# The cost-effectiveness of population level interventions to lower cholesterol and prevent Coronary Heart Disease: extrapolation and modelling results on promoting healthy eating habits from Norway to the UK

*Final Phase 2 Report for the project "Health economic analysis of prevention and intervention approaches to reducing incidence of Coronary Heart Disease"*

Gethin Griffith
Julia Fox-Rushby
Martin Buxton

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Health Economics Research Group,
Brunel University, Uxbridge, Middlesex UB8 3PH, UK

HERG
Health Economics Research Group

# Executive Summary


## Aim and Objectives

The aim of this report is to present the best available model(s), given resources and deadlines set, of the cost-effectiveness or cost-utility of at least one intervention/programme designed to change knowledge, attitude and behaviour in the population or specific communities (including families and individuals) in order to help to promote healthier lifestyles and reduce the risk of developing coronary heart disease.

## Methods

Having examined the evidence statements from the five effectiveness reviews commissioned by NICE in 2006 it was agreed with the NICE behaviour change team that none of the reviews provided suitable information to select an intervention to model. As available resources precluded modelling from scratch the interventions identified in the economic review would provide the intervention to be modelled. Applying sequential criteria (see Table 1), two interventions were identified for modelling, a personally-focussed intervention (Olsen et al, 2005) and a population level intervention (Kristiansen et al., 1991). This report focuses on replicating, transferring and developing Kristiansen et al.'s model of promoting healthy eating.

## Results

The base case analysis resulted in a cost per QALY ICER of £87 (£116 per life year). Multi-way sensitivity analysis assuming the least favourable parameters for cost-effectiveness provided an ICER of £10,679. One-way sensitivity analysis indicated that the most influential parameters in terms of affecting the ICERs unfavourably were low participation, increased cost of delivering the population intervention and the cost of medication post infarction.

## Main Conclusions

There was evidence of cost effectiveness for the population-based 'mass-media and school based' intervention targeting males aged 40+ years. A number of limitations were identified with the intervention, including the age of the data upon which the effectiveness of the intervention was based, as well as underestimating the costs and benefits when applying a population wide intervention to a single disease (MI) and specific sector of the population (males 40-49).

The modelling procedure did highlight the potential benefits of applying economic modelling to new behaviour change interventions when compared to current practice. With sufficient resources, including medical and epidemiology support, a probabilistic model would allow the synthesis of data from multiple trials to be used, identification of variables that influence cost effectiveness significantly and the assessment of the value of collecting further data.

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This work was funded by the National Institute of Clinical Excellence. We thank Professor Ivar Kristiansen and Jens Olsen for providing additional background materials to their work and for being willing to help us with our enquiries - especially when we were asking about work from nearly two decades ago. We also thank Roberta Ara for explaining some of the methods used by her and her colleagues in their work looking at statins as a CHD intervention. We are grateful for advice on, and review of, the models by David Wonderling and Dr Stephen Morris.

## SECTION 1: BACKGROUND

### 1.1 Disease burden

Coronary heart disease (CHD) is a leading public health problem and the leading single cause of death in the UK. Around one in five men and one in six women die from the disease (Petersen et al., 2005) and, of the 110,000 people a year who die from CHD in England, 41,000 are under the age of 75 (Wanless 2002). There are large disparities across ethnic groups with death rates from CHD not falling as fast in South Asians, for example, compared with the rest of the population (Petersen et al., 2005).

In addition to the impact on people, CHD also places a heavy financial burden on the UK health care system - £1.73 billion in 1999 (Liu et al 2002). CHD accounted for 4.1% of the total health expenditure in the UK in 2003 and is among the highest healthcare costs in the EU (Leal et al, forthcoming). Wanless (2002) estimated that an additional £2.4 billion a year by 2010-11 is required to implement the NSF, which would be a doubling of NHS expenditure on CHD.

As CHD is largely preventable (Wanless, 2002), the Government aims to reduce the death rate from CHD, stroke and related diseases in people under 75 by at least two fifths by 2010 (DH 1999). The 'fully engaged' scenario (Wanless 2004) set out a framework for action to tackle key health problems such as smoking and obesity that contribute to CHD. However, this scenario requires improved monitoring of the health of the UK population and improvements in the cost-effectiveness of the NHS. There is also concern that "even effective programmes for lifestyle changes in diet, exercise and behaviour can be intensive and expensive" (Avenell et al, 2004).

### 1.2 Development of NICE guidance

The paucity of knowledge about the cost-effectiveness of prevention methods, coupled with the need to ensure that effective interventions are used efficiently (Wanless 2002 & 2004) explains why NICE has been asked, by the Department of Health, to develop guidance on "*the most appropriate means of generic and*

*specific interventions to support attitude and behaviour change at population and community levels*."

This public health programme guidance will consist of recommendations on broad-ranging (those that may apply across a range of topics or behaviours) and specific interventions (those that relate to a particular activity like smoking) that aim to promote or support attitude, knowledge and behaviour change, in order to help reduce the risk of developing preventable diseases or conditions or help to promote healthier lifestyles. This guidance will provide recommendations for good practice, based on the best available evidence of effectiveness, including cost effectiveness.

Six reviews have been commissioned and completed to inform the development of this guidance and these are as follows:

1. A review of the use of the Health Belief Model (HBM), the Theory of Reasoned Action (TRA), the Theory of Planned Behaviour (TPB) and the Trans-Theoretical Model (TTM) to study and predict health related behaviour change (Taylor et al 2006a).

2. A review of the social and cultural context on the effectiveness of health behaviour change interventions in relation to diet, exercise and smoking cessation (Taylor et al 2006b)

3. A review of the effectiveness of general interventions delivered outside public health (e.g. marketing) at changing knowledge, attitudes and behaviour, in particular road safety and environmental interventions (Stead et al, 2006)

4. A review of the effectiveness of public health interventions including policy and legislative measures in changing knowledge, attitudes and behaviour (Jepson et al 2006).

5. A review of the effectiveness of interventions to support and maintain health producing knowledge, attitudes and behaviour (Harrop et al 2006).

6. A review of evidence on the cost-effectiveness of interventions and programmes designed to change knowledge, attitude and behaviour in the whole population and specific communities (including families and individuals) in order to help to promote healthier lifestyles and reduce the risk of developing CHD (Fox-Rushby et al 2006)

The development of this guidance needs to draw on, and fit within, existing NICE frameworks for evaluating health technologies although the process of developing guidance could also provide an opportunity to consider the relevance of the 'reference case' (evaluation guidelines NICE 2004 & 2006) to evaluating public health interventions.

### 1.3 Development of work on cost-effectiveness of public health interventions to reduce CHD prior to this report

At the commissioning stage, NICE chose to narrow the scope of the economics work to the cost-effectiveness of behaviour change strategies aimed reducing CHD. This was designed with a longer term strategy in mind - to help move towards comparisons of the effectiveness and efficiency of behaviour change interventions with treatment strategies for CHD, the latter of which have been the subject of several reviews. Using QALYs as the key health outcome measure is one way of moving towards informing the development of guidance, whilst recognising that prevention is concerned with maintaining healthy behaviours. The focus on CHD also reduces the complexity of modelling as the impact of interventions on multiple diseases at one time is not required. Nevertheless, it is recognised that any estimate of overall health benefit will be conservative precisely for this reason.

The invitation to tender by NICE recognised that "applying economic models to this area of work can be difficult. The literature searches carried out to develop the guidance may find insufficient evidence to perform a formal economic analysis. If this is the case, the economic evaluation carried out may be a more

developmental piece of work than is usual in NICE guidance." Our response also noted that "there is an unusually short time period available (even for NICE) for the development of an economic model (34 days), particularly in an area unlikely to be supported by a relevant systematic review of cost-effectiveness from NCCHTA or NICE. Therefore it is possible that an economic model will be provided at a more developmental stage than is usual for NICE guidance". Nevertheless, the spirit of endeavour promulgated by this process aims also to help inform other aspects of NICE's work including future guidance documents and methodological developments in health economic analyses of public health interventions.

This health economics component was conceived in three phases:

*Phase 1:* Identify, review and summarise existing evidence on the cost-effectiveness of behaviour change interventions.

Results were presented in Fox-Rushby et al (2006) and at the behavioural change PDG in December 2006. The main findings are summarised in Appendix 1 of this report.

*Phase 2:* Use, adapt or develop model of the cost-effectiveness of one or more behaviour change interventions.

The aims, methods and results are presented in this report.

*Phase 3:* After submission of the evidence to the PDG, critically review the process and findings of the economic evidence and consider the implications for future work with respect to interventions to change behaviour as well as to control CHD.

This report will be presented to the Public Health Research Team at NICE on 19th March.

## 1.4 Setting the scene for this report

The previous report showed that no high quality UK relevant study existed on this topic (i.e. an intervention set in a UK context, with RCT level evidence in the short and longer term showing evidence of effectiveness, and an ICER <£30,000/QALY and whose conclusions were supported with similar evidence from outside the UK). If there had been, our first best solution would have been to use the results directly. As there were not, modelling was necessary.

We therefore searched for slightly more limited UK models but none existed with a strong enough basis to aid modelling. At this stage we would ideally have been able to turn to the effectiveness reviews and been guided by the PDG towards a particular behaviour change intervention that with good quality evidence of effectiveness at reducing CHD and then developed a model from scratch. Unfortunately this was not possible for a number of reasons: almost none of the reviews on the effectiveness of behaviour change interventions, commissioned by NICE, provided evidence on final outcomes; few made links to impact on CHD specifically; it was a little early for the PDG to have settled on their recommendations of the most effective interventions; and, given the time and resources available modelling from scratch was not possible.

Therefore this report reflects a fourth-best approach to modelling the cost-effectiveness of behaviour change interventions, but the best available option at the time. In conjunction with the public health team at NICE, we set a series of criteria from which to select the choice of intervention for modelling. The methods are spelt out clearly in the report.

## 1.5 Aim and structure of the report

The aim of this report is to present the best available model(s), given resources and deadlines set, of the cost-effectiveness or cost-utility of at least one intervention/programme designed to change knowledge, attitude and behaviour in the population or specific communities (including families and individuals) in order to help to promote healthier lifestyles and reduce the risk of developing coronary heart disease.

This report is set out in five further sections:

- Selection of intervention for modelling
- The methods, results and issues raised in using forensic modelling to replicate selected paper(s)
- A transfer of the replicated model to England and Wales using local parameter values
- The development of, and results from, a new Markov model to estimate cost-effectiveness of the intervention in the UK
- Results of sensitivity analysis conducted with the Markov model
- Discussion of findings and initial discussion of methods[1]

[1] A full discussion of the implications of the process of research for the future will be provided in a third report to be submitted in March.

## SECTION 2: SELECTION OF INTERVENTION FOR MODELLING

In consultation with the NICE behaviour change team it was agreed that, for an intervention to be suitable for assessment using economic modelling,

- evaluations of interventions should show evidence of effectiveness in terms of impact on CHD;
- effectiveness data was needed to demonstrate the link to a final outcome indicator comparable with other interventions, facilitating calculation of an incremental cost per life year or QALY;
- the description of the programme evaluated needed to be sufficiently detailed to allow a reasonable estimation of resources used, so that costs could be estimated.

All evidence statements, provided by NICE in October 2006, from the five effectiveness reviews were consulted. Four of the five reviews provided information on effect sizes from interventions[2]. Evidence statements graded with either a 1+ or 1++ for quality and either an A or B for relevance were grouped into evidence for implementation and evidence to halt implementation.

In grouping the evidence statements from Jepson et al (2006), Taylor et al (2006b) and Stead et al (2006)[3] it was notable that no evidence statement was written in terms of impact on final health gain either in terms of additional life year or QALYs. Evidence statements predominantly focussed on intermediate indicators such as quit rates, reduction of smoking or alcohol intake, prevention of uptake (of cigarettes or illicit drugs), reaching a predetermined level of physical activity, physical activity level, increased knowledge of safety and correct behaviour, ability of drivers to see pedestrians, consumption of healthy food (e.g. fruit, less salt), blood pressure, cholesterol levels, or weight gain. The only exception to this was a reference to Brunner et al (2005) who noted that sustained diet related behaviour change could permit relatively large public health gains (Taylor et al 2006b), specifically “11 to 12 per cent reduction in stroke and

[2] Taylor et al (2006a) did not provide such information as the paper was focussed on theories of health behaviour.
[3] Evidence statements by Harrop et al (2006) for their question No 5 only reached a 1-2C or 3+A level at best.

coronary heart disease incidence (assuming) reductions in risk attributable to the changes in cholesterol and diastolic BP can be combined additively".

As none of the reviews of effectiveness reviews provided usable information to guide a starting point and because the resources available precluded modelling from scratch, it was agreed that the papers and results of the economic evaluation review would form the basis for selection.

Early discussions with NICE concluded that it was unlikely to be beneficial to model the cost-effectiveness of smoking cessation programs because confining an evaluation to the effect on CHD alone would grossly underestimate the health benefits of the intervention e.g. ignoring the impact on cardiovascular disease and cancer etc. Given that 80% of the literature identified in the economic evaluation review related to single (65%) or mixed (15%) interventions with respect to diet, it was recognised that it was most likely that a dietary intervention would be considered for modelling especially as they most frequently fell in the' likely to be very cost-effective' category (Fox-Rushby et al 2006). We also agreed that it would be useful to consider interventions at more than one level, such as a population wide and personally-focussed interventions and that, as CHD risk factors affect cost effectiveness, sub-group analysis may be relevant – although only useful if of decisional value.

The following criteria were agreed with NICE and applied to interventions in a hierarchy:

1. only interventions whose cost-effectiveness was assessed in terms of cost per life year or cost per QALY were included, in line with NICE guidance;
2. only interventions whose ICERs were reported to be below or approaching the threshold of £30,000/QALY (£30,000-£36,000);
3. the evidence and intervention itself (and its control) must be transferable to the UK. As a proxy for this, we used an arbitrary cut-off of 50% of Pang's transferability index (see Fox-Rushby, 2006). We noted which studies had been conducted in the UK (which showed where these papers dropped out of the choice of interventions for modelling).

