THE UNIVERSITY
*of* LIVERPOOL

# MODELING CORONARY HEART DISEASE IN THE UK: PAST TRENDS AND FUTURE IMPLICATIONS

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by

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# SUMMARY

## Introduction

Coronary heart disease (CHD) is the largest cause of mortality in the United Kingdom (UK), accounting for over 120,000 deaths annually. Like most developed countries, UK mortality rates from CHD have been falling since the 1970s. These trends need to be explained in order to explore different policy options for CHD prevention.

## Objectives

The objectives of this thesis were:

1. To document and critically review CHD data, and define the burden of CHD mortality and morbidity in England and Wales;
2. To explain most of the recent fall in CHD mortality in England and Wales;
3. To estimate the life-years gained by modern cardiological treatments, and by changes in cardiovascular risk factor levels;
4. To examine the potential benefits of increasing the uptake of cardiological treatments;
5. To estimate the potential benefits of reducing cardiovascular risk factors in England and Wales.

## Methods

All potentially relevant CHD data were identified, critically reviewed, and then used to assess the burden of disease for England and Wales. The main data sources were official statistics, clinical audits, national surveys and peer-reviewed publications.

The cell-based IMPACT Mortality Model, previously validated in Scotland, New Zealand and Finland was extensively developed and refined to synthesise data for England and Wales describing: a) CHD patient numbers, b) uptake of specific medical and surgical treatments, c) treatment effectiveness d) population trends in major cardiovascular risk factors, and e) effectiveness of risk factor changes, using published trials and meta-analyses.

'Analysis of extremes' sensitivity analyses were performed in each study.

## Results

CHD data were surprisingly patchy and mixed in quality. In 2000, an iceberg of disease was demonstrated in the England and Wales population of 51 million, with approximately 60,000 patients undergoing revascularisation each year, almost 3 million patients living with CHD and over 32 million possessing one or more elevated risk factors.

Between 1981 and 2000, England and Wales CHD mortality rates fell by 62% in men and 45% in women aged 25-84. This resulted in 68,230 fewer deaths in 2000, when compared with the 1981 baseline. Approximately 42% of this mortality fall was

attributable to treatments in individuals (including 8% from initial treatments of acute myocardial infarction, 11% from secondary prevention, 13% from heart failure treatments, and 3% from hypertension treatments). Some 58% of the mortality fall was attributable to population risk factor reductions (principally smoking 48%, blood pressure 9.5% and cholesterol 9.6%). Adverse trends were seen for obesity, diabetes and physical activity. Overall, the model explained approximately 96% of the mortality fall in men, and 79% in women.

The 68,230 deaths prevented or postponed in 2000 corresponded to approximately 994,610 life-years gained. Specific treatments for CHD patients gained approximately 194,145 life-years *(minimum estimate 142,500, maximum estimate 259,220)*. Population changes in the major risk factors (smoking, cholesterol, blood pressure) accounted for over three times as many life-years gained *(*approximately 800,465, *minimum estimate 602,690, maximum 879,420)*. Adverse changes in physical activity, obesity and diabetes resulted in a loss of approximately 92,600 life-years *(minimum 68,350, maximum 100,760)*.

In 2000, all medical and surgical CHD treatments together prevented or postponed approximately 25,760 deaths. However, treatment uptakes were generally poor, between 30% and 60%. Increasing treatment uptake to reach 80% of eligible patients (the NSF CHD target) would have prevented or postponed approximately 20,910 further deaths *(minimum 11,030, maximum 33,495)*, almost doubling the actual gain from therapies.

Using 2000 as the baseline, continuation of recent risk factor trends should result in approximately 15,145 fewer coronary deaths in 2010 *(min 12,170, max 17,290)*. However, achieving the modest additional risk factor reductions already seen in the USA and Scandinavia could potentially result in approximately 51,185 fewer deaths in 2010 *(minimum 39,395, maximum 72,330)*.

**Conclusions**

Coronary heart disease represents a massive burden of disease in England and Wales. Recent falls in CHD mortality rates reflect a combination of risk factor improvements and modern therapies. However, much greater mortality reductions appear possible. Future strategies should therefore maximise the delivery of appropriate therapies to all eligible CHD patients. Most crucially however, effective policies for tobacco control and healthy nutrition might potentially halve current CHD deaths in England and Wales.

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# LIST OF ABREVIATIONS

| | |
|---|---|
| ACE | Angiotensin converting enzyme |
| AMI | Acute myocardial infarction |
| BRHS | British Regional Heart Study |
| BMI | Body mass index |
| CABG | Coronary artery bypass graft |
| CHD | Coronary heart disease |
| CPR | Cardiopulmonary resuscitation |
| CVD | Cardiovascular disease |
| DALY | Disability adjusted life years gained |
| DPPs | Deaths prevented or postponed |
| HDL-C | High density lipoprotein cholesterol |
| HES | Hospital Episode Statistics |
| HSE | Health Survey for England |
| LDL-C | Low density lipoprotein cholesterol |
| LYG | Life years gained |
| NHS | National Health Service |
| OR | Odds ratio |
| PAR | Population attributable risk |
| PG IIb/IIIa | Platelet glycoprotein IIb/IIIa inhibitors |
| PTCA | Percutaneous transluminal coronary angioplasty |
| QALY | Quality adjusted life years |
| RCT | Randomised controlled trial |
| RR | Relative Risk |
| UK | United Kingdom |
| US | United States |

# 1 INTRODUCTION

Cardiovascular diseases (CVD) are the most common causes of death among both men and women in all developed countries. It is estimated that coronary heart disease (CHD) will be the largest single cause of disease burden globally by the year 2020[1]. CHD causes over 120,000 deaths in the UK annually, 26% of all premature deaths in men and 16% in women[2].

Increasing health care demands require policy decisions based on good evidence, particularly since resources are limited. By combining local data with trial based effectiveness, models can potentially offer increased transparency to the decision making process (provided their assumptions are clearly stated)[3]. Models have been extensively used in policy making and resource allocation, since they allow policy makers to simulate the effects of different scenarios within a population.

In 1996, Capewell and colleagues developed and refined a CHD mortality model (IMPACT) combining data from many sources on patient numbers, treatment effectiveness and risk factor trends to estimate the deaths prevented or postponed (DPPs) over a specified time period[4]. Initially, the IMPACT Model was used to examine the CHD mortality declines over a 20 year time period and estimate the proportion that could be attributed to falls in various risk factors or specific treatments. The IMPACT model was first validated against the actual mortality fall observed in Scotland, and then replicated in New Zealand[5].

In collaboration with the National Public Health Institute (KTL) in Helsinki, Finland, validation and development of the model then progressed, using high quality linked data on deaths and hospital activity, plus MONICA data on risk factors.

While interesting and useful, these projects highlighted various limitations of the original IMPACT methodology. As well as further developing and refining the IMPACT model, it was clearly desirable to apply it to England and Wales using local data, before using the basic model in a variety of further projects.

## 1.1 AIM

To achieve a refined coronary heart disease model, which

a) explains most of the recent fall in CHD mortality in England and Wales

b) quantifies the years of life gained by such mortality falls,

c) explores potential gains from medical and surgical treatments and

d) compares potential gains from future changes in cardiovascular risk factors

in order to explore future policy options for CHD prevention.

## 1.2 OBJECTIVES

1. To identify, select and review critically CHD data from various national and local UK sources

2. To define the burden of CHD in England and Wales using the existing data

3. To update and transform the original Scottish IMPACT Model (1975-94) into an English IMPACT Model, and incorporate relevant English and Welsh data.

4. To explore, test and develop a variety of methodological refinements to the existing CHD IMPACT Model, including:

    – reviewing $\beta$ coefficients for smoking, cholesterol and blood pressure

    – seeking $\beta$ coefficients for diabetes, obesity and physical activity

5. To explain most of the recent falls in CHD mortality in England and Wales

6. To estimate the life-years gained attributable to modern cardiological treatments, and to changes in cardiovascular risk factor levels.

7. To estimate the potential benefit of increasing the uptake of effective cardiological treatments.

8. To estimate the potential for cardiovascular risk factor changes to reduce CHD deaths in England and Wales by 2010.

# 2 CORONARY HEART DISEASE EPIDEMIOLOGY

## 2.1 CORONARY HEART DISEASE: Definition

The term 'coronary heart disease', also known as ischaemic heart disease, covers a group of clinical syndromes that includes angina pectoris, acute myocardial infarction (fatal and non-fatal) and sudden cardiac death. It may also include those forms of heart failure resulting from ischaemic heart disease. The common underlying pathology is atherosclerosis of the coronary arteries. One or more atheroma plaques grow beneath the coronary artery endothelium. This atheroma expansion results in narrowing of the lumen and may progress to rupture of the endothelial surface, thus triggering thrombosis and hence partial or complete occlusion[6].

## 2.2 CARDIOVASCULAR RISK FACTORS

The concept of 'risk factors' refers to any characteristic, which increases the probability of an individual developing CHD. Risk factors can be fixed or modifiable. This concept was first developed during the early epidemiological studies of CHD[7]. The principal fixed risk factors are age, sex and family history[8]. Modifiable biochemical and physiologic factors relate to environment and lifestyle, these include potentially alterable personal characteristics such as smoking, high blood pressure, hyperlipidemia and diabetes. These modifiable factors can then be targeted by interventions aiming to prevent CHD in individuals, or in the population.

### 2.2.1 Age

In industrial countries, absolute risk for CHD increases exponentially with age in both men and women[9-11] as the result of progressive accumulation of coronary atherosclerosis with ageing. For example, among British men, there is a 2-3 fold increase in mortality rate with each additional decade[12].

### 2.2.2 Sex

There is a striking difference in CHD mortality between men and women. Death rates among women lag behind those of men by approximately 10 years, more so in younger age groups[13]. This difference diminishes with increasing age, so that women aged 85 years or over have almost the same mortality rate as men[12]. Women are apparently

protected to some degree by their hormonal function, but this protection diminishes progressively during and after menopause[12]. However, it is worth emphasising that the sex differences in CHD are complex, and probably cannot be explained purely on an endocrine basis[8].

## 2.2.3 Smoking

Tobacco smoking is a powerful risk factor for CVD. Compared with non-smokers male and female smokers demonstrate at least a two fold increase in the incidence of CHD[14-16]. Relative risk is even higher, four or five fold, in younger groups[17]. Smoking predisposes to CHD in several ways. Partly through enhanced thrombosis (blood clotting)[18], and also by promoting atherosclerosis[19,20] and coronary plaque development[21]. If the main effect of smoking is thrombogenic rather than atherosclerotic, it would be plausible to expect that risk might rapidly decline following smoking cessation. Among persons with previously diagnosed myocardial infarction or CHD, smoking cessation reduces the risk for recurrent heart attack and mortality by 40% within two years[22]. However, the 1990 US Surgeon General's Report states that although the risk is halved within 1-2 years, risk only returns to that of a non-smoker after 15 years of abstinence[23]. Hence, all these mechanisms appear potentially important.

## 2.2.4 Blood Pressure and Hypertension

There is a continuous relationship between the level of blood pressure and the risk of cardiovascular events[24]. The mechanism whereby hypertension increases coronary events results from both the direct vascular injury which promotes atherogenesis, and also from its effects on the myocardium, including wall stress and increased myocardial oxygen demand[25].

Both systolic and diastolic blood pressure levels show a strongly positive log-linear relationship with CHD[24]. Overall, a two to three fold increase in CHD rate is apparent in hypertensive groups compared to normal blood pressure groups[24]. In the British Regional Heart Study a two-fold increase in risk of CHD was evident at a systolic blood pressure of over 148 mmHg, with little or no gradient of risk apparent below this level[26]. However, more recently the Prospective Studies Collaboration analysed

outcome in over one million subjects. A threshold was difficult to detect. They found risk extended down to 75 mmHg diastolic blood pressure[27].

However, the arbitrary definition of hypertension has contributed to a plethora of statements issued by national and international authorities over the decades. Although the International Society of Hypertension recently defined 'hypertension' as a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg in people not taking antihypertensive medication[28], this is unlikely to be the last word on the subject.

## 2.2.5 Serum Lipids

Total cholesterol and a variety of lipid sub fractions have been consistently reported to increase CHD risk.

## Total Cholesterol

In most population studies, mean total cholesterol increases with age, mainly between the second and fifth decades. Framingham and other US studies traditionally suggested a total cholesterol level <200 mg/dl as desirable (<5.2 mmol/l), 200 to 239 mg/dl (5.2-6.2 mmol/l) as "borderline-high" and 240 mg/dl (6.2 mmol/l) or over 'high' for both men and women[29]. However, serum total cholesterol levels are associated with a continuous log-linear graded CHD risk to below 160 mg/dl (<4 mmol/l)[30].

Law and colleague's meta-analysis estimated that a change in plasma cholesterol of 0.6 mmol/1 (about 10%) is associated with an overall change of approximately 27% in mortality from CHD in cohort studies, international comparisons and RCTs of lipid lowering in men[31]. A strong age gradient was also observed; a change in serum cholesterol concentration of 0.6 mmol/l was associated with a change in incidence of ischaemic heart disease of 54% at age 40 years, 39% at age 50, 27% at 60, 20% at 70, and 19% at 80[32].

## Low Density Lipoprotein Cholesterol (LDL-C)

LDL-C is the major fraction of total cholesterol and increases with age, a saturated fat rich diet, and obesity. In the US, the National Cholesterol Education Program (NCEP) Adult treatment panel II has stratified the risk of LDL-C levels as ≥ 160 mg/dl (or ≥4.1

mmol/l) being 'high risk'; 130-158 mg/dl (or 3.4 mmol/l - 4.1 mmol/l) being 'borderline high risk'; and <130 mg/dl (or <3.4 mmol/l) being a 'desirable LDL-C'[29].

LDL-C has a stronger association with CHD than total cholesterol, and is sometimes used as the primary target for cholesterol-lowering therapy[29]. Therapeutic lowering of LDL-C appears highly effective in primary and secondary prevention. In a recent large study, a 35% reduction in LDL-C lowering with the HMG-CoA reductase inhibitor, simvastatin, reduced coronary mortality by 42% and total mortality by 30%[33].

A substantial benefit from LDL-C lowering is also reported in primary prevention, with a 1% change in LDL-C level being associated with 2% or 3% change in CHD risk[29]. Thus in a meta-analysis of primary prevention trials, lipid lowering drugs reduced the odds of a CHD event by 30%[34].

**High Density Lipoprotein** *(HDL-C) Cholesterol*

HDL-C is protective against CHD. HDL-C is generally increased by regular exercise, or moderate alcohol consumption[35]. Despite the strong epidemiological association, the biological mechanisms underlying the HDL-CHD link remain poorly understood. Some researchers propose that HDL-C attenuates the atherogenicity of LDL-C; if so low levels of HDL-C may directly promote atherogenesis.

The NCEP[29] defines 3 categories of HDL-C: low (<35 mg/dl or <0.9 mmol/l), normal (35 to 60 mg/dl or 0.9 to 1.6 mmol/l), and high (>60 mg/dl or >1.6 mmol/l). The NCEP classifies low HDL-C as a major risk factor; conversely, a high level is considered a "negative" (protective) factor[29].

**Lipoprotein a**

Lipoprotein (a) (Lp a) consists of an LDL-C particle bound by a disulfide bridge to apolipoprotein (a), a structure resembling plasminogen. Lp (a) demonstrates genotypic and phenotypic variation, which then affects plasma LDL-C levels. A high level of Lp(a) (>0.30 g/l) is an important risk factor for premature atherosclerosis and CHD [36].

## Apolipoprotein A-I (Apo-AI) and Apolipoprotein B (Apo B)

Apo-AI is a lipid- binding protein and is the major component of HDL. Apo-AI stimulates cholesterol removal from cells and it has antioxidant activity, which prevents atherosclerotic damage[37].

Apo B is the main apolipoprotein of chylomicrons and LDL. It is a measure of small, dense LDL particles known to be more atherogenic than LDL. Some mutations in Apo B genes reduce LDL affinity for the LDL receptor. This delays the clearance of LDL from the plasma resulting in hypercholesterolemia and premature atherosclerosis[38].

## Triglycerides

Elevated triglyceride levels have been variably associated with an increased risk of CHD in men and women[39;40]. In univariate analyses, triglyceride often emerges as a positive risk factor for CHD. However, in multivariable analyses it frequently appears not to have an independent association with CHD[41].

### 2.2.6 Diabetes and Glucose Intolerance

Diabetes is an independent risk factor for CHD[21;42]. Glucose intolerance is an intermediate state between 'normoglycemia' (a fasting blood glucose level less than 110 mg/dl or a random blood glucose level less than 140 mg/dl) and frank diabetes. Current evidence suggests that development of glucose intolerance or diabetes is initiated by insulin resistance and is worsened by the compensatory hyperinsulinemia. The progression to type II diabetes is influenced by genetics and environmental factors that promote obesity such as a sedentary lifestyle and dietary habits[43].

Patients with diabetes demonstrate an increased risk for CHD. Although CHD can occur at very young age in insulin dependent (Type I) diabetes, type II diabetes is far more common. In the Framingham Study the risk ratio for CHD was 2.4 ($p<0.05$) in men and 5.1 ($p<0.01$) for women with diabetes[44]. Up to 80% of adult diabetic patients die of CVD, and 75% of these deaths are caused by CHD[45]. In addition to the independent risk factor, hyperglycaemia, and insulin resistance, patients with diabetes commonly have other cardiovascular risk factors (e.g. hypertension, low serum HDL-C, high LDL-C and high triglyceride); these additional risk factors increase CHD risk in many diabetic patients[46]. Type II diabetes is sometimes considered part of a dysmetabolic

syndrome (Syndrome X) that includes insulin resistance, hyperinsulinemia, obesity, hypertension, and dyslipidemia.

In diabetic patients, myocardial ischemia due to coronary atherosclerosis more commonly occurs without symptoms such as anginal pain[47]. As a result, multivessel atherosclerosis may be present before ischaemic symptoms occur and hence before treatment is instituted. The delayed recognition of various forms of CHD undoubtedly further worsens the prognosis for many diabetic patients.

## 2.2.7  Other Risk Factors

There are many more risk factors, which may increase the likelihood for developing CHD apart from the major risk factors summarised above. These risk factors include physical inactivity, family history of premature CHD, obesity, diet, antioxidants, the Barker effect, the life course, increased serum homocysteine, and abnormalities in coagulation factors.

### Obesity

Obesity, defined as a body mass index (BMI)>30, is widely used as a measure of body fatness in surveys[48]. The increasing prevalence of obesity in many countries is now considered a pandemic; in Britain, over half the adult population are currently overweight or obese[48].

Visceral or central abdominal obesity, which can be quantified by the waist to hip ratio has been shown to increase CHD risk[49]. Desirable waist to hip ratio appears to be <0.9 for men and <0.8 for women[49].

Obesity is associated with other major cardiovascular risk factors, including hypertension, diabetes, dyslipidaemia, and physical inactivity. Much of the increased CHD risk associated with obesity is mediated by these associations. However in several prospective studies obesity was found to be a significant independent risk factor for CHD incidence[50;51]. An ongoing analysis of Prospective Studies Collaboration suggests that CHD risk is increased by approximately 10% for each 5 kg additional weight *(Personal Communication Gary Smith, PSC, Oxford)*.

## Physical Inactivity

Physical inactivity appears consistently associated with an approximately twofold increase in CHD risk. In an early meta-analysis by Berlin et al., relative risk of death from CHD was 1.9 (95%CI 1.6-2.2) for sedentary compared with active groups[52]. However, not all studies have shown an independent benefit of physical activity after adjusting for potential confounders such as obesity, diabetes, hypertension and deprivation, and adjustments for these factors consistently weaken the beneficial effect of physical activity[53]. Conversely, physical activity is notoriously difficult to measure accurately, and non-differential misclassification may weaken estimates of its independent effect on CHD risk. A recent British Regional Heart Study (BRHS) paper suggests a modest but statistically protective effect in sedentary individuals who subsequently become more active[54].

The protective cardiovascular effect of physical activity may be attributable to both direct and indirect mechanisms. Direct physiologic adaptations in response to regular exercise result in more efficient oxygen delivery, and oxygen uptake by exercising muscles[55]. Other important indirect mechanisms include a reduction in blood pressure and improved control of body weight[54].

Earlier studies and guidelines recommended vigorous exercise for cardiovascular benefit[56] More recent evidence suggests that moderate exercise (such as walking) also has a cardiovascular benefit. In an 8 year follow up study of 7,735 middle aged men who participated in the British Regional Heart Study an inverse association was observed for moderate levels of activity such as involved sporting activity once a week or lighter activities such as walking, gardening and 'Do It Yourself'[53].

The current guidelines from the Centers for Disease Control and Prevention and the Surgeon General's report[57] therefore recommend at least 30 minutes of moderate intensity physical activity on most or preferably all days of the week (whereas earlier guidelines recommended vigorous aerobic exercise for at least 20 minutes 3 or more times per week).

## Alcohol use

Individuals reporting moderate amounts of alcohol intake (approximately one to three units per day) have a 40% to 50% lower CHD risk compared with individuals who are abstinent[58;59]. However, higher intakes are associated with raised blood pressure, increased CHD mortality and increased total mortality[60]. Although some cohort studies have suggested that wine may be more beneficial than beer or spirits most studies do not support an association between type of alcoholic beverage and prevention of heart disease [61]. Although regular low to moderate consumption of alcohol appears protective against CHD, a general recommendation for alcohol use was not encouraged in the latest WHO/FAO report [62] because of other cardiovascular and health risks.

## Homocysteine

Increased CHD is seen in various genetic conditions causing increased homocysteine levels. The normal plasma homocysteine levels range from 5-15 μmol/L; levels grater than 15 μmol/L are defined as hyperhomocysteinemia[63]. Higher levels of homocysteine may be a weak independent risk factor for CVD[63-65]. A recent systematic review reported that the summary odds ratios (OR) for a 5-μmol/l increase in homocysteine concentration were 1.06 (95% CI: 0.99–1.13) for 2 cohort studies, and 1.23 (95% CI: 1.07–1.41) for 10 nested case-control studies. The authors concluded that it was premature to formulate public health recommendations on recommended homocysteine levels, screening policies, and prevention measures in the general population. Data from ongoing randomised trials are awaited[66].

## Vitamins and Antioxidants

Diet appears to be a major factor in the aetiology of CVD. However, there is still considerable scientific uncertainty about the relationship between specific dietary components and CVD risk. The Antioxidant Hypothesis suggests that vitamin C and E, β-carotene and other carotenoids, antioxidant minerals such as selenium, zinc and other antioxidants such as flavonoids are protective against CVD[67]. A systematic review of observational studies suggested a weak protective effect of fruit and vegetable consumption for CHD[68]. However RCTs have generally failed to show beneficial effects of antioxidants as food supplements added to diet (β carotene, tocopherol and ascorbic acid) on the risk of myocardial infarction, stroke or CHD mortality[67,69]

Currently recommendations for primary prevention focus on increasing intake of fruit and vegetables, rather than using antioxidant supplements[70;71]. A meta-analysis of cohort studies, reported that the relative risk reduction of CHD in high consumers of fruits and vegetables might be around 15%[72]. Furthermore, the EPIC Norfolk study suggested a 20 μmol/L rise in plasma ascorbic acid concentration (equivalent to about 50 g per day increase in fruit and vegetable intake) was associated with about a 30% reduction in risk of CHD mortality[73].

## Coagulation factors

Thrombosis has a central role in CHD pathology. Plasma fibrinogen is clearly a risk marker for atherothrombotic events[74], while some studies suggest that factor VII, factor VIII, von Willebrand factor, and other coagulation markers have significant but weaker effects[75], with odds ratios typically around 1.2 or 1.3[76;77].

Thrombotic factors are important in determining the clinical expression of CHD and in some pharmacological therapies. However their measurement in healthy adults does not alter primary prevention based on the major risk factors[78].

## Socio-economic factors across the life course

The UK CHD epidemic in the 1950s-1960s particularly affected affluent groups. This class differential then slowly reversed so that people in lower social classes now have higher rates of morbidity and mortality from CVD than those in higher classes[79;80]. This particularly relates to deaths from premature CHD, which are approximately 3 times higher among unskilled manual workers than professionals[81]. It is estimated that each year 5,000 lives and 47,000 working years are lost in men aged 20-64 years due to social class inequalities in CHD death rates in England and Wales[82]. Furthermore, since the 1970s, death rates from CHD have fallen more slowly in lower socio-economic groups[83].

Childhood and adult deprivation have independent adverse effects on health[84]. Social class in childhood seems to be particularly important for mortality from CVD whereas social class in adulthood is more related to all cause mortality[80]. There is a continuing debate about the extent to which this is related to early life experience or to a higher prevalence of major risk factors[85].

Changes in socio-economic status can be measured in a variety of ways. In Chapter 8, I will describe how change in household income, indexed to 1981, was used as a crude measure of change in deprivation.

## Foetal and infant origins of adult disease

It is suggested that CHD is increased by specific patterns of disproportionate fetal growth that result from foetal under-nutrition in middle to late gestation[86]. In other words, a baby's nourishment before birth, "programmes" the subsequent development of risk factors such as raised blood pressure, glucose intolerance, concentrations of fibrinogen, and coagulation factor VIII and hence CHD[87].

Studies of men born in Britain and in Finland suggested that low birth weight or low weight at one year or both were associated with increased CHD prevalence and mortality rates [88-90].

## Genetic factors

The incidence and mortality from atherosclerosis and CHD vary considerably among races, populations and ethnic groups[91]. Some individuals with apparently low levels of risk factors show disease symptoms while many others with a high-risk profile do not. CHD may cluster in families, and may be substantially increased in first-degree relatives of persons with an early onset of the disease. The genetics of CHD can be divided into three categories: Family history, phenotypes, and genotypes.

### *Family History*

Family history of CHD provides useful additional information about an individual's risk status[92]. The earlier that clinical CHD or sudden death affected a first-degree relative, the higher the risk [93,94]. However, the independent genetic effect of a positive family history is difficult to determine. Familial influences on risk status are almost certainly mediated in part through blood pressure, serum lipid levels and the sharing of other environmental factors. A positive family history of premature CHD should therefore be considered as a reason to screen, detect and management of other family members who may carry heritable risk factors, such as familial hypercholesterolemia[94].

## Phenotypes

A number of prospective studies have reported an inverse association between height and CHD, which persisted even after adjusting for possible confounding factors, such as social class and smoking[95;96]. Furthermore, in a prospective study, taller men and women had more favourable cardiovascular risk profiles than shorter people[97]. Possible explanations for this association include, height is a marker for exposures influencing childhood growth such as diet, infection, or psychological stress[98], increasing coronary vessel diameter with height[99], genes influencing height might be closely linked to those affecting CHD risk or residual confounding, because social class is often poorly measured and controlled for.

