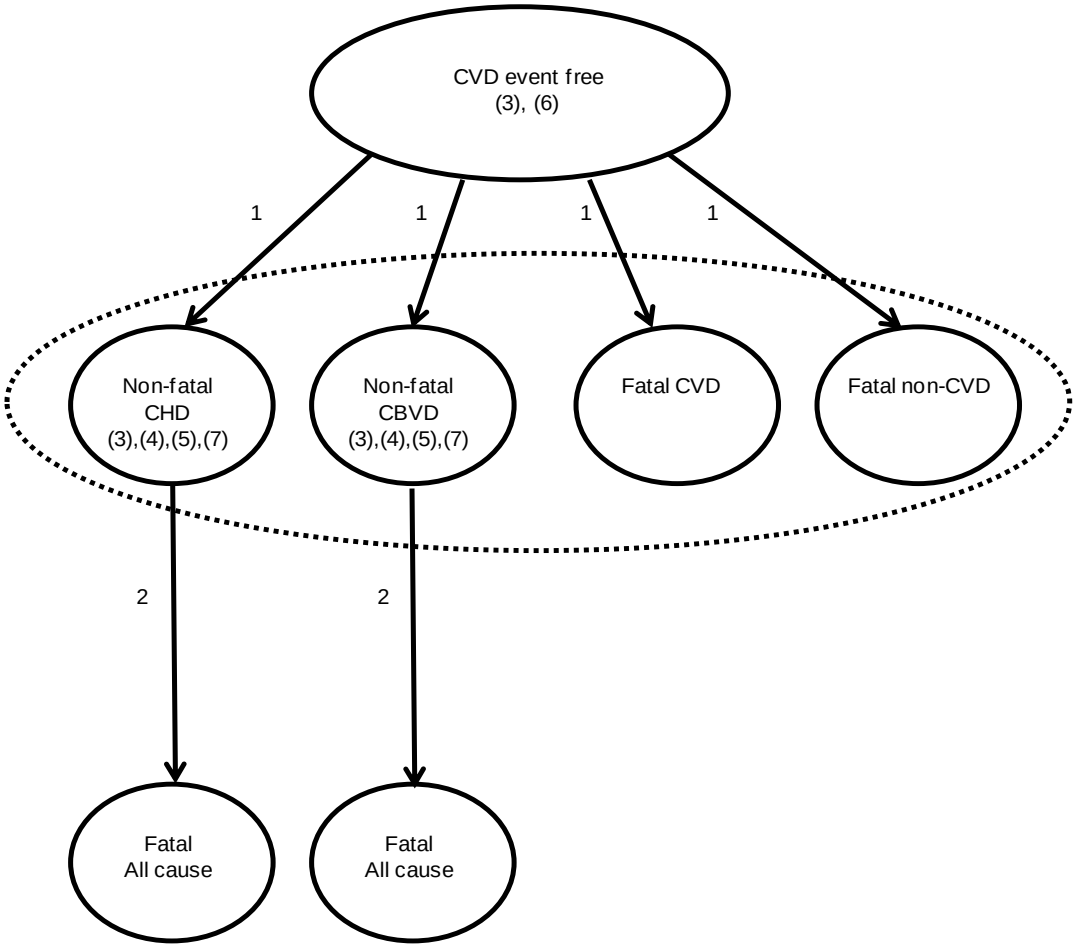
Part 2 – Development of the Scottish CVD Policy Model

The overall purpose of Part 2 of the thesis was to develop a new and a comprehensive policy model that could be used to help address the research questions. There was an opportunity to start from first principles and develop a single model, that could be used as both a clinical tool and as an economic tool to produce outcomes congruent with the ultimate aims of primary prevention.

The key to the development of the model was access to the longitudinal dataset used to create the ASSIGN score. This linked the Scottish Heart Health Extended Cohort (SHHEC) to Scottish Morbidity Records (SMR) which audits all hospital events (CVD and non-CVD) and all deaths. The dataset consisted of over 16,000 individuals defined by the ASSIGN variables. These were divided into non-modifiable and modifiable factors. The former included age, sex, family history, diabetes and socio-economic deprivation as defined by the Scottish Index of Multiple Deprivation (SIMD). The latter included systolic blood pressure, total cholesterol, HDL-cholesterol and smoking (cigarettes smoked per day).This dataset was central to developing a simple model structure but which could produce a wide range of outputs.

Chapter 4 detailed the model structure and statistical approaches to estimating life expectancy from individual risk factor profiles, as defined by the same variables as used in the ASSIGN 10-year risk score. A simple model structure was developed (see Figure 10-1) where from a CVD

Figure 10-1 The Scottish CVD Policy Model



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

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

Equation 3: Background morbidity = Function (age, deprivation)

Equation 4: Morbidity impact of non-fatal CVD events = Function (age, CVD events, SIMD)

Equation 5: Risk of subsequent CVD events = Function (age, family history, SIMD)

Equation 6: Costs prior to 1st event = Function (age, family history, SIMD)

Equation 7: Costs post 1st event = Function (age, family history, SIMD)

free state an individual can incur one of four first events: non-fatal CHD, non-fatal CBVD, CVD death and non-CVD death. If the first event was non-fatal then individuals transit directly to a final death state. This structure is congruent with a primary prevention model to assess the impact of changes to risk factors in asymptomatic individuals on the lifetime risk of a first event and consequent life expectancy (including competing events).