4. Evidence in the short or long run was required to have some level 1 evidence, and thus draw on a randomised controlled trial.
5. Because of the political difficulties associated with cutting services in practice, NICE agreed that it would be advisable to concentrate on interventions in the north-east quadrant for a first modelling exercise.
6. Papers needed to provide a reasonable amount of data to allow modelling. Our phase 1 review used a "relevance to modelling" score based on a number of criteria. We selected the highest scoring paper.

After applying criteria 1-5 to all papers, Table 1 shows that only an intervention reported in D12 (Olsen et al, 2005) was selected - nutrition counselling by a GP or dietician. As this was a personally-focussed intervention and NICE were keen for a population-level intervention we selected out just the papers included a population focussed intervention and dropped the criteria about transferability. This led to the selection of the population based promotion of better eating habits reported in D15 (Kristiansen et al, 1991), which also happened to have the highest 'relevance to modelling' score of all 26 papers reviewed.

The nature of interventions in both selected papers was discussed with NICE during a teleconference to allow them to make a judgement on whether the interventions (and control) selected were applicable to the UK. It was concluded that the population focussed intervention 'D15: Kristiansen et al. (1991)' be modelled.

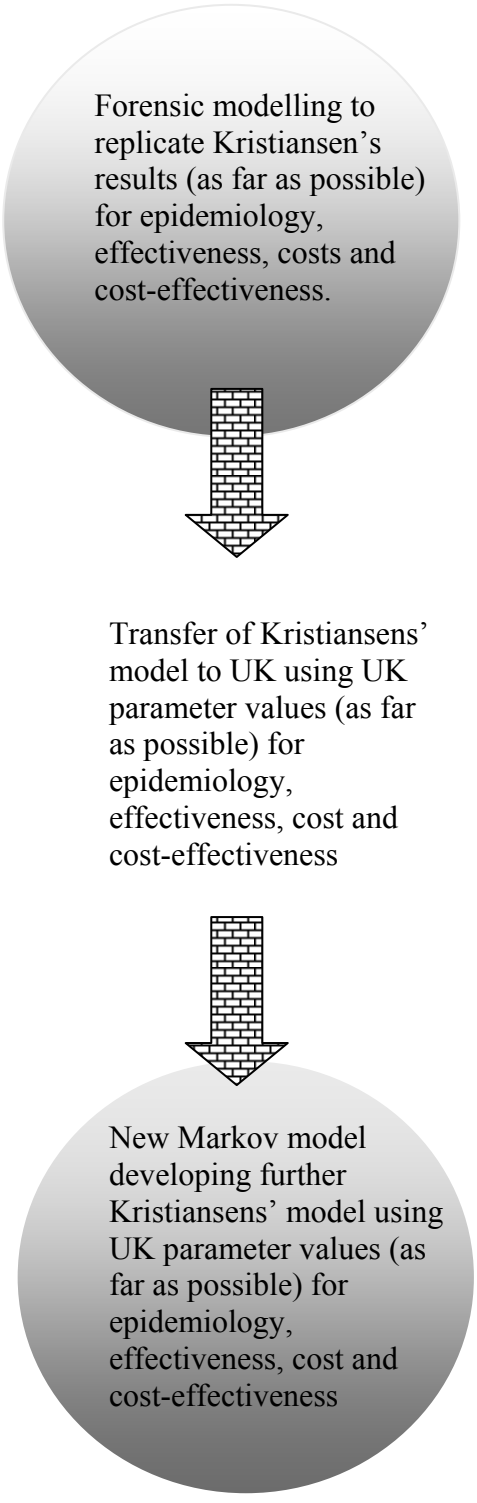
**Table 1: Inclusion and exclusion criteria applied to select intervention for modelling (see Appendix 2 for key)**

| | All studies (n=26) | | Non-personal interventions (community, work and population) (n=16) | |
|---|---|---|---|---|
| **Criteria** | **In** | **Out** | **In** | **Out** |
| All studies | C1, C2, C3, C4, D1, D2, D3, D4, D6, D5, D7, D8, D9, D10, D11, D12, D13, D14, D15, D16, D17, E1 (UK), E2, S1, S2, S3 (UK) | | *Community:* C4, E1 (UK) *Population:* C2, D2, D3, D5, D7, D8, D9, D13, D14, D15, D16, E2, S1, S3 (UK) | |
| Cost per QALY or survival data recorded | C1, C2, C3, D1, D4, D5, D7, D8, D9, D10, D11, D12, D13, D14, D15, D16, D17, E1 (UK), E2, S2, S3 (UK) | C4, D2, D3, D6, S1 | E1 (UK), C2, D5, D7, D8, D9, D13, D14, D15, D16, E2, S3 (UK) | C4, D2, D3, S1 |
| <=£36,000 | C1, C2, C3, D4, D5, D7, D8, D9, D10, D11, D12, D13, D14, D15, D16, D17, E1 (UK), E2, S2, S3 (UK) | D1 | E1 (UK), C2, D5, D7, D8, D9, D13, D14, D15, D16, E2, S3 (UK) | |
| Transferability scores >=50% | C3, D4, D9, D10, D11, D12, D13, D16, E1 (UK), E2, S2, S3 (UK), | C1, C2, D5, D7, D8, D14, D15, D17 | Not applied | Not applied |
| RCT effectiveness data (short/ long term level = 1) | C3, D4, D9, D12, D16 | D10, D11, D13, E1 (UK), E2, S2, S3 (UK) | D9, D14, D15, D16 | E1 (UK), C2, D5, D7, D8, D13, E2, S3 (UK) |
| ICER in north-east quadrant | C3, D4, D12 | D9, D16 | D14*, D15 | D9, D16 |
| **Intervention selected** | **D12** | | **D15** | |

(*paper provides virtually no description of intervention)

The process of modelling the cost-effectiveness of a population level healthy eating promotion programme based on Kristiansen et al (1991) was undertaken in three steps, as indicated in Figure 1. Each circle is the subject of one of the following sections of the report. The first step of 'forensic modelling' is required to understand the basis for evidence prior to proceeding to transfer findings – can the model be reproduced (tested by replication of results using the same input data)? It is a necessary first step for questioning and understanding assumptions of the original evidence as well as the degree of understanding of those transferring evidence. Having understood the starting position, or at least what is replicable, the second step is to transfer the model into a UK situation, using as many UK relevant parameters as possible. The final step is to consider how a model could be improved and to move on to further developments.

**Figure 1: Process of modelling adopted in this report**



## SECTION 3: REPLICATING KRISTIANSEN ET AL'S MODEL

This first part of this section describes the focus of Kristiansen et al's paper and outlines the model. The second part presents the methods and results from replicating the model.

### 3.1 Focus of Kristiansen et al's paper

In 1991 Kristiansen and colleagues evaluated, by means of mathematical estimation, three alternative strategies designed to reduce cholesterol with the explicit aim of reducing myocardial infarction morbidity and mortality. The strategies were:

1. Population based promotion of health eating
2. Screening tests for cholesterol followed by dietary treatment via a doctor plus additional blood sampling at intervals depending on results.
3. Diet and (unspecified) lipid lowering drug treatment for those at highest risk with additional visits to a doctor.

The individual approaches (No. 2 & 3) were based upon the Norwegian cholesterol-lowering programme which provided guidance for the treatment of high blood cholesterol. However, for the purposes of this research we are interested in the first intervention only, compared with 'doing nothing'. A summary of the intervention, study design and findings are presented in Appendix 3. The only information in the paper to describing the content of the programme to promote healthy eating is:

- "*The population approach, entail(s) ….promoting health eating habits*";
- *The Norwegian nutrition policy … is based on two* (unreferenced) *government white papers. The Norwegian Nutrition Council has an important role as a broker of information among the scientific community, the agricultural sector, the food industry, and health authorities, as well as schools and the general public. The impact on eating habits may be enforced by a more targeted use of the mass media as well as through levying taxes on fatty foods or subsidising low fat foods";*

- *"We assumed a stronger commitment to health education programmes in schools and the increase use of the mass media*" (and a budget increase for the Norwegian Nutrition Council).

The costs and effects (in life years and QALYs) for the strategy were compared with 'doing nothing' for a population of 200,000 40-49 year old men in Denmark against a comparator of 'do nothing' and assuming that 10% of the overall costs of the intervention were allocated to this sub-group of the population. They concluded that, over 10 years, 648 non-fatal MI's and 325 fatal MI's would be avoided (see Table 2). The incremental cost per life year saved over a 20 year period was £12 and incremental cost per QALY was £10 for the population based strategy. Appendix 3 provides our phase 1 summary (Fox-Rushby et al 2006) of evidence on results and methods for Kristiansen et al (1991).

**Table 2: Kristiansen et al. (1991) – Health outcomes**

| | | **No intervention** | | | **Mass media (population strategy)** | |
|---|---|---|---|---|---|---|
| Serum Cholesterol | N0. Men | Non-fatal MI | Fatal MI | Total MI's | **Reduction in** non-fatal MI | **Reduction in** fatal MI |
| 1st 10 years of the intervention | | | | | | |
| ≤4.9 | 40,000 | 0 | 0 | 0 | 0 | 0 |
| 5.0 – 5.9 | 40,000 | 640 | 320 | 960 | 64 | 32 |
| 6.0 - 6.9 | 70,000 | 1,960 | 980 | 2940 | 245 | 123 |
| 7.0 – 7.9 | 30,000 | 1,240 | 620 | 1860 | 155 | 78 |
| ≥8 | 20,000 | 1,226 | 614 | 1840 | 184 | 92 |
| **Total** | **200,000** | **5,066** | **2,534** | **7600** | **648** | **325** |
| | | | | | Subsequent 10 years of the intervention | |
| ≤4.9 | 40,000 | 0 | 0 | 0 | 0 | 0 |
| 5.0 – 5.9 | 40,000 | 1,920 | 960 | 2,880 | 192 | 96 |
| 6.0 - 6.9 | 70,000 | 5,880 | 2,940 | 8,820 | 735 | 369 |
| 7.0 – 7.9 | 30,000 | 3,720 | 1,,860 | 3,720 | 465 | 234 |
| ≥8 | 20,000 | 3,678 | 1,842 | 5,520 | 552 | 276 |
| **Total** | **200,000** | **15,198** | **7,602** | **22,800** | **1,944** | **975** |

Source: Kristiansen et al. (1991)

The research was first published in Norwegian in the journal 'Tidsskr Nor Laegeforen' in 1989 (Eggen et al, 1989) and covered a 10-year analysis period. Subsequently, the myocardial incidence estimates were revised for the 10-year period, estimated for a following 10 year period and translated into English for the

BMJ (personal communication with Professor Ivar Sønbø Kristiansen, 15th January 2007).

Kristiansen et al. (1991) applied estimates of the number of myocardial infarctions that would be expected in a 10 year period for males based on total serum cholesterol concentrations (Westlund and Nicolaysen, 1972). In a prospective cohort study Westlund and Nicolaysen (1972) found, for a cohort of 3751 males aged 40-49 years, that the best predictor of myocardial infarction from the independent variables used (weight-height, serum cholesterol, systolic and diastolic blood pressure) was total serum cholesterol alone. The estimates of the number of myocardial infarctions for the 40-49 year old males were split into 2/3 non-fatal and 1/3 fatal in each of the serum cholesterol categories. This method was then applied for the subsequent decade assuming that the incidence of myocardial infarction was three times that seen in the first decade. Table 2 shows that 1944 non-fatal MI's are avoided in years 10-20 compared with 648 in years 1-10.

For illustrative purposes, the implicit model behind Kristiansen et al's model has been represented graphically in the form of a decision tree. In Figure 2 males begin by being free of MI progress and through the tree to experience one of three states; fatal MI, non-fatal MI or no MI. The numbers of avoided MI's recorded for the first decade are given in Table 2. Males that are free of MI at the end of the first decade then proceed through the tree again and can fall into one of the three same states but with a different probability of doing so. The avoided MI's are then added to the results for the first decade (see Table 4).

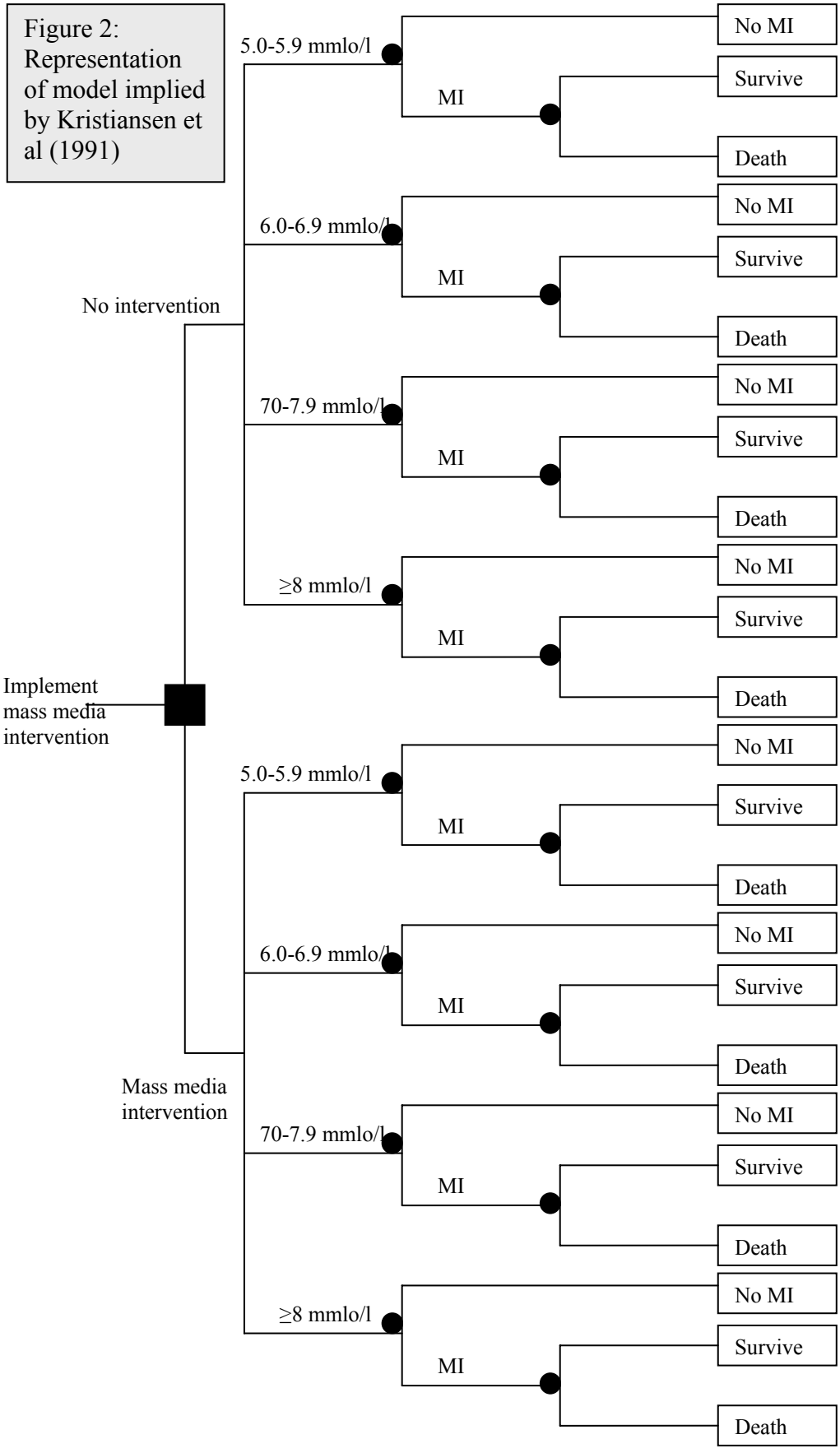



**Figure 2: Kristiansen's spread-sheet model represented as decision tree**

Table 3 sets out the principal parameters and sources of data used by Kristiansen et al (1991) in estimating the costs and effects of the population based healthy eating promotion programme under six categories; demography, epidemiology, effectiveness, utilities, costs and discounting.