## Genotypes

Functional polymorphisms can affect genes. This may induce variability of biological mechanisms, which have neutral, beneficial or detrimental consequences. However, Keavney's authoritative review recently concluded that common polymorphisms, with frequent alleles that have relatively small effects and interact with each other and environmental factors are likely to account for most of the genetic component of coronary disease[100]. More definitive answers may need to await completion of the UK Biobank Project[101].

## 2.3 CHD RISK SCORING SYSTEMS

CHD is a multifactorial disease. As described above, the major independent risk factors for CHD are elevated serum total cholesterol, cigarette smoking, elevated blood pressure, diabetes mellitus, and age. The quantitative relationship between these risk factors and CHD risk has been elucidated by the Framingham Heart Study[42] in USA and other studies in Europe such as PROCAM[102], Dundee[103] and British Regional Heart study[104]. These studies suggest that the major risk factors are generally additive in predictive power[42]. Therefore, the total risk of a person can be estimated by a summing the risk from each of the major risk factors.

The absolute risk of developing CHD over the next 10 years can be calculated using the Framingham equation[42] or a variety of other risk scores[103-105]. The Framingham equation in UK subjects tends to overestimate risk slightly higher compared with the Dundee equation but substantially higher (by approximately 50%) compared with the BRHS[106]. The reason for this was not clear and it is suggested that Framingham equation could be used for relative risk estimation rather than absolute risk for CHD[106]. Although preventive efforts should target each major risk factor, an assessment of total risk based on the summation of all major risk factors can be clinically useful for identification of high-risk patients who merit prioritisation for more intensive intervention[107;108].

Most risk scores estimate risk for persons without clinical manifestations of CHD[42] and are therefore useful for primary prevention in individuals. For secondary prevention in patients with CHD, there are many guidelines for the management of individual risk factors developed by American[93;109;110] and European bodies[111]. However, CHD risk scores are less useful for policy makers at the population level. A CHD policy model can be more useful which incorporates a wide range of risk factors and treatment interventions to explain CHD morbidity or mortality trends seen in the population.

I will consider prevention in more detail in the next chapter.

# 3 CHD PREVENTION AND TREATMENT

Control of CHD is a broad concept and includes primary and secondary prevention strategies.

**"Primary prevention"** means delaying or preventing CHD in healthy subjects. by modifying lifestyle and environmental factors, and their social and economic determinants that are underlying cause of CHD. Primary prevention can use two main approaches:

In *population-based approaches*, interventions are directed at all individuals in the whole population regardless of their risk factor or disease status. Examples include national legislation to ban tobacco advertising and food policies which promote the consumption of fresh fruit and vegetables and which discourage the dietary intake of excessive salt or saturated fat[112;113]. **Primordial prevention** is a relatively new term that used interchangeably with population-based approaches. It is defined as attempts to prevent the risk factors in the whole population that may eventually lead to CVD[114].

In the *high-risk approach* the target is the individual with one or more elevated risk factors and who is therefore more likely to develop disease in the future. Interventions for these people can be more sophisticated and aggressive. For instance, the detection and treatment of elevated cholesterol or blood pressure, or helping the individual to quit smoking.

The term **"secondary prevention"** denotes interventions in patients with established CHD, aiming to reduce the likelihood of further events and decrease coronary mortality. Secondary prevention strategies can be aimed at control of risk factors either by lifestyle changes or drug therapies (for instance by using aspirin, beta-blockers, statins or ACE inhibitors). This dual approach has led some authors to consider secondary prevention efforts and treatment of CHD as synonymous terms. In contrast, most clinicians would not use the term secondary prevention to describe the initial treatment of AMI, unstable angina or heart failure or revascularisation.

Secondary prevention targets all manifestations of atherosclerotic disease, which includes angina pectoris or a documented myocardial infarction, a history of coronary

artery revascularisation procedure (bypass graft or angioplasty), peripheral artery disease, aortic aneurysm, stroke or heart failure secondary to CHD[29,93].

A comprehensive strategy for CHD prevention should therefore consider all four components, primary and secondary prevention in both individuals and populations.

## 3.1 EFFECTIVE INTERVENTIONS FOR CHD PRIMARY PREVENTION

Causal relationships between CHD and major risk factors such as smoking, cholesterol, blood pressure and physical activity are well established[115]. Interventions to change these risk factors through life style changes or medical interventions have been studied widely in many different populations.

### 3.1.1 Reducing smoking

Many countries started tobacco control programmes in 1970s and have had considerable success in reducing smoking rates. Sweden, Norway, Finland and Iceland all introduced advertising bans back in the 1970s which were followed by substantial reductions in smoking rates or tobacco consumption[116;117]. In US, smoking prevalence amongst the adults decreased from 37% in 1970 to 23% in 2000[118]. Smoking prevalence declined even faster in California when more intensive programmes were active, and visibly slowed when these programmes were suspended[119]. In all these countries CHD mortality decreased significantly in the last few decades.

The risk of CHD declines rapidly in those who quit smoking, to a level comparable with that of people who had never smoked after 2–3 years, independent of the number of cigarettes smoked before quitting[23].

Effective interventions and policies to reduce smoking differ according to the targeted population. Physician's cessation advice is often directed at older smokers and is designed to encourage them to quit smoking. Simple short advice by a physician has a small but significant (2.5% absolute difference in cessation rates) effect on cessation rates[120]. Anti-tobacco media campaigns can be targeted at all people and convey messages like "don't start", "quit now" or "don't relapse". Such campaigns are more likely to be effective as part of a larger campaign aimed primarily at adults[121].

## 3.1.2 Reducing cholesterol

Population cholesterol level is widely influenced by diet. It is suggested that a diet rich in saturated fat is associated with higher CHD risk. Therefore dietary modification remains the cornerstone of CHD prevention[122].

Interventions at the community level can substantially reduce cholesterol levels in the population. In Finland, the North Karelia Project started in 1972, aiming to reduce risk factors, and a similar national programme followed this. A major decline in CVD risk factors was observed in the following 20 years in Finland. Cholesterol levels decreased approximately 18% among both men and women (from 6.9 mmol/l to 5.7 mmol/l in men and from 6.8 mmol/l to 5.6 mmol/l in women) between 1972 and 1997[123].

After an alarming increase in CVD and risk factors in Mauritius, an intensive national non-communicable disease intervention programme was introduced in 1988. The intervention programme aimed at modifying levels of risk factors related to lifestyle, including glucose intolerance, hypertension, hyperlipidaemia, obesity, cigarette smoking, alcohol misuse, and physical inactivity. Primary prevention components of the programme included extensive use of the mass media; fiscal and legislative measures; and widespread community, school, and workplace health education activities. All these components have promoted healthy nutrition, increased exercise, smoking cessation, and reduction in alcohol intake. As well as promoting healthy lifestyles, the government also introduced unsaturated soya bean oil as cooking oil instead of saturated fat rich palm oil. The mean total cholesterol concentration decreased by 14-15% (from 5.5 to 4.8 mmol/l), among adult Mauritians during the five years from 1987 to 1992[124].

Lowering cholesterol levels in individuals without CHD using drugs is also an option. In a recent systematic review of four randomised clinical trials (RCT) of statins, fibrates and cholestyramine it was found that drug treatment for cholesterol reduction significantly reduced CHD events and CHD mortality, but found no significant effect on overall mortality (OR for treatment *versus* placebo; 0.70, 95% CI 0.62 to 0.79 for CHD events; 0.71, 95% CI 0.56 to 0.91 for CHD mortality; 0.94, 95% CI 0.81 to 1.09 for overall mortality)[34].

### 3.1.3  Reducing blood pressure

**Population blood pressure**

Population blood pressure has been decreasing in many western countries[125]. Substantial changes in food processing have taken place in the last three decades and intake of preserved foods decreased. This might have largely reduced the salt intake in the populations and caused the secular trend observed in blood pressure in the western countries.

It has been much debated whether a general reduction in sodium intake could decrease the blood pressure of a population and thus reduce cardiovascular mortality and morbidity. To answer this question many studies have been performed in different populations with normal blood pressure and high blood pressure. Evidence from a systematic review shows a small effect of salt restriction in the people with normal blood pressure and therefore does not suggest a general recommendation to reduce sodium intake in the general population[126]. However, reducing sodium intake in people with high blood pressure is very effective, leading to 4 mmHg systolic and 2 mmHg diastolic blood pressure reductions in people with high blood pressure[126].

**Hypertension treatment**

Control of hypertension is very important to prevent CHD, stroke and other target organ damage such as kidney diseases, peripheral vascular disease, and retinopathies[127]. However, prevention and treatment of hypertension remain important public health challenges[128]. A survey in England has shown that, whilst most patients with hypertension are detected, those diagnosed as hypertensive often do not continue on treatment and those treated are often not controlled satisfactorily[129]. An increase in hypertension treatment and control in England was reported between 1994 and 1998, but compared with international standards these measures were still low[130].

Hypertension treatment should start with detailed cardiovascular risk assessment using established CHD risk scoring methods based on Framingham equation[131-133]. For this purpose the SIGN guideline development group recommends the use of the most recent version of the Joint British chart, which can be used to formulate decisions about antihypertensive, lipid lowering and antiplatelet therapy[131].

Management is based on risk stratification. The treatment target for hypertensive patients is recommended to be a blood pressure of <140/90 mmHg[128]. However, this field continues to change rapidly, thus a target of 115/75 mmHg was recently proposed[134]. To reach this target lifestyle modification and drug treatments are recommended, together or interchangeably in hypertensive patients.

## Lifestyle modification to reduce blood pressure

A change in **diet** is recommended, including a diet high in fruit and vegetables; high in pulses and whole grains; high in fat-free and low fat dairy, poultry, fish, shellfish, and meat products; high in all essential nutrients; reduced in salt; reduced in total fat, saturated fat and cholesterol; no more than one or two drinks of alcohol per day; and controlled in calories to prevent or correct obesity[135]. Obese or overweight hypertensive patients should be encouraged to **lose weight**[136]. **Sodium intake** should be reduced by minimising intake of processed food and by not adding salt at table towards a target of <5 g/day[128]. **Increase in physical activity**, at least 30-45 minutes brisk walking most days should be encouraged. Smoking should be actively discouraged[128]. These methods can be used alone or in combination with drugs. Increased potassium intake from fresh fruit and vegetables is also beneficial.

## Antihypertensive drug therapies

Effective treatment options for hypertensive patients include thiazide diuretics, beta-blockers, calcium channel antagonists, and angiotensin converting enzyme (ACE) inhibitors[128].

**Diuretics** are inexpensive, effective, generally well tolerated in low doses, and diuretic-based treatment regimens have been clearly shown to prevent major cardiovascular events, including stroke and CHD[137]. Diuretics should be used in low doses (maximum of 25 mg daily of hydrochlorothiazide) and often half or less this dose, in order to reduce the adverse effects. Diuretics are recommended as first choice for the treatment of elderly patients[128].

**Beta-blockers** are safe, cheap and effective for reducing blood pressure. They can be used as alternative or supplementary therapy to diuretics and calcium antagonists[128]. A meta-analysis of 7 RCTs, aimed to quantify hypertension treatment effect (beta-blocker

and/or diuretics) for stroke, CHD and, total and specific mortality, in men and women[127]. In that analysis hypertension treatment effect was significant for all coronary events, stroke and mortality outcomes in men. However in women hypertension treatment was significant only for stroke, treatment reduced stroke risk by 38% in women and 34% in men. The difference was attributed to untreated risk in women[127].

**Calcium antagonists** are effective and well tolerated in lowering blood pressure. Long-acting calcium antagonists are preferred and rapid-onset short acting calcium antagonists should be avoided. Calcium antagonists are particularly recommended for elderly patients with systolic hypertension. Adverse effects include tachycardia, flushing, ankle oedema and (with verapamil) constipation[137].

**ACE inhibitors** have been proven useful in blood pressure reduction; can reduce cardiovascular mortality and morbidity after myocardial infarction. ACE inhibitors are specifically indicated as first line therapy for hypertension in patients with type 1 diabetes, proteinuria, or left ventricular dysfunction[128]. Angiotensin II antagonists are recommended as alternatives to ACE-inhibitors when cough is a limiting adverse effect.

### 3.1.4 Reducing obesity

Effective interventions to reduce weight or obesity at the population level have been researched. Systematic reviews and RCTs have found that a combination of advice on diet and exercise, supported by behavioural therapy, is probably more effective in achieving weight loss in obese or overweight people than either diet or exercise advice alone[138]. A low energy, low fat diet is the most effective lifestyle intervention for weight loss. Weight regain is likely, but weight loss of 2–6 kg may be sustained over at least 2 years. Combined personal and computerised tailoring of weight loss programmes may improve maintenance of weight loss[139]. However most studies were carried out on overweight or obese volunteers, not on the general population. Besides these interventions in high-risk people, interventions targeting life styles (such as promoting physical activity and healthy diet) for the whole population may also be required.

### 3.1.5 Increasing physical activity

There is good observational evidence that moderate to high levels of physical activity reduce the risk of non-fatal and fatal CHD and stroke[140]. People who are physically

active (those who undertake moderate levels of activity daily or almost daily, e.g. walking) typically experience 30–50% reductions in relative risk of CHD compared with people who are sedentary, after adjustment for other risk factors[140].

Effective interventions to encourage people to increase their physical activity were evaluated in a systematic review[141]. Community wide campaigns, school based interventions such as modifying the curricula and individually adapted health behaviour change programmes were reported as the most effective interventions to increase physical activity[141]. However, studies in this review were mostly from USA, there was little research in the UK. Interventions that encourage walking and do not require attendance at a facility are most likely to lead to sustainable increases in physical activity[142]. Brisk walking has the greatest potential for increasing overall activity levels of a sedentary population[139;142].

## 3.2 EVIDENCE BASED CARDIOLOGICAL THERAPIES

Life expectancy is greatly reduced by symptomatic CHD. For instance median survival in a 65 year old man falls to 5 years after a first admission for AMI, and 17 months after a first admission for heart failure[143;144]. A wealth of evidence from randomised trials and meta-analyses underpins an expanding range of treatments for different forms of CHD. These can improve symptoms, or survival, or both.

The **therapies** considered in this thesis are detailed in *Box 8.9, Chapter 8*. They included cardio-pulmonary resuscitation, thrombolysis, primary PTCA, aspirin, beta blockers, and ACE inhibitors for the initial treatment of acute myocardial infarction; all secondary prevention medications including aspirin, beta-blockers, ACE inhibitors, statins, warfarin and cardiac rehabilitation; aspirin, CABG surgery and angioplasty with stenting for angina; heparin, aspirin, and platelet IIB/IIIA inhibitors for unstable angina; ACE inhibitors, spironolactone and beta blockers for heart failure; plus anti-hypertensive drugs and statins for primary prevention. The mortality benefits are summarized in *(Box 8.10)*.

### 3.2.1 Angina

Angina is the commonest symptomatic manifestation of CHD, affecting approximately two million people in the UK[2]. Angina typically presents with central chest pain

induced by exercise, cold or stress. This reflects reversible myocardial ischemia. If the chest pain rapidly disappears with rest or nitrates, it is often termed 'stable' or 'chronic' angina. Such patients are usually given nitrates for symptom relief plus regular aspirin, and beta-blockers or calcium antagonists. Depending on factors including severity of symptoms and the location of the stenoses in the coronary vessels, patients may be referred to a rapid access cardiopulmonary clinic for further assessment, often leading to angiography and CABG surgery or PTCA procedures if indicated[145,146].

### 3.2.2 Unstable angina

Unstable angina presents as angina pain, which occurs with increasing frequency or severity, and which may persist even when a patient is at rest. Unstable angina patients are at increased risk of myocardial infarction or sudden cardiac death. They are generally admitted to hospital, where they are usually treated with nitrates, beta-blockers, aspirin, anti-coagulants such as heparin, and sometimes platelet glycoprotein IIb/IIIa (PG IIb/IIIa) inhibitors or clopidogrel[147]. Unstable angina patients are often strong candidates for revascularisation with increasing numbers receiving PTCA stent plus PG IIb/IIIa inhibitors or clopidogrel[147].

### 3.2.3 Revascularisation

There is good evidence that many people with atheromatous plaques and narrowed coronary arteries can have their anginal symptoms relieved and reduced by restoring blood flow through blocked coronary arteries (revascularisation) or their risks of dying may also be decreased[148]. The two most widely used techniques are coronary artery bypass surgery (CABG) and percutaneous transluminal coronary angioplasty (PTCA).

### 3.2.4 Coronary Artery Bypass Graft Surgery (CABG)

CABG is the surgical procedure to restore blood flow around narrowed or blocked coronary arteries. The goal of the surgery is to improve blood flow and provide relief from chest pain and other symptoms[149]. This involves the careful removal of a "clean" vein (graft) from the leg, or arm, and attaching it to bypass the stenosed section of the artery. The majority of the CABG procedures now involve the transfer of one or both internal mammary arteries. Long term results are much better than venous grafts[146].

### 3.2.5 Percutaneous transluminal coronary angioplasty (PTCA)

PTCA is a procedure in which a cardiac catheter is passed through the skin into an artery, most commonly the femoral artery in the groin or radial artery. The catheter is then threaded into the coronary arteries. The position of the tip of the catheter can be followed using radio opaque dye on X-ray screening. When the tip of the catheter is in the narrowed section of the coronary artery, a small balloon at the tip of the catheter is inflated dilating the narrowed section of the coronary artery. A tubular mesh splint – a stent – is then usually inserted into the dilated artery to act as scaffolding to help keep it open[149]. The risk of subsequent restenosis at that site can now be further reduced by medications including PG IIb/IIIa inhibitors, or drug eluting stents[150].

However there is no convincing evidence that PTCA is superior to medical treatment with regard to the risk of myocardial infarction or death in patients with chronic stable angina. PTCA is more effective at relieving anginal symptoms than medical treatments such as beta-blockers, nitrates and calcium channel antagonists[151]. This advantage decrease over time with little difference remaining at 3 years because of the high rate of restenosis[151]. PTCA also appears equivalent to CABG in terms of angina relief in the short term, but not long term[152]. However evaluation of PTCA and CABG remains difficult as the technology is evolving rapidly. Large RCTs inevitably require long timescales to produce definitive results on therapies, which may then already be obsolete.

### 3.2.6 Acute Myocardial Infarction

Acute myocardial infarction (AMI) occurs in over 200,000 individuals in the UK each year[2]. AMI is the death of cardiac myocytes due to prolonged ischaemia[153]. AMI most commonly occurs following a complete occlusion of a coronary artery due to plaque rupture and thrombosis[154]. It is a severe clinical condition and in approximately 50% of cases leads to sudden death[155]. Even after admission to hospital, mean case fatality of AMI in the first month is about 20% (even higher in the elderly) and about one-half of these deaths occur within the first two days[156;157].

AMI is thus a life threatening clinical condition, and patients are usually rapidly admitted to hospitals through emergency departments.

**Cardiac arrest** is the main cause of sudden cardiac death. This sudden complete loss of cardiac output is most commonly due to a major arrhythmia, either ventricular fibrillation, or asystole[158]. The patient will die unless adequate circulation is achieved within minutes. This can be achieved by cardiopulmonary resuscitation (CPR) now (mouth-to-mouth breathing and closed chest compressions using the recommended timing and a specific sequence) as well as defibrillation[158].

Adequate CPR may be provided by trained bystanders, paramedics, ambulance staff or hospital staff. Survival after cardiac arrest varies from less than 5% to 60% according to the characteristics of the cardiac arrest event (e.g. cardiac aetiology or not, witnessed or not, ventricular fibrillation or not)[158]. However only 5-15% survive long term[159]. This still represent a substantial salvage rate, 'saving' approximately as many lives as thrombolysis[159].

All AMI patients should be considered for fibrinolytic treatment (thrombolysis) as soon as possible after symptom onset. Thrombolysis is beneficial up to about 12 hours after the AMI. According to the Fibrinolytic Therapy Trialists' (FTT) meta-analysis, for those presenting within 6 h of symptom onset, approximately 30 deaths are prevented per 1000 patients treated, with 20 deaths prevented per 1000 patients treated for those between 7 and 12 h. Beyond 12 h there is little convincing evidence of benefit[160]. Although survival benefit from fibrinolytic therapy in elderly patients was initially considered small, a more recent meta analysis has demonstrated statistically significant benefit in patients over 75 with a relative risk reduction of almost 20%[161]. Newer thrombolysis agents such as tPA may have marginal additional mortality benefits, compared with the original agent, streptokinase[162].

Additional benefit from aspirin treatment combined with thrombolysis was clearly demonstrated in the ISIS 2 trial, with a reduction of approximately 50 lives per 1000 patients treated[163]. The first 150–325mg dose of Aspirin should ideally be chewed, and a lower dose (75–160mg) given orally daily thereafter[153].

In selected cases, primary angioplasty can be performed, ideally within 90 min after the first medical contact[153]. This can achieve an additional relative mortality reduction of approximately 30% compared with thrombolysis[164].

Depending on the site and the severity of occlusion, various complications might occur during AMI. Cardiogenic shock, heart failure, and arrhythmia are the most frequent and most important. Intravenous beta-blockers can be useful in AMI, particularly because of their potential to limit infarct size, reduce the incidence of fatal arrhythmias, and to relieve pain[153]. ACE inhibitors are also beneficial. ACE inhibitors were originally just given to patients who had an impaired ejection fraction (ejection fraction <40%) or who experienced heart failure within the first 24 h[153]. However, more recent data suggest benefit when given to majority of AMI survivors, irrespective of their left ventricular function[165].

## 3.2.7 Secondary Prevention

Secondary prevention treatments are indicated for patients following AMI or revascularisation and, increasingly, for patients with angina or heart failure. These include lifestyle changes in diet, physical activity and smoking cessation, along with a wealth of effective medications. These include antiplatelet and anticoagulant treatment (aspirin, or, occasionally, warfarin), beta-blockers, ACE-inhibitors, statins and cardiac rehabilitation.

The Antiplatelet Trialists Collaboration meta-analysis demonstrated about a 25% reduction in reinfarction and death in post MI and other CHD patients[160]. A recent meta-analysis by Freemantle et al suggested that beta-blockers reduce mortality and reinfarction by 20%–25% in those who have recovered from AMI[166]. Several meta-analyses have likewise demonstrated that ACE inhibitors reduce mortality after AMI by approximately 23%[167]. There is therefore a growing tendency to administer ACE inhibitors to all patients surviving an AMI admission, provided there are no contraindications[153].

The Scandinavian Simvastatin Survival Study (4S) demonstrated the benefits of lipid lowering by a statin in 4444 post-infarction or anginal patients with serum cholesterol levels of 212–308 mg/dl (5.5-8.0 mmol/l). Overall mortality was decreased from 12% to 8%, a relative reduction of approximately 30%, representing 33 lives saved per 1000 patients treated over a median of 5.4 years. There were corresponding substantial reductions in coronary mortality, and in the need for coronary bypass surgery[33]. A 29%

reduction in mortality has now been demonstrated in cardiac patients with 'normal' cholesterol levels of 4-5 mmol/l[34].

### 3.2.8  Cardiac Rehabilitation including physical exercise

The definition of cardiac rehabilitation defined as 'the process by which patients with cardiac disease, in partnership with a multidisciplinary team of health professionals, are encouraged and supported to achieve and maintain optimal physical and psychosocial health[168].

Cardiac rehabilitation includes the facilitation and delivery of secondary prevention through risk factor identification and modification in an effort to prevent disease progression and the recurrence of cardiac events[169]. Individual tailored advice on life style changes such as smoking, dietary modification, cholesterol lowering and physical exercise are the main interventions[170;171]. Cardiac rehabilitation is also beneficial in heart failure[172].

In CHD patients an increase in physical activity level and improvement in cardio-respiratory fitness are associated with better quality of life and survival[171]. A recent systematic review of cardiac rehabilitation RCTs, including exercise versus usual care in CHD patients, found that exercise based cardiac rehabilitation reduced the major CHD events (mortality, non-fatal AMI, CABG or PTCA) by 24%[171].

### 3.2.9  Heart Failure

Depending on the extent of the cardiac muscle damage during an AMI, patients may develop acute or chronic heart failure. Acute heart failure is defined as acute dyspnoea characterized by signs of pulmonary congestion sometimes including pulmonary oedema. Chronic heart failure is defined as 'the pathophysiologic state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues'[173]. CHD accounts for just over half the cases of chronic heart failure in the UK[174;175]. Heart failure patients have a very poor survival particularly those requiring hospital admissions. Heart failure patients are eligible for a broad range of treatment including ACE-inhibitors, diuretics, beta-blockers, aspirin and statins. Diuretics are essential for symptomatic treatment peripheral and pulmonary oedema and it is now recommended

to combine with ACE-inhibitors[173]. Diuretics alone do not appear to decrease mortality[176]. ACE-inhibitors reduce mortality and hospital admissions in heart failure patients by approximately 26%, independent of age, sex and baseline use of diuretics, aspirin or beta-blockers[167]. Several meta-analyses have shown that beta-blockers in heart failure patients reduce all cause mortality, cardiovascular mortality and hospital admissions by approximately 37%, and 34%[176;177].

### 3.2.10 Smoking cessation in CHD patients

Smoking cessation is a very effective intervention in smokers with CHD. Total mortality rates are reduced by about 36% in patients after angiography, myocardial infarction, bypass surgery or PTCA[22]. The improvement in survival after smoking cessation is thus comparable to that achieved by bypass surgery 40%[170] and more than that achieved with aspirin 15%[160] or statins 29%[34]. In smoking cessation, individual counselling, support from physician and nicotine replacement is the most successful approach[139]. Group therapy, behaviour modification techniques, and advice pamphlets are potentially useful additional interventions for smoking cessation[139].

### 3.2.11 Dietary modification

Diet modification generally means an emphasis on lowering intake of saturated animal fats and trans- fatty acids (TFAs), and an adequate supply of mono or polyunsaturated fats. This can be achieved by eating less red meat, taking a moderate amount of low fat dairy products, plus at least two fish meals per week. Increased amounts of high fibre with plenty of fruit and vegetables is also desirable for all patients with CHD, independent of their cholesterol level [170]. RCT evaluation suggests that such diets may reduce mortality in post AMI patients by 24% or 29% compared with usual diet[178;179].


There is thus wealth of evidence –based therapies available to combat CHD. In the next chapter, I will consider the scale of CHD in the world and in the UK.