To estimate the transitional probabilities from a CVD free state to the four first events a competing risk analysis was undertaken. The cause specific hazards were estimated in a parametric analysis using all the ASSIGN variables as covariates (linear predictor), and using a Gompertz ancillary parameter (Equation 1). This approach generates cumulative incidence estimates, where for any given cycle the sum across the probabilities of the five model states always sums to 1. Importantly, over a lifetime all individuals leave the CVD free-state and incur one of the first four events within a particular annual model cycle. Therefore, once the model has exhausted all 100 annual cycles the sum of probabilities across the four events must sum to 1 (i.e. an individual must incur one of the first four events over a lifetime).

If the first event was non-fatal then a survival analysis was conducted where the risk of death was estimated conditional upon the type of first non-fatal event (CHD or CBVD), and using the covariates of: year of the event since screening and the non-modifiable risk factors (Equation 2). Separate risk equations were estimated for men and women.

The model estimates overall life expectancy directly from a CVD-free state in four stages. First, the model conducts a "what-if" analysis and estimates the remaining life years from incurring each one of the first four events. This is calculated by summing the years before a first event and the survival time post non-fatal event. Given the model runs for 100 annual model cycles, and within each cycle any one of the four events could be experienced, this generates 400 different scenarios that an individual could face upon entering the model (i.e. type and timing of the first event). Each scenario is then associated with a particular life expectancy estimate.

Second, the probability of incurring each one of these 400 scenarios is weighted by the probability of incurring a specific event in a particular year by using the annual addition to the cumulative incidence estimates. This weighting generates average remaining life expectancy. Third, the age of the individual upon entering the model is added which then gives an overall life expectancy estimate.

The purpose of Chapter 5 was to quality adjust survival in the model and to estimate average annual health service costs as an individual ages in the model, and accumulates expected comorbidities. Summing over a lifetime would then provide quality adjusted life expectancy and cumulative lifetime health service costs.

Quality adjustment took into account background morbidity and non-fatal CVD events. Background morbidity was estimated specific to age group, sex and fifths (quintiles) of a SIMD score (Equation 3). The impact of experiencing a non-fatal CHD and CBVD was also estimated (Equation 4). Further, survival from first event was quality adjusted by estimating the probability of incurring further five non-fatal events (Equation 5) weighted by quality of life impact of incurring further non-fatal CVD events (Equation 4).

All hospital events were recorded in the SMR and then costed taking into account the primary cause of admission, additional events within stay, and hotelier costs incurred as a function of length of stay. Costs prior to a first event were estimated (Equation 6), and also after a first event and prior to death (Equation 7).

Extensive validation tests were undertaken. Face validity was checked via an expert group of clinicians, an epidemiologist, a medical statistician and a health economist. This group met four times to discuss the model rationale, structure, function and capacity to generate credible outputs. The group was content that the model was fit-for-purpose. Internal validity was tested to see how well the model could predict observed first events within the SHHEC-SMR population. The model performed well. A more difficult test is external validity to test how well the model could predict first event outcomes in a dataset not used in its construction. The West of Scotland Coronary Prevention Study (WOSCOPS) was used, which was a trial of pravastatin affects in reducing CVD outcomes in asymptomatic men aged between 45 and 64 years. The model also performed well, predicting outcomes for both the placebo and intervention group. An additional test of the model is how well it could predict life expectancy in a contemporary Scottish population in 2009. The model did not perform particularly well, which is unsurprising given life expectancy increases over time. Therefore, the model was consequently recalibrated. This was done by adjusting the risk of first events, by adding a multiplicative factor to the linear predictor. Life expectancy predictions now match observations to within 1 year or less across sex and age categories.

The chapter ended by briefly illustrating that the policy model was ready to be used in evaluation. The model can simulate the impact of changes to risk factors on (undiscounted and discounted) life expectancy, quality adjusted life expectancy and lifetime health service costs. Importantly, the model is also able to assess the impact on health inequalities.

Overall, part 2 built the model with the intention that it could be used to either conduct ‘what-if’ modelling exercises or to project forward actual trial evidence. The modelling approach is

flexible is that it can include any intervention that impacts on the ASSIGN variables; including single or multiple interventions and estimates can adjusted for compliance estimates. Further, the model can conduct extensive sensitivity analysis, either one-way, analysis of extremes or probability sensitivity analysis; and adjust key structural parameters, such as the discount rate. The key focus of the thesis was to demonstrate the model's ability to discriminate between individuals in terms of QALE and costs, in a similar manner as 10-year risk scores.

Part 3 – Demonstrating the Scottish CVD Policy Model

Part 3 of the thesis was designed to demonstrate how the policy model may be used to help address the research questions. This was attempted in four short chapters, each focussing on a specific issue. Chapter 6 showed how the model can identify optimal screening strategies. It is likely that the current practice of using 10-year scores will continue to be used for the foreseeable future; however, the analysis showed that the impetus to screen the entire population is not efficient. The most cost effective approach is to screen the most deprived fifth in the population and those with family history. This could then identify 84% of all individuals in the general population that are at premature risk of CVD – the key target group when it comes to primary prevention.