**Table 3: Parameter estimates and sources of data in Kristiansen et al (1991)**

| | Parameter | Source of data |
|---|---|---|
| Demography | Estimate of Norwegian males 40-49. See Table 2 | Unrecorded |
| Epidemiology | The number of males by lipid concentration (5-5.9, 6-6.9, 7-7.9, ≥8)[4][5]. See Table 2 | Based on Tromso heart study population (E Arensen, personal communication) |
| | Number of myocardial infarctions at different lipid concentrations (applied to Norwegian male population 40-49). See Table 2 | Based on a 10 year follow up of 3725 men aged 40-49[3] |
| | One third of myocardial infarctions are fatal. | Based on a 10 year follow up of 3725 men aged 40-49[3] |
| | A threefold increase in myocardial infarctions occurs in the next 10 year follow-up. | Norwegian cause of death statistics used behind assumption. |
| | Mass media intervention reduces cholesterol by 5% | 4% reduction shown in North Karelia project[1] and 5% reduction shown in Norwegian studies[2] |
| Effectiveness | 5% reduction in cholesterol resulted in a reduction in MI risk of 10% for individuals with cholesterol levels of 5.0-5.9, 12.5% for cholesterol = 6.0-6.9, 12.5% for cholesterol = 7.0-7.9 and 15% for cholesterol ≥ 8.0. | Authors' view that a 2% reduction in the incidence of CHD is normally assumed when serum cholesterol is reduced by 1% (referenced to and RCT in JAMA[4] and Norwegian findings on personal focussed interventions[5]) ... "may be too conservative" |
| | Full participation and compliance with the programme was assumed (100%). | Author assumption |
| | Cholesterol lowering begins in the 3rd year of programme. | Gradually increasing effect of a cholesterol reduction programme taken from 2 clinical trial papers in JAMA[4] |
| | To calculate life years (and subsequently QALYs) all myocardial infarctions in the first ten year were assumed to occur at the mid-point year 7 in the first 10 years (as the first 2 years were not assumed to have a reduction in cholesterol) year 15 in the second 10 year period. | Author assumption, but possibly based on Norwegian 'Cause of Death Statistics', although not clear how. |

[4] [4] Sometimes cholesterol is quoted in mg/dl (milligrams per decilitre). Converting mmol/l to mg/dl is done by dividing the mmol/l figure by 0.0259; the opposite conversion is achieved by multiplying by 0.0259.

[5] NHS Direct recommends total cholesterol of under 5.0 mmol/l, and consider a level above 6.0 mmol/l as high and a health risk factor (NHS Direct 2007)

| | | |
|---|---|---|
| | Reduced cholesterol was assumed to reduce the number of coronary artery bypass graft operations for angina pectoris | Unspecified 'records of the total number of such operations in Norway'. No data provided on estimates used. |
| Utilities | Avoided fatal myocardial infarction =1.0 incremental utility | Read et al. (1984) |
| | Avoided non-fatal myocardial infarction =0.1 incremental utility | |
| Costs | The authors state that only heath care costs were considered. However, the costs of the intervention bourn by the Norwegian Nutrition Council include brokering information to schools as well as using the mass media | Author choice based on previous approach used separately by M.Weinstein and A.Williams |
| | The mass-media strategy had a unit cost per year of £454,545 | Estimated by increasing the annual National Nutrition Council Budget 10 fold (£4545,450) and allocating 10% to males 40-49. |
| | Cost saving from the unspecified number of reduced CABG operations was £9922 per operation. | |
| | 25% of patient with avoided fatal myocardial infarction were assumed to have the cost savings of an avoided inpatient hospital stay (£2318 per hospital stay) | |
| | Savings from reduced treatment costs following infarction (beta blockers). £227 per year | |
| | Costs resulting from survival. Annual health care costs of £455 (£0-£363) per year | |
| Discounting | Future costs and benefits were discounted at 7%. | Rate recommended by Norwegian Treasury |
| | Unit costs of inputs | 'current fee schedules or recent cost calculations' |

[1] Salonen J et al (1981) Changes in smoking, serum-cholesterol and blood pressure during a community-based cardiovascular disease prevention programme – the North Karelia project *Am J Epidemiol* 114, 81-94

[2] National Health Screening Services. (1988) The cardiovascular disease study in Norwegian Counties – results from the second screening. Oslo, National Health Screening Service

[3] Westlund K and Nicholaysen R (1972) Ten year mortality and morbidity related to serum cholesterol. *Scand J Clin Lab Invest* 30 (suppl 127) 3-24

[4]The Lipid Research Clinics Coronary Primary Prevention Trial results (1984) 1 & 11. *J Am Med Assoc* 251, 351-364 and 251, 365-374

[5]Bjartveit K et al (1988) A cholesterol lowering programme for the adult population *Tidsskr Nor Lægeforen* 108, 2285-8

### 3.2 Can the model be reproduced?

The first key step in reproducing this model was to ascertain how the numbers of fatal and non-fatal myocardial infarctions (MI) for the 'no intervention' serum cholesterol groups were estimated and to replicate this step.

There are two ways in which MI estimates, in the form of the percentage of patients expected to develop an MI in a 10 year period for males 40-49, can be ascertained from the Westlund and Nicholaysen (1972) paper; using coefficients from the regression equations presented or reading the results in tables from the paper.

By means of regression analysis Westlund and Nicholaysen (1972) produced an estimate of the percentage of 40-49 year old males likely to develop MI (incidence= 0.00629[serum cholesterol in mg/dl] + 1.651) and die from MI (mortality= 0.00641[serum cholesterol in mg/dl] + 1.170) over a 10 year period. The minimum, maximum and mid point (e.g. 5.0 mmol/l, 5.9 mmlo/l and 5.45 mmlo/l) and rounding of their transformed values (mmlo/l * 0.0259) was not the same percentage for incidence and mortality reported by Kristiansen et al. (1991) (see Tables 4 and 5)[6].

**Table 4: Incidence and mortality applied by Kristiansen et al.**

| Serum Cholesterol | Number of men | Non-fatal infarctions | Fatal infarctions | Number of infarctions | Non-fatal MI % | Fatal MI% | Total % |
|---|---|---|---|---|---|---|---|
| 5-5.9 | 40,000 | 640 | 320 | 960 | 1.6 | 0.8 | 2.4 |
| 6-6.9 | 70,000 | 1,960 | 980 | 2,940 | 2.8 | 1.4 | 4.2 |
| 7-7.9 | 30,000 | 1,240 | 620 | 1,860 | 4.1 | 2.1 | 6.2 |
| ≥ 8 | 20,000 | 1,226 | 614 | 1,840 | 6.1 | 3.1 | 9.2 |
| Sum | 160,000 | 5,066 | 2534 | | | | |

[6] The results of the MI mortality and incidence were also combined as MI incidence minus MI mortality. However, these calculations did not match the percentage of MI estimated for males receiving no cholesterol reducing interventions as reported by Kristiansen. For example, for 5.0mmol, incidence (2.86%) minus mortality (2.41%)= 0.45%, whilst Kristiansen et al. record a value of 1.6% non-fatal MI, 0.8% fatal MI and a total of 2.4% (see Table XX and XX).

**Table 5: Incidence and mortality calculated from Westlund and Nicholaysen's (1972) regression/prediction equations**

| Chole-sterol mmlo/l | Chole-sterol mg/dl | Cholesterol coefficient for mg/dl | Constant | Incidence | Chole-sterol coefficient for mg/dl | Constant | Mortality |
|---|---|---|---|---|---|---|---|
| 5 | 193 | 0.00629 | 1.651 | 2.86 | 0.00641 | 1.17 | 2.41 |
| 5.45 | 210 | 0.00629 | 1.651 | 2.97 | 0.00641 | 1.17 | 2.52 |
| 5.9 | 228 | 0.00629 | 1.651 | 3.09 | 0.00641 | 1.17 | 2.63 |
| 6 | 232 | 0.00629 | 1.651 | 3.11 | 0.00641 | 1.17 | 2.66 |
| 6.45 | 249 | 0.00629 | 1.651 | 3.22 | 0.00641 | 1.17 | 2.77 |
| 6.9 | 266 | 0.00629 | 1.651 | 3.32 | 0.00641 | 1.17 | 2.88 |
| 7 | 270 | 0.00629 | 1.651 | 3.35 | 0.00641 | 1.17 | 2.90 |
| 7.45 | 288 | 0.00629 | 1.651 | 3.46 | 0.00641 | 1.17 | 3.02 |
| 7.9 | 305 | 0.00629 | 1.651 | 3.57 | 0.00641 | 1.17 | 3.13 |
| 8 | 308 | 0.00629 | 1.651 | 3.59 | 0.00641 | 1.17 | 3.14 |
| 5 | 190 | 0.00629 | 1.651 | 2.85 | 0.00641 | 1.17 | 2.39 |
| 5.45 | 210 | 0.00629 | 1.651 | 2.97 | 0.00641 | 1.17 | 2.52 |
| 6 | 230 | 0.00629 | 1.651 | 3.10 | 0.00641 | 1.17 | 2.64 |

The incidence and mortality statistics reported by Westlund and Nicholaysen (1972) are reported for cholesterol ranges that span but don't match two of Kristiansen et al.'s (1991) ranges, e.g. Westlund and Nicholaysen (1972) report for 225-249 mg/dl (5.8 – 6.45 mmlo/l) whilst Kristiansen et al. (1991) report incidence and mortality for 5.0-5.9 and 6.0 to 6.9 mmlo/l. It is therefore unclear how Kristiansen et al. (1991) estimated the number of males developing MI. They do not appear to have assumed approximately equivalent groups to select incidence and mortality from the Westlund and Nicholaysen (1972) tables as neither the percentage of total or definite recorded MI's in Norway correspond with the results in Table 4 . For example Westlund and Nicholaysen (1972) record total and definite MI incidence of 6.8% and 4.8% respectively for men with cholesterol of 7.1 to 7.7 mmlo/l, whilst Kristiansen et al. record 4.1% of men with cholesterol of 7.0-7.9 mmlo/l having nonfatal MI's. Whilst replicating the number of MI's is not possible there is no reason to believe that the estimates calculated by Kristiansen et al. (1991) are incorrect and therefore we have proceeded with the ones they used.

The second step in attempting to replicate the results of the Norwegian study was to estimate the incremental difference in life years between the 'no intervention' (control) and the population strategy of 3,100 life years. Based upon the assumptions stated and examination of the tables in Eggen et al. (1989) we would expect 325 less fatalities in the first decade and 975 in the second. The savings are reported to occur from year 7 and 15 respectively and are discounted at 7% a year. From the original Eggen et al. (1989) paper it emerged that discounting occurred from the base year and not the subsequent year, as is more conventional (Drummond et al 1997). Applying these assumptions (see Table 6) provided 3,095 incremental life years. Allowing for rounding this was considered a successful replication of Kristiansen et al.'s (1991) results (within 0.16% of the Kristiansen estimate).

**Table 6: Reproducing Kristiansen et al.'s (1991) incremental life years saved**

| Year | Incremental life years gained | Incremental life years discounted @ 7% (from base year) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 0 | 0 |
| 3 | 0 | 0 |
| 4 | 0 | 0 |
| 5 | 0 | 0 |
| 6 | 0 | 0 |
| 7 | 325 | 202 |
| 8 | 325 | 189 |
| 9 | 325 | 177 |
| 10 | 325 | 165 |
| 11 | 325 | 154 |
| 12 | 325 | 144 |
| 13 | 325 | 135 |
| 14 | 325 | 126 |
| 15 | 975 | 353 |
| 16 | 975 | 330 |
| 17 | 975 | 309 |
| 18 | 975 | 288 |
| 19 | 975 | 270 |
| 20 | 975 | 252 |
| Sum | 8,450 | 3,095 |

The third step was to estimate QALYs. In this particular study quality of life was assumed to improve by 10% when a non-fatal MI was avoided (incremental utility of 0.1). Kristiansen's model assumed that avoiding an MI provided additional years in perfect health (incremental utility of 1.0). Applying these utilities to the number of avoided non-fatal and fatal myocardial infarctions resulted in 3713 QALYs discounted at 7% (See Table 7). This was considered a successful replication as it was within 2.3% of the incremental QALYs reported by Kristiansen of 3800 QALYs. The difference was attributed to rounding in Kristiansen's calculations and results.