# 4 HOW BIG IS THE GLOBAL CHD PROBLEM?

Cardiovascular diseases are the commonest causes of death among both men and women in all developed countries. In 2001 CVD deaths accounted for 29.3% of the global deaths and almost 50% of these occurred in developed countries[180]. According to WHO estimates, 16.6 million people around the globe die of CVD each year. In 2001 there were 7.2 million deaths from CHD[180]. It is estimated that CHD will be the largest single cause of disease burden globally by the year 2020[1].

CVD also cause substantial disability. It is estimated that 10% of the total disease related burden, in terms of disability adjusted life year lost (DALYs) were attributable to CVD in year 2001[180].

## 4.1 International Comparisons

CHD shows dramatic geographic variations. Countries differ up to tenfold in CHD death rates and the prevalence of atherosclerosis *(Figure 4.1)*[156]. However, part of this difference may reflect variations in the diagnosis, coding, reporting and validity of CHD deaths between countries. For instance, the true CHD mortality in France and Japan may be two fold higher than suggested by routine statistics[181;182]. However in the USA CHD might be over-estimated by 7.9% to 24.3% and by as much as two-fold in older persons as a cause of death on death certificates[183]. Therefore within country comparisons are generally more secure than between country comparisons[184].

The MONICA Study was planned to overcome this difficulty. Its aim was to use a standardised methodology to measure the trends in cardiovascular mortality and CHD and cerebrovascular disease morbidity and to assess the extent to which these trends are related to changes in known risk factors, life style, health care and major socioeconomic features. These variables were measured at much the same time (1986 and 1994) in 39 defined communities in 26 different countries. The MONICA Study thus aimed to provide comparable data on CHD mortality, morbidity and risk factor trends[185;125].

The MONICA cross sectional comparison generally suggested a ten-fold difference in coronary event rates among countries[185]. For example age-standardized annual CHD event rates in men aged 35 to 64 ranged from 76 per 100,000 in Beijing, China to 915 per 100,000 in North Karelia, Finland. For women, rates ranged from 30 per 100,000

for Catalonia, Spain to 256 per 100,000 for Glasgow, UK, [185]. This represented a 12-fold gradient in men, and 8-fold in women.

In contrast to most studies such as the Seven Countries Studies[186] and Beaglehole's recent review [115], the major risk factors apparently explained only part of the large variations in CHD mortality between the MONICA countries[185]. However, MONICA Study has been repeatedly criticized for 'ecological bias' and may underestimate the relationship between changes in risk factors and population trends in CHD [185;187]. This is because a) decreasing response rates to the MONICA surveys was observed over the course of the study[125] b) possible regression dilution bias; adjusted coefficients may be as much as 60% higher[32] c) no allowance for a possible lag time between changes in the risk factor levels and changes in population CHD mortality[125].

**Figure 4.1 Death rates from CHD, men and women aged 35-74, 1998, selected countries.**
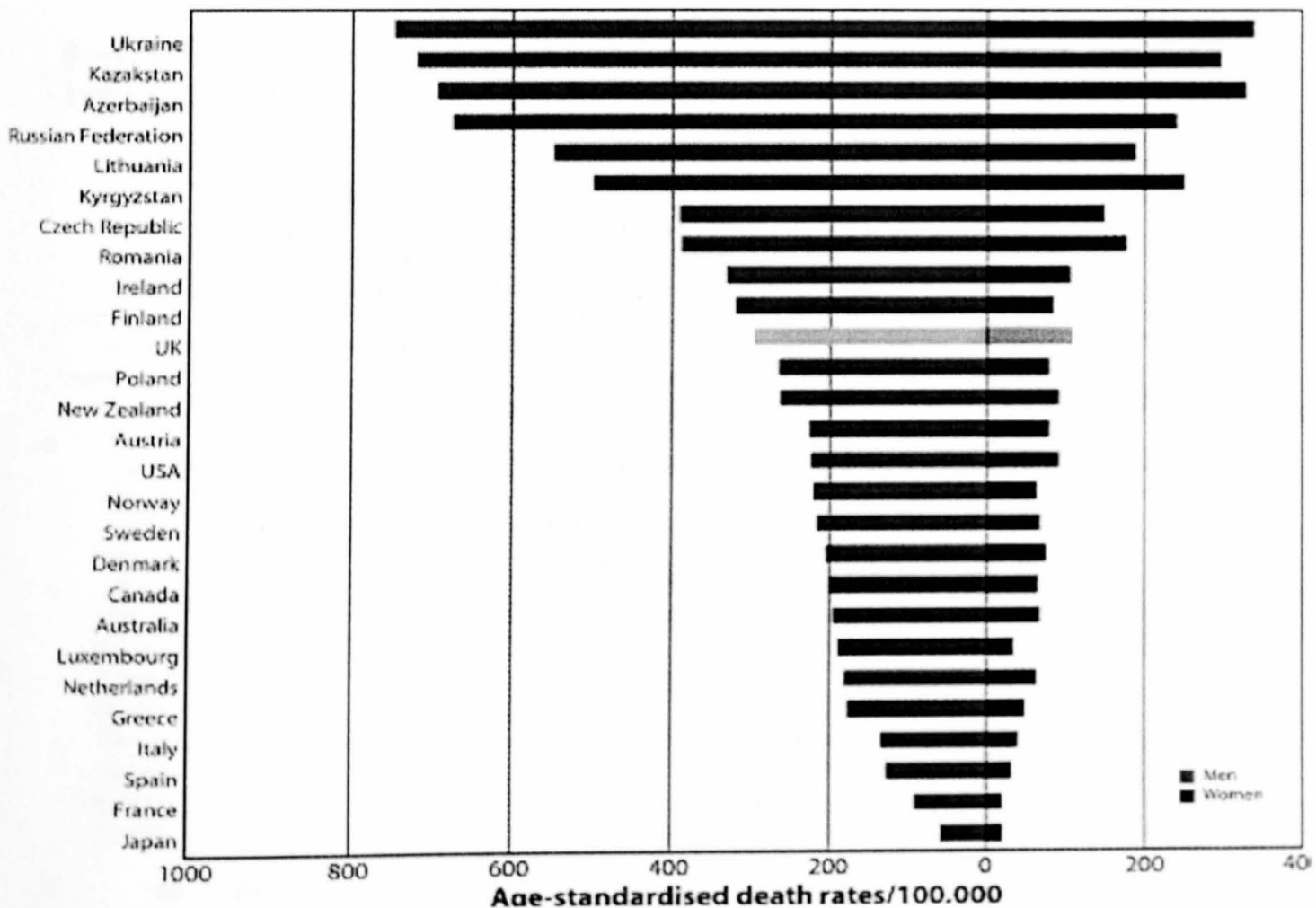


Source: World Health Organisation (2002) http://www.who.ch/-

## 4.2 CHD Trends

CVD were recognised as a public health problem early in the 20th century. Cardiovascular morbidity and mortality rates increased in most industrialised countries until the 1970s or 1980s before starting to decline[188]. In the 1970s CHD death rates were quite high in the majority of developed countries including Finland, Ireland, UK and USA[189]. In many of these countries CHD death rates have halved since then. Over the same period death rates in countries from Eastern and central Europe have been rising rapidly *(Figure 4.2)*. In Croatia, for example, between 1988 and 1998 death rates rose by over 60% in both men and women[2] *(Figure 4.2)*.

These trends may partly reflect the removal of competing causes of death, the artifactual consequences of shifts in the age distributions of populations, and changes in diagnosis and reporting[190]. However such factors cannot entirely explain either the huge international differences or the very consistent mortality trends, with decreases in so many developed countries, and increases in many developing countries.

**Figure 4.2 Changes in deaths from CHD, men and women aged 35-74, between 1988 and 1998, selected countries**
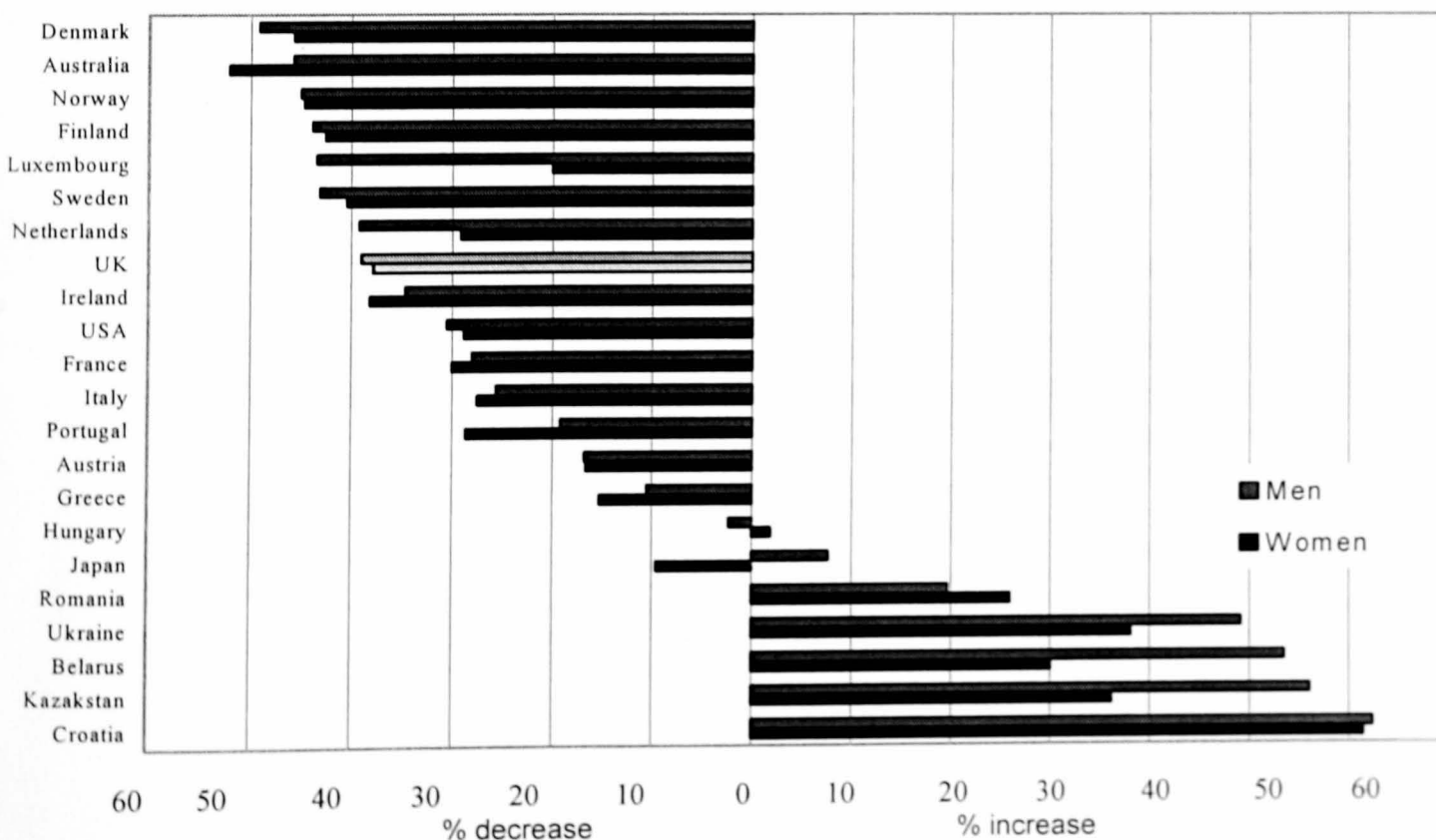


**Source: World Health Organisation (2001) http://www.who.ch/-**

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Furthermore if large increases and decreases in CHD incidence have truly occurred within a very few decades, this strongly suggests that the main determinants of CHD are environmental rather than genetic or cohort-related. They are therefore potentially preventable[191].

The decline in CHD incidence and mortality in developed countries is often attributed to medical innovations in CHD treatment (coronary care units, fibrinolytic therapy, CABG surgery and drugs)[192;193]. However, it is important to note that substantial falls in mortality occurred in the US and the UK before the introduction of most modern treatments. These falls must therefore have been principally attributable to environmental factors, the strongest candidates being lifestyle changes (cigarettes smoking, diet, and exercise) and reductions in other risk factors[193;194].

## 4.3 How big is the CHD problem in the UK?

After consideration of world trends, in this section, I will now focus on UK CHD burden.

### 4.3.1 Introduction

Despite substantial declines since 1970s, CHD remains as a major public health problem in the UK. Effective policy decisions to prevent the disease were overlooked for decades. Documenting the CHD burden in the UK provides a useful tool to communicate the importance of the disease with the community and health policy decision makers. Therefore in this section of my thesis, using data from national surveys and statistics I attempted to estimate the current CHD burden in Britain.

### 4.3.2 Methods

Data were extracted on all patients with established CHD and all subjects with elevated cardiovascular risk factors in the England and Wales population of 52.9 million.

The data sources included: Office for National Statistics[195;196], British Heart Foundation Coronary Heart Disease Statistics[2], special registers[197;198], population surveys[48;199;200], published papers[143], grey literature and correspondence with UK experts *(Personal communication with David Cunningham, 2002) (Box 8.11).*

**Estimating the number of CHD patients**

The specific patient groups comprised acute myocardial infarction, post myocardial infarction, unstable angina, chronic angina, CABG surgery, angioplasty, and heart failure.

The numbers of patients who had CABG or PTCA in 2000 were reported in the relevant national registers[197;198]. The numbers of unstable angina, AMI and heart failure patients admitted to hospital were gathered from Hospital Episode Statistics (HES)[196]. These HSE numbers were then adjusted using an 8% reduction to reflect individual patients rather than episodes[196]. The numbers of angina patients in the community were estimated using the corresponding age specific prevalence rates reported in the Health Survey for England (HSE '98) applied to the England and Wales population in that age and sex group[48]. The number of heart failure patients in the community was estimated

using age-sex specific prevalence rates reported in Key Health Statistics from General Practice 1998 [201]. To avoid double counting, the number of patients admitted to hospital with heart failure was deducted from figures for community heart failure.

The number of patients surviving after an AMI was based on all patients admitted to hospital between 1990 and 2000, using HES data[196;202]. One month case fatality rates obtained from the SLIDE study[143] were applied to the total numbers of AMI patients. [143]

The risk factors included were current smoking, elevated cholesterol (>6.5 mmol/l), hypertension (treated and untreated, >160/95 mmHg), physical inactivity (less than 3 times a week moderate activity), obesity (BMI>30 kg/m$^2$) and doctor reported diabetes (using standard definitions)[48]. Where alternative sources provided discrepant data, the best estimate was selected on the basis of coverage, generalisability and validity.

The number of people with risk factors was estimated by simply applying the prevalence reported in Health Survey in England to the age and sex categorised population of England and Wales (Table 4.2).

### 4.3.3 Results

### CHD Mortality

CVD are the main cause of death in UK: accounting for over 200,000 deaths in 2002 and CHD itself caused 110,000 deaths. This represents one quarter of all male deaths and one sixth of all female deaths. CHD is also the most common cause of premature death in the UK causing 26% of premature deaths in men and 16% of premature deaths in women$^2$.

### CHD Morbidity

CHD morbidity is less well defined, and tends to be described in isolated groups such as admissions for acute myocardial infarction or patients undergoing CABG surgery[148].

### Incidence

The MONICA Project included two UK centres; Glasgow and Belfast. These regions reported some of the highest CHD rates in the world. Average annual coronary event

rates per 100,000, between 1985-1994, were 777 and 265 in Glasgow men and women respectively and only slightly lower in Belfast, 695 and 188 respectively *(Figure 4.3)*[156].

**Figure 4.3 Age-standardised coronary event rates per 100,000 population, men aged 35-64, MONICA Populations.**
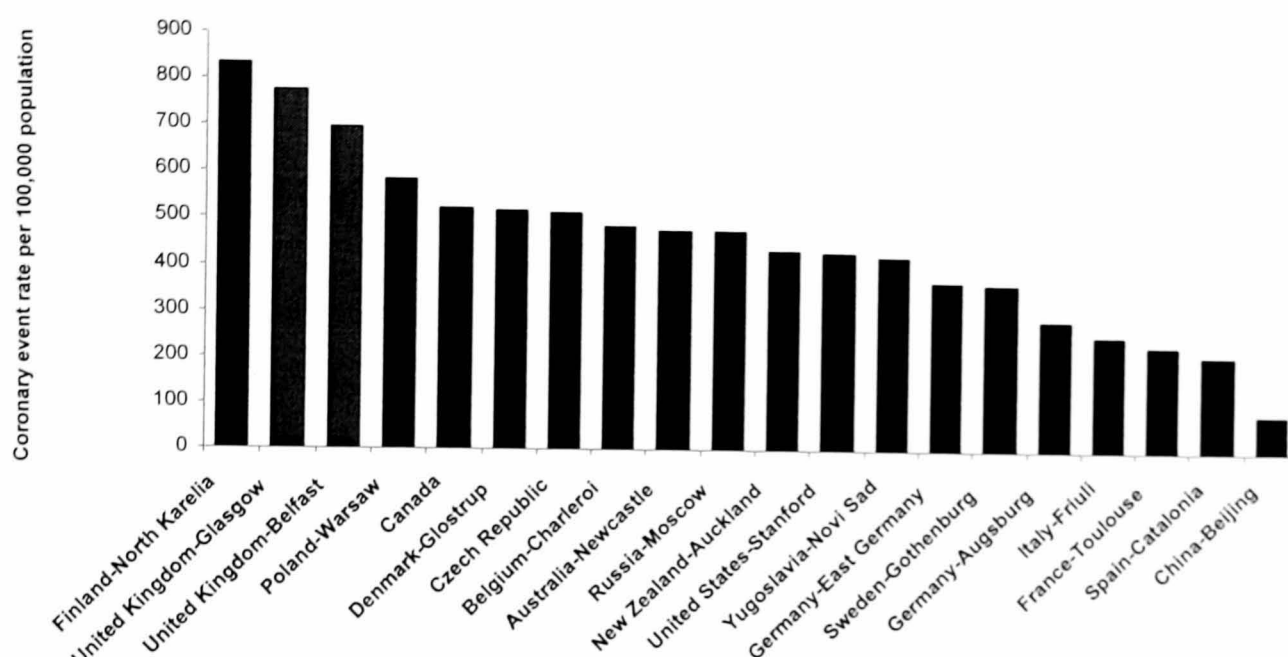


Source: Tunstall-Pedoe H et al for the WHO MONICA Project. Lancet (1999) 353; 1547-57.

## Prevalence

The Health Survey for England has been carried out annually since 1991. The 1998 survey, which focused on CVD, suggested that the overall self reported prevalence of ischaemic heart disease (angina or heart attack) in adults was 7.1% in men and 4.6% in women. Prevalence of ischaemic heart disease increased with age; 4.3% in men and 1.8% in women aged 45-54, 13.6% in men and 6.3% in women among 55-64 and 23.4% in men and 18.4% in women aged 75 years and over *(Table 4.1)*. This means that over 2.5 million people in the UK were living with CHD in 1998[2].

**Table 4.1 Prevalence (%) of coronary heart disease, by age and sex, England, 1998.**

| CHD* (%) | Age Groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 16-24 | 25-34 | 35-44 | 45-54 | 55-64 | 65-74 | 75 + | Total |
| Men | 0.1 | 0.4 | 0.9 | 4.3 | 13.6 | 20.2 | 23.4 | 7.1 |
| Women | - | 0.3 | 0.6 | 1.8 | 6.3 | 12.5 | 18.4 | 4.6 |

* CHD: reported as doctor-diagnosed heart attack or angina.

**Source:** Health Survey for England 1998[48].

## The iceberg of CHD

In England and Wales in 2000, there were thus over 2.5 million patients with recognised CHD (approximately 1.4 million men and 1.1 million women) *(Table 4.2 and Figure 4.4)*. In 2000 there were approximately twice as many men as women with MI, and three times as many men underwent CABG surgery or angioplasty (44.258 men versus 13,349 women respectively).

Over 30 million adults in the UK demonstrated one or more elevated major risk factors (21.5 million physically inactive, 14.4 million hypertensive, 9.5 million smokers, 8.0 million with elevated cholesterol, 7.7 million with obesity and 1.1 million with diabetes) *(Figure 4.4)*.

## Costs

The NHS direct health care costs of CHD in 1999 came to £1.73 billion on the basis of more than half a million hospital admissions, approximately 35,000 CABG surgical operations, 25,000 angioplasties and 2 million GP consultations[203].

In 2000 there were 634,000 individuals consulting to a GP with angina in the UK. The direct cost of the disease was estimated to be £669 million or 1.3% of total NHS expenditure. This cost was due to mainly hospital bed occupancy and revascularisation procedures performed in this patients[204].

Every year CHD accounts for 2.5 million life-years lost due to premature deaths in the UK. Totally direct health care costs, cost for productivity loss and informal care costs altogether accounted £7 billion a year[205]. Which represents a higher cost than for any other single disease for which a comparable analysis has been carried out. In this paper, the number of angina patients (estimated using GP records) seems small in comparison with other reports of angina prevalence; some were almost three fold higher *(Table 4.2)*. Overestimation because of self-reported status, or inflation attributable to the Rose questionnaire detected angina appears likely.[48] However, there might also be angina patients in the community without any GP consultation. If these hidden patients ever presented, addressing this currently unmet need would further increase the total cost of angina to the UK NHS.

**Table 4.2 Estimated numbers of subjects with recognised coronary heart disease or with elevation of one or more cardiovascular risk factors in England and Wales, 2000.**

| | Estimated Patient Numbers | | |
|---|---|---|---|
| **Established coronary heart disease** | **Men** | **Women** | **Total** |
| CABG Surgery[197] | 20,786 | 5,525 | **26,331** |
| Angioplasty[198] | 23,472 | 7,824 | **31,296** |
| Acute myocardial infarction[196] | 56,082 | 33,309 | **89,391** |
| Post infarction survivors[143;196;202] | 213,992 | 142,661 | **356,653** |
| Heart failure: hospital admissions[196] | 20,576 | 20,812 | **41,388** |
| Heart failure: patients in the community[201] | 149,329 | 206,617 | **355,942** |
| Unstable angina admissions[196] | 45,728 | 26,872 | **72,600** |
| Angina patients in the community[48] | 895,837 | 716,678 | **1,612,515** |
| **Total coronary heart disease patients** | **1,425,802** | **1,160,298** | **2,586,116** |
| **Cardiovascular risk factors** | | | |
| Physical Inactivity (less than 3 times a week moderate activity)[48] | 9,508,260 | 12,018,500 | **21,526,760** |
| Total hypertensives (>160/95mmHg)[48] | 7,431,791 | 6,920,245 | **14,352,036** |
| *(Treated hypertension)[48]* | *(1,559,072)* | *(2,253,449)* | *(3,812,521)* |
| Smoking[200] | 4,920,830 | 4,608,280 | **9,529,110** |
| High Cholesterol (>6.5 mmol/l)[48] | 3,392,288 | 4,637,437 | **8,029,725** |
| Obesity (BMI>30 kg/m²)[48] | 3,499,377 | 4,163,699 | **7,663,076** |
| Reported Diabetes[48] | 616,922 | 522,685 | **1,139,607** |
| **People with one risk factor[199]** | 6,031,600 | 5,838,230 | **11,869,830** |
| **People with two risk factors[199]** | 6,386,400 | 6,968,210 | **13,354,610** |
| **People with 3 or 4 risk factors[199]** | 3,193,200 | 4,143,260 | **7,336,460** |
| **People with one or more risk factors[199]** | **15,611,200** | **16,949,700** | **32,560,900** |
| **England and Wales Population, 25+ in 2000[195]** | **17,740,000** | **18,833,000** | **36,573,000** |

**Figure 4.4 The iceberg of coronary heart disease in England and Wales, 2000.**

| | |
|---|---|
| Revascularisation | 57,625 |
| AMI | 89,390 |
| Post Infarction | 356,650 |
| Heart Failure | 397,330 |
| Angina | 1,685,115 |

Total coronary heart disease patients: **2,586,115**

| | |
|---|---|
| Physical Inactivity | 21,526,760 |
| Hypertensives | 14,352,035 |
| Smokers | 9,529,110 |
| High Cholesterol | 8,029,725 |
| Obesity | 7,663,075 |
| Diabetes | 1,139,605 |

People at least with one risk factor: **32,560,900**
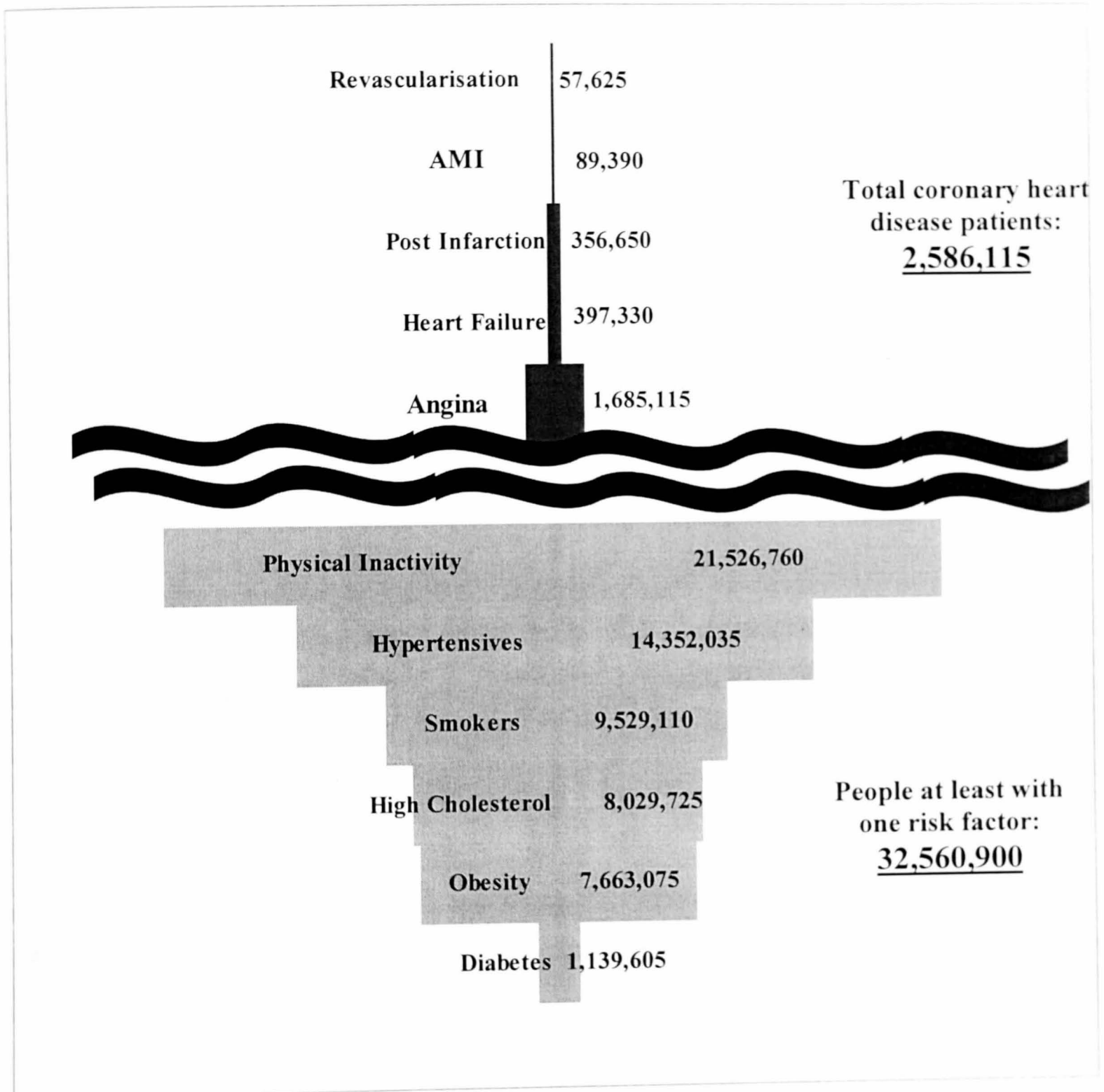
### 4.3.4 Interpretation

An iceberg of disease was defined for CHD, with CABG surgery and angioplasty at the tip and, at the base, asymptomatic subjects with one or more risk factors.