Chapter 7 then illustrated how the model could be used as a clinical tool to replace the use of ASSIGN 10-year scores, which are driven by age and where the use of a 20% threshold results in prioritisation of older patients. There is a lack of trial evidence, especially regarding the impact of multi-factorial interventions. It is important to have a clinical tool which can estimate the potential benefits from risk factor modification. The policy model was used to estimate maximum potential benefits in terms of additional life expectancy. For exposition, the estimates generated were a theoretical maximum, assuming 100% compliance and immediate and full reversibility of risk. In practice, these assumptions are unlikely to hold; however, the benefit of using the model in this way was also to articulate the need for such research. Using this measure of potential benefit, rather than 10 year risk, would likely result in a switch in which individuals receive prioritisation, including younger patients, females, smokers and a greater focus on deprived individuals. Nonetheless, the model is flexible in that these assumptions can be easily updated as and when new evidence becomes available.

The models ability to be used as an economic evaluation tool was then illustrated. Chapter 8 illustrated how the model could be used to evaluate Keep Well, Scotland flagship primary

prevention programme. Keep Well consists of screening deprived individuals using the ASSIGN risk tool and then prioritising high risk individuals for a mix of tailored pharmaceutical and lifestyle interventions. At present, there has not been a rigorous evaluation of impacts on risk factors or events. The policy model was used to demonstrate the considerable uncertainty of Keep Well through an analysis of extremes approach, as this could most easily illustrate the origins of the uncertainty, and consequent assumptions that policymakers themselves are making by rolling out the model without evidence. Baseline screening data were run into the model, and both the academic literature and expert opinion was sought to generate appropriate assumptions regarding the probable impact of the Keep Well interventions, over and above usual care. The central expectation is that the programme is unlikely to be cost effective. However, under an extreme best case scenario, (e.g. using the most optimistic expectations of intervention efficacy and compliance estimates) Keep Well may be cost effective.

The only other comparable analysis to date was by the Department of Health which developed an economic model to inform the roll-out of England's national screening programme. The model however is not available for peer review. In reviewing the associated literature, it was particularly notable that the compliance assumptions were extremely optimistic. For instance, it was assumed that compliance with statins would be 70%; whereas the literature finds 50% is the upper limit, and in Glasgow it was estimated to be less than 30%.

Finally, Chapter 9 demonstrated that the model can be used to estimate the impact of population wide interventions, which could have enormous impacts in increasing (discounted) QALYs and reducing (discounted) hospital costs. The act of discounting is very important here, especially for cost estimates. Interventions tend to increase life expectancy, postpone events and individuals accumulative additional co-morbidities before death. This actually results in higher undiscounted health service costs. However, discounting, by weighting the future less than the present, results in the cumulative sum of lifetime costs being lower in individuals who have successfully lowered risk factor levels (as events are avoided or postponed).

It is notable that legal and regulatory changes could also improve health inequalities, given the distribution of inflated risk factors is greater in more deprived communities and such interventions do not require the engagement of individuals, which is normally lower in deprived areas. An analysis also found that national screening could plausibility increase

health inequalities, conditional upon differential engagement rates across groups. Further, an approach to primary prevention that combined targeted screening with population wide interventions may have a better opportunity to be effective, cost effective and reduce health inequalities.

Overall, the intention of Part 3 was that decision makers (clinicians and policy makers) could use the model flexibly to produce outcomes of interest. Further, given the model can be used to simulate the impact of a wide range of interventions, there may be an opportunity to use the model to develop more strategic approaches to primary prevention, regarding the optimal combination of interventions; rather than viewing targeted and population wide approaches as competing approaches.

10.3 Strengths and limitations

Strengths

(i) Data sources:

In general, Scotland has excellent data sources. A key strength of the thesis was the robustness of the particular data sources used to construct, populate and validate the model. To build the Scottish CVD Policy Model access to the Scottish Heart Heath Extended Cohort (SHHEC) was granted, which consisted of five baseline surveys from the mid-1980s to the early 1990s. SHHEC was then linked to the Scottish Morbidity Records (SMR) until 2009. SMR records all hospitalisations and death, with up to 6 diagnostic codes, and recording length of stay. SHHEC was also linked to the General Registrars Office for Scotland (GROS) to record all deaths. Overall, the longitudinal dataset consisting of over 16,000 individuals, with a maximum follow-up of 25 years and an average follow-up of 21 years (given SHHEC consists of multiple surveys in different years).

To populate the model to quality adjust survival estimates, the Scottish Health Survey was used to estimate background morbidity and the morbidity impact of experiencing non-fatal CVD events, as discussed further below. Further, to test the model's external validity, the West of Scotland Coronary Prevention Study (WOSCOPS) was used. Using Scottish data sources enhances the internal validity of the model for use in Scotland.

(ii) Consistency with ASSIGN Score:

This was a similar dataset to the one used to create the ASSIGN 10-year score. The difference was that the dataset used in this thesis has an additional 3 years of liked SMR

data. Given the analysis is using the same variables as the ASSIGN score this may enhance the acceptability of the policy model as a natural extension to the 10-year risk score. On the one hand, the model can now be used to evaluate interventions using the same variables that were used to prioritise individuals. On the other hand, using the data to create a new clinical tool (based on potential benefit) may enhance its acceptability also.