**Table 7: Reproducing Kristiansen et al.'s (1991) incremental QALYs gained**

| | Number of avoided | | Incremental QALYs gained from avoided | | | |
|---|---|---|---|---|---|---|
| Years | Non-fatal MI | Fatal MI | Non-fatal MI | Fatal MI | Sum QALYs | Discounted QALYs |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7 | 648 | 325 | 65 | 325 | 390 | 243 |
| 8 | 648 | 325 | 65 | 325 | 390 | 227 |
| 9 | 648 | 325 | 65 | 325 | 390 | 212 |
| 10 | 648 | 325 | 65 | 325 | 390 | 198 |
| 11 | 648 | 325 | 65 | 325 | 390 | 185 |
| 12 | 648 | 325 | 65 | 325 | 390 | 173 |
| 13 | 648 | 325 | 65 | 325 | 390 | 162 |
| 14 | 648 | 325 | 65 | 325 | 390 | 151 |
| 15 | 1944 | 975 | 194 | 975 | 1169 | 424 |
| 16 | 1944 | 975 | 194 | 975 | 1169 | 396 |
| 17 | 1944 | 975 | 194 | 975 | 1169 | 370 |
| 18 | 1944 | 975 | 194 | 975 | 1169 | 346 |
| 19 | 1944 | 975 | 194 | 975 | 1169 | 323 |
| 20 | 1944 | 975 | 194 | 975 | 1169 | 302 |
| Sum | | | | | | 3713 |

The final step was to replicate the cost data reported in the paper. Information on how cost estimates were applied to incremental survival data was particularly sparse in the BMJ paper (Kristiansen et al., 1991). Further detail was sought from the authors, but has yet to be supplied.

Kristiansen et al (1991) provided one table of the components of cost. Table 8 below records the costs relevant to the population strategy. Unfortunately no quantity data was provided in the paper as a result we don't know how many people were assumed to need a CABG. This omission makes it is more difficult to work out how total cost and any cost savings were calculated. However, based upon available detail, total cost was assumed to be:

*Equation 1:*

Total cost = [population intervention costs$^{A}$ + (average health care costs * avoided fatal MI$^{7\ to\ 20)}$] – [(treatment of coronary heart disease (hospital) cost * 25% avoided fatal MI$^{7\ \&\ 15}$) + (Coronary artery bypass grafting * undisclosed % of avoided fatal MI $^{7\ \&\ 15}$) + (treatment after infarction costs * avoided MI)]

*Where: A*= all 20 years; CABG= Coronary artery bypass graft; 7 & 15= Years 7 and 15; 7 to 20= Years 7 to 20.

**Table 8: Costs used in Kristiansen's model**

| Component | Unit of cost | Cost | Source |
|---|---|---|---|
| Average health care cost | Per person per year | £363 | Max in sensitivity analysis |
| Average health care cost | Per person per year | £0 | Min in sensitivity analysis |
| Treatment of coronary heart disease | Per hospital stay | £2318 | Base case |
| Coronary artery bypass grafting (CABG) | Per operation | £9,922 | Base case |
| Treatment after infarction | Per person year | £227 | Base case |
| Population intervention | Per year | £4545,545 | Base case |

The above equation could be solved to estimate the number of CABG; unfortunately we discovered a second problem with the data which made any estimation potentially less robust. The 'base case' cost presented in the paper recorded a value of £455 for 'average health care cost per year'. In Table 8, however, we show that the high and low case values used in the sensitivity analysis were £0 and £363; the highest of which is actually lower than the recorded base case unit cost. The quoted value of £455 in the base case for cost of drugs was linked to an ICER cost per life year of £12 whilst the value of £363 used in the sensitivity analysis produced an ICER of £200 life year. Given that

one-way sensitivity analysis was used an ICER results of £12 per life years using an average health care cost per year of £455 does not make intuitive sense.

Taking Kristiansen et al.'s (1991) sensitivity analysis cost and ICER results rather than the questionable base case result for the cost variable 'average health care cost per year', it was possible to estimate a total cost per life year gained of £620,000. Assuming that equation 1 is correct, the undisclosed percentage of avoided MI patients assumed to avoid the need for CABG was solved. Substituting a value of 32% resulted in a total cost of £619,119 (see Table 9, £619,119/3,095 = £200 per life year). Using the minimum health care costs and maintaining all other values constant resulted in an incremental cost of -£504,542 (ICER of -£163) (see Table 10).

**Table 9: Incremental costs**

| | Survival | | Costs | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Expenditure | | Savings | | | Total costs | Incremental costs discounted @ 7% |
| Years | Inc non-fatal MI | Inc fatal MI | Intervention | Health care costs of survival | Inpatient stay | Post MI costs | CABG | | |
| 1 | 0 | 0 | £454,545 | £0 | £0 | £0 | £0 | £454,545 | £424,808 |
| 2 | 0 | 0 | £454,545 | £0 | £0 | £0 | £0 | £454,545 | £397,017 |
| 3 | 0 | 0 | £454,545 | £0 | £0 | £0 | £0 | £454,545 | £371,044 |
| 4 | 0 | 0 | £454,545 | £0 | £0 | £0 | £0 | £454,545 | £346,770 |
| 5 | 0 | 0 | £454,545 | £0 | £0 | £0 | £0 | £454,545 | £324,084 |
| 6 | 0 | 0 | £454,545 | £0 | £0 | £0 | £0 | £454,545 | £302,883 |
| 7 | 648 | 325 | £454,545 | £117,975 | £188,338 | £147,096 | £2,057,426 | -£1,820,339 | -£1,133,616 |
| 8 | 648 | 325 | £454,545 | £117,975 | £0 | £147,096 | £0 | £425,424 | £247,601 |
| 9 | 648 | 325 | £454,545 | £117,975 | £0 | £147,096 | £0 | £425,424 | £231,402 |
| 10 | 648 | 325 | £454,545 | £117,975 | £0 | £147,096 | £0 | £425,424 | £216,264 |
| 11 | 648 | 325 | £454,545 | £117,975 | £0 | £147,096 | £0 | £425,424 | £202,116 |
| 12 | 648 | 325 | £454,545 | £117,975 | £0 | £147,096 | £0 | £425,424 | £188,893 |
| 13 | 648 | 325 | £454,545 | £117,975 | £0 | £147,096 | £0 | £425,424 | £176,536 |
| 14 | 648 | 325 | £454,545 | £117,975 | £0 | £147,096 | £0 | £425,424 | £164,987 |
| 15 | 1994 | 975 | £454,545 | £353,925 | £565,013 | £452,638 | £6,331,030 | -£6,540,210 | -£2,370,473 |
| 16 | 1994 | 975 | £454,545 | £353,925 | £0 | £452,638 | £0 | £355,832 | £120,533 |
| 17 | 1994 | 975 | £454,545 | £353,925 | £0 | £452,638 | £0 | £355,832 | £112,647 |
| 18 | 1994 | 975 | £454,545 | £353,925 | £0 | £452,638 | £0 | £355,832 | £105,278 |
| 19 | 1994 | 975 | £454,545 | £353,925 | £0 | £452,638 | £0 | £355,832 | £98,391 |
| 20 | 1994 | 975 | £454,545 | £353,925 | £0 | £452,638 | £0 | £355,832 | £91,954 |
| | | | | | | | **Sum** | -£876,152 | £619,119 |

CABG= Coronary artery bypass graft

**Table 10: Incremental costs**

| | Survival | | Costs | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Expenditure | | savings | | | | |
| Year | Inc non-fatal MI | Inc fatal MI | Intervention | Health care costs of survival | Inpatient stay | Post MI costs | CABG | Total costs | Incremental costs discounted @ 7% |
| 1 | 0 | 0 | £454,545.00 | £0 | £0 | £0 | £0 | £454,545 | £424,808 |
| 2 | 0 | 0 | £454,545.00 | £0 | £0 | £0 | £0 | £454,545 | £397,017 |
| 3 | 0 | 0 | £454,545.00 | £0 | £0 | £0 | £0 | £454,545 | £371,044 |
| 4 | 0 | 0 | £454,545.00 | £0 | £0 | £0 | £0 | £454,545 | £346,770 |
| 5 | 0 | 0 | £454,545.00 | £0 | £0 | £0 | £0 | £454,545 | £324,084 |
| 6 | 0 | 0 | £454,545.00 | £0 | £0 | £0 | £0 | £454,545 | £302,883 |
| 7 | 648 | 325 | £454,545.00 | £0 | £188,338 | £147,096 | £2,057,426 | -£1,938,314 | -£1,207,085 |
| 8 | 648 | 325 | £454,545.00 | £0 | | £147,096 | | £307,449 | £178,938 |
| 9 | 648 | 325 | £454,545.00 | £0 | | £147,096 | | £307,449 | £167,232 |
| 10 | 648 | 325 | £454,545.00 | £0 | | £147,096 | | £307,449 | £156,291 |
| 11 | 648 | 325 | £454,545.00 | £0 | | £147,096 | | £307,449 | £146,067 |
| 12 | 648 | 325 | £454,545.00 | £0 | | £147,096 | | £307,449 | £136,511 |
| 13 | 648 | 325 | £454,545.00 | £0 | | £147,096 | | £307,449 | £127,580 |
| 14 | 648 | 325 | £454,545.00 | £0 | | £147,096 | | £307,449 | £119,234 |
| 15 | 1994 | 975 | £454,545.00 | £0 | £565,013 | £452,638 | £6,331,030 | -£6,894,135 | -£2,498,752 |
| 16 | 1994 | 975 | £454,545.00 | £0 | | £452,638 | | £1,907 | £646 |
| 17 | 1994 | 975 | £454,545.00 | £0 | | £452,638 | | £1,907 | £604 |
| 18 | 1994 | 975 | £454,545.00 | £0 | | £452,638 | | £1,907 | £564 |
| 19 | 1994 | 975 | £454,545.00 | £0 | | £452,638 | | £1,907 | £527 |
| 20 | 1994 | 975 | £454,545.00 | £0 | | £452,638 | | £1,907 | £493 |
| | | | | | | | | **Sum** | -£504,542 |

CABG= Coronary artery bypass graft

## SECTION 4: APPLICATION OF THE KRISTIANSEN ET AL (1991) MODEL TO ENGLAND AND WALES

This section describes the application of Kristiansen et al.'s model to the UK. It sets out the issues concerning the comparability of UK and Danish delineations of the cholesterol concentrations in the population and how this defines and affects the methods of applying Kristiansen et al's model. The delineation of parameters is set out in the same ordering as the previous chapters

### 4.1 Issues in applying the Kristiansen et al model to England and Wales

Data identified on UK cholesterol levels for males was frequently recorded as a single statistic indicating the percentage above or below 5.0 mmlo/l (Allender, 2006). The National Diet and Nutrition Survey (NDNS) (Ruston et al., 2004) does provide a more detailed breakdown of total serum cholesterol. However, cholesterol ranges for the NDNS and Kristiansen's model did not match exactly, and so it has been necessary to use the Nutrition Survey categorisations for the England and Wales model. Also cholesterol scores were not available for males aged 40 to 49 in the Diet and Nutrition Survey so the nearest age band of 35-49 was used.

No suitable UK data was found upon linking cholesterol and myocardial infarction for the cohort to be modelled in this study (males 40-49 MI free with specific serum cholesterol concentrations) at the time of conducting this particular analysis[7]. A systematic search for meta-analysis evidence upon clinical parameters (total serum cholesterol and myocardial infarction was conducted on the Ovid Medline database from 1950 to December 2006. A copy of the Medline search strategy is included in Appendix 4. Twenty two papers were identified (see Appendix 5). However, they were not suitable. A further search for all types of paper retrieved 1796 papers. It was not possible to review all abstracts and retrieve potentially relevant papers given the time and resource constraints of this project.

[7] Suitable information linking cholesterol to myocardial infarction was identified for he Markov modelling.

The discrepancy between Kristiansen et al. (1991) and the NDNS (Ruston et al., 2004) cholesterol groupings resulted in:

a. MI risk in the Kristiansen model was linked to serum cholesterol levels, and as a result the discrepancy in cholesterol groupings impacted on this parameter. The cholesterol groupings for the two data sources Kristiansen et al. (1991) and the NDNS (Ruston et al., 2004) were sufficiently close to consider the first two cholesterol categories (5.2-5.79 mmlo/l=5.0 – 5.9 mmlo/l and 5.8 – 6.49 mmlo/l 6.0 – 6.9mmlo/l) approximately equivalent. Equivalence could not be assumed for the England and Wales maximum cholesterol group of ≥ 6.45 mmlo/l and the Kristiansen et al. (1991) grouping of 7.0 – 7.9 and ≥ 8.0 mmlo/l with the respective MI estimates of 6.2% and 9.2%. The mid point of 7.7% was taken for the highest categorisation of ≥ 6.5 mmlo/l used in the following analysis. Both the values of 6.2% and 9.2% were used in the sensitivity analysis.

b. As the MI risk reduction in the Kristiansen model was linked to serum cholesterol levels, the discrepancy in cholesterol groupings impacted on this parameter. As Kristiansen et al. (1991) estimated a 10% reduction in the number of MI's for individuals with a baseline cholesterol score of 5.0 – 5.9 mmlo/l, 12.5% for 6.0 - 6.9 mmlo/l and 7.0 – 7.9 mmlo/l, and 15% for ≥8 mmlo/l, but, the England and Wales cholesterol levels were 5.2 – 5.79 mmlo/l, 5.8 – 6.49 mmlo/l and ≥ 6.5 mmlo/l. As a result MI reductions were varied in the following way:
   Base case - 5.2 - 5.79 =10%, 5.8 - 6.49 = 12.5%, ≥ 6.5 = 12.5%.
   Sensitivity values - 5.8 - 6.49 = 10% and 12.5%, ≥ 6.5 = 12.5% and 15%.

The principal parameters and sources of data used in the following model of a population based healthy eating promotion programme applied to England and Wales are set out in Table 11 in the same format as was done for the Kristiansen et al (1991) model.