CHD thus accounts for a massive burden of mortality and morbidity in England and Wales. However, high cost, high profile revascularisation for the selected few should not distract attention from the huge iceberg beneath.

Coronary heart disease in the UK typifies the iceberg of disease principle. Politicians and health service managers generally concentrate on the relatively few but prominent patients receiving revascularisation, less than 60,000 annually[148]. This diverts attention from ten times as many myocardial infarction survivors and heart failure patients (over 700,000) who are also at high risk of death or further events, and who are equally eligible for effective secondary prevention.

I estimated that in England and Wales in 2000, there were over 2.6 million patients with recognised CHD, including chronic angina. This total is consistent with estimates from the British Heart Foundation[2]. Furthermore, for each of these 2.6 million recognised patients, there were more than ten times as many individuals with one or more cardiovascular risk factors.

The quality of data on CHD appeared remarkably patchy and poor, despite CHD being the largest cause of death[2;206], as presented in detail in the next chapter. Some imprecision is therefore inevitable. However, this chapter may well represent a reasonable estimate for each defined and mutually exclusive group of patients, using all currently available data sources.

My thesis principally focuses on UK CHD trends. However, before examining trends in more detail, it was clearly important to critically review the quality of the available UK CHD data. This work will be described in a later chapter. But first, I would like to consider the potential value of modelling diseases such as CHD, and, in the following two chapters, give an overview of CHD policy models in use.

# 5 MODELLING

**"All models are wrong but some are useful"** (G.E.P. Box. 1978)[207]

Improving population health through effective interventions remains the fundamental challenge for public health practitioners and policy makers. Decision-makers at the population, clinical, and individual levels often need to choose the 'best intervention' for a health problem. However, limitations on resources, time and information can make the decision process very complex. Assessing the value of a health intervention requires consideration of many elements including the size of the target population, the prevalence of the disease, and the intervention's effectiveness and cost[208].

Models are tools that potentially allow users to take into account all these points together and evaluate the intervention options.

## 5.1 What is a model and why are models used?

A model is a simplification of reality. Models range widely, from simple, descriptive tools (such as a plan of a house), to systems of mathematical equations, which can explain past disease trends[209;210], or which predict future events such as disease epidemics[211;212]. Models are also widely used in environmental surveillance[213] and predicting impact of natural disasters[214]. Such models, therefore, intend to increase understanding, facilitate prediction, or assist in decision making[209].

Weinstein et al recently defined a model as an **'analytic methodology that accounts for events over time and across populations, based on data drawn from primary or secondary sources, whose purpose is to estimate the effects of an intervention on valued health consequences and costs'**[215]. In other words, a model is a logical mathematical framework that permits the integration of facts and values, and which links these data to outcomes that are of interest to health-care decision makers. Models can thus potentially synthesize available evidence on risk factors, health outcomes and costs from many different sources, including data from clinical trials, observational studies, case registries, surveys and routine health statistics[216].

Models are used to guide, or even dictate, policy decisions in many areas that affect human life and health[215]. Increasing health care demands require policy decisions based on good evidence, particularly since resources are usually limited. By openly and

explicitly combining local data with trial based effectiveness evidence, models can offer increased transparency to the decision making process (particularly if their assumptions are clearly stated).

Models can also allow a large amount of evidence to be considered simultaneously; by combining and integrating into a coherent whole different types of data from controlled trials, routine surveillance and expert consensus[3]. Models have been extensively used in policy making and resource allocation, since they permit policy makers to examine future policy options, or to simulate the effects of different scenarios within a population[217]. However, improved technology potentially allows both practitioners and policy-makers to use these models, without necessarily understanding the modelling assumptions or the limitations of the data[3].

## 5.2 General types of models

There are many models in the health literature. They differ greatly in their methods.

Models can be classified in many different ways, based on their intended use (descriptive or prescriptive), their use of probabilities (descriptive, deterministic or probabilistic)[218], their analytical methodology (a decision tree or state transition model), their application to a population (longitudinal or cross-sectional), or their purpose (risk assessment, cost, effectiveness etc.). However these classifications are not mutually exclusive, and a model can therefore belong to more than one classification.

### Intended use of model

**Descriptive models** are designed to predict or illustrate the result of a clinical process. **Prescriptive models** are used to compare two or more interventions to estimate the optimal treatment option[209]. With respect to intended use, Weinstein also distinguishes between **clinical decision models**, designed to guide clinicians or patients, and **health policy models**, which will help decision makers or organisations with choosing the appropriate strategy and allocating healthcare resources[219].

### Use of probabilities

Models can be classified into two broad groups based on their use of probability. **Deterministic models** use probabilities based on fixed-point estimates. Thus, the probability experienced in a branch is a single fixed value. However, in **stochastic**

**(probabilistic) models,** the probability of experiencing a certain condition is not a single fixed value but a range of values from a defined distribution. Deterministic models are simpler, require less expertise to develop and can be run on less complex computer softwares[220]. The majority of models are used to evaluate health care costs and outcomes are deterministic.

## The analytical methodology

Models can also be classified according to their use of time. Simple **decision trees** are very useful for modelling if the events or health states do not occur repeatedly and the likelihood of the event does not change over time. This modelling approach fits very well for acute conditions such as bacterial infection, antibiotic therapy or adverse events in a hospitalised patient. **Recursive trees** involve treatment patterns or health states that can repeat over time. The model starts with a cohort of individuals and follows them for a period. In each year, individuals have a risk (probability) of developing the outcome. The probability of developing the outcome may change every year, but otherwise each year is a single decision tree. **Markov Modelling** and other **state transition models** are the logical extension of recursive trees for more complex events occurring over time[221]. One limitation of Markov models is that they do not have memory; therefore the chain of preceding events does not influence the likelihood of a given event at a specified time. This limitation could be important for certain clinical outcomes, for example the likelihood of a major depressive patient experiencing an acute episode may depend on the number and timing of previously experienced depressive episodes[220]. In general, recursive trees and Markov models are more complex than decision trees models and require more effort, time and expertise.

## Longitudinal and cross-sectional models

All models include a population or group to estimate the outcomes. **Longitudinal models** calculate expected outcomes for 'typical' patients or cohorts and follow them longitudinally through time to evaluate health outcomes resulting from alternative interventions[218]. It is therefore not possible to take into account demographic trends in the population or changes in treatment practice[217]. This approach is used more in decision tree models, and outcomes might for instance be QALYs.

**Cross-sectional models** record the health outcomes of a cross-section of an entire population or substrata, and then follow each person until the end-point of the analysis[218]. The main difference between the two is that cross-sectional models are based on the general population (stratified into different age and sex groups) whereas longitudinal models are based on a cohort of identical subjects. For instance. patients who survived MI and now eligible for statin therapy could be used to assess cost-effectiveness of this therapy in secondary prevention.

## The unit of the model on which estimations are based

Models can be divided into two large groups, working on groups or at the individual level. Spreadsheet or cell based models generally work on groups of individuals whereas microsimulation models work on individual level. Since this difference is the main determinant of the outcomes and estimations, these models need to be considered here in more detail.

**Microsimulation models** (for example CHD Policy Model[222], POHEM[210], Mui's Model[223], and CHD Policy Analysis[224]) can simply project future outcomes for a given individual, based on his or her sociodemographic, behaviour, and clinical characteristics. Here, data from different observational studies such as Framingham Heart study are used for risk estimates.

Microsimulation models could start with a representative sample or subsample of individuals from a census or survey. They can be developed using an entirely synthetic population, which resembles the population of interest. In this process, each individual in the cohort is generated separately, and can be subjected to the probability of certain events (such as death or development of a disease) over the simulation period. This kind of model usually uses probabilistic rather than deterministic techniques. Since microsimulation models are based on individual data, they may avoid bias due to aggregation. Also, since they work on individual data, they can easily incorporate many risk factors, and outcomes can be easily broken down according to specification of individuals. However, despite their richness, these models have encountered criticism because of their complexity. Furthermore, development and maintenance of these models can be costly in terms of time and money[217].

**Cell-based models** (IMPACT[4], PREVENT[225]) are widely used in decision-making. Their growing popularity can probably be attributed to increases in computer literacy and computer power, plus easier access to organizational data[226].

Cell-based models vary widely in size and complexity. To construct a cell-based model, a population can be divided into subgroups, for instance, by age, sex, treatment and risk factor exposure. It is assumed that all the individuals within any given subgroup are similar if not identical. The probability (or rate) of an event occurring during a specified time period is applied to the specific subgroup. The estimated events for each of the categories are then summed to produce outcomes for the whole population.

Cell-based models can have considerable detail on the population; for instance, sometimes projections can be based on age-sex-race or marital status groups. However, these models do not typically include individual-based longitudinal information, and their estimations are aggregated[226].

Cell-based models have several potential advantages compared to other model types:

- Spreadsheet software is widely available
- Depending on the complexity, the time, cost of building and maintaining it is usually less expensive than microsimulation approaches
- While some require extensive training, most are relatively simple and user-friendly
- Many are very accessible; however, detailed assumptions should ideally be available for review[226].

These models also have some limitations:

- Spreadsheets may include erroneous formulae, incorrect ranges, omitted factors, data input errors, incorrect use of built in functions and duplication of effort[226,227]
- With addition of new variables, the number of cells can become unmanageable

Model classifications are not mutually exclusive; therefore a model can belong to more than one category.

## 5.3 The steps involved in developing a model

There are important steps to consider in developing a model[217]:

### 5.3.1 Problem definition

The question that the model is to answer must be explicitly defined before starting to build it. The disease(s) or outcome(s) being modelled, interventions under consideration and the population should all be specified. The problem would usually have a clinical relevance, and cause and effect relation should usually be well established[220].

### 5.3.2 Model specification

The choice of model will influence the assumptions that need to be made and which will therefore impact on the output. Microsimulation approaches provide flexibility but may require technical experts to help develop and interpret them. Cell-based models are simpler but generally provide aggregate estimates of outcome[217]. However, they can be useful in determining population impact of an intervention.

It is important that models are developed co-operatively with epidemiologists and clinicians. In particular, the researchers must decide whether to include the prevalent population and/or incident population, and how to determine the base scenario against which to compare other scenarios[217].

### 5.3.3 Data gathering and incorporating

Once the type of model is decided, the type of outcome parameters must then be determined and estimates of event probabilities obtained or developed.

Deaths prevented can provide useful information but can be relatively limited since it does not consider the length and the quality of that life[217]. In the evaluation of health care interventions a commonly used outcome is life-years-gained (LYG). In this process the intervention that maximizes life expectancy will be identified. However LYG does not take account of the quality of life. Quality adjusted life years (QALY) are therefore another useful measure of effectiveness and has the advantage of unifying mortality and morbidity in one measure[217]. Disability adjusted life years (DALYs), an internationally standardised form of QALY, have been used widely in the WHO Global Burden of Disease Project. DALY expresses years of life lost to premature death and years lived

with disability of specified severity and duration. One DALY is thus one lost year of healthy life[228].

**What type of data should be used in the models?**

Models require considerable data input and data sources need to be recent and credible. However, the availability of comprehensive high quality data remains a problem.

The data may come from a variety of sources including clinical trials, meta-analyses, surveys, databases, medical records, audits, Delphi panels (expert opinion) and official tariff lists for health care resource use[229].

**Clinical trials** produce the best evidence of efficacy of an intervention. However, since their study groups are restricted with inclusion and exclusion criteria, generalisation is always an issue so that the outcomes may not reflect the usual practice[220;229;230].

**Meta-analyses** may be a good source of efficacy data, if the outcomes are potentially generalisable to the target population. However, they are often subject to certain biases either from studies available (publication bias) or from the selection of studies for the analysis (inclusion bias; if criteria are chosen to produce intended results). The method of meta-analysis is also important. If there is significant heterogeneity, the results should usually not be combined[220].

**Expert opinion** can be a useful source when there is no published or reliable information on a particular area[229]. General practitioners or specialists can provide information based on their own experience on compliance or treatment uptake. However, such opinions can be subjective, and will differ between experts. Therefore a representative sample of the actual practicing physicians is generally desirable[220;229].

**Surveys and observational studies** can provide vital prevalence data for the models. However, their main objective may be different so that they can provide only limited detail on certain variables. Cohort studies and repeated cross-sectional studies can provide valuable and relatively unbiased information on the natural history of a disease and risk factors and lag times[220;229].

**Official statistics** are often very useful sources for population and mortality information. However, depending on the practice, they can be subject to reporting and

coding inaccuracy. Furthermore, in some countries their precision and ease of access can be questionable [220].

The data sources used in modelling should therefore be explained in adequate detail. The selection criteria for studies and data sources should be described and the strengths, weaknesses and possible sources of bias should be discussed[220].

All models therefore need to be validated and subjected to sensitivity analysis to identify the impact of different parameters[217].

### 5.3.4 Sensitivity analysis

In modelling studies uncertainty in data is a particularly problematic area. Sensitivity analyses should therefore be employed to quantify this uncertainty. There are different types of sensitivity analyses. The most common form is **simple sensitivity analysis,** where one or more parameters of an evaluation are varied across a plausible range[231]. If only one parameter is changed at a time while the others retain their base-case specifications, it is called *'one-way sensitivity analysis'*. If more than one parameter is changed at the same time then it is called *'multiway-sensitivity analysis'*. Any confidence intervals presented for the estimations can usually be included into sensitivity analyses. Multiway sensitivity analysis can take the form of scenarios, which explore the implications of alternative 'states of the conditions'[231].

*Threshold analysis* is concerned with identifying the critical value of parameters above or below which the conclusion of a study will change[232]. It can produce a useful graphical presentation, and is quite helpful when a parameter in the model is continuous and indeterminate. This approach is most often used in cost effectiveness analyses.

*The Analysis of Extremes Method* involves incorporating the best and worst estimates of inputs, and then generating extreme estimates for output. This kind of sensitivity analysis can be very efficient in dealing with uncertainties in data input. However, this method does not usually provide information about the likelihood of these 'best' or 'worst' scenarios. In most cases, the probability that all the worst cases or good cases occur simultaneously is small[231].

*Probabilistic sensitivity analysis* is more complex than the analysis of extremes, but it usefully allows the modeller to assign ranges, distributions and probabilities to uncertain variables[231].

## 5.4 Assessing model quality

When assessing the quality of a model, one should consider the system being modelled, the elements included and excluded, the model structure, the risk factors and the probable effects of known trends and the model assumptions-stated and unstated[217]. In the ISPOR Task Force Report, Weinstein et al[216] recommended three dimensions: Model structure, data and validity:

### 5.4.1 Model structure

The model should be structured to ensure its inputs and outputs are relevant to the decision making process. The health states defined in the model should correspond to the natural history of the disease. The structure of the model should be consistent with the theory of the health condition and with the available evidence on causal relationships between variables. The structure of the model should be as simple as possible while capturing the underlying essentials of the disease process and interventions. The description of the model should be sufficiently detailed so that the model can be replicated mathematically. The assumptions and input parameters, and the logic connecting them to outputs should all be stated clearly (Transparency).

The time horizon of the model should also be long enough to reflect the impact of the interventions[216].

### 5.4.2 Data

Systematic reviews of the literature should be conducted on key model variables. Where the data are not available or not reliable, assumptions have to be made and they can be tested with sensitivity analyses. All models should include extensive sensitivity analyses for key parameters. Ranges should accompany the estimates from the model. Data quality and availability should be evaluated and the inclusion or exclusion criteria should be defined for data sources[216].

Data modelling refers to the mathematical steps that are taken to transform empirical observations into a form that is useful for decision modelling. This involves methods of incorporating estimates of treatment effectiveness from randomised clinical trials, combining disease specific and all-cause mortality rates or risk factor prevalence and interventions. These should be defined in enough detail in the model.

## 5.4.3 Validation

In the ISPOR Task force report, the validation of models was grouped into three categories:

### Internal validation

Models should only be used after careful testing to ensure that the mathematical calculations are accurate and consistent with the specifications of the model. This process can be done by using null or extreme input values and checking whether they produce the expected outputs[216]. Checking the model formulas, inputs and outputs by a second author may also help. The results of the model should make sense in terms of both the theoretical considerations, and also in intuitive terms (face validity) [216].

Models should be calibrated against the actual data when possible. However, calibration is possible only if inputs and outputs are available over the time frame being modelled.

### Between model validation

Models can also be validated against each other (convergent validity)[216]. Models addressing the same problem would be expected to produce similar results with similar assumptions and input parameters (corroboration).

### External validation

Models should be based on best available evidence at the time that they were built. Model outputs or estimates should be consistent with the observed data. Tests of predictive validity -the ability of the model to make accurate predictions of future events- are valuable, but not essential. In some models splitting the data into two time-periods can be useful to check the predictive validity of a model[233]. For example data for years 1990-1996 are used to generate a regression model, which is then applied to

the 1997-1999 dataset, and used to predict outcome for 1997-1999 period. These predictions are then compared against the observed outcomes for 1997-1999. This method may provide information on model's validity for different datasets and periods. Models should never be considered as complete and unchangeable tools to predict future. They should be updated according to new evidence and scientific knowledge[216]. A model should not necessarily be criticized for failing to predict the future. However, it should be possible for a good model to be recalibrated or re-specified to adapt to new evidence as it becomes available[215].

In the next chapter, I will briefly review existing CHD models.

# 6 EXISTING CHD HEALTH POLICY MODELS

Models are being increasingly used in health policy decision-making. In terms of CHD health policy models a wide variety exist. Some CHD models consider risk factors alone[234], risk factors and cardiovascular treatments[4], secondary prevention such as cholesterol lowering treatment[235] or estimates of general practice workload[236]. Their quality and utility may vary. In this section, I will describe a systematic review in which I evaluated the strengths and limitations of existing CHD policy models.

## 6.1 Methods

For this systematic review, we defined a CHD policy model as a tool that may help to explain or predict the outcome of CHD interventions (specific treatment or cardiovascular risk factor change, or the implementation of a new strategy) at the population level.

### Search strategy

A search strategy was developed, piloted and run in MEDLINE and EMBASE electronic databases supplemented by screening reference lists of relevant articles and reviews. Electronic searching within the databases included 'coronary heart disease or synonyms' and 'model or synonyms' as key words. Both key words and MeSH headings were used *(Appendix 1)*. The search strategy was validated using ten key papers already known to the authors; all ten papers were captured by the search strategy. The search identified 4,531 articles initially, and a further 17 were identified by checking the references. All the records were imported to 'Reference Manager'. By checking the titles and abstracts for the terms 'model', 'coronary heart disease' or 'population', the number of articles reduced to 275. Two independent reviewers (BU, SC) checked the titles and abstracts of all papers initially identified, and then screened the articles for inclusion and appraisal. The two reviewers independently classified each article and agreement was good (Kappa = 0.76).

### Inclusion and exclusion criteria

Any CHD modelling study was included if it reported on a key outcome (deaths prevented, life years gained, prevention cost, treatment cost, mortality, prevalence, incidence or disability) in a defined population. Models simply describing animals,

cell lines, clinical series, cohorts or estimates of individual risk were excluded.

*Figure 6.1* illustrates the flowchart for the search and review process. Excluded articles are listed in Appendix 4. In total, 75 articles were critically appraised and 26 articles were excluded.

**Figure 6.1 Flowchart of search strategy for CHD policy models**

Results of searches:
4,531 hits

Screening by
Title, Keywords,
Abstract and
Inclusion criteria
applied

101 articles identified

Data Extraction/
Study Selection

**Included articles: 75**
CHD Policy Model: 13
Cardiovascular Life Expectancy Model: 9
Prevent model: 5
Impact: 5
Global Burden of Disease: 4
CHD policy analysis: 2
Other models: 37

**Excluded articles: 26**
Not modelling study: 8
No CHD outcome reported:8
Review paper: 6
Other: 4

## Data extraction and assessment of model quality

A pre-piloted form was used for data extraction *(Appendix 2)*. Articles were categorised according to the specific models that they described. Each paper was then critically appraised using explicit quality criteria. There are no universally accepted lists of appropriate quality criteria for model papers. However reviews by Weinstein[215], and Edwards[226], and recent guidelines International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[216] have suggested useful quality criteria. Using these sources[215;216;226], we created a grading system, based on sensitivity, validity and transparency of the model *(Appendix 4)*.

## Scoring system

Papers were graded on the basis of whether a sensitivity analysis carried out, the validity was checked, data quality presented, illustrative examples were provided, assumptions stated, if model was potentially available to the reader and if potential limitations such as assumptions, confounding, lag times and competing causes were discussed. A simple scoring system was developed, with maximum of ten points available. A point was awarded for each key feature listed above. Each paper was scored and given an overall grading as methodologically 'poor= overall score 0-3', 'adequate=4-7' or 'good=8-10' on an a priori basis.

## 6.2 Results

A total of 75 articles describing 42 different CHD policy models were finally included from 4,531 initial papers *(Figure 6.1)*. Due to space restriction, we presented here summaries of the six principal CHD policy models used to address several health policy questions, all based on large populations, and all with more than one publication *(Table 6.1 and 6.2)*. Critical appraisals of each paper are provided in *Appendix 4*.

### Papers excluded from the review

Papers excluded and the reasons for exclusion are listed alphabetically in the *Appendix 4, Table 8*. The main reasons for exclusion were that the paper was not a modelling study, it did not report on CDH outcomes, or it was only a review paper.

## Model methodology and structure

Model methodology varied widely. 12 (29%) of the 42 models were microsimulation or state transition Markov models, eight (19%) were cell based spread sheets, eight (19%) were life table analyses, four (9%) used Monte Carlo simulation techniques, four (9%) used logistic or linear risk functions, three (7%) used population attributable risk fraction estimations and three (7%) used a variety of other methods such as decision analysis *(Appendix 4).*

### Box 6.1 Summary of structures and methodology used in the six major models

*The Coronary Heart Disease Policy* (CHDP) Model was developed in 1980s as a state-transition, cell based model[222]. It was used to examine trends in CHD mortality[233;237] and expected gains in life expectancy from risk factor modifications[238]. This model was also used to evaluate the cost effectiveness of medical interventions for primary and secondary prevention of CHD[239-242] and health promotion activities[243].

The model was based on the 1980 US population and mortality statistics. It consists of three sub-models:

- A *demographical/ epidemiological* model, which represents the disease-free population aged 35-84 years. Here the population is stratified by sex, age groups and cardiovascular risk factors. This model includes risk factors as categorical variables, therefore in total over 5,000 cells are required. It then uses a logistic risk function based on the Framingham equation to calculate the annual incidence rates of CHD events for each cohort.

- A *bridge* model, which covers subjects for the first 30 days after they develop coronary disease. Using a CHD incidence data from Minnesota, the model initially determines whether the first event is angina, AMI or cardiac arrest[222].

- A *disease history model*, which includes the survivors after the first 30 days, places them in 12 CHD states by age and sex, and then follows them through treatment pathways.

This model allows the user to simulate the effects of an intervention (either risk factor modification, or therapeutic) by changing case fatality rates and observing the effect on mortality, morbidity and costs for up to 30years.

*CHD Policy Analysis Model,* is a microsimulation model being developed for the Department of Health by the London School of Hygiene and Tropical Medicine and Universities of Southampton and Birmingham[224;244]. The primary prevention component of the model aims to simulate the impact of different primary prevention strategies on benefits and costs [244]. The treatment component of the model evaluates the impact of different treatments given to different groups of CHD patients, commencing with stable angina[224].

*PREVENT* is a cell based simulation model developed by Gunning-Schepers in the 1980s the Netherlands[225]. It can be used to estimate the health benefits of changes in population risk factor prevalence comparing i) continuation of existing trends with ii) alteration of the proportions of the population with given levels of risk factors. The model allows one risk factor to be associated with more than one disease and one disease to be associated with more than one risk factor. Demographic evolution is also taken into account in simulations[225].

*Cardiovascular Life Expectancy Model* was developed by Grover et al (1992) in Canada to examine the cost-effectiveness of different treatment options for CHD[234]. The model includes primary and secondary prevention parts. The primary CHD part calculates the annual probability of dying from CHD or other causes and the annual risk of CHD events (with or without intervention) for a person without symptomatic CHD at entry to the model. The annual risk of developing specific CHD endpoints is based on data from the Framingham Heart Study.

After developing CHD, a person then moves to the secondary CHD model. This part calculates the risk of dying during the 12 months following a nonfatal myocardial infarction. The risk estimations are based on the Framingham logistic equations for primary events but after adjustment for the presence of CHD[234].

The predicted annual cumulative mortality difference with and without the intervention over the remaining total life expectancy represents the total years of life saved after intervention.

*The IMPACT CHD mortality model* is a cell-based model originally developed by Capewell and colleagues in 1996[4]. Using an MS EXCEL spreadsheet, this model

combines data from many sources on patient numbers, treatment uptake. treatment effectiveness and risk factor trends to estimate the deaths *prevented or postponed* (DPPs) over a specified time period. It can therefore be used to estimate the proportion of a mortality decline over a certain time span that might be attributed to specific treatments or risk factor changes.

*The Global Burden of Disease* (GBD) model developed at WHO by Lopez and Murray, is an example of models which use population attributable risk percentage (PAR %) estimations. The model can calculate the attributable burden of disease for a specific risk factor, population and time, which is defined as 'the difference between currently observed burden and the burden that would be observed if past levels of exposure had been equal to a specific reference distribution of exposure'. The reference distribution of exposure is defined as the risk factor exposure with lowest relative risk[245;246].