(iii) Modelling approach:

There are a range of policy models in existence and all have considerable merits. However, other models can either be very complicated, both in the structure and statistical estimation (e.g. CHD policy Model, IMPACT model); or overly simple in the sense that the scope is limited (e.g. NICE's PDG which projected benefits of population interventions only on CVD death avoided and only over 10 years).

The Scottish CVD Policy Model may offer several innovative model features relative to standard cohort state transition models. This opportunity to develop the modelling approach was mainly the result of having developed a comprehensive longitudinal dataset.

First, estimates between risk variables and events were made continuously where possible. This enhances the discriminatory ability of the model so that no averaging across groups is required, which is common in cohort state transition models.

Second, in estimating first events risks the annual addition to the cumulative incidence estimates are read directly into the model. This is more elegant approach than the manual fix normally applied in state-transition models, where event risks in each cycle of model are calculated by multiplying hazards by the (decreasing) proportion still at risk. The cumulative incidence approach automates this process, and given cumulative risk must sum to 1, this approach provides an automatic model verification check.

Third, by concentrating on primary prevention the total downstream consequences from experiencing a first event were directly estimated. This avoids the need for recurrent states and individuals moving between model states, both of which can complicate the model structure. Further, using a single dataset to estimate transition risks may enhance the transparency of the model estimates; as opposed to combining multiple sources from different time periods and contexts, which most other policy models have to do. This is not a criticism of models that have had to do this, given data limitations.

Fourth, the simple model structure (a maximum of three states) means that the model can track patient history. Age at screening determines the risk of a first event, and the age (time) at which an event occurs determines survival. This avoided the “memoryless” feature common in cohort state transition models. Normally, time to event and individual history is associated with discrete event simulation.

Fifth, to predict average (quality adjusted) life expectancy and lifetime costs a method most commonly associated with decision trees was used. That is, all possible scenarios in the model were given a life expectancy estimated, which were then weighted by the associated probability. To be clear, for each specific covariate profile, there are 400 possible scenario defined by the type of the first event experienced and the timing of that event (4 first events x 100 model cycles). As an individual must incur one of these four first events, the sum of probabilities across all 400 scenarios must sum to 1.

All of these model features enhance the simplicity and transparency of the model, reducing the risk that the model may be perceived to be a “black box”, which can be a general criticism of models. Overall, the model doesn’t easily fall into conventional categories as it shares features common to different models. The model is described as an individual state transition model, but could also be described as a ‘hybrid model’, as discussed in the ISPOR 2012 best practice guidelines.

(iv)Focus on primary prevention:

Given policymakers are currently focused on primary prevention, the modelling problem did not consider secondary prevention. This approach simplified the modelling problem, and facilitated a simple model to be develop, which contributes to the transparency of the modelling.

(v) Estimating the impact of risk factor changes in non-CVD death:

The SHHEC-SMR dataset permitted a competing risk analysis to be undertaken (using the competing cause of non-CVD death). As such, the impact of changes to risk factors on life expectancy takes account not only of CVD event, but also non-CVD death events, such as cancers and respiratory diseases. This is particularly important when considering the impact of changes to certain variables such as smoking. Other economic models either estimate the life expectancy through the avoidance of CVD events, or use general population lifetables. The latter is perfectly legitimate, though less elegant than the competing risk approach.

(vi)Quality adjustment:

An analysis of the Scottish Health Survey allowed morbidity (background morbidity and event utility decrements) to be estimated enabling life expectancy to be quality-adjusted. Background morbidity estimates were made specific to sex and age categories, and most notably conditional upon deprivation status. This allows the model to more accurately estimate background morbidity and account for the underlying social gradient, that exists in terms of health related quality of life (in addition to life expectancy). The impact of experiencing non-fatal events was also made for five event categories, which is a wider set of CVD conditions that other comparable studies.

Further, the SHHEC-SMR dataset permitted estimation of the lifetime risk of further non-fatal CVD events to be estimated following a first event. Consequently, quality adjustment was made throughout an individual's lifetime. Most models do not make quality adjustments, and where it is done, it is not as comprehensive.

(vii) Lifetime costs:

The SHHEC-SMR dataset was also used to model and cost all events. This enabled estimation of expected lifetime hospital costs directly from a risk factor profile. From reviewing the literature, it appears that no other policy model estimates the impact of prevention and extending life expectancy on cumulative lifetime costs. It is important that this is done to more fully take into account the impact of prevention. Prevention essentially postpones fatal events, and it is important to account for the impact of longer life expectancies on health service costs.

(viii) Possibility of greater congruence between clinical and economic approaches:

The policy model was developed using the same ASSIGN variables currently used in clinical practice. This means that the variables used to prioritise individuals can now be used to model the lifetime impacts of changes to modifiable risk factor. Further, by using the same variables to develop a new clinical tool (based on potential benefit) this may enhance the possibilities of implementation in primary care.