## Table 11: Application of the Kristiansen model to England and Wales

| | Parameter | Source of data |
|---|---|---|
| | Population estimates for males 40-49 years in 2006. See Table 12. | Latest (2004 based) Government Actuaries Department (GAD) population estimates (GAD, 2007). |
| Epidemiology | The number of males by lipid concentration (5.2-5.79, 5.8-6.49, ≥6.5). See Table 12. | (National Diet and Nutrition Survey (Ruston et al., 2004) applied to (GAD) population estimates. |
| | The percentage of MI's by lipid concentration. See Table 12. As the category ≥6.5 mmlo/L was between Kristiansen's highest lipid concentrations a mid point of 7.7% was used the Kristiansen values of 6.2 and 9.2 in sensitivity analysis. | Calculation and application of the percentages applied by Kristiansen et al. to the population of England and Wales |
| | One third of myocardial infarctions are fatal. | As for Kristiansen et al. and Petersen et al. (2005)* |
| | A threefold increase in myocardial infarctions occurs in the next 10 year follow-up. | As for Kristiansen et al. |
| | Mass media intervention reduces cholesterol by 5% | As for Kristiansen et al. |
| Effectiveness | 5% reduction in cholesterol resulted in a reduction in MI risk of 10% for individuals with cholesterol levels of 5.2-5.79, 10-12.5% for cholesterol = 5.8-6.49, 12.5-15% for cholesterol ≥ 6.5 | Amendment of Kristiansen et al. to accommodate UK lipid concentrations |
| | Full participation and compliance with the programme was assumed (100%). | As for Kristiansen et al. |
| | Cholesterol lowering begins in the 3rd year of programme. | As for Kristiansen et al. |
| | To calculate life years (and subsequently QALYs) all myocardial infarctions in the first ten year were assumed to occur at the mid-point year 7 in the first 10 years (as the first 2 years were not assumed to have a reduction in cholesterol) year 15 in the second 10 year period. | As for Kristiansen et al. |
| | Reduced cholesterol was assumed to reduce the number of coronary artery bypass graft operations for angina pectoris | As for Kristiansen et al. |
| Utilities | Avoided fatal myocardial infarction | 0.87-0.0 (kind et al. 1999; Ward et al., 2005) |
| | Avoided non-fatal myocardial infarction | 0.87-0.76 (kind et al. 1999; Goodacre et al., 2004) |
| Costs | The authors state that only heath care costs were considered. However, the costs of the intervention bourn by the Norwegian Nutrition Council include brokering information to schools as well as using the mass media | As for Kristiansen et al. |
| | The mass-media strategy had an annual unit cost of £606,045.4. | As for Kristiansen et al. increased to 2006 ppp £ |
| | Cost saving from the reduced number CABG operations | We estimate that a figure of approximately 32% was used by Kristiansen et al and have |

| | | |
|---|---|---|
| | | applied this figure to the 2006 ppp £, £13,229.0 (per CABG) |
| | 25% of patient with avoided fatal myocardial infarction were assumed to have the cost savings of an avoided inpatient hospital stay. £3,090.6 per hospital stay | As for Kristiansen et al. increased to 2006 ppp £ |
| | Savings from reduced treatment cost following infarction (beta blockers). £302.7 per year | As for Kristiansen et al. increased to 2006 ppp £ |
| | Costs resulting from survival. Annual health care costs of £484.0 per year | As for Kristiansen et al. increased to 2006 ppp £ |
| | Unit costs of inputs | 'current fee schedules or recent cost calculations' |
| | Future costs and benefits were discounted at 3.5% | Rate recommended by NICE |

* The number of fatal to non-fatal MI's was spit 2/3 to 1/3 as in Kristiansen et al.'s model. This split corresponds to UK findings Petersen et al. (2005) estimate non-fatal MI's to be 2 to 2.5 times the number of fatal MI's.

**Table 12: Number of males by total serum cholesterol (England and Wales)**

| Serum cholesterol 2004 | % Males 40-49 | Number of Males 40-49 |
|---|---|---|
| <5.2 mmlo/l (K<4.9) | 44.00% | 1,702,343 |
| 5.2 - 5.79 mmlo/l (K=5-5.9) | 20.00% | 773,792 |
| 5.8 - 6.49 mmlo/l (k=6-6.9) | 21.00% | 812,482 |
| ≥ 6.5 mmlo/l K=7-7.9 & 8+ | 15.00% | 580,344 |
| Sum | 100.00% | 3,868,962 |

The total number of myocardial infarction for the control group of 'no intervention' over a 10 year period and for the population based intervention for twenty years are presented in Table 13.

**Table 13: Fatal and non-fatal myocardial infarction over 20 years of a mass-media intervention for men aged 40-49 years**

| | | | | | *Reduction in incidence of infarction* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No intervention | | | Mass-media (1st decade) | | | | Mass-media (2nd decade) | | |
| **Serum cholesterol (mmlo/l)** | **Total no males** | **Total MI** | **Non-fatal MI** | **Fatal MI** | **MI reduction** | **Total MI** | **Non-fatal MI** | **Fatal MI** | **Total MI** | **Non-fatal MI** | **Fatal MI** |
| <5.2 | 1,702,343 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 |
| 5.2 - 5.79 | 773,792 | 18,571 | 12,381 | 6,190 | 2.00% | 1,857 | 1,238 | 619 | 5,571 | 3,714 | 1,857 |
| | | | | | | | | | | | |
| 5.8 - 6.49 | 812,482 | 34,124 | 22,749 | 11,375 | 2.00% | 3,412 | 2,275 | 1,137 | 10,237 | 6,825 | 3,412 |
| 5.8 - 6.49 | 812,482 | 34,124 | 22,749 | 11,375 | 2.50% | 4,266 | 2,844 | 1,422 | 12,797 | 8,531 | 4,266 |
| 7 .7% develop MI (fatal + non-fatal) | | | | | | | | | | | |
| ≥ 6.5 | 580,344 | 44,687 | 29,791 | 14,896 | 2.50% | 5,586 | 3,724 | 1,862 | 16,757 | 11,172 | 5,586 |
| ≥ 6.5 | 580,344 | 44,687 | 29,791 | 14,896 | 3.00% | 6,703 | 4,469 | 2,234 | 20,109 | 13,406 | 6,703 |
| 6.2% develop MI (fatal + non-fatal) | | | | | | | | | | | |
| ≥ 6.5 | 580,344 | 35,981 | 23,988 | 11,994 | 2.50% | 4,498 | 2,998 | 1,499 | 13,493 | 8,995 | 4,498 |
| ≥ 6.5 | 580,344 | 35,981 | 23,988 | 11,994 | 3.00% | 5,397 | 3,598 | 1,799 | 16,192 | 10,794 | 5,397 |
| 9.2% develop MI (fatal + non-fatal) | | | | | | | | | | | |
| ≥ 6.5 | 580,344 | 53,392 | 35,594 | 17,797 | 2.50% | 6,674 | 4,449 | 2,225 | 20,022 | 13,348 | 6,674 |
| ≥ 6.5 | 580,344 | 53,392 | 35,594 | 17,797 | 3.00% | 8,009 | 5,339 | 2,670 | 24,026 | 16,018 | 8,009 |

**Health outcomes**

The base case with 7.7% of individuals with total serum cholesterol ≥ 6.5 mmlo/l developing MI (fatal and nonfatal) and the population intervention reducing the risk of MI by 10%, 12.5% and 12.5% respectively for the cholesterol levels of 5.2 - 5.79, 5.8 - 6.49 and ≥ 6.5 provided 62,480 incremental life years and 62,229 QALYs discounted at 3.5% from 12 months post commencement of the intervention.

**Sensitivity of health outcomes**

Assuming that only 6.2% of individuals with total serum cholesterol ≥ 6.5 mmlo/l developing MI and the mass-media campaign reducing the risk of MI as in the base case for cholesterol levels of 5.2 - 5.79 mmlo/l and ≥ 6.5 mmlo/l, but declines to 10% for cholesterol levels 5.8 - 6.49 mmlo/l provided 52,121 incremental life years and 55,248 QALYs discounted at 3.5%.

Assuming that 9.2% of individuals with total serum cholesterol ≥ 6.5 mmlo/l developing MI (Fatal and nonfatal) and the mass-media campaign reducing the risk of MI by 10%, 12.5% and 15% respectively for the cholesterol levels of 5.2 - 5.79, 5.8 - 6.49 and ≥ 6.5 provided 75,410 incremental life years and 79,934 QALYs discounted at 3.5%.

**Incremental costs and ICERs**

All costs are discounted at 3.5% unless stated otherwise. Total costs including savings, when discounted at 3.5%, for the base case provided a saving of £75,921,144. The base case gave a discounted incremental cost per QALY of -£1,146 (-£1,215 per life year gained); both ICERs were in the South East Quadrant (ICERs in SE-Q).

**Sensitivity analysis of ICERs**

Even when the intervention cost was increased 9-fold to £5,454,408 the ICER achieved was cost saving (ICER=-£69, ICER in SE-Q). Cost savings would have to be reduced to a 10th of their original unit costs before the ICER value resulted in a positive cost per QALY to the NHS (£6.51 per QALY, ICERs in NE-Q)

**Limitations of Kristiansen et al's model and its application to the UK**

Almost by definition models have limitations, as they simplify reality, and over time expectations of the reporting and building of models has changed. Therefore it is not surprising to be able to point to a number of limitations in the Kristiansen et al model. However, we also consider limitations in its application to the UK today. Both are raised with a view to considering potential improvements in modelling.

Of note first is a lack of transparency in the calculation of model parameters. The derivation of the estimated percentage and subsequent number of individuals developing MI's for the controls (no cholesterol lowering intervention) is unclear. These estimates are arguably the most important parameters in the model given that all subsequent parameters are applied to, or derived from these parameters.

The majority of unit costs reported are aggregated and the underlying resources used applied to estimate these costs are not provided. This prevents assessment of the appropriateness of the assumptions made for Norway and assessment of the applicability of the costs to other settings. There is also a lack of detail on how some of the resource estimates have been applied. For example, there is no data on how many reduced coronary artery bypass grafts were assumed when calculating the associated cost savings. Kristiansen et al. (1991) noted that they used approximate costs for resource consumption but there is no indication of the approximation. In a personal communication, Prof. Kristiansen noted that with hindsight that the beta-blocker cost estimates used were too high.

The model is confined solely to males aged 40 to 49. This appears to be due to the availability of suitable epidemiology data at that time. However, MI's occur in women and in all age groups (particularly older groups) (Allender et al. 2006), and as a result the model underestimates the potential health benefits of a population wide programme designed to reduce MI's. Additionally, only 10% of the costs of the programme were attributed to this

population sub-group, which raises questions about how realistic the cost attribution is as many costs could be a lump sum. If this group of males is likely to gain most relative to other groups, then cost-effectiveness may lessen when applied to broader age ranges and to females.

Confining the model to MI's ignores the other CHD conditions frequently modelled, such as stable and unstable angina (Lindgren et al., 2003; Ward et al., 2005). A cholesterol programme targeting diet is also likely to produce health benefits for health conditions other than CHD, such as the CVD conditions of transient ischemic attack and stroke, cancers, diabetes and general health (reduced BMI) and wellbeing.

Two other strong assumptions are that the model confines costs and effects to a 20-year period and assumes all morbidity and mortality occur at the mid-point in two time periods, and hence two specific years of the 20-year period considered. The first assumption means that both lifetime risk of MI and future costs are ignored, the impact of which is testable. The second, whilst indefensible from a clinical perspective, may not affect substantially affect the results of the model within a 20-year period.

The health states in the model are inadequate for the condition being modelled. All individuals developing MI are immediately split into fatal and non-fatal MI. There is no possibility of individuals in the non-fatal MI state dying of a secondary or a subsequent MI/CHD related cause[8]. This is likely to overestimate survival benefits, even in a 20-year period.

Assuming that the epidemiology /risk data is available, limitations five and six could be overcome by using a Markov model. Markov models are frequently used currently to consider decision problems, which involve continuous risk over time, where timing may be important e.g. age and events can occur repeatedly (Sonnenberg and Beck, 1993).

[8] Non-infarction mortality is assumed to be equal for and cancel each other out in this incremental analysis.

Kristiansen et al.'s paper was published in 1991, and medical practice has developed substantially in the past 20 years. Patients are given thrombolytic drugs following a heart attack and more use is made of Percutaneous Coronary Intervention revasculation procedures. As a result mortality rates have changed since 1991, potentially affecting the incremental benefits and costs of the population intervention.

## SECTION 5: THE COST-EFFECTIVENESS OF A HEALTHY EATING PROMOTION PROGRAMME IN ENGLAND AND WALES: DEVELOPMENT AND RESULTS OF A NEW MARKOV MODEL

In the discussion of the limitations of the spread-sheet modelling conducted by Kristiansen et al (1991) it was apparent that the transition from being at risk of myocardial infarction to having and infarction and ultimately death was unrepresentative of the disease progression. For example, only allowing transition between health states to occur in years 7 and 15. Such a method may overestimate survival gains and underestimate costs as all mortality occurs relatively late in the model when the largest discounting impact occurs.

Markov models allow the possibility of transition (moving) from one health state to another for every cycle of a model (in the following model a cycle is one year). In using this type of model, over-estimation of survival would no longer be an issue and the long-term impact of the intervention could also be assessed.

### Model design

A deterministic Markov cohort chain simulation model was developed and run on Microsoft Excel to estimate the cost-effectiveness of a population wide cholesterol lowering strategy compared to no intervention for England and Wales in terms of cost per quality adjusted life years (QALYs). The health states included in the model were: CHD free (segregated according to cholesterol level), nonfatal myocardial infarction and Death (see figure 3). In addition there was a tunnel state (immediate transition from this state after entry) of heart attack. Individuals entering the state heart attack either died from the event within 0-35 days or moved to the non-fatal myocardial infarction state. In addition to mortality from MI, other cause mortality (all cause less MI mortality) was applied in the model. For MI free patients in the high-risk cholesterol groups, other cause mortality was applied when it exceeded the risk of a heart attack (positive mortality risk). Once in the heart attack state individuals had a 0-35 day mortality risk applied. Heart attack

survivors had a mortality risk from subsequent MI events and when other cause mortality exceeded this risk the incremental differential was also applied to this group.