The GBD Model has five components: causes of death, descriptive epidemiology of disabling sequel, burden attributed to selected risk factors, projections of burden for the future and sensitivity analyses. Cause of death data are obtained from vital registrations or other sources. Data on 107 disorders and selected disabling sequel were investigated regarding average age of onset, duration, incidence and prevalence. Burden of disease and injury attributable to ten major risk factors were calculated. The model uses attributable fractions, taken from reviews and meta-analyses, applied to the population of a region to calculate the burden of disease of these risk factors[246]. Burden of disease is measured using disability adjusted life years (DALYs) calculated as the sum of years lost and years lived with disability[228].

## Comprehensiveness

Among the 42 models, 29 (69%) included only risk factors for primary prevention and 8 (19%) only considered treatments. Only 5 (12%) models included risk factors and treatments together. The CHD Policy and the IMPACT model were the most comprehensive since they both included a wide range of risk factors, CHD categories and effective treatments *(Box 6.2)*. The CHD Policy Analysis Model represents a derivative of the CHD Policy Model[244]. The CHD Policy Analysis Model eventually aims to include many treatment categories but has not been completed *(Box6. 2)*.

**Box 6.2 CHD risk factors and treatment categories included in the six major models.**

*The Coronary Heart Disease Policy Model* includes major risk factors such as smoking, total cholesterol, DBP and relative weight, which are necessary to estimate CHD risk using Framingham Equations. The model considers disease categories such as angina, AMI, sudden death, post MI, CABG, PTCA. Individual CHD treatments are also considered such as statins, aspirin, and beta-blockers in different publications based on this model.

The *PREVENT* Model is a primary prevention model and therefore only considers risk factors: smoking, cholesterol, hypertension, obesity, physical activity and alcohol use.

*The Cardiovascular Life Expectancy Model* estimates the annual risk of developing specific CHD endpoints based on data published from the Framingham Heart Study. It therefore includes risk factors of age, sex, diastolic blood pressure, total cholesterol, HDL cholesterol level, left ventricular hypertrophy, glucose intolerance and smoking status[247].

*The CHD Policy Analysis Model* resembles CHDP model by Weinstein et al. It has primary prevention and CHD treatment parts. The primary prevention component includes risk factors such as age, sex, systolic blood pressure, total cholesterol, and smoking[244]. The disease events included are stable angina, unstable angina, myocardial infarction, sudden cardiac death, stroke death, other cardiovascular death, cancer death and death from other known and unknown cause[244].

*The IMPACT* Model considers comprehensive risk factors and CHD categories and treatments. For primary prevention the model includes smoking, cholesterol, blood pressure deprivation, obesity, diabetes and physical activity. It also includes primary prevention with statin therapy.

The Disease categories (and treatments) (included: **AMI: Cardiopulmonary** resuscitation, thrombolysis, aspirin, PTCA, Beta blockers, ACE inhibitors); **Secondary prevention following MI, CABG or PTCA):** (Aspirin, Beta blockers, ACE inhibitors, Statins, Warfarin, Rehabilitation); **Chronic angina:** (CABG surgery, Angioplasty, Aspirin, Statins); **Unstable angina:** (Aspirin, Aspirin & Heparin PG HB/HA inhibitors); **Heart failure:** (ACE inhibitors special lactose, aspirin, statins); **Hypertension treatments:** (All).

*The Global Burden of Disease model* includes ten major risk factors for global disease burden. They are malnutrition, poor water quality, unsafe sex, alcohol, occupation, tobacco use, hypertension, physical inactivity, illicit use of drugs, and air pollution[246]. CHD is included in the model, and is modelled as being caused by tobacco use, hypertension and physical inactivity, and reduced by alcohol at all levels of consumption.

## Model Population

Most (33, 79%) of the 42 models included this review considered specific populations, 4 (10%) and 5 (11%) of them were based on patients and hypothetical cohorts respectively.

Most of the models were restricted to young and middle-aged groups, generally 15 to 64 years *(Table1-7 in Appendix 4)*. However the CHD Policy Model, IMPACT and CHD Policy Analysis Model considered groups aged up to 84 years. None of the models specifically considered non-Caucasian populations.

## Model outcomes

Most common outcomes reported in the models were number of deaths prevented 25 (60%), 17 (41%) life years gained, 17 (41%) CHD incidence and 27 (64%) cost/cost effectiveness. Fewer papers reported on CHD deaths 10 (24%), CHD prevented 9 (21%), prevalence 6 (14%), QALY 6 (14%), DALY 4 (10%) admissions 3 (7%).

## Model quality

Relatively few papers included in this review reported on model quality. Although sensitivity analyses were reported in 20 (48%) of the models, the majority were one-way rather than multi-way sensitivity analyses.

Validity of the model was assessed in 10 (24%) of the models. In the CHD Health Policy Model this was done by comparing the CHD deaths estimated by the model to the actual CHD deaths observed in 1990 using US vital statistics[233]. In the IMPACT Model, validity was likewise checked by comparing estimated fall in CHD deaths with observed fall[4;248]. Six other models also compared model estimates with observed figures[125;223;249-252]. In PREVENT, model validity was checked by comparing model

estimates with another estimation method[253]. In the Cardiovascular Life Expectancy Model, predictive validity was checked by comparing the model estimates with events observed in primary and secondary prevention trials[254;255]. Only two models (7%) reported on calibration of the model estimates against observed data. CHD Health Policy model was calibrated using life years estimated from the model compared with life expectancy from 1980 national statistics[238]. Kottke's model used actual mortality rates from the North Karelia cohort for calibration[256]. Only two of the models had been replicated in different populations (PREVENT[257;258] and IMPACT[5]).

On *Table 6.2* quality evaluation of six major models were presented in detail. CHD Policy Model and IMPACT Model appeared to be better in reporting the model quality compared with the others.

## Transparency and Limitations of the Models

Most models (36, 86%) explicitly stated their key assumptions. Illustrations or examples for estimations were provided in 14 (33%). Working versions of the models were potentially available in only (4, 10%). However, barely one fifth of the models reported on limitations of the models such as competing causes 8 (19%), lag times 7 (17%) or confounding 8 (19%).

The majority of the model papers received intermediate scores of 4-7 points *(Appendix 3)*.

## Table 6.1 Existing CHD Policy Models

| Name of the model | Type of model | Model setting & Study population(s) | Risk factors included | Disease groups & treatments included | Outcomes | Sensitivity analysis | Validation | Strengths and limitations |
|---|---|---|---|---|---|---|---|---|
| **CHD Policy Model (Weinstein and Goldman)** | State transition Markov Model | USA, Men and Women aged 35-84 | Smoking, total cholesterol, DBP and weight to estimate CHD risk using Framingham Equations | Angina, AMI, sudden death, post MI, CABG, PTCA  Individual CHD treatments were considered in different studies such as statins, aspirin, beta-blockers etc | Number of deaths prevented, LYG, CHD incidence (number of arrests, angina, AMI), CHD prevalence, CHD mortality, cost per life year | In the initial model none. Subsequently papers reported one way sensitivity analysis | Model was calibrated using 1986 mortality data. Validity: model Estimates were compared with 1990 observed-92-98% fit reported. | First policy model rather basic. Steadily refined since then. Many papers in high impact journals |
| **PREVENT (Gunning-Scheppers)** | Cell based | Netherlands;Denmark, England  Depending on the purpose aged <65 | Smoking, cholesterol, hypertension, obesity, physical activity, alcohol | None | Number of deaths prevented, life years gained | One way, different scenarios | Not checked | Mainly a primary prevention model. Developed and adopted in many different populations. |
| **CHD Life Expectancy Model (Grover et al)** | Life table analysis, Cost-effectiveness model | Canada, Adult men and women, age group not clear | Smoking, total cholesterol, DBP, glucose intolerance, age | Did not consider CHD disease categories but treatments can be considered for primary prevention  None ? | Years of life saved, cost per life year saved, years of life without CHD symptoms | One-way | Calibrated | This model uses hypothetical cohorts of participants. In most of the papers, time and the specific population are not clear. |
| **CHD Policy Analysis (Sanderson and Davies)** | Micro simulation | England and Wales,  Up to 85 years. Men and women | Smoking, cholesterol, systolic blood pressure | Angina (stable-unstable), AMI, postMI, CABG, PTCA  None - ? | Deaths prevented, morbidity prevented, CHD & noncardiac deaths, unstable angina | | No validation reported | Future model may include secondary prevention treatments. NO sensitivity analyses. Model fit appears better for men |

| Name of the model | Type of model | Model setting & Study population(s) | Risk factors included | Disease groups & treatments included | Outcomes | Sensitivity analysis | Validation | Strengths and limitations |
|---|---|---|---|---|---|---|---|---|
| | | | | | admissions, investigations, angiograms, PTCA, CABG | | | than women. |
| **IMPACT (Capewell, Critchley and Unal)** | Spread-sheet | Scotland, England &Wales, New Zealand, and, Initially M-F aged 45-84. IMPACT Model for England and Wales includes M-F 25-84 | Initially smoking, cholesterol, blood pressure deprivation- then obesity, also diabetes and physical activity | This model is comprehensive and considers Vine CHD categories and over 20 specific CHD treatments | Deaths prevented or postponed, life years gained. | Multi way sensitivity analysis using Analysis of extremes | Estimated falls in CHD mortality were compared with observed falls | Considers all major effective treatments available for CHD and all major risk factors. Data quality adequate, used trial and meta-analyses: National population statistics and results from representative studies |
| **Global Burden of Disease** **Murray & Lopez** | Population Attributable Parish method | World divided into eight geographic regions M-F all ages | Malnutrition, poor water, unsafe sex, alcohol, tobacco occupation, hypertension, physical activity, illicit drugs, and air pollution | None | Disability adjusted life years (DALYs) | Multi-way sensitivity analysis-discounting and age weighting | None | A comprehensive and global model for WHO strategies. Well documented and described. CHD is included, and modelled as caused by tobacco use, hypertension and physical inactivity, and reduced by alcohol. Data quality: Extremely variable depending on the region |

\* **Abbreviations:** AMI- acute myocardial infarction, CABG- Coronary artery bypass graft, MI- Myocardial infarction, LYG- Life years gained, PTCA- Percutaneous transluminal coronary angioplasty

**Table 6.2 Quality assessment for major CHD policy models**

| | Model Structure | | | | | Data Quality | | | | Validation | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Natural history of disease | Sufficient description | Assumptions | Inputs | Outputs | Inclusion criteria | Exclusion criteria | Data sources defined | Sensitiviy analyses carried out | Internal | External | Corroboration | |
| CHD Policy Model | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 34 |
| PREVENT | 1 | 3 | 3 | 2 | 3 | 3 | 3 | 3 | 2 | 1 | 1 | 1 | 26 |
| CHD Life Expectancy Model | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 1 | 3 | 3 | 0 | 24 |
| CHD Policy Analysis | 3 | 3 | 2 | 3 | 3 | 2 | 2 | 3 | 0 | 2 | 2 | 0 | 25 |
| IMPACT | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 1 | 2 | 33 |
| Global Burden of Disease | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 0 | 0 | 28 |

Appraisal criteria: The elements of the model assessment were listed in table. A general opinion was developed after reviewing all the papers published from that individual model. Each one of the criteria was scored on a 0 to 3 point scale. 0: not reported/ not done, 1: reported superficially/done simply 2:reported with detail 3: discussed

## 6.3 Interpretation

This is the first comprehensive systematic review of CHD policy models. Previous reviews were restricted to a particular type[259-261] or particular application[261]. The increasingly wide use of modelling has thus far resulted in few attempts to evaluate model quality. We therefore aimed to systematically assess the quality of the modelling methodology rather than simply report on the reported results. A wide variety of CHD policy models have been developed with over 70 publications now available. CHD models have become more complex and comprehensive as a result of improving computer technology and wider usage[3]. In general, the quality of the models has also improved over time so that more recent papers tend to explicitly report on sensitivity analyses and assumptions and limitations.

Quality assessment of publications, is well described especially for randomised controlled studies[262]. However, there are no widely accepted quality criteria for modelling papers in general nor specifically for CHD policy models. We therefore developed simple evaluation criteria based on sensitivity analyses, validity, and these comprehensive reporting of assumptions and limitations. These criteria explicitly reflect the main quality components suggested in the recent ISPOR Guideline[216].

Models can allow a large amount of evidence to be considered simultaneously, by combining and integrating into a coherent whole different types of data from controlled trials, routine surveillance and expert consensus[3]. Models have been extensively used in policy making and resource allocation, since they permit policy makers to examine future options, or to simulate the effects of different scenarios within a population[217]. However, improved technology potentially allows both practitioners and policy-makers to use these models without necessarily understanding the inherent assumptions or data limitations [3].

Models require considerable data input and data sources need to be appropriate and credible. However, the availability of comprehensive high quality data remains a problem. The data may come from a variety of sources including clinical trials, meta-analyses, surveys, databases, medical records, audits, Delphi panels (expert opinion), routine statistics and official tariff lists for health care resource use[229]. Every modelling paper should therefore explicitly report and discuss data quality

methodological limitations and assumptions to address these discrepancies. However, few of the papers reviewed here critically evaluated their data quality.

Uncertainties about data are a perennial problem in modelling studies. Sensitivity analyses should therefore be employed to quantify the degree of uncertainty. In general, CHD models have only recently started to report sensitivity analyses[233;255;263].The most common approach is where one or more parameters of an evaluation are varied across a plausible range[231]. Confidence intervals can also be easily included in sensitivity analyses. *One-way sensitivity analysis* (where only one parameter is changed at a time while the others retain their base-case specifications) is obviously less rigorous than *multiway-sensitivity analysis* (where more than one parameter is changed at the same time). However, multiway sensitivity analyses remain uncommon[3;4;248;264].

Many of the papers reviewed here failed to provide sufficient detail to allow thorough evaluation. When assessing the quality of a model, one should ideally consider the system being modelled, the elements included and excluded, the model structure, the probable effects of existing trends in mortality and risk factors and the model assumptions- both stated and unstated[216;217] . The description of the model should be sufficiently detailed so that the model can be replicated mathematically.

In conclusion, CHD models offer a potentially valuable tool for policy development. However, existing models vary widely in their depth, breadth and quality. Few models have been calibrated, replicated or validated against a gold standard. Before being accepted as a policy aid, any model should explicitly include a statement of its aims, assumptions, strengths, outputs and limitations.

# 7  AN EVALUATION OF UK DATA SOURCES FOR CHD

## 7.1 Introduction

*Chapter 4* described the massive burden of disease generated by CHD in the UK, and also raised potential concerns about the quality of the data describing CHD. This chapter will therefore focus on CHD data quality in the UK.

Policy decisions on health and health care require good evidence, particularly since resources are limited[3]. Good evidence to describe the current situation means not just information on the effectiveness of interventions, but also valid and reliable data on the disease burden and the provision of health care.

Modelling studies can provide decision makers with good evidence based results and they are based on data availability and quality[3]. In my thesis I will use IMPACT CHD Mortality model to explore recent CHD mortality trends in England and Wales. I therefore decided to evaluate the availability and quality of UK CHD data sources since 1981. I considered all 'public health' information sources for CHD, as defined in the recent 'Department of Health CHD Information Strategy'[265]. This included information on patterns of mortality and morbidity (including hospital admissions and episodes) and major cardiovascular risk factors by age, sex, and ethnicity.

## 7.2 Methods

UK data sources on CHD were initially identified and categorised according to the IMPACT CHD mortality model, which aims to explore CHD mortality trends in England and Wales during 1981-2000[248].

To build the IMPACT Model, information was required on a) population based mortality rates and patient numbers with different categories of CHD -acute myocardial infarction, unstable and chronic angina, heart failure, hypertension, CABG surgery and angioplasty; b) uptake of specific medical and surgical treatments; c) effectiveness of specific cardiological treatments and risk factor reductions and d) population trends in major cardiovascular risk factors (smoking, cholesterol, hypertension, obesity, diabetes, physical activity and deprivation)[248].

**Search Strategy**

Potential data sources were identified and obtained by various methods including comprehensive electronic searches using keywords and MeSH headings. Databases searched included MEDLINE, EMBASE and DISSERTATION ABSTRACTS. This search was further supplemented by cross-checking reference lists of the key articles retrieved during the electronic search. I also examined conference proceedings, audit reports, relevant official web sites and personal correspondence *(Appendix 5)*.

The main data sources for population and patient data were the Office for National Statistics (ONS)[266] and the British Heart Foundation's Annual CHD Statistics[2]. Information on treatment prescription and uptake were obtained from various national and local clinical audits[267-269] and surveys[157;201;270;271]. Data on efficacy of interventions and risk factor changes were reviewed from published randomised controlled trials, meta-analyses and population studies.

The British Regional Heart Study[272], General Household Survey[273], and Health Survey for England[48] were the main data sources for risk factor data.

Each data source was evaluated in terms of the following criteria: coverage and completeness (population of interest), coding accuracy (where these are reported in the primary data source), validity (the degree to which a variable measures what it purports to measure[274]- where this is reported in the primary data source) and generalisability (critical appraisal of the studies for their methodology), ease of access (availability of information either published or electronically), and inclusion of information on age and sex breakdowns, ethnic and socio-economic categories.

## 7.3 Results

### *Population and patient data sources*

The main data sources for population and patient data are presented in *Table 7.1*. Data from ONS official statistics[195;266] were easily accessible both electronically and in published form. However Official statistics are not based on autopsies, therefore may over estimate CHD deaths in the elderly. The British Heart Foundation provided another useful source of annually updated CHD statistics for the UK[2]. The source includes data on CHD morbidity, mortality, prevalence, incidence and cost in the UK.

Information on patient numbers undergoing CABG surgery has been available from the United Kingdom Cardiac Surgical Register since 1977[197]. The register was based on voluntary and anonymous reporting of activity and hospital mortality for CABG, valvular and congenital heart disease surgical procedures performed in NHS Hospitals. Each unit was asked to return a standard questionnaire annually to the Society of Cardiothoracic Surgeons[197]. These data were then analysed and published as annual reports. However while reasonably complete, the Register lacks details on age, sex, ethnicity, social status and long-term survival.

**Angioplasty** patient numbers have been available from the British Cardiovascular Intervention Society's Audit returns since 1989[198]. These referred to angioplasty activity in all interventional centres in the UK, both NHS and private. The data had details on procedures and success, but lacked details on age, sex and other individual specific information.

The number of **acute myocardial infarction, angina** and **heart failure** admissions to hospitals was available from Hospital Episode Statistics (HES)[196]. HES provided information on in-patient care delivered by NHS hospitals in England since 1989. HES collected almost 12 million records per year, and each record contained over 50 items of information. Since these records related to named individuals, it was not possible to access them directly. The database contained information on diagnoses, operations, admission method, patients' age, sex and ethnic group, length of stay, waiting time, maternity care, psychiatric care, Healthcare Resource Groups (HRGs), NHS Trusts and Health Authority areas[196].

HES records described *episodes* of continuous in-patient care under the same consultant[196]. In cases where responsibility for a patient's care transferred to a subsequent consultant, there would be two or more records for the same patient. In 1999-2000, approximately 8% of admissions fell into this category[196]. HES could not provide details of the drugs used in hospitals, nor information concerning outpatients or patients treated in accident and emergency departments and then discharged home immediately. Another major limitation of the database was being unable to distinguish between first admissions and readmissions.

The number of **angina patients in the community** could be estimated using prevalence of 'ever experienced angina', available from the Health Survey for England(HSE) '98[48].

This was a series of annual surveys about the health of people in England carried out since 1991. The HSE contained a 'core', which was repeated each year, and each survey year has one or more modules on subjects of special interest. The HSE 1993, 1994 and 1998 had CVD modules and could therefore provide useful information on CHD, stroke, hypertension and other cardiovascular risk factors.

In the HSE, angina prevalence was measured as 'self reported angina'. In addition to this, the Rose questionnaire on angina and heart attack[48] was used as an alternative estimation method. Overall angina prevalence was lower with Rose Questionnaire (2.6% in men and 3.1% in women) than that based on self-reported 'doctor-diagnosed' angina (5.3% and 3.9%). This suggests a possible overestimation in angina prevalence with self reported angina. However, Rose Questionnaire measures current angina rather than ever-experienced angina and prevalence of self reported 'current angina' was closer to prevalence measured by Rose questionnaire (3.2% and 2.5% in men and women)[48]. Angina patient numbers based on GP consultation rates could be expected to be substantially smaller than these prevalence based estimations[204].

The population surveyed in HSE has been the population living in private households. Those living in institutions have not been covered. They are likely to be older and, on average, in poorer health than those in private households. Furthermore, a response rate for the survey varied substantially by survey year but was generally low. Interviews were carried out on 69% of individuals targeted, 58% had their blood pressure measured and only 47% gave a blood sample[48].

The number of **heart failure patients in the community** was estimated using prevalence of 'treated heart failure' from Key Health Statistics from General Practice, 1998[201]. This report gave the prevalence of various morbidities and treatment data derived from general practitioner records and it provided data for age-sex groups.

Since this source was based on general practitioner consultations, it omitted those symptomatic subjects who did not present to the NHS, but who were detected by epidemiological surveys[275,276]. Furthermore, there is evidence of substantial limitations in coding accuracy and appropriate treatment of the condition[175]. Therefore, the actual number of heart failure patients in the community may be slightly higher than the estimated numbers using prevalence data from Key Health Statistics from General Practice[175].

Table 7.1 Population and patient data sources of information on CHD in the UK, 1981-2000.

| Information | Source | Evaluation |
|---|---|---|
| Population statistics (1981-2000) (number) | Office for National Statistics [195] | Easily accessible, accurate and up-to-date |
| Deaths by age and sex (1981-2000) (number) | Available online from Office for National Statistics[266] and as published reports[277] | Death certification complete standardised coding. Only minority based on autopsy. May over estimate CHD deaths in elderly. |
| CHD Mortality (rates) | Available as mortality statistics from Office for National Statistics [277;278] and from British Heart Foundation Annual CHD Statistics online or published reports[2] | Little information on ethnic minority or socio-economic difference. |
| CABG surgery patients (number) | CABG numbers from 1991-2000 available online on UK Society for Cardiothoracic Surgeons of Great Britain and Ireland's web site (http://www.scts.org/doc/2102)[197]. To obtain figures for England and Wales CABG numbers for Scotland and Ireland deducted from UK's figures. | Appear accurate. Lack detail on age, sex, ethnic group, social status and long-term survival. |
| Angioplasty patients (number) | Angioplasty numbers for 1991-2000 available online on British Cardiovascular Intervention Society's web site http://www.bcis.org.uk/audit/Bcis00.ppt[198]. | Age and sex split not provided. |
| Angina patients admitted to hospital (number) | Number of angina patients admitted to hospital available from Hospital Episode Statistics 1999-2000 (http://www.doh.gov.uk/hes/index.html)[196]. | Episodes not individuals. Coding accuracy improving. Lack detail of subgroups. No data on therapy. |
| Angina patients in the community (number) | Prevalence of 'ever experienced angina' is available from Health Survey for England 1998[48], and British Regional Heart Study[279]. | Only prevalence not incidence. |
| Heart failure patients admitted to hospital (number) | Number of angina patients who admitted to hospital was available from Hospital Episode Statistics 1999-2000 (http://www.doh.gov.uk/hes/index.html)[196] | As for angina admissions. |
| Heart failure patients in the community (number) | Prevalence of treated heart failure patients in the community available from Key Health Statistics from General Practice 1998 report[201] | GP consultations; therefore omits subjects not presenting to NHS. |

## Cardiological treatments

Data sources on cardiological treatments in primary and secondary level are presented in *Table 7.2*.

The precise number of CHD patients who had cardio-pulmonary resuscitation (CPR) in the community (before reaching hospital) was not known, neither was the number of CHD patients who had CPR in hospital. These two figures could only be estimated from various surveys[157;280;281].

Information about **hospital admissions** in 2000 was available online from HES[196]. However, trend data, and details of hospital interventions were very limited.

**Treatment uptake data** were not available routinely, and came principally from isolated surveys and registers. For **treatment at the primary care level**, limited prescription and uptake data were available from the Prescribing Analysis and Cost Tabulate (PACT)[282], and a few published local audits and studies[166;283-287]. Broadly consistent uptake levels were reported for treatments in primary care settings in two different surveys[288;289]. The EUROASPIRE II Study provided treatment levels for the secondary care of CHD from a small number of selected UK hospitals, but age and sex breakdowns were not generally available[269]. Furthermore, generalisability of EUROASPIRE II results to whole UK practices is questionable.

**Table 7.2 Data sources on CHD treatments in primary care and secondary care in the UK, 1981-2000.**

| Information | Source | Quality & Comments |
|---|---|---|
| **Initial Treatments For Acute Myocardial Infarction** | | |
| **Community CPR** | Estimated using data from UK Heart Attack Study[157] and Scottish Heartstart[290]. Number of myocardial infarction admissions to hospital obtained from HES. | Ad hoc surveys and ambulance data only. |
| **Hospital CPR** | Number of hospital CPR patients estimated using 2000 HES data. Approximately 11 % of the patients admitted to hospital need CPR (The United Kingdom Heart Attack Study Collaborative Group[271] and BRESUS Study[280]) | Isolated surveys only. |
| **Thrombolysis** **Aspirin** **Beta-blocker** **ACE inhibitor** | The United Kingdom Heart Attack Study Collaborative Group[271], Nottingham Heart Attack Register[269;291] | Isolated surveys, plus some data on numbers given thrombolysis. Routine information on hospital treatments for acute myocardial infarction not available. |
| **Secondary Prevention Following Acute Myocardial Infarction, CABG Surgery or PTCA** | | |
| Aspirin Beta-blocker ACE inhibitor Statins Warfarin Rehabilitation including exercise | Limited data on secondary prevention from General Practice Research Database report[289] and EUROASPIRE II Study[269] | Isolated surveys[288] and a few ad-hoc audits only. |
| **Unstable Angina in Hospital admissions** | No routine data on therapy | No routine data. |
| **Aspirin for Community Angina** | Data mainly from a General Practice Research Database report [289] | Isolated surveys only. |
| **Heart failure treatment in hospital** | - | Isolated audits only. |
| **Heart failure treatment in the community** | Key Health Statistics From General Practice 1998[201] | Isolated papers. |
| **Treatment of individual patients for hypertension** | British Regional Heart Study [292] Caerphilly papers[293] and the Health Survey for England 1998[48] | Information limited especially in elderly. |

## Cardiovascular risk factor data sources

Population based cardiovascular risk factor data sources and their evaluations are presented in *Table7.3.*

The risk factors considered were blood pressure, smoking, total cholesterol levels, obesity, physical activity, diabetes, and deprivation. Population based risk factor data were available mainly from the British Regional Heart Study[272;292;294], the General Household Survey[273], and the Health Survey for England[48]. Information was very limited for the 1980s, but more extensive by the year 2000.