(viiii) Wide range of applications:

As discussed, the model can be used to inform the entire approach to primary prevention, from identifying optimal screening strategies, prioritising individuals for intervention, and evaluating interventions, including single and multiple risk factor interventions at both the individual and population level.

(x) Validation:

The validation exercises were more comprehensive than current policy models. In particular, external validation and recalibration to contemporary populations has not been done by other models. Overall, the policy model has high internal validity using Scottish data sources and calibrating to contemporary populations.

Limitations

(i) Data sources:

Within the SHHEC-SMR dataset there is much greater proportion of those in the most socio-economic deprived quintile than would be expected in a truly representative sample. However, when modelling event risk adjustment was made for deprivation status when estimating event risks (the cause specific hazards of Chapter 3), the model itself is representative of Scotland.

Within the SHHEC-SMR dataset there remained a substantial amount of people alive and/or event free: 57% of men and 69% of women in SHHEC. However, of particular note is that there were just 9% of men and 5% of women who had died following a non-fatal event. This may be an important limitation. While there was sufficient power to undertake the analysis, this provides an opportunity to re-estimate the model equations in the future.

The baseline screening population (SHHEC) dated from the 1980s, and it is likely that survival rates post-event would now be higher. Conditional upon appropriate evidence, the model can be re-calibrated to account for such changes. This issue is revisited in the next section when discussing further research.

(ii) Costing analysis:

A limitation of the costing analysis is that only hospital costs are included. The implications for primary care costs are not considered as such information is not routinely available. This may be a particularly important limitation when estimating health service costs post–stroke, where stroke patients are increasing treated at the community level, rather than within secondary care. Further, in estimating the consequences of extending life expectancy the analysis found that costs increase, as expected, due the onset of more co-morbidity. It would be expected that this would impact upon primary care also.

(iii) Socioeconomic deprivation modelled as a non-modifiable risk factor:

Socioeconomic deprivation is measured by the Scottish Index of Multiple Deprivation (SIMD). This was classed as a non-modifiable risk factor. This is an important limitation given an increasing policy discussion on the social determinants of health. The decision to treat SIMD as a non-modifiable risk factor was taken for two reasons. First, there is no direct evidence linking area–level interventions (aimed at changing relative deprivation status) and consequent changes in CVD risk. Second, the perspective of the model is from the Health Service. The interventions that would change relative deprivation status (driven by income, education, area etc) do not reside with the NHS. Nonetheless, the model can incorporate such evidence if available. This would mean that the potential benefit calculation made in Chapter 6 would be revised.

(iv) Socioeconomic deprivation status measured as an area-based variable

SIMD is an area based measure, where households are grouped into small datazones of 740 households, and a (continuous) score is given to represent socioeconomic status. The downside of this measure is the ecological fallacy, treating all individuals with a similar postcode the same. A better measure may be more specific to the individual household. Possible options being explored in Scotland is council tax band. However, at present no measure is perfect. To reiterate, the modelling used is essentially as extension of the same variables used in clinical screening.

(v) Constraints regarding generalisability:

While the model has high internal validity, this may also be considered a weakness. In particular, the use of socioeconomic deprivation may limit its generalisability. SIMD is specific to Scotland. The variable is not equivalent to England's Index of Multiple Deprivation (IMD), and other countries do have similar measure of socioeconomic deprivation.

Overall, there are important strengths and limitations of this research. In reflecting upon these, there may be the opportunity for further research. The chapter now turns to a discussion of key areas that may be particularly fruitful.

10.5 Further research

10.5.1 Improvements to the current model

The following is divided into two sections. First, consideration is given to how the present model could be improved in terms of its estimation and validation. Second, discussion then turns to how the model itself can evolve and expand its scope and application.

(i) Widen the range of CVD risk factors:

It was important to build the Policy Model using the nine CVD risk factors that are used in the ASSIGN risk score. The intention was that clinicians and policy makers could view the Policy Model as a natural extension of the ASSIGN 10-year risk score. Nonetheless, there is the possibility to explore further increasing the number and/or changing the risk factors. Candidates may include (a) biomarkers, such as c-reactive protein (CRP), (b) particular conditions (e.g. hypertension, atrial fibrillation); (c) behavioural (e.g. alcohol, physical activity); and genetic factors.

However, there is the possibility of diminishing marginal returns with respect to adding risk factors. From an epidemiological perspective, if the addition of risk factors improves predictions in CVD events and life expectancy predictions then the research is worth pursuing. Regarding a dataset, a good candidate would be the Scottish Health Survey, a cross-sectional survey of the Scottish population that dates from 1995. At present, record linkage would extend to 2010, giving 15 years of follow-up.

However, from an economics perspective, the key issue is whether the risk is modifiable and how will this help to improve the models ability to discriminate between individuals to inform the targeted approach to prevention. That is, it is important to assess whether the addition of risk factors are also cost effective. Research in this area is lacking.

(ii) Accuracy of self-reported events:

It would be important to respond to the limitations that we outlined previously. The accuracy of self-reported CVD events within the SHeS 2003 by linking the survey to historical hospital data via patient ID. This type of linkage is readily available in Scotland for the purposes of research, subject to Government permission.