A simulated cohort of 40 year old males was followed until members were 100 years of age at which point all members were assumed to die in the next cycle, giving a maximum of 60 cycles of one year's duration each. Transition between health states was assumed to occur annually; as an incremental cost-utility analysis conducted and not an attempt to precisely estimate survival gains, half cycle corrections were excluded from the model. Risk estimates of transition from one state to another were transformed into one year transition probabilities (Briggs, Sculpher and Claxton, 2006) using the density method (Miller and Homan, 1994); see Appendix 6 for formulae.

**Model parameters**

All sources are referenced below in Table 14. Model parameters were sought in the same fashion as for the application of the Kristiansen et al model to England and Wales.

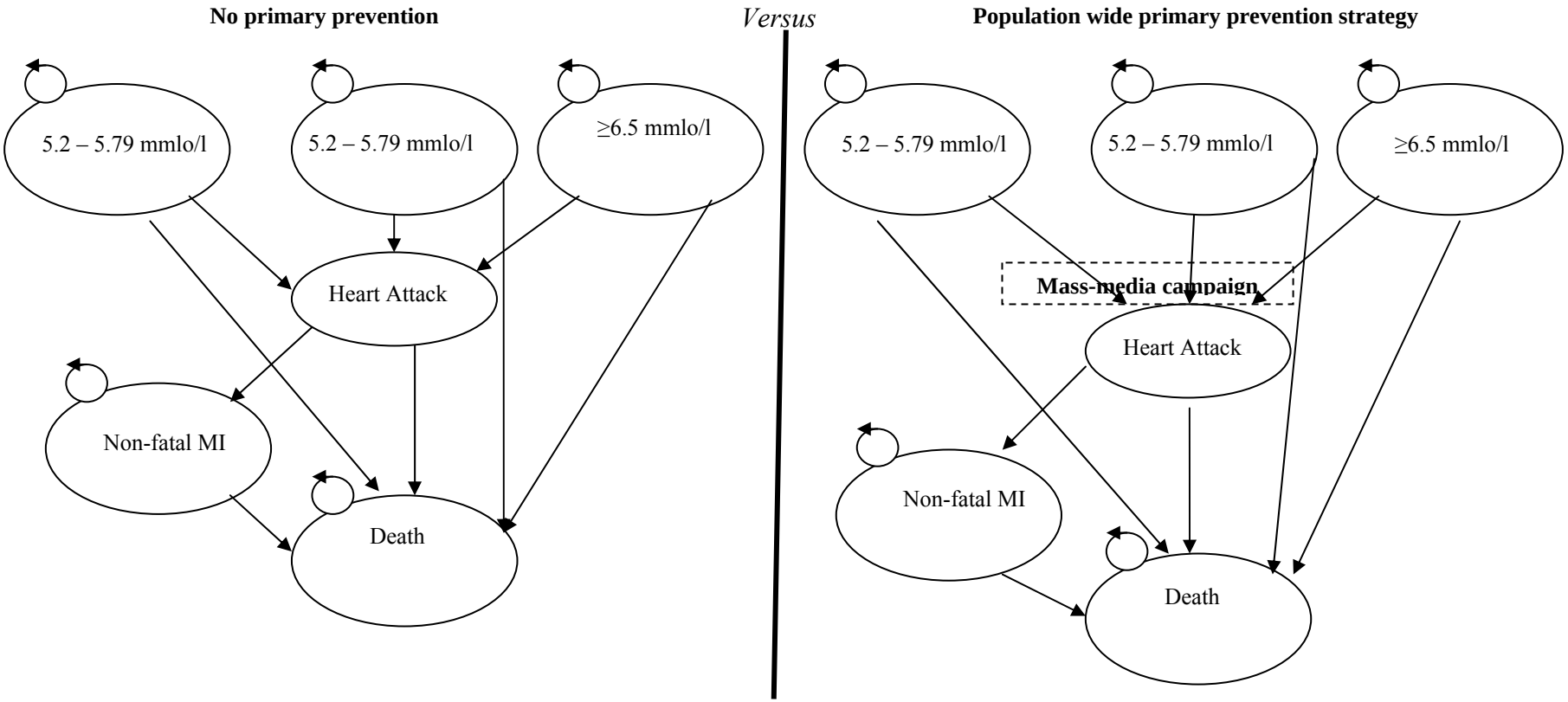



**Figure 3: Markov state diagram of no primary prevention versus population wide CHD/MI prevention strategy**

**Table 14: The cost-effectiveness of a health eating promotion programme in England and Wales: Development and results of a new Markov model**

| | Parameter | Source of data |
|---|---|---|
| | Population estimates for males 40 years in 2006. See Table 12. | As application of Kristiansen to England and Wales |
| Epidemiology | The number of males by lipid concentration (5.2-5.79, 5.8-6.49, ≥6.5). See Table 12. | As application of Kristiansen to England and Wales |
| | Risk of developing MI | Anderson et al. (1990) algorithm applied to cholesterol mid point scores* |
| | Mass media intervention reduces cholesterol by 5% | As for Kristiansen et al. |
| Effectiveness | 5% reduction in cholesterol resulted in a reduction in MI risk of 10% for individuals with cholesterol levels of 5.2-5.79, 12.5% for cholesterol = 5.8-6.49 and ≥ 6.5 | As for Kristiansen et al. The largest potential reduction of 15% was not modelled. |
| | Participation of 100% was assumed in the base case. | |
| | Cholesterol lowering begins in the 3rd year of programme. | As for Kristiansen et al. |
| | All transitions between health states occurred annually | |
| | Mortality within 35 days of myocardial infarction 12.2% | (Baigent et al., 1998) |
| | Mortality from 36 days after infarction to 10 years. 24.8% | (Baigent et al., 1998) |
| Utilities | Non-fatal myocardial infarction, 0.87 | kind et al. (1999) |
| | Avoided non-fatal myocardial infarction, 0.76 | Goodacre et al., 2004) |
| Costs | Intervention and health care costs | As Kristiansen et al. except for annual medical costs as a result of avoided mortality |
| | The mass-media strategy had an annual unit cost of £606,045.4. | (Kristiansen et al., 1991)(1) |
| | The number of coronary artery bypass graft operations for angina pectoris (+ other PCI procedures)was assumed to be 9% | Fox et al., 2000 |
| | Cost of CABG operations £8,241 | (NHS Reference Costs, 2006 (DOH, 2007)) (2) |
| | 25% of patient with avoided fatal myocardial infarction were assumed to have the cost savings of an avoided inpatient hospital stay. £1,309.50 per hospital stay | Kristiansen et al. (1991), DOH (2007) (3) |
| | Savings from reduced treatment cost following infarction. £281.0 per year | (BNF, 2006) (4) |
| | Future costs and benefits were discounted at 3.5% | Rate recommended by NICE |

* Parameter values used to generate risks from the Anderson et al. (1990) myocardial infarction risk estimates (Framingham study) were age (40 to 100), constants systolic blood pressure of 109 and HCL cholesterol of 45, with the three mid point total serum cholesterol scores of 210, 240 and 280 mg/dl.

**Table 15: Sensitivity analysis parameters**

| | Sensitivity estimates | |
|---|---|---|
| Parameters | Min | Max |
| Intervention participation | 50% | - (base case 100%) |
| Age | 40 (Base case) | 50 (Increase), 60 (Max) |
| *Effectiveness* | | |
| MI risk 5.2-5.79 mmlo/L | - | Framingham CHD risk equations (D'Agostino et al., 1990). |
| MI risk 5.8 – 6.49 mmlo/L | - | |
| MI risk ≥ 5.5 mmlo/L | - | |
| *Utilities* | | |
| At increased risk of MI | 0.84 (kind et al. 1999) | 0.91 (kind et al. 1999) |
| Non fatal MI | 0.72 | 0.80 |
| Death | | |
| Discounting effects and costs | 0% | 7% (Norwegian Treasury, Kristiansen et al., 1991) |
| *Costs* | | |
| Number receiving inpatient treatment for MI (fatalities) | 12.5% | 50% |
| Inpatient treatment of MI | £860.90 (DOH, 2007) (1) | £1,901.20 (DOH, 2007) (1) |
| Number receiving coronary artery bypass graft (CABG & other PCI procedures) (non-fatal MI) | 2.8% (Palmer et al., 2002) | 23% (Fox et al., 2000) |
| Coronary artery bypass graft (CABG) (non-fatal MI) | £1926.40 (DOH, 2007) (2) | £14,350 (Sculpher et al. 1994) (3) |
| Drug treatment after infarction (annual costs) | £34.40 (BNF) (4) | £645.33 (North of England Evidence Based Circulars) |
| Cost of mass-media strategy (annual costs) | £303022.70 (5) | £1212090.80 (6) |

All costs were inflated to 2006 £ if not already in 2006 £.

(1) Non-elective admissions costs.

(2)Lower quartile of FCE weight for elective and non-elective.

(3)Inflation of Sculpher et al (1994) CABG costs by Vela to 2006 prices and adjusted using Hill et al. Methods (2004) for adjusting to include additional FCE through and ICU stay. Costs do not account for subsequent revasculation.

(4) Kristiansen's assumption of only costing beta blockers (lowest costs).

(5) Half of Kristiansen's base estimate in 2006 ppp £.

(6) Double Kristiansen's base estimate in 2006 ppp £.

**Results**

The base case parameters provided an incremental cost effectiveness ratio (ICER) of £87 per QALY (£116 per life year) (ICERs NE-Q) with costs and effects discounted at 3.5%. One-way sensitivity analysis was conducted by varying participation rate, age of the cohort when the intervention commenced, coronary risk estimates, utilities (QALY weights), discount rate, percentage receiving inpatient treatment for MI and the accompanying cots, parentage having CABG and the accompanying costs, the cost of drug treatment following MI and the cost of the population intervention.

**Table 16: One-way sensitivity analysis**

| Parameters | Value | ICER (£/QALY) |
|---|---|---|
| Participation in intervention | 50% (**Min**) | £2,853 |
| Age | 50 (**Increase**) | -£2,372 |
| | 60 (**Max**) | -£2,290 |
| Coronary risk | Framingham CHD risk (**Max**) | -£335 |
| *Utilities* | | |
| At increased risk of MI | 0.84 (**Min**) | £98 |
| | 0.91 (**Max**) | £75 |
| Non fatal MI | 0.72 (**Min**) | £77 |
| | 0.80 (**Max**) | £99 |
| Discounting cost and outcomes | 0% (**Min**) | £1,195 |
| | 7% (**Max**) | -£2,903 |
| *Costs* | | |
| Number receiving inpatient treatment for MI | 12.5%(**Min**) | £145 |
| | 50% (**Max**) | -£29 |
| Inpatient treatment of MI | £860.90(**Min**) | £127 |
| | £1,901.20 (**Max**) | £35 |
| Number receiving coronary artery bypass graft (CABG) | 2.8% (**Min**) | £125 |
| | 23% (**Max**) | £1 |
| CABG | £1926.4 (**Min**) | £13 |
| | £14,350 (**Max**) | -£815 |
| Drug treatment after infarction | £34.40 (**Min**) | £2,288 |
| | £645.33 (**Max**) | -£3,165 |
| Cost of mass-media strategy | £303,022.70 (**Min**) | -£1,296 |
| | £1,212,090.80 (**Max**) | £2,853 |

The one-way sensitivity analysis results are presented in Table 16. The one-way sensitivity analysis revealed that the largest impact upon the base case ICER in terms of increasing cost per QALY was seen when intervention costs were doubled to £1.2 million or a reduction in participation to 50% of males

(e.g. as a result of poor message dissemination or a reluctance to comply with the intervention's message of cholesterol reduction through diet) was applied, resulting in ICERs of £2,853 (ICERs NE-Q). The next largest increases in cost were recorded for a reduction of drug treatment costs after infarction (ICER £2,288, ICER NE-Q) and finally a 0% discount rate (£1,195, ICER NE-Q).

Negative ICERs arose when: the base case parameters were combined with the number receiving inpatient treatment for MI increased to 50% from 25%; there was a greater risk of a heart attack; the maximum CABG costs or minimum intervention costs were applied; age increased; discount rates increase, and; the maximum post infarction medication costs are used (see Table 16). Post infarction medication yielded the greatest impact on lowering the ICER value (-£3,165, ICER SE-Q).

Multi-way sensitivity analysis of all parameters to produce the least favourable circumstances to yield a cost-effective ICER (≥ £30,000), comprising of 50% participation in the intervention (40 years of age at commencement), with minimum NHS costs, maximum intervention costs and base case utility weights, provided an ICER of £10,679 (ICER NE-Q, discounted at 3.5%). The most positive model parameters (100% participation, maximum NHS costs - highest percentage of patients needing surgery and inpatient care at maximum cost), maximum risk of a heart attack, with base case utility weights and minimum intervention cost) provided and ICER of -£7,276 (ICER SE-Q).

Threshold analysis of a £30,000 ICER value for the base case parameters was conducted with the three most influential parameters identified from the one-way sensitivity analysis being varied. Even if post myocardial infarction medication were free it would not result in an ICER value approaching £30,000; free medication resulted in an ICER of £2,596 (ICER NE-Q). Participation in the intervention would have to fall to 9% in each cholesterol group to produce an ICER of £30,256 (ICER NE-Q). The annual intervention cost would have to increase to £6.7 million to produce an ICER of £30,409 (ICER NE-Q).

## SECTION 6: DISCUSSION

### 6.1 Replicating Kristiansen et al. (1991)

It was not possible to replicate exactly the calculation of CHD risks for the Norwegian male population of 40-49 year old males despite retrieving the effectiveness paper underlying this calculation. Professor Kristiansen was consulted on this matter and he has agreed to forward any details he has in the future. Making the assumption that the risk estimates of the number of MI's was correct, both the incremental life years and the QALYs were successfully replicated. It was not possible to fully replicate the Norwegian costs due to a lack of detail on unit costs and their application.