**Blood pressure** data were relatively limited until recently. The British Regional Heart Study provided some blood pressure data in 1981, but only for men aged 40-59[272]. The Dietary and Nutritional Survey of British Adults[295] reported blood pressure data from 1990 onwards and provided sex and limited age breakdowns (up to 65). The Health Survey for England has included blood pressure data since 1993[296].

**Smoking prevalence** was the exception among the cardiovascular risk factors with good data on trends easily available from successive General Household Surveys[200;273]. Age, sex and socio-economic status breakdowns were also available.

Data on **cholesterol levels** were very limited during the 1980s[294]. The Health Survey For England included cholesterol levels from 1993. However, changing laboratory methods used between surveys made the interpretation of these recent trends difficult[48].

Blood samples were analysed by different laboratories in different Health Surveys. The Royal Victoria Infirmary laboratories in Newcastle upon Tyne analysed blood samples in 1991 to 1993 and 1998 Health Surveys. However, the laboratories of the West Middlesex University Hospital had undertaken analysis of blood samples collected in the 1994 to 1997 Health Surveys. Although they both used the same method (DAX Cholesterol Oxidase) in 1994 and 1998, the equipment used was different. Some caution is therefore necessary when interpreting these results[48].

Data on **obesity** (defined as BMI>30kg/m$^2$) were available from two Department of Health surveys in early 1980's[297], and also HSE[295]. However, data on other anthropometric measures such as waist-to-hip ratio, were not available in the early 1980's but only from more recent population surveys[48].

Some indirect evidence of a decline in **physical activity** (an increase in car journeys and decrease in miles walked) was available from the Department of Transport's Statistics for Great Britain[298]. However, no comprehensive population-based measures were available before the Allied Dunbar Survey in 1990[299]. The British Regional Heart Study provided physical activity data limited to men aged 40-59[53;300]. However, definitions of physical inactivity have varied in different surveys, so comparable trend information were not available.

There were some studies on **diabetes** starting from the 1970s mainly focusing on treatment efficacy (The United Kingdom Prospective Diabetes Study)[301] and mortality in diabetic patients (British Diabetic Association Cohort Study)[302]. However, early information on trends in diabetes prevalence was available only from one population survey in Poole commencing in 1983[303]. The Health Survey for England provided self reported information on diabetes prevalence since 1991[296]. Trends in general practice consultations between 1994 and 1998 are also now available from the General Practice Research Database[304].

**Socio-economic information** was available on household income, adjusted for tax and benefits, and housing tenure from various sources including Social Trends[305] and the General Household Survey [200;273]. However, because deprivation scores describe relative deprivation on the basis of cross-sectional data, trend data for deprivation scores have not been generated. Data on socio-economic characteristics defined the occupation of the head of household, equalised income and health authority area type was available from Health Survey for England.

The **Barker hypothesis** states that low birth weight is associated with increased rates of CHD in later life[87]. To estimate the impact of birth weight trends, population birth weight data is necessary. However birth weight data is routinely available only from 1950s[306]. Data on earlier years is only available from small population registries. In Hertfordshire, from 1911 to 1948 weight at birth and at age 1year were recorded routinely[307].

# Table 7.3 Data sources on cardiovascular risk factors in the UK, 1981-2000.

| Cardiovascular Risk factors | Source | | Evaluation |
|---|---|---|---|
| **Information** | **Initial Year (1981)** | **Most Recent Year (2000)** | |
| **Population blood pressure** | The Dietary and Nutritional Survey of British Adults[295] and British Regional Heart Study[272] | Health Survey for England 1998[48] | Blood pressure data very limited until recent times. For early years The Dietary and Nutritional Survey of British Adults and British Regional Heart Study (only for men) provided mean blood pressure levels. Health Survey for England included these data since 1993. |
| **Smoking prevalence** | General Household Survey 1980[273] | General Household Survey 2000[200] | Good data for trends in smoking prevalence easily available from General Household Surveys and British Household Panel Survey categorised by age and sex. |
| **Cholesterol** | British Regional Heart Study[272] | Cholesterol levels measured in Health Survey for England 1994 and 1998[48]. MONICA Glasgow and Belfast trends 1985-1995 available for comparison[308]. | Limited data available for the early 1980s. Changing laboratory methods used in the Health Survey for England (1994-1998) made interpretation of recent trends difficult, even when supported by trends from UK MONICA surveys. |
| **Obesity** | The Heights and Weights of Adults in Great Britain[297] | Health Survey for England 98[48] | Data on obesity (defined BMI >30) available from two DoH surveys in early 1980s. Data on other anthropometrical measures i.e. waist to hip ratio, were not available in early 1980's but these data available from some more recent population surveys (Health Survey for England). |
| **Physical activity** | British Regional Heart Study[272] | Allied Dunbar Survey 1990[299] | No comprehensive population-based measures were available before Allied Dunbar Survey 1990. British Regional Heart Study data limited to men aged 40-59. Definitions of physical inactivity varied in different surveys so comparable trend information not available directly. Some indirect evidence of a decline in physical activity available from Department for Transport's Transport Statistics for Great Britain report[298]. |
| **Diabetes** | Poole Diabetes Study[303] | Health Survey for England 98[48], General Practice Research Database[309] | Data on diabetes prevalence is either not available or not comparable for early 1980s. More recent trend information is available from Health Survey for England and General Practice Research Database[309]. |
| **Deprivation** | 1981 Census data | 2001 Census data awaited | Standardised trend data for deprivation score not available. Information available on: household income, adjusted for tax and benefits, housing tenure. |

## 7.4 Interpretation

Information on CHD in the UK is frequently patchy, obsolete or simply not available. Although routinely collected data provide large quantities of health information, often covering the whole population over a long period of time, such sources have limitations and are underused[310]. The Office for National Statistics provides useful updated population and mortality statistics. Furthermore, much of the Office for National Statistics information is available electronically, which makes it much more accessible for users. Likewise Hospital Episode Statistics, which summarise admissions to the NHS hospitals, are also available electronically; however they lack detail on interventions at the hospital level. The British Heart Foundation's HEARTSTATS website is also developing rapidly, and provides an increasingly wide range of CHD statistics plus brief comments *(http://www.heartstats.org/homepage.asp)*.

Public health information on CHD in the UK must be improved. At present, the NHS annually spends over £2 billion on a range of evidence-based initiatives for the treatment of CHD. However, evaluation of these initiatives using existing routine data is simply not possible. Furthermore, monitoring this common and devastating disease is almost confined to analysis of mortality statistics. Over 35,000 CABG operations are performed each year, however survival even two years later is not routinely available[311]. Thirty day case fatality following admission for AMI or CABG surgery have been used as Department of Health performance indicators[312]. However, variations in performance indicators between individual hospitals are vulnerable to differences in coding practices and case-mix[313].

Other Northern European countries have developed and implemented better CHD monitoring systems. The Information and Statistics Division (ISD) in Scotland collects good data on all patients treated for CHD and the procedures they receive. Scotland's routine NHS data is of high quality and data linkage allows the investigation of the epidemiology and treatment of heart disease across the population, with comprehensive analyses then being possible on different forms of the disease, including myocardial infarction and heart failure[123,144,192,313,314].

CHD mortality rates in Finland were once the highest in the world[315]. A series of regional risk factor surveys (FINRISK) have been carried out there every five years since the early 1970s[192,315,316]. These use a standardised methodology, include all the major CHD risk factors, with high participation rates and a large sample size (approximately 14,000 for the

2002 survey). Reliable estimates of trends and their contributions to CHD mortality declines can therefore be made over a 30-year period. They also allow relatively quick identification of adverse developments such as the increase in smoking among women observed in the 1980s to early 1990[317].

Monitoring of risk factors and of secular trends in risk factor epidemiology is also available in Norway[318]. Cardiovascular risk factor studies have been conducted in different regions since the late 1950s. Since the 1970s, the National Health Screening Service (SHUS) cardiovascular disease screening and prevention programmes visit all municipalities, every three years and achieve high response rates[318].

In the USA, the National Health and Nutrition Examination Survey (NHANES) has been periodically conducted since the early 1960s to obtain nationally representative information on health, nutritional status, risk factors and health behaviours in the population. NHANES III (1988-94) is the seventh of these[319] and data from NHANES 1999-2000 is currently available from (webpage: http://www.cdc.gov/nchs/data/nhanes/frequency/filelist%204-2003.pdf)

In England and Wales, the CHD NSF, NHS Plan and CHD Information Strategy all explicitly recognise the huge importance of disease monitoring and service evaluation. All have made a number of specific and sensible recommendations. However, at present over 99% of the £2 billion NHS CHD budget is spent on medical interventions, particularly revascularisation. Less than 1% is currently spent on the monitoring of CHD[2;265]. These are inadequate resources for even basic information strategy or technology. Furthermore, although some national datasets (such as the Health Survey for England) can support the Information Strategy, such datasets are not 'locally owned' and lack the scale to analyse specific local population groups, such as ethnic minorities[320].

In conclusion, future CHD disease monitoring and evaluation will require more comprehensive and accurate population-based information on trends in patient numbers, treatment uptake and risk factors. This will require adequate resources to improve existing information systems. Regular and comprehensive surveys (including women and elderly people), using standardised methodology will also be essential.

In terms of my thesis, these findings mean that all data, whether routine statistics or surveys have to be treated with some caution. The need for a sensitivity analysis will therefore be explicitly discussed in the next chapter.

# 8 DESCRIPTION OF THE IMPACT MODEL

In *Chapter 6*, I discussed the concept of modelling and reviewed some of the CHD models in use today. In this chapter, I will describe the IMPACT Model in detail and explain the methodology.

In 1996, Capewell et al. developed and refined IMPACT CHD mortality model[4]. Using an MS EXCEL spreadsheet, this cell-based CHD model combines data from many sources on patient numbers, treatment uptake, treatment effectiveness and risk factor trends to estimate the *deaths prevented or postponed* (DPPs) over a specified time period. It can therefore be used to estimate the proportion of a mortality decline over a certain time span that might be attributed to various risk factor changes or to specific treatments. For example, in Scotland CHD mortality declined by 29% between 1975 and 1994. Using the IMPACT model, it was possible to attribute approximately 40% of the fall to medical therapies and one third to the reduction in population levels of smoking[4].

The IMPACT model was validated against the actual mortality fall observed in Scotland[4], and then replicated in New Zealand[5]. It was then used to estimate how many additional deaths could potentially have been prevented by simply increasing the uptake of appropriate treatments by eligible patients[321] in Scotland in 1994 (approximately 4,000). The model was also used to estimate the additional deaths which might potentially be prevented in Scotland by further reductions in risk factors such as smoking, cholesterol and blood pressure[322].

In collaboration with the National Public Health Institute (KTL) in Helsinki, Finland, validation and development of the IMPACT model has recently been completed. This used high quality linked data on deaths and hospital activity, plus MONICA data on risk factors[192]. The findings suggested that cholesterol reductions were much more important in explaining trends in CHD mortality (1982-1997) in Finland compared with UK *(personal communication with Julia Critchley, 2003)*.

The original IMPACT model was thus restricted to the Scottish population of 5.1 million. Furthermore it demonstrated a number of methodological limitations, including being restricted to 1994, considering only three risk factors and omitting modern therapies such as primary angioplasty for AMI, and PG IIb/IIIb antagonists for unstable angina. The aim of my PhD project was therefore to further develop the IMPACT Model methodology, update it and

apply it to the much larger and more complex England and Wales population[248]. I would then be in a position to examine LYGs, potential impact of improvements in uptake of treatments, or reductions in major risk factors, as well as mortality trends in England and Wales between 1981 and 2000.

## 8.1 Building an IMPACT Model for England and Wales

### Selection of an appropriate population and time frame

**The England and Wales population** was chosen to examine recent CHD mortality trends because:

i)      The National Service Framework for Coronary Heart Disease, published in 2000 highlighted an obvious need for such work to support the NSF and to evaluate its impact

ii)     No comprehensive analysis of UK trends in CHD mortality, risk factors and treatments had been published

iii)    Relatively extensive data were available for England and Wales describing the population, mortality trends and, to a lesser extent, morbidity trends

### Age range

The model was initially built without an upper age limit. However, it became increasingly clear that data were sparse over the age of 85 years. Furthermore, there was some evidence that the accuracy of CHD on death certificates decreased in the elderly[183]. It was therefore decided to restrict the model to between ages 25 to 84 years.

**The baseline (1981) and final years (2000) were chosen on the basis of several factors:**

i)      The total duration needed to be at least 10 years in order to cover a reasonable change in mortality rates.

ii)     There needed to be adequate data on risk factors and treatments for the base year

iii)    The final year needed to be as recent as possible to maximise its value to clinicians and policy makers.

After some pilot work, a **20-year period between 1981 and 2000** was chosen to model the mortality trends in England and Wales.

## Refining and developing the IMPACT mortality model

The cell-based IMPACT mortality model was further developed and refined during my PhD studies. I added new treatments and new risk factors to the model. I also introduced new methods to quantify the cumulative effects of multi therapy in secondary prevention groups. The methodology sections will provide further detail around these issues. A list of these changes is presented below, and the approaches developed to address these issues are explained in the appropriate sections and boxes *(flagged in italics)*.

**Box 8.1 Principal changes and refinements made in English IMPACT Model**

**New treatments added to the IMPACT Model**

- Primary angioplasty for AMI patients
- Platelet glycoprotein IIB/IIIA inhibitors for unstable angina
- Spironolactone, aspirin and statins for angina and heart failure patients
- Statins for primary prevention *(Box 8.9)*

**– New risk factors added to the IMPACT Model**

- Obesity
- Diabetes
- Physical activity
- Deprivation *(Page 99-100, Box 8.11)*

**– Mant and Hicks correction was applied for secondary prevention therapies** *(Box 8.3)*

**– New possible overlaps between patient groups considered** *(Box 8.4)*

**– Impact of risk factor changes in CHD patients was estimated** *(Appendix 9)*

The model was then revised to incorporate data for England and Wales. Data were identified and incorporated for men and women aged 25 to 84 years in England and Wales detailing;

a) CHD patient numbers,

b) uptake of specific medical and surgical treatments,

c) population trends in major cardiovascular risk factors (smoking, total cholesterol, hypertension, obesity, diabetes, physical activity and socio-economic deprivation),

d) effectiveness of specific cardiological treatments, and

e) relationship between specific risk factor reductions and CHD mortality.

A flowchart is presented to describe the IMPACT Mortality Model and parameters included in *Figure 8.1*.

**Figure 8.1 Flowchart of the IMPACT Mortality Model parameters**



**MODEL PARAMATERS**
- Population eligible
- **Change in risk factor levels**
- **Beta coefficient***

**Risk Factors**

Cholesterol
Smoking
Blood Pressure
Obesity
Inactivity
Deprivation
Diabetes

**Acute CHD**

Myocardial Infarction
Angina
CABG & PTCA
Unstable Angina

- Patients number eligible
- Acute treatments
- Treatment uptake
- Compliance
- Efficacy

**Chronic CHD**

Post MI- CABG- PTCA
Heart Failure

- Patients number eligible
- Secondary prevention
- Treatment uptake
- Compliance
- Efficacy

**Outcomes**

Deaths Prevented or Postponed
Life years gained

## The fall in coronary heart disease deaths

The number of CHD deaths expected in 2000 if the mortality rates in 1981 had persisted was calculated by indirect age standardisation, using 1981 as a base year. The CHD deaths actually observed in 2000 were then subtracted to give the fall in CHD deaths between 1981 and 2000 *(Appendix 7)*.

## Patient categories included in the IMPACT England and Wales model

ICD9 Codes 410-414 (prior to 2000) and ICD10 codes I20-I25 (since 2000) correspond to Coronary Heart Disease. This definition consists of mainly myocardial infarction or angina. The specific patient groups comprised acute myocardial infarction, post myocardial infarction, unstable angina, chronic angina, CABG surgery, angioplasty, and heart failure.

## Treatment categories included in the IMPACT England and Wales model

The model aimed to include all medical and surgical treatments given in 1981 and 2000 in England and Wales. These interventions are listed in *Box 8.9* and included all the interventions considered in earlier versions of the IMPACT Model[4;5] plus primary angioplasty for myocardial infarction, statins for primary prevention, platelet IIB/IIIA inhibitors for unstable angina, and spironolactone and beta-blockers for heart failure.

## Mortality Reduction Estimation by treatments

The mortality reduction for each treatment was calculated using the relative mortality reduction reported in published meta-analyses and trials listed in *Box 8.2* applied to the case fatality observed in unselected patient cohorts[143;144]. Case fatality rates for patient groups are presented in *Appendix 8*. Survival benefit over a one-year time interval was used for all treatments, thus only DPPs for at least one year were counted in the calculations.

The deaths prevented or postponed for at least a year were therefore calculated as:

*Patient numbers eligible X treatment uptake X relative mortality reduction X one-year case fatality*

An example of calculation method is presented below in *Box 8.2*:

**Box 8.2 Example of DPP calculation: Men aged 55-64 given aspirin for acute myocardial infarction**

In the Antithrombotic Trialists' Collaboration meta analysis, aspirin reduced relative mortality in men with AMI by 15%[160]. In England and Wales in 2000, 10,699 men aged 55-64 were eligible, and 95% were given aspirin[289]. One year case fatality in men aged 55-64 admitted with an AMI was approximately 17%[143].

The DPPs for at least a year were therefore calculated as:

*Patient numbers x treatment uptake x relative mortality reduction x one-year case fatality =*

*10,699 x 95% x 15% X 17% = 259 DPPs.*

**Polypharmacy Issues**

Individual CHD patients may receive a number of different medications. However, RCT data on efficacy of treatment combinations are sparse. Mant and Hicks[323] suggested a **cumulative relative benefit** method to estimate the case-fatality reduction achieved by polypharmacy. The potential effect of multiple treatments in an individual patient were therefore examined using the Mant and Hicks approach:

*Relative Benefit = 1 - [(1 -Treatment A) X (1-Treatment B) X.... (1-Treatment n)*[323].

An example of this approach and its use for IMPACT Model is presented in *Box 8.3* below:

**Box 8.3 Example of Mant and Hicks calculation for secondary prevention following acute myocardial infarction.**

If we take the example **of secondary prevention following AMI;** good meta-analysis evidence suggests that, for each intervention, the relative reduction in case fatality is approximately:

Aspirin 15%[160], beta-blockers 23%[166], ACE inhibitors 23%[167], statins 29%[34] and rehabilitation 27%[324].

The Mant and Hicks[323] approach, recently used by Wald and Law[325], suggests that in individual patients receiving all these interventions, case-fatality reduction is very unlikely to be simply additive ie not **117%** (15% + 23%+ 23% + 29% + 27%). Indeed, 117% is clearly absurd, implying immortality. Instead, having considered the 15% case fatality reduction achieved by aspirin, the next medication, in this case a beta-blocker, can only reduce the **residual** case fatality (1-15%). Likewise, the subsequent addition of an ACE inhibitor can then only decrease the **remaining** case fatality, which will be 1 - [(1- 0.15) X (1-0.23)].

The Mant and Hicks approach therefore suggests that a **cumulative relative benefit** can be estimated as follows:

*Relative Benefit = 1 - [(1 -Treatment A) X (1-Treatment B) X (1 -Treatment C) X (1 - Treatment D) X (1 -Treatment E)]*

In considering appropriate treatments for AMI survivors, applying relative reductions for aspirin, beta-blockers ACE inhibitors statins and rehabilitation then gives:

*Relative Benefit = 1 - [(1 -aspirin) X (1 - beta-blockers) X (1 - ACE inhibitors) X (1- statins) X (1- rehabilitation)]*

$$= 1 - [(1- 0.15) \text{ X } (1-0.23) \text{ X } (1-0.23) \text{ X } (1- 0.29) \text{ X } (1- 0.27)]$$

$$= 1 - [(0.85) \text{ X } (0.77) \text{ X } (0.77) \text{ X } (0.71) \text{ X } (0.73)]$$

**= 0.74   ie a 74% lower case fatality**

**Potential overlaps between patient groups: avoiding double counting**

There are potential overlaps between CHD patient groups *(Figure 8.1).* For example, approximately half the patients having CABG surgery have a previous AMI[326], 20-30% of AMI survivors develop heart failure within 12 months[174], and over 50% of CHD patients have a history of hypertension[143] *(Figure 8.1).*

**Figure 8.2 Potential overlaps between CHD patient groups**
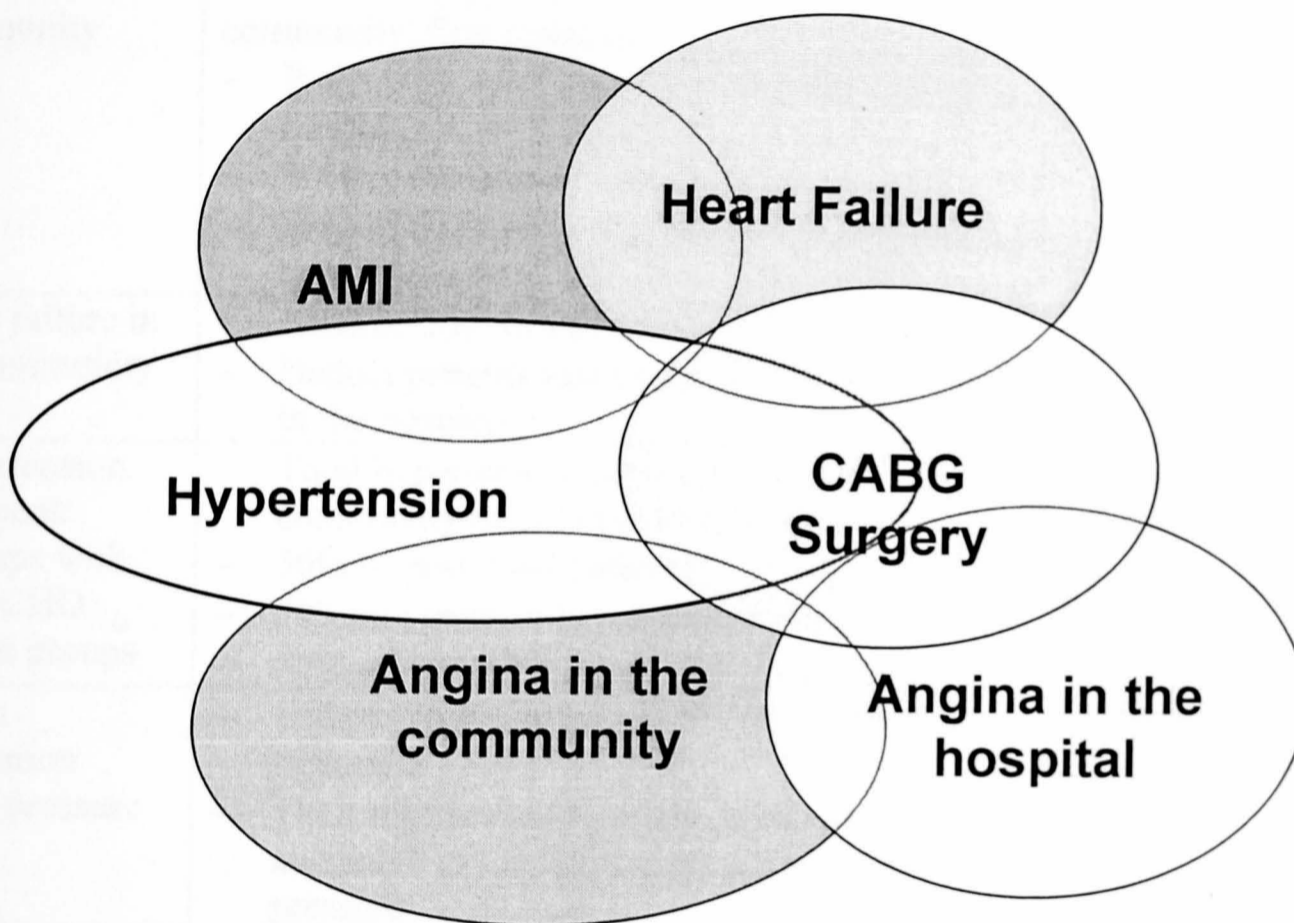


Therefore, to avoid double counting, potential overlaps between different groups of patients were identified and appropriate adjustments were made by subtracting one group from another. For instance, I subtracted the number of severe heart failure patients treated in hospital from the total number of heart failure patients in the community (because community heart failure patients could be admitted to hospital on one or more occasions).

A comprehensive list of overlap assumptions is presented in *Box 8.4.*

**Box 8.4 Assumptions and overlap adjustments used in IMPACT Model.**

| Treatment category | Assumptions and Overlap Adjustments | Justification |
|---|---|---|
| PTCA patients progressing to CABG surgery | – PTCA numbers multiplied by 0.8, assuming that 20% of PTCA go to CABG | Martin (2002)[327] |
| Efficacy of PTCA in Angina | - Assumed equivalent to CABG surgery for two vessel disease (maximum estimate), or equal to medical therapy (minimum estimate) | Sculpher (1994)[328] Folland (1997)[329] Yusuf (1994)[330] |
| Angina in the community | From the total patient numbers with angina in the community, first deducted: <br> – Patients already treated for unstable angina in hospital, <br> – 50% of those receiving CABG for angina, <br> – 50% of those receiving secondary prevention post AMI/post CABG/Post Angioplasty, | Capewell (2000)[143] |
| Heart failure in the community | – Assume 50% of heart failure is due to CHD <br> – Deduct patients treated for severe heart failure in the hospital | Fox (2001)[174] |
| Hypertension treatment: overlaps with other CHD patient groups | – Total hypertensive patient numbers in community calculated, then deduct: <br> – 50% of post AMI patients <br> – 50% of community angina patients <br> – 50% of community heart failure patients | Health Survey for England 1998[48] |
| Fall in population blood pressure | – Estimate the number of DPPs by hypertension treatment <br> – Then subtract this from the total DPPs attributed to the fall in population blood pressure | Capewell (1999)[4] Capewell (2000)[5] |
| Post MI patients | – Assume 50% overlap between post-MI and post-CABG patients | Capewell (2000)[5] |

## Patient compliance and adherence

Low compliance to prescribed medical interventions is a complex problem especially for patients with chronic diseases. In this model, compliance, the proportion of treated patients actually taking therapeutically effective levels of medication, was assumed to be 100% in hospital patients (because of their continuous supervision by health care staff), 50% in asymptomatic community patients (on the basis of available evidence[331]) and 75% in symptomatic community patients (as a value intermediate between 50% and 100%). Each assumption was subsequently tested in a sensitivity analysis, as described later in this chapter.