(iii) Primary costs:

To improve the cost analysis, it would be worthwhile to access primary care records in Scotland to expand the analysis. It is estimated that primary care accounts for 7% of total CVD costs, with 80% hospital care and medications, which the model should includes. At present, access to primary care records is not routinely available.

(iv) Improving a potential benefit approach:

A potential benefit approach was illustrated by estimating the theoretical maximum gain in life expectancy from changes to modifiable risk factors. These estimates are overly optimistic. In practice, there is lack of evidence regarding the reversibility of risk factors and how this may differ by age, gender and deprivation status. A benefit of the model is to make these issues explicit and illustrate the importance of applied research in this area. The model has been programmed with the ability to adjust potential benefit estimates based upon evidence of intervention efficacy and effectiveness, including intervention engagement and compliance estimates.

(v) Moving from a potential benefit approach based on cost effectiveness:

From a health economics perspective, patient discrimination and prioritisation for intervention should be on the basis of potential cost effectiveness using QALE. At present, economic evidence is limited regarding the cost effectiveness of multi-factorial and lifestyle interventions. The model can be used to help generate this evidence. However, this is conditional upon policymakers developing a more rigorous evaluation agenda.

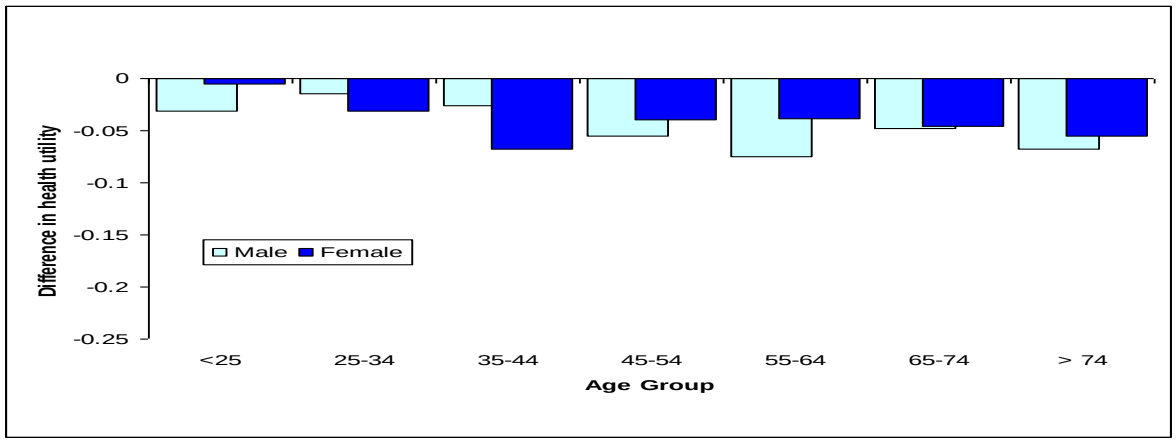
(vi)The impact of interventions on improving background health utility:

At present, the model estimates the health related quality of life impact of interventions on avoiding non-fatal events. However, it may also be the case that by reducing risk factor levels may result in improvements to background mortality irrespective of changes to event rates.

As a proof of concept analysis, the cross-sectional SHeS 2003 was used to re-estimate population background morbidity conditional upon smoking status, finding striking differences. Smoking is associated with considerably lower health utility in both males and females, including the youngest age groups (Figure 1). Average health utility in men who smoke was 0.779 (0.804-0.753) compared to 0.816 (0.802-0.83) in non-smokers – an average reduction of 0.037 (4.5%). For women the average health utility in smokers was 0.762 (0.74-0.784) compared to 0.796 (0.783-0.808) – an average reduction of 0.034 (4.3%). For comparative

purposes, the size of these reductions is (approximately) equivalent to experiencing a myocardial infarction (see Table 5-8).

Figure 1 Absolute differences in background morbidity (health utility): smokers versus non-smoking



A similar analysis could be undertaken for other risk factors. For those measured on a continuous scale (e.g. systolic blood pressure, total cholesterol and HDL cholesterol) these could be dichotomised into high and low according to clinical guidelines (e.g. hypertensive versus non-hypertensive patients).

However, given the cross-sectional nature of this dataset these estimates infer associations, not causation. That is, it does infer that the act of quitting smoking would result in smokers acquiring the utilities of non-smokers (at least not in the early stages of quitting). To test causal relationships, this analysis would need to be repeated using a longitudinal dataset. If evaluations take into account the impacts of interventions on background morbidity (in addition to mortality impacts and the impact of experiencing a non-fatal event) this would likely result in more favourable cost effectiveness results for primary prevention interventions.

(vii) Make explicit equity judgements:

In demonstrating the policy model, equal weight is given to an additional life year gained irrespective of deprivation status. This is consistent, with the assumption of reimbursement agencies such as the Scottish Medicine Consortium (SMC) or the National Institute for Health and Care Excellence(NICE).

However, this assumption of equal value appears to be odds with government initiatives that have an explicit aim to close health inequalities. This signals that an extra year of life within

deprived communities is (all things remaining equal) valued more highly than an extra of year of life in the general population. However, it is important to formalise such value judgements explicitly into a set of equity weights which can then be used to adjust potential benefit calculations across the population. This process could then result in a more pronounced deprivation gradient in terms of the potential benefit across deprivation groups. The Policy Model provides a transparent conceptual framework upon which the impact of different equity judgement can be made.