### 6.2 Application of the Kristiansen Model to England and Wales

The Kristiansen model was applied to 40-49 year old males resident in England and Wales, assuming the Norwegian MI incidence (calculated from Kristiansen's reported results) and incidence to mortality ratio, costs and mortality rates (using UK utilities) suggest that such a population intervention would be cost-effective (ICERs in the North East and South East quadrants and all ICERs below £7.00 per QALY). However, a number of limitations were identified with Kristiansen's original application in Norway. For example, the spread-sheet model could not model the disease states adequately in terms of routes to mortality (immediate fatality, mortality post one month and other cause mortality). The model did not account adequately for continuous lifetime risks and assumed all health state transitions occurred simultaneously. In light of these and other limitations (see section 4) a Markov model was designed and populated with data appropriate for England and Wales.

### 6.3 The cost-effectiveness of a healthy eating promotion programme in England and Wales: Development and results of a new Markov model

The base case (most likely) and the most negative scenario produced in the multi-way sensitivity analysis, both resulted in cost-effective ICERs (<£20,000, North East and South East quadrants). The most influential parameters in terms of affecting the ICERs unfavourably were low participation, increased cost of delivering the mass-media intervention and the cost of medication post

infarction. Threshold analysis suggests that participation and intervention costs could result in unfavourable ICERs and for this to occur participation would have to fall to 9% of 40 year old males or intervention costs must increase to £6.7 million per year.

### 6.4 Limitations of the intervention modelled

As previously discussed, in the limitations of the Kristiansen model, confining the intervention population males aged 40 to 49 underestimates the potential health gains of such an intervention. Myocardial infarction occurs in women and in all age groups (particularly older groups) (Allender et al. 2006). Confining the model to MI's also ignores other CHD conditions frequently modelled; stable and unstable angina (Lindgren et al., 2003; Ward et al., 2005). A cholesterol programme targeting diet is also likely to produce health benefits for health conditions other than CHD, such as the CVD conditions of transient ischemic attack and stroke, cancers, diabetes and general health (reduced BMI) and wellbeing. Therefore the estimates of total benefit could be considerably underestimated.

In addition to underestimating the health benefits, total costs were also underestimated, as only 10% of the costs of the programme were attributed to this population sub-group by Kristiansen et al. Targeting 10% of the population with a population wide intervention does not mean that the costs incurred would only be 10%. A mass-media campaign would incur 100% costs irrespective of the percentage of the population that benefit or benefit most. In light of this fact the cost of the intervention is more likely to be £6,060,454 giving an ICER of £27,490 (ICER in NEQ) which is much less cost-effective than in the Kristiansen et al. cost allocation scenario. However, this is clearly too pessimistic as no benefits at all are assigned to improved health outcomes for other age groups of men and for women. If a broader age range of men and women were included, and if these groups added proportionally fewer QALYs, it suggests the ICER would fall between £27,490 and £87 per QALY. Despite underestimating both costs and benefits ICERs are still likely to be cost-effective (<£30,000) especially as the upper ICER does not include benefits to the broader population.

The health gains modelled in this study and those of Kristiansen et al. (1991) are based upon two parameters, both of which could be argued to over-estimate benefits. First, the population intervention is assumed to reduce total serum cholesterol by 5% and secondly, a 1% reduction in serum cholesterol would result in a 2% reduction in coronary risk. The first assumption is based upon the findings from two studies, the North Karelia project (Salonen et al., 1981) and the 'cardiovascular disease study in Norwegian countries – second screening' (National Health Screening Service, 1988). The former found a 4% reduction in cholesterol and the latter a 5% reduction. Kristiansen et al. (1991) note that The Lipid Research Clinics Coronary Primary Prevention Trial Results I (1981) and Bjartveit et al. (1988) only found a 2% reduction in coronary risk to accompany a 1% serum cholesterol reduction. Therefore assuming that a 2.5% reduction is seen for males with cholesterol levels of 5.8 mmlo/l or above may be too optimistic. In addition, studies such as the Framingham study have shown that CHD risk is multifactorial and a simplistic intervention merely targeting cholesterol may not affect risk in the way assumed in 1991 (Kristiansen et al.). In addition medical practice has developed substantially in the past 20 years. Patients are given thrombolytic drugs following a heart attack and there is much greater use of percutaneous coronary interventions and other revasculation procedures. However, as PCI and mortality data from 1998/2000 was applied in the Markov model this is less of an issue in that particular analysis than in Kristiansen's.

The modelling conducted by Kristiansen et al. (1991) and subsequently adopted in this study is based upon a comparator of 'do nothing'. Whilst this was possibly appropriate in Norway in 1991, in the UK there is an active health promotion program in operation. For example, the food standards agency is promoting the traffic light labels on food through TV advertisement, food stuffs aimed at reducing cholesterol are advertised on TV, coronary heart statistics and advice are readily available on the internet as are sites devoted to promoting improved general health and calculating risk for CHD, CVD and other diseases. It could be argued that, in the absence of a 'do nothing' option, that the risks estimated for England and Wales using the US based

Framingham Coefficients gives an indication of the gains that would have been made in relation to MI risk amongst Males 40-49 years of age in 2006 £ had the population intervention modelled been implemented in 1991. Consequently, this would suggest that the ICERs are too low.

**Methodological issues**

It should be noted that the mass-media intervention identified in this study does not adhere strictly to the NICE economic perspective, although we have modelled it as such. Whilst the objectives of the intervention (reducing mortality and morbidity), are in keeping with NICE's objectives, the costs do not comply. Kristiansen et al include the costs of mass-media and education, neither of which in practice may fall on the health service, although the cost savings would benefit the NHS. However we have modelled as if all costs and benefit apply to the NHS.

In retrospect we wonder if we did use the right criteria as our choice was one very old paper and so much of the context of treatment and epidemiology of CHD has changed since this paper was written. Practices in economic evaluation have also changed dramatically in the intervening time. For example, it is now considered good practice to provide resource use and unit cost data separately, which helps transfer of results across settings. The age of the paper also affected our ability to get active support even though some of the original authors were kind enough to provide their foreign language reports and help us on some issues. Finally we are concerned that limiting our choice of papers to the 26 papers reviewed means that we missed some good models. For example, interventions which included Statins or other drugs were excluded from our search strategy in phase 1 (e.g. Ward et al, 2005).

**Implications of the modelling results**

Allowing for all the limitations of the modelling, the two primary outcomes of the modelling are as an indicator of the cost-effectiveness of a population centred behaviour change intervention and as an example of how economic

modelling can be used to provide evidence to inform public health decision making.

The modelling discussed in this report begins to quantify the potential cost and benefits associated with health promotion programmes. The results of the modelling (in Norway and England and Wales) suggest that health promotion can be cost-effective when targeted through schools and the mass-media. However, each new intervention should be assessed against current practice in as rigorous a fashion as possible, accounting for all costs and benefits.

The Markov model rapidly developed in this study, ideally would have been populated with data from meta-analysis of literature in the field. In the absence of such data the model is based on single trials and quasi-experimental design studies. As a result we cannot be as confident in the data as we would like to be. Ideally we would have liked to produce a probabilistic Markov model. This was not done for two main reasons. Firstly, the key parameter in this model the risk reduction in coronary incidence was only available within our time line as a percentage risk reduction and not a relative risk. Secondly, identifying the relevant literature for CHD free and medication free UK adults from the wealth of peer reviewed literature devoted to CHD was difficult given time constraints.

If adequate resources can be allocated, including medical and epidemiology support, economic evaluation using modelling techniques can be an extremely useful decisional aid. Allowing the synthesis of all relevant data in the form of probabilistic parameters from meta-analysis of the relevant effectiveness data and costs to be assessed. The value of conducting further trials to ascertain data on a specific parameter could also be assessed using the value of perfect information analysis. Our final phase III report will consider the implications of the approach adopted in this research and debate the future directions for economic evaluation in this area.

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## Appendix 1: Summary of main findings from Phase 1

1. Prevention in childhood

There is no economic evaluation of a solely child-focussed disease prevention programme targeted at reducing CHD

2. General prevention in adulthood

Three out of the four papers that focussed on combined packages of interventions aimed at multiple risk factors fell into the 'likely to be very cost-effective' category[9]. These included a mix of population and individual focussed interventions for adults over the age of 30. Whilst short term effects in two papers were based on RCTs, none of the studies were conducted in the UK and none investigated alternative packages of interventions. Two papers compared the combination programme with no programme at all and one against a screening based alternative.

3. Intervention in adulthood to change the behaviour of people with specific risk factors for CHD (eg. smoking, poor diet, lack of physical activity)

*Exercise:* Both papers on the cost-effectiveness of interventions designed to increase exercise fall into the category 'likely to be very cost-effective' when compared with no intervention and a largely sedentary population aged over 35. However, the quality of short term effectiveness data was not strong.

*Smoking:* Two out of three papers[10] on smoking fall into the category 'likely to be very cost-effective'. One paper was the advice to individuals in Spain and the other was Heartbeat Wales. Unfortunately the quality of short term effectiveness data from Spain was not strong and the data from Wales very poor quality.

*Diet:* Of the 17 papers on diet, the cost-effectiveness of professional advisors in changing diet was consistently in the 'very cost-effective' category whereas there is no consistent pattern for any other types of diet interventions (population or screening based or diet alone) which fell in all categories between very likely and very unlikely to be cost-effective, including the 'standard' Step 1 diet which could be considered a more 'standardised' intervention.

Two non-advisory interventions also remained in the likely to be very cost-effective group; food labelling with trans fatty acid content (Services DoH, 2003) and a population-based health promotion programme on healthy food (Kristianson 1991). However, one of the reasons why the food labelling may rest only in one category is because neither sensitivity nor sub-group analysis was conducted, which is surprising given that only level 2 data was (and could be) available. Kristianson's (1991) model used a range of levels of data and undertook a basic sensitivity analysis.

When specified (n=12/17), most papers on diet focused on populations over the age of 35 with the exception of Murray et al (2003) who modelled the entire population. The quality of evidence varied by category of cost-effectiveness, with most RCT data for specifications of interventions in the >£50,000 category, followed by £0-20,000 and then £30-50,000. No RCT data supported interventions in the cost saving or £30-50,000 level of cost-effectiveness.

4. Treatment (primary, secondary and tertiary care) in adulthood for people with CHD (e.g. statins, coronary heart by-pass, heart transplant).

The majority of treatments provided and evaluated are not behaviour change interventions or are provided in conjunction with behaviour change interventions. This project was also defined with NICE to exclude secondary and tertiary care. This reviews found no evidence on the effectiveness of behaviour change interventions

[9] The remaining paper(s) did not provide QALYs or number of life years saved.
[10] The remaining paper(s) did not provide QALYs or number of life years saved.

alone. Several papers were excluded because the effects of behaviour change interventions could not be isolated, particularly from pharmacological intervention.

5. Other findings

- A blanket statement on cost-effectiveness of targeted or population strategies cannot be made as the evidence is mixed; in some cases targeted strategies are more effective and in other cases mass treatment is.
- There is evidence suggesting that the cost-effectiveness of behavioural change interventions varies by age, gender and risk level but in an inconsistent way across intervention type.
- There is considerable uncertainty for a number of interventions around the threshold value of £30,000/QALY, indicating that future modelling may provide useful decisional information for a UK setting.
- Data from studies citing ICERs of between 0-£50,000/QALY was heavily reliant on uncontrolled primary studies
- Few economic evaluations rely on primary data and few modelling studies provide sufficient description to ascertain the methods used.

*Gaps in content of evidence*

- With the exception of evaluations that cover the whole population, no evidence is provided on the cost-effectiveness of behaviour change interventions for specified sub-groups e.g. age group 19-30yrs, low income groups, pregnant women, particular ethnic groups or specified disadvantaged groups.
- There is no economic evaluation of a solely child-focussed disease prevention programme targeted at reducing CHD.
- No cost-effectiveness analysis of interventions to reduce smoking or increasing exercise to reduce CHD has included children.
- Very few economic evaluations of behaviour change interventions to reduce CHD have been conducted from a UK perspective
- There is a lack of research looking at patient preferences. Little attention was paid to patient preferences for the type of interventions that would be preferred or how they would be delivered. In turn preference is likely to affect compliance, which needs to be addressed (Murray et al, 2003) as it is key to the success of any behaviour intervention.
- Future research needs to include QALY weights for life years to facilitate comparison across a range of interventions

*Gaps in quality of evidence*

- Few economic evaluations of behaviour change interventions to reduce CHD are conducted alongside level 1 effectiveness evidence
- A lack of reliable data from which to extrapolate the long term health outcomes of behaviour change interventions from short term effects of behaviour change interventions (Kristiansen et al., 1991). For example, Kinlay et al. (1994) cited a lack of adequate information upon the impact of cholesterol and cholesterol reduction upon the risk of CHD among women.

## Appendix 2: List of papers considered


E1: Munro, J., Brazier, J., Davey, R., & Nicholl, J. (1997). Physical activity for the over-65s: could it be a cost-effective exercise for the NHS? *Journal of Public Health Medicine*, 19, 397-402.

E2: Jones, T. F., & Eaton, C. B. (1994). Cost-benefit analysis of walking to prevent coronary heart disease. *Archives of Family Medicine*, 3, 703-710

S1: Ong, M. K., & Glantz, S. A. (2004). Cardiovascular health and economic effects of smoke-free workplaces.[erratum appears in Am J Med. 2005 Aug;118(8):933]. *American Journal of Medicine,* 117, 32-38

S2: Plans-Rubio, P. (2004). Allocation of resources between smoking cessation methods and lovastatin treatment of hypercholesterolaemia: based on cost effectiveness and the social welfare function. *Pharmacoeconomics*, 22, 55-69.