## Deaths prevented or postponed by therapies in 1981

A number of effective therapies were already in limited use in 1981. These included CABG surgery, cardiopulmonary resuscitation, beta-blockers for acute myocardial infarction, diuretics for acute left ventricular heart failure, and therapy for moderate and severe hypertension (defined as a diastolic blood pressure >105mmHg). Precise patient data for some of these interventions, including CABG, and eligible hypertensives, were available from the data sources detailed below. Others, such as beta-blocker use for post MI patients and heart failure treatment in hospital and in the community were estimated after consultation with cardiologists in practice in 1981. Again, each assumption was subsequently tested in a sensitivity analysis.

## Risk factors included in the model

The review of CHD epidemiology in *Chapter 2*, identified and discussed the key risk factors for CHD. The original Scottish IMPACT only considered the major risk factors, smoking, cholesterol and blood pressure. These were retained in the IMPACT Model for England and Wales, and attempts were made to incorporate additional risk factors such as diabetes, obesity, physical activity and deprivation.

As I discussed in *Chapter 2,* diabetes is an independent risk factor for CHD[21;42] and it is estimated that up to 80% of adult diabetic patients die of CVD, and 75% of these deaths are caused by CHD[45]. For modelling purpose, diabetes trend data was available from various studies and surveys in England and Wales, although with some limitations.

Obesity is also found to be a significant independent risk factor for CHD incidence[50;51] and data on obesity trend was available from national surveys.

Physical inactivity is associated with at least a twofold increase in CHD risk[52]. Although adjusting for other cardiovascular risk factors weakens this association, the beneficial effect of physical activity remains statistically significant[53].

CHD showed a strong social class gradient. The death rate from CHD is approximately 3 times higher among unskilled manual men of working age than among professional men[81]. Data on deprivation and household income were available from routine statistics in the UK[305;332].

While inclusion of a number of other risk factors were considered desirable, pilot work demonstrated the lack of reliable population-based data in 1981, or 2000 or both eg low birth weight for foetal origins of disease. However, the model still included all the main risk factors which together have been generally considered shown to explain at least 75% of CHD risk[333].

## Calculating the mortality benefits from changes in specific risk factors

For risk factor changes, the model employs regression ($\beta$) coefficients obtained from large cohort studies and MONICA analyses. Each $\beta$ coefficient quantifies the independent relationship between population change in a specific CHD risk factor, (such as smoking, cholesterol, or blood pressure) and the consequent change in population CHD mortality rate, having adjusted for all other factors considered in that particular analysis. These coefficients were reviewed and summarised in *Box 8.12*.

It has been shown in several studies that the association between blood pressure and CHD is continuous and that a threshold was difficult to detect [24;27]. Similar findings apply to serum total cholesterol levels and CHD risk. A $\beta$ **coefficient** is therefore very appropriate to quantify the population mortality impact of change in each specific risk factor.

The **population attributable risk fraction** method offers an alternative approach when a) there is a threshold or b) there are insufficient data to generate a reliable $\beta$ coefficient (for instance diabetes, obesity, activity and deprivation).

The $\beta$ coefficient approach is preferable for several reasons. Firstly, it is usually more stable across populations, particularly when based on a meta-analysis. Secondly, it usually involves a more reliable adjustment for other factors in a multi-variate analysis. Thirdly, PARs may overestimate achievable impact from a risk factor change (they are often based on RRs obtained from a dichotomised risk factor and population prevalence). Fourthly, the RR of a risk factor is very sensitive to how many other risk factors were included or excluded in the original statistical model[334]. For instance, the PAR quoted for physical inactivity can range from less than 10%[335]up to 37%[336].

The DPPs between 1981 and 2000 by the fall in each risk factor was then calculated as the product of three variables:

*CHD deaths in that group in 1981 base year X relative risk factor decline X $\beta$ coefficient*

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An example of this calculation is given below:

**Box 8.5 Example of mortality fall estimation attributable to change in population risk factor (smoking).**

*Mortality fall due to reduction in smoking prevalence in women aged 55-64:*

In England and Wales smoking prevalence in women aged 55-64 fell from 39% to 23% between 1981-2000, an absolute reduction of 16%, and a relative reduction of **41%, (16/39)**.

Pooling of studies from Finland, Iceland and elsewhere[187;192;337] produced a β coefficient value of **0.51**. (That is to say for every percent fall in smoking prevalence, the population CHD mortality would be expected to fall by 0.51%.)

The DPPs between 1981 and 2000 were then calculated as:

*CHD deaths in that group in 1981 base year X risk factor decline X β coefficient:*

Thus

$$5,555 \; X \; 41\% \; X \; 0.51 = 1,162 \; DPPs.$$

This calculation was then repeated

a) for men and women in each age group, and

b) for each risk factor

c) using maximum and minimum values in each group, to generate a sensitivity analysis

**Population Attributable Risk Fraction Method**

A separate method was used for obesity, diabetes, physical activity and socio-economic deprivation, because of the absence of suitable β coefficients[4;5]. Population attributable risk fraction (PAR) was calculated using the conventional formula *(Box 8.6).*

These risk factors were dichotomised and prevalences were obtained from population studies and surveys[48]. Obesity was defined as BMI>30 kg/m$^2$, diabetes was defined as clinically diagnosed diabetes[303], physical inactivity as moderate activity less than 3 times a week[48].

The number of CHD deaths attributable to each specific risk factor was calculated for 1981 and for 2000. The difference between the two values then represented the DPPs due to the change in that specific risk factor in the population.

An example of this calculation method is presented below in *Box 8.6.*

**Box 8.6 Example of CHD mortality change estimation due to change in diabetes prevalence**

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*Mortality change due to change in diabetes prevalence in men aged 75-84*

The number of CHD deaths attributable to diabetes in 1981 and in 2000 was calculated using the PAR fraction. This required estimates of **P**, diabetes prevalence in both years[48,303,304], and **RR**, the relative risk of diabetes for CHD mortality (obtained from the EPIC Study[338]), and the number of deaths from CHD in each year. The population attributable risk fraction was then calculated as;

$$\text{Prevalence x (Relative Risk -1)}$$

$$\text{PAR} = \frac{}{\text{(Prevalence x (Relative Risk -1)) +1}}$$

In England and Wales, the diabetes prevalence in men aged 75-84 was 4% in 1981 and 7% in 2000. Thus 12% of CHD deaths were attributable to diabetes in 1981 and 18% in 2000 respectively *(Table below)*. The number of actual deaths attributed to diabetes was then calculated: 2865 in 1981 and 3,916 in 2000. The difference between these (1,051) represented the change in the number of deaths attributable to the change in diabetes prevalence in the population between 1981 and 2000 (Table).

**Table. CHD deaths due to diabetes in 1981 and 2000 in men aged 75-84**

| | Diabetes Prevalence | | | CHD deaths | | PAR Fraction | | Deaths attributable to Diabetes | | Mortality Increase |
|---|---|---|---|---|---|---|---|---|---|---|
| Aged | 1981 | 2000 | RR | 1981 | 2000 | 1981 | 2000 | 1981 | 2000 | |
| 65 - 74 | a | b | c | d | e | $f^i$ | $g^{ii}$ | f*d | g*e | (f*d) – (g*e) |
| Best | 0.04 | 0.07 | 4.00 | 24205 | 21772 | 0.12 | 0.18 | 2865 | 3916 | -1051 |

i  f=(a x (c-1)/((a x (c-1))+1)),    ii  g=(b x (c-1)/((b x (c-1))+1))

This calculation was then repeated
a) for men and women in each age group,  b) for obesity, physical inactivity and deprivation and
c) using maximum and minimum values in each group, to generate a sensitivity analysis

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# Estimating deaths prevented or postponed by changes in deprivation using the PAR approach

Since satisfactory independent beta coefficients did not exist for deprivation, a population attributable risk (PAR) approach was used.

## Deriving the age-specific PARs for deprivation

No recent England and Wales data were available on the socio-economic gradients in CHD mortality. I therefore used the best available alternative. social gradients in AMI mortality rate per 100,000 in the Scottish men categorised by quintiles of deprivation measured as Carstairs deprivation score (Unpublished data from SLiDE Study)[339] *(Table 8.1).*

**Table 8.1 Social gradients in AMI mortality rates (per 100,000) in the Scottish population 1986-1995 (quintiles of deprivation in men)**

| | AGE GROUPS | | |
|---|---|---|---|
| **Deprivation Quintile** | **25-64 years** | **65-74 years** | **>75 years** |
| **Most affluent (1)** | 1.63 | 16.08 | 27.92 |
| **2** | 1.99 | 17.99 | 30.18 |
| **3** | 2.13 | 18.49 | 29.63 |
| **4** | 2.50 | 19.17 | 16.54 |
| **Most deprived (5)** | 2.81 | 20.07 | 29.52 |
| **Rate Ratio** | **1.72** | **1.25** | **1.06** |
| **PAR 5 v 1\*** | **0.126** | **0.047** | **0.011** |

*Prevalence of people in the fifth quintile of deprivation category is 20%.

Rate ratios estimated for most deprived quintile were 1.72, 1.25 and 1.06 in men aged 25-64, 65-74 and >75 respectively. These RRs were consistent with the RRs reported in other studies[340]. The crude PAR values for AMI mortality in the most deprived quintile compared with the most affluent were then calculated as: 0.126 for ages 25-64 years, 0.047 for 65-74 and 0.011 for men aged >75 years *(Table 8.1).*

*Changes in deprivation in England and Wales 1981-2000*

After considering and testing various options, the most dependable measure of change in deprivation was considered to be the data available on Final Household Income, adjusted for tax and benefits, and adjusted for inflation between 1981 and 2000[332]. Between 1981 and 2000, income in the most deprived quintile increased from £3,220 to £4,410, after adjusting for tax, benefits, and inflation *(Table 8.2)*.

**Table 8.2 Changes in household income 1981-2000, adjusted for tax, benefits and inflation**

| | Household income (£) | | | | | |
|---|---|---|---|---|---|---|
| | **1981** | **1999 Crude** | **Inflation adjustment** | **1999 adjusted** | **Absolute change indexed to 1981** | **% change** |
| **Quintiles** | **a** | **b** | **c** | **d=b/c** | **e=d-a** | **f=e/a** |
| **Most affluent** | 12,260 | 35,440 | 2.0 | 17,720 | 5,460 | 0.45 |
| **2** | 7,670 | 20,380 | 2.0 | 10,190 | 2,520 | 0.33 |
| **3** | 5,790 | 15,840 | 2.0 | 7,920 | 2,130 | 0.37 |
| **4** | 4,130 | 11,470 | 2.0 | 5,735 | 1,605 | 0.39 |
| **Most deprived** | **3,220** | **8,820** | **2.0** | **4,410** | **1,190** | **0.37** |

It was then (generously) assumed that reduction in deprivation was equal to increase in household income.

***Estimating the number of CHD deaths prevented or postponed by improvement in deprivation***

31,632 CHD deaths occurred in men aged 65-74 in 1981 *(Appendix 7)*. If the PAR is 0.038, then approximately 1,195 of these deaths could be attributable to being in the lowest deprivation quintile (0.038 x 31,632), *(Table 8.3)*.

Thus, approximately 442 deaths were prevented or postponed by a 37% improvement in income deprivation 1981-2000 *(Table 8.3)*.

**Table 8.3 Deaths prevented or postponed by improvements in deprivation, using PAR methodology**

|  | CHD deaths 1981 | Attributabl e fraction (PAR) | CHD deaths attributable to deprivation in 1981 | Relative reduction in deprivation | Mortality Reduction 1981/2000 |
|---|---|---|---|---|---|
|  | a | b | (a x b) | c | (a x b x c) |
| Men, aged 65-74 | 31,632 | 0.038 | 1,195 | 0.37 | 442 |

## Model Validation: Comparison with observed mortality falls

The model **estimate** for the total DPPs by all treatments plus all risk factor changes (or increase in the case of obesity, diabetes and physical inactivity) was summed and then compared with the **observed** falls in mortality for men and women in each specific age group. On an *a priori* basis, any shortfall in the overall model estimate was then formally attributed to other, unmeasured risk factors[3-5].

## Sensitivity Analyses

Because of the uncertainties surrounding many of the values, a multi-way sensitivity analysis was performed using Brigg's analysis of extremes method[231;341]. Minimum and maximum mortality reductions were generated for therapeutic effectiveness, using 95% confidence intervals for relative risk obtained from the most recent meta-analyses or large randomised controlled trials and the minimum and maximum plausible values for the remaining key parameters: Patient numbers, treatment uptake and adherence were based on the quality of the available data: eligible patient numbers $\pm$ 10%[196;201], treatment uptake $\pm$ 50%, and compliance $\pm$30%[331]. Corresponding sensitivity analyses were constructed for risk factors, the key parameters being the $\beta$ coefficient, relative risk, change in risk factor and CHD death numbers in base year.

Illustrative examples of sensitivity analyses and calculations are shown in the *Box 8.7:*

**Box 8.7 Example of sensitivity analysis for benefits from treatments given to CHD patients.**

*Sensitivity analysis for mortality reduction estimation for men aged 55-64 given aspirin for acute myocardial infarction:*

In the ATT meta analysis. aspirin reduced relative mortality in men with acute myocardial infarction by 15%[160]. In England and Wales in 2000. 10.699 men aged 55-64 were eligible, and 95% were given aspirin[289]. One year case fatality in men aged 55-64 admitted with an acute myocardial infarction was approximately 17%[143].

The DPPs for at least a year were therefore calculated as:

*Patient numbers x  treatment uptake x relative mortality reduction x one-year case fatality = 10,699 x 95% x 15% X 17% = 259 DPPs.*

| | Patient numbers | Treatment Uptake | Relative Mortality reduction | One year case fatality | DPPs |
|---|---|---|---|---|---|
| | a | b | c | d | (a x b x cxd) |
| **Best Estimate** | 10,699 | 0.95 | 15% | 17% | 259 |
| Minimum estimate | 9,629 | 0.48 | 11% | 14% | 71 |
| Maximum estimate | 11,769 | 0.99 | 19% | 22% | 487 |

This may be described as a "robust" approach for two reasons.

a) maximum and minimum values for each variable were deliberately forced to provide a wider range rather than a narrower one. eg relative mortality reduction $\pm20\%$ rather than say. $\pm10\%$.

b) the resulting product. for instance the minimum estimate. was generated by assuming that the lowest feasible values all occurred at the same time, a most unlikely situation.

## 8.2 Identification and assessment of relevant data for IMPACT Model

In *Chapter 7*, I presented and evaluated the CHD data sources in the UK. The review showed that available information on CHD in the UK is frequently patchy, obsolete or not available. Although the data are scarce with a good assessment of data quality and assumptions or extrapolations they might still be used for modelling. In this section I would like to present how I identified and assessed the data used for IMPACT Model.

To build the IMPACT Model a wide range of data was needed from many different sources. Information on population, demographic changes, mortality and myocardial infarction incidence was principally obtained from routine health statistics from the Office for National Statistics (ONS) and the British Heart Foundation's Annual CHD Statistics[2]. The number of patients admitted to hospital with myocardial infarction, angina and heart failure was obtained from Hospital Episode Statistics (HES). Patients undergoing cardio-pulmonary resuscitation (CPR) in the community or in hospital were enumerated from various surveys. Information on patients undergoing CABG surgery and angioplasty came from the United Kingdom Cardiac Surgical Register and the British Cardiovascular Intervention Society's Audit returns respectively[197;198]. Surviving patients eligible for secondary prevention therapies after myocardial infarction, CABG surgery or angioplasty were calculated using routine statistics and revascularisation registers *(Box 8.8)*.

The number of patients in the community with treated or untreated hypertension or angina was calculated using the 1998 Health Survey for England and the British Regional Heart Study. The number of treated and untreated heart failure patients in the community was obtained from General Practice returns and survey data *(Box 8.8)*.

**Box 8.8 Population and patient data sources for England and Wales, 1981-2000.**

| Information | Source |
|---|---|
| **Population (1981-2000)**<br><br>**Deaths by age and sex (1981-2000)**<br>**CHD mortality rates** | Office for National Statistics[195,266,277,278] and British Heart Foundation Annual CHD Statistics[2]. |
| **Acute myocardial infarction patients** | Hospital Episode Statistics(HES)[196]<br>British Heart Foundation Annual CHD Statistics[2]. |
| **CABG surgery patients** | UK Society for Cardiothoracic Surgeons of Great Britain and Ireland's web site (http://www.scts.org/doc/2102)[197]. Figures for England and Wales obtained by deducting numbers for Scotland and Ireland from UK total. |
| **Angioplasty patients** | British Cardiovascular Intervention Society's web site http://www.bcis.org.uk/audit/Bcis00.ppt. |
| **Patient numbers eligible for secondary prevention** | AMI survivors from Hospital Episode Statistics (HES)[196] plus SLiDE[143]. CABG and angioplasty patients from websites above. |
| **Angina patients admitted to hospital categorised as a) emergencies or b) elective** | Hospital Episode Statistics 1999-2000 (http://www.doh.gov.uk/hes/index.html)[196]. |
| **Angina patients in the community** | Prevalence of 'ever experienced angina' from Health Survey for England 1998[48], and British Regional Heart Study[279]. |
| **Heart failure patients admitted to hospital** | Hospital Episode Statistics 1999-2000 (http://www.doh.gov.uk/hes/index.html)[196] |
| **Heart failure patients in the community** | Prevalence from Key Health Statistics from General Practice 1998 report[201]and Stewart et al[286]. |

*Information on treatment prescription and uptake* was obtained from various national and local clinical audits and surveys *(Box 8.9)*.

**Box 8.9 Medical and surgical treatments included in the model: data sources for treatment uptake levels**

| TREATMENTS | Treatment Uptake in 2000 (average) | Source (year) |
|---|---|---|
| **ACUTE MYOCARDIAL INFARCTION** | | |
| **Cardio-pulmonary resuscitation** | | |
| **Community** | 46% | Julian (2002)[159], UKHAS-Norris, 1998[157] |
| **Hospital** | 99% | Julian (2002)[159], UKHAS-Norris, 1998[157] |
| | 88% | Sayer (2000)[342] |
| | 65% (aged <65) 57% (aged>65) | BRESUS- Tunstall-Pedoe (1992)[280] |
| **Thrombolysis** | 54% | UKHAS-Norris, 1998[157] |
| | 55% | Julian (2002)[159] |
| | 50% | French (1996)[343] |
| | 85% | Birkhead (1999)[284] |
| | *Age gradient* | Barakat (1999)[344] |
| **Aspirin** | 79% | UKHAS-Norris, 1998[157] |
| | 70% | Brown(1997)[270] |
| | 86% | French (1996)[343] |
| **Primary angioplasty** | <1% | David Cunningham, Myocardial Infarction National Audit Project (MINAP) (2002)- *personal communication* |
| **Intravenous beta-blockers** | <5% | Hardy (1999)[345], Owen (1998)[346], Woods (1989)[347] |
| | 6.6% | Ferguson (1999)[348] |
| | 32%- 56% | Brown(1997)[270] |
| | 19% | UKHAS-Norris (1998)[157] |
| **ACE inhibitors** | 19% | UKHAS-Norris (1998)[157] |
| | 6%-17% | Brown(1997)[270] |

| SECONDARY PREVENTION IN CHD PATIENTS | | |
|---|---|---|
| **Aspirin** | 61%-70% | Ryan (2001)[289] |
| | 81% | EUROASPIRE II (2001)[269] |
| | | |
| **Beta-blockers** | 44% | EUROASPIRE II (2001)[269] |
| | 80% | Myocardial Infarction National Audit Project (MINAP) (2002) |
| **ACE inhibitors** | 27% | EUROASPIRE II (2001)[269] |
| | 25% | Ryan (2001)[289] |
| | | |
| **Statins** | 20% | Reid (2002)[349] |
| | 36% | Whincup (2002)[350] |
| | 69% | EUROASPIRE II (2001)[269] |
| | 10%-60% Men 9%-35% Women | Ryan (2001)[289] |
| | 33% | British Regional Heart Study (2001)[351] |
| | 55%M, 40%F | DeWilde (2002)[352] |
| | 50% | Benner (2002)[353] |
| | 36% | Jackevicius (2002)[354] |
| | | |
| **Warfarin** | 4% | EUROASPIRE II (2001)[269] |
| | | |
| **Rehabilitation** | 14%- 23% post AMI 33%- 56% post CABG | Bethel (2001)[355] |
| | 34% | EUROASPIRE II (2001)[269] |
| CHRONIC ANGINA | | |
| **CABG surgery** | 100% | Society of Cardiothoracic Surgeons of Great Britain and Ireland[197], Martin (2002)[327] |
| **Angioplasty** | 100% | British Cardiac Intervention Society (2002)[198], Martin (2002)[327] |

| Aspirin in community | 50% | Ryan (2001)[289] |
| --- | --- | --- |
| Statins in community | 10% | Ryan (2001)[289] |
| | 23% | Whincup (2002)[350] |
| | 21% | BRHS (2001)[351] |
| | 35% and 25% | Reid (2002)[349] |

## UNSTABLE ANGINA

| Aspirin & Heparin | 60% | PRAIS Study- Collinson (2000)[356] |
| --- | --- | --- |
| Aspirin alone | 30% | PRAIS Study- Collinson (2000)[356] |
| Platelet glycoprotein IIB/IIIA inhibitors | 50% | PRAIS Study- Collinson (2000)[356] |

## HEART FAILURE IN THE HOSPITAL

| ACE inhibitors | 58% | Cleland (2002)[357] |
| --- | --- | --- |
| Beta-blockers | 28% | Cleland (2002)[357] |
| Spironolactone | 10% | Cleland (2002)[357] |
| Aspirin | 50% | Cleland (2002)[357] |
| Statins | 32% | Cleland (2002)[357] |

## HEART FAILURE IN THE COMMUNITY

| ACE inhibitors | 68% | Ellis (2001)[358] |
| --- | --- | --- |
| Beta-blockers | 17% | Cleland (2002)[357] |
| Spironolactone | 12% | Cleland (2002)[357] |
| Aspirin | 38% | Ellis (2001)[358] |
| Statins | 43% | Cleland (2002)[357] |

## HYPERTENSION TREATMENT

| | 59% | Health Survey for England 1998(2001)[130] |
| --- | --- | --- |

## STATINS FOR PRIMARY PREVENTION

| | 3% | Packham (2000)[359] |
| --- | --- | --- |

*Data on the efficacy of therapeutic interventions* were obtained from published randomised controlled trials, meta-analyses and cohort studies *(Box 8.10)*.

**Box 8.10 Clinical efficacy of interventions: relative risk reductions obtained from meta-analyses, and randomised controlled trials***

| TREATMENTS | Relative Risk Reduction | Source paper: First author (year) |
|---|---|---|
| **ACUTE MYOCARDIAL INFARCTION** | | |
| **Cardio-pulmonary resuscitation (CPR)** | | |
| **Community CPR** | 10% | Julian (2002)[159], BRESUS Study-Tunstall-Pedoe(1992)[280], Cobbe(1996)[360] |
| **Hospital CPR** | 30% aged <65 15% aged >65 | Julian (2002)[159], BRESUS Study- Tunstall-Pedoe(1992)[280] |
| **Thrombolysis** | 20%-30% | FTT, Collins(1996)[361] , Estess(2002)[362] |
| **Aspirin** | 15% | Antithrombotic Trialists' Collaboration (2002)[160] |
| **Primary angioplasty** | 30% | Cucherat (2000)[164] |
| **Beta-blockers** | 4% | Freemantle (1999)[166] |
| **ACE inhibitors** | 7% | Latini (1995)[165] |
| **SECONDARY PREVENTION IN CHD PATIENTS** | | |
| **Aspirin** | 15% | Antithrombotic Trialists' Collaboration (2002)[160] |
| **Beta-blockers** | 23% | Freemantle (1999)[166] |
| **ACE inhibitors** | 23% | Flather (2000)[167] |
| **Statins** | 29% | Pignone (2000)[34] |
| **Warfarin** | 15% | Lau (1992)[363] |
| **Rehabilitation** | 27% | Brown (2003)[324] |
| **CHRONIC ANGINA** | | |
| **CABG surgery** | 39% | Yusuf (1994)[330] |
| **Angioplasty** | 8% | Yusuf (1994)[330], Pocock (1995)[152], Folland (1997)[329] |
| **Aspirin** | 15% | Antithrombotic Trialists' Collaboration(2002)[160] |
| **Statins** | 29% | Pignone (2000)[34] |

| UNSTABLE ANGINA | | |
|---|---|---|
| Aspirin alone | 15% | Antithrombotic Trialists' Collaboration (2002)[160] |
| Aspirin & Heparin | 27% | Oler (1996)[364] |
| Platelet glycoprotein IIB/IIIA inhibitors | 9% | Boersma(2002)[365] |
| HEART FAILURE IN HOSPITAL PATIENTS | | |
| ACE inhibitors | 26% | Flather (2000)[167] |
| Beta-blockers | 37% | Shibata (2001)[177] |
| Spironolactone | 30% | Pitt (1999)[176] |
| Aspirin | 15% | Antithrombotic Trialists' Collaboration (2002)[160] |
| Statins | 29% | Pignone (2000)[34] |
| HEART FAILURE IN THE COMMUNITY | | |
| ACE inhibitors | 26% | Flather (2000)[167] |
| Beta-blockers | 37% | Shibata (2001)[177] |
| Spironolactone | 41% | Pitt (1999)[176] |
| Aspirin | 15% | Antithrombotic Trialists' Collaboration (2002)[160] |
| Statins | 29% | Pignone (2000)[34] |
| HYPERTENSION TREATMENT | | |
| | 11% | Collins (1990)[366] |
| STATINS FOR PRIMARY PREVENTION | | |
| | 29% | Pignone (2000)[34] |

*Relative Risk calculated as 1- Odds Ratio

**Population risk factor trend data** were obtained mainly from The British Regional Heart Study, the General Household Survey, and the Health Survey for England *(Box 6.11)*.

**Box 8.11 Data sources on cardiovascular risk factors in the UK, 1981-2000.**

| Cardiovascular Risk factors | Source | |
|---|---|---|
| Information | Initial Year (1981) | Most Recent Year (2000) |
| Smoking prevalence | General Household Survey 1980[273] | General Household Survey 2000[200] |
| Cholesterol | British Regional Heart Study[272] | Health Survey for England 1994 and 1998[48]. Glasgow MONICA and Belfast MONICA trends 1985-1995 also available for comparison[156] |
| Population blood pressure | The Dietary and Nutritional Survey of British Adults[295] and British Regional Heart Study[272] | Health Survey for England 1998[48] |
| Obesity | The Heights and Weights of Adults in Great Britain[297] | Health Survey for England 1998[48] |
| Physical activity | British Regional Heart Study[272] | Allied Dunbar Survey 1990[299], Department of Transport's Transport Statistics for Great Britain[298] |
| Diabetes | Poole Diabetes Study[303] | Health Survey for England 98[48], General Practice Research Database[304] |
| Deprivation | Trends in Household Income[332] | Trends in Household Income[332] |

In general data sources provided necessary information for modelling with some limitations. These limitations were discussed in detail in *Chapter 7*.