(viii) Event and life expectancy predictions:

In the future there will be an opportunity to acquire a further SHHEC-SMR linkage where more first CVD events and deaths will have been observed. This provides an opportunity to re-estimate the model equations.

(viiii) More accurate estimation of life expectancy:

To estimate this area under the survival curve, the standard practice in state transition models as recommended for instance by the National Institute of Clinical Excellence, is to use the trapezoid method; by dividing the area under the curve into a series of segments into rectangles and triangles, defined by cycles of the model, and summing across the area. However, this is approach is an approximation and introduces avoidable error. That is, the area between the hypotenuse of the triangle and the survival curve is omitted. This problem can be reduced by smaller cycles of the model, and so more refined segments. However, a more elegant method, given survival is estimated in continuous time is to calculate the area under the curve by using integrals. However, in a practical sense the model will continue to be in error given the historical dataset. Recalibration of model outputs as illustrated in Chapter 5 will likely be a continual requirement over time.

(viiii) Validation in more up-to-date population(s):

The model was developed and validated on populations that date from the 1980s. It is important to assess how the model predictions perform on a more contemporary population, especially in terms of a population exposed to an intervention(s).

(x) Developing optimal intervention strategies: combining the 10-year risk and potential benefit approach:

The greatest benefits from interventions are potentially in younger individuals. However, it is the older individuals that are at most immediate risk. A switch to a potential benefit approach for prioritisation does not imply similar interventions offered. The concern expressed by

advocates of a population wide approach that a targeted approach necessarily leads to medicalising the population is premature. That is, using 10 year risk scores can be used to define caseness where pharmaceutical interventions could be offered given the urgency of the problem. On the other hand, younger individuals could be expected to have a greater opportunity to live a healthier lifestyle, and have more chance for reversibility of risks. As such, younger individuals could be offered lifestyle interventions. Indeed, this is aligned with how policymakers and clinicians tends to behave. The benefit of the model is to estimate the cost effectiveness of different approaches, and be used to further discriminate between individuals in terms of interventions offered, if necessary.

(xii) Further re-calibration of life expectancy predictions

The model is currently calibrated to a 2009 population. This can be redone for more contemporary populations, as lifetables are made available.

(xiii) Generalisability outside of Scotland:

As discussed earlier, the immediate application of the Policy Model is within Scotland. If the model were to be used in England then a mapping exercise between SIMD and England's Index of Multiple Deprivation (IMD) would need to be undertaken. An alternative option, when considering using the model in England or elsewhere would be to drop SIMD from the model and simply recalibrate to the population. A precedent is that the Framingham risk score was developed in the US and originally in a 1970s population; but is still recommended (JBS2 Guidelines) for use in England with the additional of intercepts intended to calibrate to the population.

10.5.2 Widening the model scope

There are a variety of ways in which the model can be developed further. We now outline the main areas.

(i) Expand scope to consider younger age groups:

The derivation and validation of the model was conducted using adults aged between 30 and 74 years. This age range is commensurate with traditional focus of policymakers. In addition, of increasing focus are concern regarding a possible obesity epidemic and, in particular, the observations of increasing BMI in children and associated unhealthy lifestyle such as sedentary behaviour and diet. There is also concern regarding the associated costs and need for interventions.

There are few economic evaluations of such interventions, or indeed economic models, which can project short term study findings into longer term outcomes. A model under development is an agent-based model based at the Brookings Institute(106-107). This appears to be an extremely complex model structure with the intention to simulate individuals as agents, and the interactions between one another and with relevant contextual variables, such as school food policies.

An example of an actual economic evaluation of a school based intervention, which was accompanied by an economic model to project longer term outcomes was conducted in England(108, 330). This is summarised below in relatively detail, as it provides an interesting approach to the modelling that informs how the Scottish CVD Policy Model might be adapted to be used in younger age groups.

The intervention was nationwide to introduce diet and nutritional requirements for school meals. The study conducted an evaluation within the North East between 2005 and 2010, and conducted a cost consequence analysis. Small, but significant reductions in the saturated fat content of school lunches were detected. To project the potential impacts on CVD, short term findings were extrapolated to estimate future CVD events, and consequent impacts on QALE.

A discrete event simulation was developed with multiple states, with transitions between states driven by QRISK (discussed in Chapter 2). The model is described as proof-of-concept, and the analysis exploratory. The reporting of the model is very transparent. The QRISK 10-year risk score were interpolated to estimate annual risk, allowing lifetime risk to be estimated. There was no significant change in discounted QALE and, taken, at face value the intervention wasn't cost effective. However, the report states the potential wider impact of the intervention on non-CVD events, and potential wider non-health impacts were not valued in a cost effectiveness approach.

In the context of this thesis the most relevant aspect is to learn from the modelling approach taken. While the model structure of the Scottish CVD policy model is different, the ASSIGN variables could be used in a similar way to how the model interpolated the QRISK variables. The Scottish CVD policy model has estimated the relationship between risk variables in continuous time (including age), and estimates lifetime risk, life expectancy, and cumulative lifetime health service costs. This process takes into account both CVD and non-CVD death

outcomes. Therefore, in taking a lead from this study, the policy model could be used in a similarly exploratory way. Nonetheless, the policy model isn't validated for such groups. Further, the policy model also ignores the potentially wider impacts beyond the health service.