S3: Phillips, C. J., & Prowle, M. J. (1993). Economics of a reduction in smoking: case study from Heartbeat Wales. *Journal of Epidemiology & Community Health*, 47, 215-223

C1: Lindgren, P., Fahlstadius, P., Hellenius, M.-L., Jonsson, B., & De Faire, U. (2003). Cost-effectiveness of primary prevention of coronary heart disease through risk factor intervention in 60-year-old men from the county of Stockholm - A stochastic model of exercise and dietary advice. *Preventive Medicine*, 36, 403-409

C2: Lindholm, L., Rosen, M., Weinehall, L. & Asplund, K.,(1996). Cost effectiveness and equity of a community based cardiovascular disease prevention programme in Norsjo, Sweden. *Journal of Epidemiology and Community Health*, 50, 190-195

C3: Finkelstein, E. A., Troped, P. J., Will, J. C., & Palombo, R. (2002). Cost-effectiveness of a cardiovascular disease risk reduction program aimed at financially vulnerable women: the Massachusetts WISEWOMAN project. *Journal of Womens Health & Gender Based Medicine*, 11, 519-526.

C4: Dalziel, K., Segal, L., & Mortimer, D. (2005). *Risk Factor Study - How to reduce the burden of harm from poor nutrition, tobacco smoking, physical inactivity and alcohol misuse: cost-utility analysis of 9 multi-risk factor interventions*. Victoria: Monash University

D1: Stinnett, A. A., Mittleman, M., & Weinstein, M. C. (1996). Cost-effectiveness of dietary and pharmacological therapy for cholesterol reduction in adults. In M. R. Gold (Ed.), *Cost-effectiveness in Health and Medicine* (pp. 349-391). New York: Oxford University Press.

D2: Phillips, C., Belsey, J., & Shindler, J. (2000). Flora pro.activ: A clinical and financial impact analysis. *Journal of Medical Economics*, 3, 61-76.

D3: Kinlay, S., O'Connell, D., Evans, D., & Halliday, J. (1994). The cost-effectiveness of different blood-cholesterol-lowering strategies in the prevention of coronary heart disease. *Australian Journal of Public Health*, 18, 105-110.

D4: Johannesson, M., & Fagerberg, B. (1992). A health-economic comparison of diet and drug treatment in obese men with mild hypertension. *Journal of Hypertension*, 10, 1063-1070

D5: Services, D. o. H. a. H. (2003). *Food labelling: trans fatty acids in nuitrition labelling; Consumer research to consider nutrient content and health claims and possible footnote or disclosure statements; final rule and proposed rule*. Rockville: Us Food and Drug Administration.

D6: Bendich, A., Mallick, R., & Leader, S. (1997). Potential health economic benefits of vitamin suplementation. *Western Journal of Medicine*, 166, 307-312.

D7: Assmann, G., & Schulte, H. (1990). Primary prevention of coronary heart disease in the Federal Republic of Germany. Analysis of cost-effectiveness. *DRUGS,* 40, 33-37.

D8: Tosteson, A. N., Weinstein, M. C., Hunink, M. G., Mittleman, M. A., Williams, L. W., Goldman, P. A., & Goldman, L. (1997). Cost-effectiveness of populationwide educational approaches to reduce serum cholesterol levels. *Circulation*, 95, 24-30.

D9: Tice, J. A., Ross, E., Coxson, P. G., Rosenberg, I., Weinstein, M. C., Hunink, M. G., Goldman, P. A., Williams, L., & Goldman, L. (2001). Cost-effectiveness of vitamin

therapy to lower plasma homocysteine levels for the prevention of coronary heart disease: effect of grain fortification and beyond.[see comment]. *Journal of the American Medical Association*, 286, 936-943

D10: Plans-Rubio, P. (1997). Cost-effectiveness of dietary treatment of hypercholesterolemia in Spain. *Public Health*, 111, 33-40.

D11: Prosser, L. A., Stinnett, A. A., Goldman, P. A., Williams, L. W., Hunink, M. G., Goldman, L., & Weinstein, M. C. (2000). Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics.[see comment]. *Annals of Internal Medicine*, 132, 769-779

D12: Olsen, J., Willaing, I., Ladelund, S., Jorgensen, T., Gundgaard, J., & Sorensen, J. (2005). Cost-effectiveness of nutritional counseling for obese patients and patients at risk of ischemic heart disease. *International Journal of Technology Assessment in Health Care,* 21, 194-202.

D13: Nallamothu, B. K., Fendrick, A. M., Rubenfire, M., Saint, S., Bandekar, R. R., & Omenn, G. S. (2000). Potential clinical and economic effects of homocyst(e)ine lowering. *Archives of Internal Medicine*, 160, 3406-3412

D14: Murray, C. J., Lauer, J. A., Hutubessy, R. C., Niessen, L., Tomijima, N., Rodgers, A., Lawes, C. M., & Evans, D. B. (2003). Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk.[erratum appears in Lancet. 2005 Jul 16-22;366(9481):204]. *Lancet,* 361, 717-725.

D15: Kristiansen, I. S., Eggen, A. E., & Thelle, D. S. (1991). Cost effectiveness of incremental programmes for lowering serum cholesterol concentration: is individual intervention worth while? *BMJ*, 302, 1119-1122.

D16: Blake, G. J., Ridker, P. M., & Kuntz, K. M. (2003). Potential cost-effectiveness of C-reactive protein screening followed by targeted statin therapy for the primary prevention of cardiovascular disease among patients without overt hyperlipidemia. *American Journal of Medicine*, 114, 485-494.

D17: Plans-Rubio, P. (1998). Cost-effectiveness analysis of treatments to reduce cholesterol levels, blood pressure and smoking for the prevention of coronary heart disease: Evaluative study carried out in Spain. *PharmacoEconomics,* 13, 623-643.

## Appendix 3. Intervention, study design and findings

### Table 1.1. Main finding of Kristiansen et al. (1991)

| Objective | **To evaluate the relative cost-effectiveness of three main strategies to reduce cholesterol concentrations.** |
|---|---|
| **Characteristics of sample** | 200,000 Norwegian males aged 40-49 |
| **Main findings and conclusions** | Population approach gave 3100 life years and 3000 QALYs over no action. The net incremental effects of dietary treatment were 400 QALYs.<br>Over 20 years of a population based strategy was projected to be £16 per life year gained. For an individual strategy based on dietary treatment the cost was about £16,533 per life year gained.<br><br>Individual intervention should be implemented cautiously and within more selected groups than currently recommended.<br><br>From perspective of health sector plus other, ICER for intervention 1 compared with no action =£13.3 per QALY. ICER for intervention 2 compared with intervention 1 = £134 per QALY |
| **Findings of Sensitivity Analysis** | Varying unit cost up and down influenced total cost in the same direction. |
| **Drummond %** | 61 |
| **Relevance to modelling%** | 57 |
| **Transferability score %** | 29 |
| **Quantity of short (long) term effectiveness data** | Short grade 2+4 long (grade 1,2+4) |

## Table 1.2. Study context

| | | |
|---|---|---|
| **Provider** | | Government |
| **Target Population** | | Individual and population |
| **Setting** | | Primary care & Community |
| **Disease/State** | | At general & at increased risk (based on serum cholesterol) |
| **Intervention** | | Intervention (I) The promotion of healthy eating habits and lowering serum cholesterol concentration. Information on food among the scientific community, the agricultural sector, the food industry, health authorities, schools, the general public and mass media.<br>Intervention (II) Two cholesterol tests: if serum cholesterol concentration >= 6.0 mmol/L ,then dietary treatment and visits to doctor and additional blood sampling at intervals dependent on cholesterol score (6-7.9= 1.5 visits per year, 8+ =2 visits per year). |
| **Comparator group** | | No intervention |
| **Time horizon of intervention** | | 20 years |
| **Funder of study** | | Not stated |
| Analytic Model | | **CEA & CUA** |
| **Perspective stated (inferred)** | | Health service/care |
| **Design** | | Unspecified modelling |
| **Health outcomes** | **Benefit Measures** | 1. Number of Myocardial Infarctions<br>2. Life Years<br>3. QALYs |
| | **Effectiveness data sources** | 1.Cost-effectiveness of cholesterol-lowering therapy in the Netherlands<br>2. The cardiovascular disease study in Norwegian counties- results from the second screening<br>3. Multiple Risk Factor Intervention Trial. Risk factor changes and mortality results<br>4. Management of hypercholesterolemia<br>5. Ten-year mortality and morbidity related to serum cholesterol<br>6.Central Bureau of Statistics: Causes of death 1985 |
| **Costs** | **Resources costed** | Screening, confirmatory screening, consultation, cholesterol testing, treating CHD, coronary artery bypass grafting, treatment after infraction, average health care costs, drugs, population strategy |
| | **Source of resource use data** | ~~Weinstein's approach for costing. Undisclosed?~~ |
| | **Source of unit costs** | Current fee schedules,<br>published unit costs ; Foundations of cost-effectiveness analysis for health and medical practices (Weinstein MC, Stason WB), Economics of coronary artery bypass grafting Williams A), Cost per patient based on DRG-classification (Slattebrekk OV |
| | **Year costs** | 1990 (inferred) |

**Table 1.3. Context continued**

| | | |
|---|---|---|
| Discount rate(s) | | **7%** |
| **Sensitivity Analysis** | **Type** | Deterministic (one-way) |
| | **Variables used** | 1. Cost per visit<br>2. Cost per screening<br>3. Health care cost per year<br>4.Discount rate<br>5.Life year gain<br>6.Cost of drugs<br>7. Mass strategy cost |
| **Time horizon of analysis** | | 20 years |

**Appendix 4 Search for epidemiology parameters to populate the Kristiense at al (2001) to England and Wales**

Ovid Medline Search 1950 – January 2006

*ab*: Abstract
*kf*: Keyword Heading Word
*sh*: MeSH Subject Heading
*ot*: Original Title
*hw*: Subject Heading Word
*ti*: Title

| | Search History | Results |
|---|---|---|
| 1 | myocardial infarction.ab,kf,sh,ot,hw,ti,kw. | 131420 |
| 2 | Serum Cholesterol.ab,kf,sh,ot,hw,ti. | 12010 |
| 3 | total cholesterol.ab,kf,sh,ot,hw,ti. | 19454 |
| 4 | Meta analysis.ab,kf,sh,ot,hw,ti. | 23885 |
| 5 | Meta-analysis.ab,kf,sh,ot,hw,ti. | 23885 |
| 6 | 2 or 3 | 29969 |
| 7 | 4 or 5 | 23885 |
| 8 | 1 and 6 | 1796 |
| 9 | 7 and 8 | 22 |
| 10 | from 9 keep 1-22 | 22 |

## Appendix 5. Results of Search strategy


Anonymous. (1995). Design, rational, and baseline characteristics of the Prospective Pravastatin Pooling (PPP) project--a combined analysis of three large-scale randomized trials: Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), Cholesterol and Recurrent Events (CARE), and West of Scotland Coronary Prevention Study (WOSCOPS). *American Journal of Cardiology*, **76,** 899-905.

Ballantyne, C.M., Riegger, G., Moore, N., Saia, F. & Serruys, P.W. (2004). Fluvastatin reduces cardiac mortality in patients with coronary heart disease.[see comment]. *Cardiovascular Drugs & Therapy*, **18,** 67-75.

Buchwald, H., Campos, C.T., Boen, J.R., Nguyen, P., Williams, S.E., Lau, J. & Chalmers, T.C. (1996). Gender-based mortality follow-up from the Program on the Surgical Control of the Hyperlipidemias (POSCH) and meta-analysis of lipid intervention trials. Women in POSCH and other lipid trials.[see comment]. *Annals of Surgery*, **224,** 486-98.

Chiodini, B.D., Barlera, S., Franzosi, M.G., Beceiro, V.L., Introna, M. & Tognoni, G. (2003). APO B gene polymorphisms and coronary artery disease: a meta-analysis. *Atherosclerosis*, **167,** 355-66.

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Jolly, K., Taylor, R.S., Lip, G.Y. & Stevens, A. (2006). Home-based cardiac rehabilitation compared with centre-based rehabilitation and usual care: a systematic review and meta-analysis. *International Journal of Cardiology*, **111,** 343-51.

Kanaya, A.M., Grady, D. & Barrett-Connor, E. (1737). Explaining the sex difference in coronary heart disease mortality among patients with type 2 diabetes mellitus: a meta-analysis. *Archives of Internal Medicine*, **162,** 1737-45.

Kanters, S.D., Banga, J.D., Stolk, R.P. & Algra, A. (1999). Incidence and determinants of mortality and cardiovascular events in diabetes mellitus: a meta-analysis. *Vascular Medicine*, **4,** 67-75.

Keech, A., Colquhoun, D., Best, J., Kirby, A., Simes, R.J., Hunt, D., Hague,

W., Beller, E., Arulchelvam, M., Baker, J., Tonkin, A. & Group, L.S. (2003). Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial.[see comment]. *Diabetes Care*, **26,** 2713-21.

Lewis, B. (1991). On lowering lipids in the post-infarction patient. *Journal of Internal Medicine*, **229,** 483-8.

Manktelow, B., Gillies, C. & Potter, J.F. (2002). Interventions in the management of serum lipids for preventing stroke recurrence. *Cochrane Database of Systematic Reviews*, **3**.

Morand, P., Roquebrune, J.P. & Fredenrich, A. (1992). [Hypolipidemic treatment after myocardial infarction]. *Archives des Maladies du Coeur et des Vaisseaux***,** 151-6.

Palmer, S and et al (2002). A cost-effectiveness model comparing alternative management strategies for the use of glycoprotein IIb/IIIa antagonists in non- st-elevation acute coronary syndrome. Report to the National Institute for Clinical Excellence. Available online: http://www.nice.org.uk/Docref.asp?d=32030.

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Taylor, R.S., Unal, B., Critchley, J.A. & Capewell, S. (2006). Mortality reductions in patients receiving exercise-based cardiac rehabilitation: how much can be attributed to cardiovascular risk factor improvements? *European Journal of Cardiovascular Prevention & Rehabilitation*, **13,** 369-74.

## Appendix 6. Density method of transforming risks to transition probabilities

Both equations 1 and 2 should be performed on time dependent risks sequentially.

Equation 1: instantaneous event rate or incidence density (ID)

$$ID = \frac{-\ln\left[1 - r\right]}{t}$$

Equation 2: time dependent probability (TDP)

$$TDP = 1 - e^{x}\left[-Id \times c\right]$$

Ln = log to base e.
$e^x$ = exponential.
r = rate to be transformed.
t = time/duration frame for initial rate.
c = cycle length to be applied in the model.