(ii) Expand the model to consider secondary prevention:

It was appropriate that the model focussed upon primary prevention, as this is the policymakers' focus. The model already predicts the (time dependent) probability of secondary events conditional upon age at event. The application was to quality adjust survival curves post-event. With further updates to the linkage over time, and greater numbers of secondary and recurrent events there may be the opportunity to expand the model to also inform secondary prevention. This would entail developing further model states representing secondary events with conditional life expectancies.

(iii) Widen focus from CVD to become a chronic disease model:

Perhaps, the most interesting research going forward is to expand the scope of the model and develop a chronic disease model. At present the model predicts non-CVD death, in addition to CVD events. To develop a wider chronic disease model this category could be disaggregated into main constituent parts, such as cancers and respiratory diseases, for instance. Given the SMR links to all hospitalisations, there would be feasible to implement. Essentially, the approach of cause specific hazards would include other diseases. However, the simple structure could remain; unless secondary prevention was also included.

(iv) Widen the perspective to estimate the broader economic impacts of prevention:

A health perspective was adopted where the model is concerned with impacts of interventions on (quality adjusted) life expectancy and health service costs. This is the standard approach for health economic evaluation. However, a more ambitious analysis would be to adopt a societal perspective, which is more in keeping with the overall aims of economics to assess the overall social value of policy. A societal approach would estimate the impacts of interventions on the carers of individuals, and the knock-on financial impacts on the wider economy through changes in productivity from reductions in premature mortality and morbidity. The approach of cost benefit analysis (CBA) is congruent with the societal perspective, where all (major) impacts are valued, and the perspective of the funding sector is a secondary consideration, rather than the prime concern of the cost effectiveness analysis approach.

A simple approach would be to estimate the productivity impacts by estimating working years lost from premature mortality and mortality, and value this using average wage levels, or imputed shadow wage prices. Estimates could be made as a function of age, sex and an individual's social deprivation status. The latter may allow more refined estimates of the value of lost productivity which is dependent on the nature of work an individual undertakes. This essentially a static analysis, conditional upon the timing of an event the model could in principle, instantly computes a productivity cost estimate. The assumptions implicit in this approach are a constant employment ratio, wage rates and costs.

A more sophisticated approach would be to build a dynamic model where the population and health sector is embedded with a larger macroeconomic model. This approach would need to follow an approach common in macroeconomic forecasting, such as computational general equilibrium models. Indeed NATSEM-CHE-CoPS Micro-Macro Chronic Disease Prevention Model has attempted to take this approach, and where CVD is just one of many disease areas under consideration. The model was developed by the National Centre for Social and Economic Modelling (NATSEM) at the University of Canberra, and the Centre for Health Economics (CHE) and Centre of Policy Studies (CoPS) at Monash University, and can be used to model a wide variety of population health initiatives.

Essentially, the model simulates the labour market, health sector and population health simultaneously. It is not clear how equations are estimates or the extent of the data sources used, however in principle this is an interesting approach. There are no examples for the primary prevention of CVD, however in principle this may be possible.

In developing a research agenda to the guiding principle will be that a model should be as simple as possible, and not more so. The key issue returns to what the modelling problem is, as outlined in Chapter 3 under modelling best practice guidelines. It may be that the simple approach as outlined, coupled with scenario analysis (e.g. future employment and wage rates) may be sufficient.

(v) Modelling a wider set of interventions

The demonstration of the model focussed on interventions that are intended to impact on risk factors directly. Further, the interventions were either traditional health sector interventions being rolled-out as part of multi-factorial interventions (drugs, lifestyle advice) or changes in legislation that do not require engagement of individuals, such as reduction in salt content of food. This was appropriate given the focus of the thesis. However, the model could in

principle consider the social determinants, conditional upon evaluation evidence that links changes in upstream interventions (e.g. employment) on CVD events directly, or through mediating health behaviours. At present, socioeconomic deprivation, as measured by the Scottish Index of Multiple Deprivation (SIMD) is considered as a non-modifiable variable. In principle, this could be treated as modifiable conditional upon evidence, or could be used in a 'what-if' modelling exercise to make the case for investment in the wider determinants.

10.6 Conclusion

To conclude, the thesis set out to build a Scottish CVD Policy Model that could be used to help inform the approach to primary prevention. The aims of primary prevention are to avoid premature mortality and morbidity, associated health service costs and to reduce health inequalities. However, it is unclear whether current approaches are best able to meet these objectives, given scarce resources. Key uncertainties concern optimal screening approaches, how best to prioritise individuals for interventions, and how to combine individually targeted and population wide interventions. The Scottish CVD Policy Model is intended to help address these uncertainties. "All models are wrong, but some are useful"(39). The model is intended to be rigorous, comprehensive and easy to understand. It appears to add value to the existing economic models regarding the model approach, validation of outputs and the wide range of applications. Nonetheless, no model should ever be considered complete(331). It is hoped that an exciting research agenda had been identified, and to be fulfilled in the future.

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