**Data on the mortality reduction from specific population cardiovascular risk factor changes: β coefficients**

These were obtained from published randomised controlled trials, meta-analyses and cohort studies. A range of different coefficients describing the relationship between each separate risk factor and CHD mortality were presented below *(Box 8.12 and Box 8.13)*. These coefficients represent % change in CHD mortality by 1 % change in mean population risk factors.

**Box 8.12 Estimated β coefficients from multiple regression analyses quantifying the relationship between changes in population mean risk factors and changes in CHD mortality for men aged under 65.**

| Study | β Coefficients | | |
|---|---|---|---|
| | **Smoking** | **Cholesterol** | **Blood Pressure (diastolic)** |
| Sigfusson 1991[337] | **0.51** | 2.22 | 1.06 |
| Law *et al.* 1994[32] | - | **1.9 – 5.4*** | |
| Vartiainen *et al.* 1994[192] | 0.70 | 2.00 | **1.67** |
| MONICA, 2000[125] | 0.73 | 1.31 | 0.53 |
| Collins/MacMahon, 1990[24;366] | - | - | 2.08 |
| Seven Countries[367;368] | - | 2.10 | 2.09 |
| **Our 'best' estimates** | **0.51** | **2.46** | **1.67** |
| Minimum | 0.40 | 1.31 | 0.53 |
| Maximum | 0.73 | 3.00 | 2.09 |

*adjusted for regression dilution bias

The MONICA study considered the impact of changes in risk factors on changes in CHD mortality at a *population* level. However, the MONICA coefficients have been criticised for 'ecological bias' and may underestimate the relationship between changes in risk factors and population trends in CHD mortality. This is because:

1) those who do not respond to risk factor surveys may be at higher risk than attendees, and a decreasing response rate to MONICA surveys was observed over the course of the study[125].

2) the major outcome from the MONICA study was all coronary events, not just CHD mortality, which may slightly dilute the β coefficients obtained.

3) MONICA coefficients do not account for possible regression dilution bias; adjusted coefficients may be as much as 60% higher[32].

4) The principal MONICA estimates made no allowance for a possible lag time between changes in the risk factor levels and changes in population CHD mortality[125].

The MONICA coefficients for cholesterol and diastolic blood pressure are generally lower than from other sources[192;368] and have thus been used in our model as minimum estimates using the data for males only. In many MONICA centres, the number of events among females was too small to obtain reliable estimates, and the smoking coefficient appeared particularly anomalous.

The coefficients derived from meta-analyses and the largest cohort studies were therefore regarded in our model as the best estimates. The best estimates were taken from the Sigfusson study in Iceland for smoking[337], from the Law meta-analysis for cholesterol[32] and Finland for blood pressure[192]. Maximum estimates for cholesterol were taken from Law *et al*[32], for smoking from MONICA[125] and for blood pressure from the Seven Countries[367;368].

Minimum estimates for cholesterol and blood pressure came from MONICA Study[125]. The coefficients were reduced in older age groups to reflect good epidemiological evidence suggesting that relative risk is attenuated by age[32].

In the sensitivity analyses, the England and Wales IMPACT model proved to be stable with a range of beta coefficients.

There were no suitable Beta coefficients describing the individual relationships between obesity, diabetes, physical inactivity, and deprivation with CHD mortality. Relative Risks were therefore taken from the largest and most recent studies available *(Box 6.13)*.

**Box 8.13 Relative risks for obesity, diabetes, physical inactivity and deprivation and coronary heart disease mortality *(Best, minimum and maximum estimates)*.**

| | Relative Risk (95% Confidence Interval) | | | |
|---|---|---|---|---|
| | **Obesity**<br>(BMI>29kg/m$^2$) | **Diabetes**<br>(clinically diagnosed)[303] | **Physical activity**<br>(moderate activity 3 times a week)[48] | **Deprivation**<br>(Carstairs score, most deprived 5$^{th}$ quintile, based on SliDE data)[339] |
| **Men** | Stevens (1998)[369], RRs ranged from 1.57 to 2.33$^#$ by age groups. | Khaw (2001)[338], RR=4.24*(1.92-9.35) | Shaper (1991)[53] RR=0.50** (0.2-0.8) | Smith (1998), Renfrew and Paisley Study[340]. RR=1.24(1.03-1.49)$^+$ |
| **Women** | Stevens (1998)[369], RRs ranged from 1.00 to 2.24$^#$ by age groups. Willett (1995)[50] RR=3.56 (2.96-4.29) | Female RRs x 1.5 higher than male, (Members of the British Diabetic Association Study)[370]. | Lee (2001)[371], RR=0.55*** (0.37-0.82) | Smith (1998), Renfrew and Paisley Study[340]. RR=1.44 (1.15-1.80)$^+$ |

$^#$ Adjusted for age, education, physical activity, alcohol consumption.

* Adjusted for age, serum cholesterol, systolic blood pressure, smoking, BMI, MI or stroke history.

** Adjusted for BMI, social class, smoking, total cholesterol, HDL cholesterol, FEV1, breathlessness and heart rate.

***Adjusted for age, treatment, smoking, alcohol, fat consumption, fibre, fruits and vegetables, use of hormones, postmenopausal status, parental history of MI at an early age.

$^+$ Adjusted for age, blood pressure, cholesterol, BMI, FEV1 score, smoking, angina, ECG ischeamia, bronchitis and social class.

In this chapter, I have described the IMPACT Model and methodology. In the next chapter, I will describe how I then attempted to use the IMPACT Model to analyse the recent CHD mortality trends in England and Wales.

# 9 EXPLAINING THE DECLINE IN CHD MORTALITY IN ENGLAND AND WALES BETWEEN 1981 AND 2000

Having described the IMPACT Model and methodology in the previous chapter, I will now describe how I then examined the CHD mortality trends in England and Wales between 1981 and 2000.

## 9.1 Introduction

Since the 1970s, CHD mortality rates have halved in most industrialised countries but somewhat less in the UK[2]. Explanations for the mortality falls remain controversial[156]. Many authors credit the increasingly widespread use of effective therapies such as thrombolysis, aspirin, ACE-inhibitors, statins and coronary artery bypass surgery[372;373]. Others highlight reductions in major cardiovascular risk factors such as smoking, cholesterol and blood pressure[119;156]. While both components are probably important, answering this complex question appears difficult.

Some researchers have therefore used models of varying degrees of sophistication to try and explain the observed declines in CHD mortality[3]. The majority consistently suggest that risk factor improvements explain more of the mortality decline than do treatments. For example, it has been estimated that the proportion of mortality decline attributable to risk factor reductions was 57% in the USA between 1980 and 1990[233], 60% in Auckland, New Zealand between 1974 and 1981[194] and 52% between 1982 and 1993[5], and 60% in Scotland between 1975 and 1994[4]. Since then, however, many effective therapies have been introduced[148].

A better understanding of the CHD mortality fall in Britain and other countries is clearly essential, both to predict future trends and to clarify policy options for CHD prevention[148;374]. I have therefore examined how much of the fall in CHD mortality in England and Wales between 1981 and 2000 can be attributed to 'evidence based' medical and surgical treatments, and how much to changes in major cardiovascular risk factors.

## 9.2 Methods

In the cell-based IMPACT mortality model, described in *Chapter 8*, I identified and incorporated data for men and women aged 25 to 84 years in England and Wales detailing; a) CHD patient numbers, b) uptake of specific medical and surgical treatments, c) population trends in major cardiovascular risk factors (smoking, total cholesterol, hypertension, obesity, diabetes, physical activity and socio-economic deprivation), d) effectiveness of specific cardiological treatments, and e) effectiveness of specific risk factor reductions.

The methods used and identification and assessment of relevant data for English IMPACT Model were presented in *Chapters 7 and 8* therefore only results and discussion will be presented here.

## 9.3 Results

In England and Wales between 1981 and 2000, CHD mortality rates fell by 62% in men and 45% in women aged 25-84. There were 68,230 fewer CHD deaths than expected from baseline mortality rates in 1981 *(Appendix 7)*.

**Medical and surgical treatments *(Table 9.1)***

Medical and surgical treatments together prevented or postponed approximately 25,765 deaths (minimum estimate 15,390, maximum estimate 45,265). This represented approximately 42% of the total CHD mortality fall, after allowing for treatments given in 1981 *(Figure 9.1)*. Substantial contributions came from treatments in individuals for secondary prevention (11.2%), heart failure (12.6%), acute myocardial infarction (7.7%), angina (7.0%), and hypertension (3.1%).

Approximately 4,740 deaths were prevented or postponed by immediate treatments for acute myocardial infarction; the biggest contributions came from cardiopulmonary resuscitation, aspirin and thrombolysis. CABG surgery and PTCA were estimated to prevent or postpone approximately 1,935 and 559 deaths respectively, accounting for 3.8% of the total *(Table 9.1)*.

*Adjustment for polypharmacy in individual patients*

Applying the Mant and Hicks equation to the uptake of multiple medications in individual patients would reduce the total DPPs (25,765) by approximately 2,118 (395 in acute myocardial infarction, 800 in heart failure patients and 923 in secondary prevention) *(Appendix 9)*.

Figure 9.1 Coronary heart disease deaths prevented or postponed by treatments and risk factor changes in the England and Wales population between 1981 and 2000.
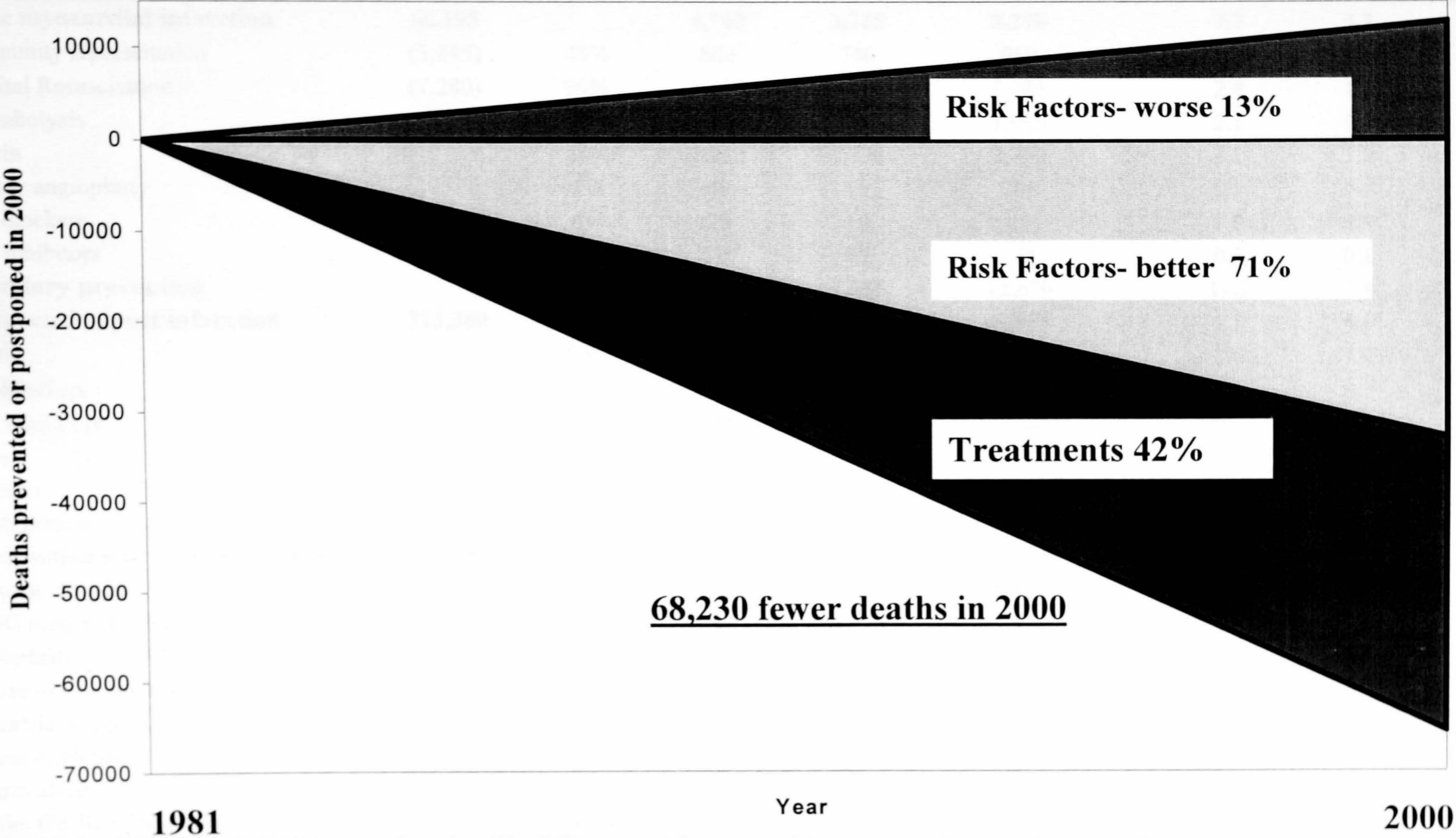
## Table 9.1 Deaths prevented or postponed (DPP) by medical and surgical treatments in England and Wales in 2000.

| TREATMENTS | Patients eligible | Treatment uptake (%)* | Deaths prevented or postponed | | | Proportion of overall DPPs (%) | | |
|---|---|---|---|---|---|---|---|---|
| | | | Best Estimate | Minimum estimate | Maximum estimate | Best Estimate | Minimum estimate | Maximum estimate |
| **Acute myocardial infarction** | **66,195** | | **4,740** | **3,225** | **8,290** | **7.7** | **5.2** | **13.5** |
| Community Resuscitation | (3,045) | 48% | 800 | 740 | 960 | 1.3 | 1.2 | 1.6 |
| Hospital Resuscitation | (7,280) | 99% | 1,455 | 680 | 2,185 | 2.4 | 1.1 | 3.5 |
| Thrombolysis | | 46% | 1,320 | 600 | 1,995 | 2.1 | 1.0 | 3.2 |
| Aspirin | | 94% | 1,950 | 1,130 | 2,780 | 3.2 | 1.8 | 4.5 |
| Primary angioplasty | | 1% | 40 | 15 | 205 | 0.1 | 0.0 | 0.3 |
| Beta-blockers | | 4% | 20 | 10 | 40 | 0.0 | 0.0 | 0.1 |
| ACE inhibitors | | 19% | 170 | 45 | 125 | 0.3 | 0.1 | 0.2 |
| **Secondary prevention** | | | **6,900** | **4,585** | **12,670** | **11.2** | **7.4** | **20.6** |
| **2' prevention post infarction** | **313,380** | | **3,844** | **2,850** | **5,060** | **6.2** | **4.6** | **8.2** |
| Aspirin | | 56% | 1,240 | 640 | 1,990 | 2.0 | 1.0 | 3.2 |
| Beta-blockers | | 34% | 970 | 570 | 1,635 | 1.6 | 0.9 | 2.7 |
| ACE inhibitors | | 19% | 440 | 335 | 1,440 | 0.7 | 0.5 | 2.3 |
| Statins | | 25% | 460 | 430 | 1,340 | 0.7 | 0.7 | 2.2 |
| Warfarin | | 4% | 100 | 60 | 235 | 0.2 | 0.1 | 0.4 |
| Rehabilitation | | 23% | 675 | 305 | 1,230 | 1.1 | 0.5 | 2.0 |
| **2' prevention post revascularisation** | **315,680** | | **3,055** | **1,735** | **7,610** | **5.0** | **2.8** | **12.4** |
| **Chronic Angina** | | | **3,425** | **1,905** | **5,890** | **5.6** | **3.1** | **9.6** |
| CABG surgery (1990-2000) | 187,415 | 100% | 1,935 | 1,125 | 2,375 | 3.0 | 1.8 | 3.8 |
| Angioplasty (1990-2000) | 112,405 | 100% | 560 | 160 | 815 | 0.8 | 0.3 | 1.3 |
| Aspirin in Community | 1,763,635 | 55% | 1,105 | 625 | 2,115 | 1.6 | 1.0 | 3.4 |
| **Unstable Angina** | **67,375** | | **910** | **620** | **1,620** | **1.5** | **1.0** | **2.6** |
| Aspirin & Heparin | | 59% | 465 | 335 | 720 | 0.8 | 0.5 | 1.2 |
| Aspirin alone | | 30% | 235 | 125 | 655 | 0.4 | 0.2 | 1.1 |
| Platelet IIB/IIIA Inhibitors | | 48% | 210 | 160 | 245 | 0.3 | 0.3 | 0.4 |

| TREATMENTS | Patients eligible | Treatment uptake | Deaths prevented or postponed | | | Proportion of overall DPPs (%) | | |
|---|---|---|---|---|---|---|---|---|
| Table 9.1 (Continued) | | (%)* | Best Estimate | Minimum estimate | Maximum estimate | Best Estimate | Minimum estimate | Maximum estimate |
| Heart failure- total | | | 7,760 | 4,162 | 13,596 | 12.6 | 6.8 | 22.1 |
| Heart failure- in hospital | 34,690 | | 4,755 | 2,295 | 7,680 | 7.6 | 3.7 | 12.5 |
| ACE inhibitors | | 62% | 1,850 | 635 | 2,625 | 3.0 | 1.0 | 4.3 |
| Beta-blockers | | 31% | 1,280 | 745 | 2,270 | 2.1 | 1.2 | 3.7 |
| Spironolactone | | 10% | 350 | 220 | 675 | 0.6 | 0.4 | 1.1 |
| Aspirin | | 50% | 870 | 405 | 1,535 | 1.4 | 0.7 | 2.5 |
| Statins | | 21% | 410 | 290 | 575 | 0.7 | 0.5 | 0.9 |
| Community heart failure | 242,090 | | 3,210 | 1,940 | 6,320 | 5.0 | 3.1 | 10.3 |
| ACE inhibitors** | | 56% | 1,535 | 1,020 | 3,050 | 2.5 | 1.7 | 4.9 |
| Beta-blockers** | | 15% | 550 | 330 | 885 | 0.9 | 0.5 | 1.4 |
| Spironolactone | | 10% | 205 | 125 | 415 | 0.3 | 0.2 | 0.7 |
| Aspirin | | 29% | 585 | 350 | 1,480 | 1.0 | 0.6 | 2.4 |
| Statins** | | 17% | 335 | 110 | 490 | 0.5 | 0.2 | 0.8 |
| Hypertension Treatment | 13,352,870 | 53% | 1,890 | 840 | 2,785 | 3.1 | 0.0 | 4.5 |
| Statins for primary prevention | 7,630,760 | 3% | 145 | 45 | 410 | 0.2 | 0.0 | 0.7 |
| Total Treatment Effects- 2000 | | | 25,765 | 15,390 | 45,265 | 41.8 | 27.7 | 73.5 |

* Treatment uptake levels are weighted averages of age specific uptake levels  **Treatment efficacy for these groups was reduced by 25% assuming that only about 50% were on the optimal treatment dose.

**Major cardiovascular risk factors** *(Table 9.2)*

Changes in the major cardiovascular risk factors together produced a best estimate of 35,830 fewer deaths (minimum estimate 23,155, maximum 62,555) *(Table 9.2)*. This therefore accounted for some 58% of the total mortality fall between 1981 and 2000. The biggest contribution came from the reduction in smoking (48.2%), along with decreases in serum total cholesterol levels (9.4%), blood pressure (9.5%) and deprivation (3.5%) *(Table 9.2)*. These mortality reductions reflected a substantial decline in smoking prevalence and smaller reductions in mean blood pressure, total cholesterol and deprivation *(Table 9.2)*.

Adverse trends were seen for obesity, physical activity, and diabetes. They, together caused approximately 7,650 additional CHD deaths *(Table 9.2)*. The prevalence of obesity increased by 186%, resulting in an estimated additional 2,095 CHD deaths. Diabetes prevalence increased by 66% with approximately 2,890 additional CHD deaths, and indirect evidence suggested a 30% decrease in physical activity (with some 2,660 additional deaths *(Table 9.2)*.

**Table 9.2 Deaths prevented or postponed as a result of population risk factor changes in England and Wales 1981 and 2000.**

| RISK FACTORS | % Change in risk factor | Deaths prevented or postponed (number) | | | Proportion of overall DPPs (%) | | |
|---|---|---|---|---|---|---|---|
| | 1981-2000 | Best Estimate | Minimum estimate | Maximum estimate | Best Estimate | Minimum estimate | Maximum estimate |
| Smoking | -34.5% | **29,715** | 20,035 | 44,675 | **48.2%** | 32.5% | 65.5% |
| Population blood pressure | -7.7% | **5,865** | 4,245 | 15,470 | **9.5%** | 5.5% | 20.6% |
| Cholesterol | -4.2% | **5,770** | 3,930 | 12,100 | **9.4%** | 8.6% | 27.0% |
| Deprivation | -6.6% | **2,125** | 1,065 | 3,190 | **3.5%** | 1.7% | 5.2% |
| Physical activity | - 30.6% | **-2,660** | -1,490 | -3,460 | **-4.3%** | -2.4% | -5.6% |
| Obesity | +186.2% | **-2,095** | -1,340 | -2,585 | **-3.4%** | -2.2% | -4.2% |
| Diabetes | +65.6% | **-2,890** | -2,565 | -4,685 | **-4.7%** | -4.2% | -7.6% |
| Total risk factor effects | - | **35,830** | 23,155 | 62,555 | **58.2%** | 37.6% | 76.2% |

**Table 9.3 Percent contribution of men and women to total DPPs by age groups in England and Wales (1981–2000).**

|  | Total | 25-34 | 35-44 | 45-54 | 55-64 | 65-74 | 75-84 |
|---|---|---|---|---|---|---|---|
| **Men** | 70% | 89% | 87% | 85% | 77% | 64% | 65% |
| **Women** | 30% | 11% | 13% | 15% | 23% | 36% | 35% |
| **Men /Women Ratio** | 2.34 | 7.95 | 6.48 | 5.52 | 3.29 | 1.81 | 1.84 |
| **Total DPPs** | 61,595 | 185 | 1,510 | 6,625 | 13,750 | 21,065 | 18,460 |

In year 2000 most of the DPPs due to cardiac treatments and risk factors changes in England and Wales came from men (70% in men and 30% in women). In younger age groups 85% to 90% of the DPPs were from men. After the age of 65, the ratio of DPPs in men compared with women decreased below 2 *(Table 9.3)*.

**Table 9.4 Percent contribution of treatments and risk factor changes to total DPPs in men and women by age groups in England and Wales (1981-2000).**

| Men | | 25-34 | 35-44 | 45-54 | 55-64 | 65-74 | 75-84 |
|---|---|---|---|---|---|---|---|
| **Treatments** | 37% | 19% | 28% | 33% | 37% | 42% | 34% |
| **Risk factors** | 63% | 81% | 72% | 67% | 63% | 58% | 66% |
| **Total DPPs** | 43,155 | 165 | 1,310 | 5,610 | 10,545 | 13,555 | 11,970 |

| Women | | 25-34 | 35-44 | 45-54 | 55-64 | 65-74 | 75-84 |
|---|---|---|---|---|---|---|---|
| **Treatments** | 54% | 69% | 51% | 50% | 50% | 48% | 63% |
| **Risk factors** | 46% | 31% | 49% | 50% | 50% | 52% | 37% |
| **Total DPPs** | 18,445 | 20 | 200 | 1,015 | 3,205 | 7,510 | 6,490 |

In general, risk factor changes prevented or postponed more deaths in men compared with treatment effects (63% versus 37%). In women, the treatment effect was relatively greater, similar to risk factor changes in all age groups *(Table 9.4)*.

## Sensitivity Analyses, Validation and Model Fit

*Figure 9.2* demonstrates the results of the sensitivity analysis. The proportional contributions of specific treatments and risk factor changes to the overall fall in CHD mortality in England and Wales between 1981 and 2000 remained relatively consistent *(Figure 9.2)*. Thus, all secondary prevention treatments together accounted for approximately 11% of the total mortality fall of 68,230. The minimum contribution was 7% and the maximum 21%. This contribution therefore remained consistently larger than that for acute myocardial infarction or hypertension *(Figure 9.2)*.

The agreement between the **estimated** and **observed** mortality falls for men and women in each age group was generally good *(Table 9.5)*. Overall, the model accounted for 90% of the total mortality fall in England and Wales between 1981 and 2000, (96% in men and 79% in women). In general, the model estimates were close to the actual falls in men in all age groups. However, in women model fit less good , 79% overall and only 56% in women aged 75-84 years. As planned, the remaining 10% was attributed to other, unmeasured factors such as dietary changes and life-course effects.

**Table 9.5 Model validation: estimated versus observed changes in CHD deaths in England and Wales 1981-2000.**

| MEN | Age Group (years) | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | 25-34 | 35-44 | 45-54 | 55-64 | 65-74 | 75-84 | |
| Estimated fall in CHD deaths | 166 | 1,308 | 5,609 | 10,545 | 13,556 | 11,969 | 43,153 |
| Observed fall in CHD deaths | 168 | 1,314 | 5,571 | 10,685 | 15,342 | 11,740 | 44,822 |
| *Discrepancy* | *-3* | *-6* | *37* | *-140* | *-1,786* | *229* | *-1,669* |
| Model Fit: Estimated fall / Observed fall in CHD deaths | 98% | 100% | 101% | 99% | 88% | 102% | 96% |
| **WOMEN** | 25-34 | 35-44 | 45-54 | 55-64 | 65-74 | 75-84 | Total |
| Estimated fall in CHD deaths | 21 | 202 | 1,015 | 3,204 | 7,510 | 6,492 | 18,444 |
| Observed fall in CHD deaths | 28 | 155 | 998 | 3,054 | 7,479 | 11,695 | 23,409 |
| *Discrepancy* | *-7* | *47* | *17* | *150* | *31* | *-5,203* | *- 4965* |
| Model Fit: Estimated fall / Observed fall in CHD deaths | 76% | 130% | 102% | 105% | 100% | 56% | 79% |

**Figure 9.2 Proportional contributions of specific treatments and risk factor changes to the CHD mortality reduction in England and Wales, 1981-2000: Results of a sensitivity analysis.**

(■ Best estimate, - minimum and maximum estimates)
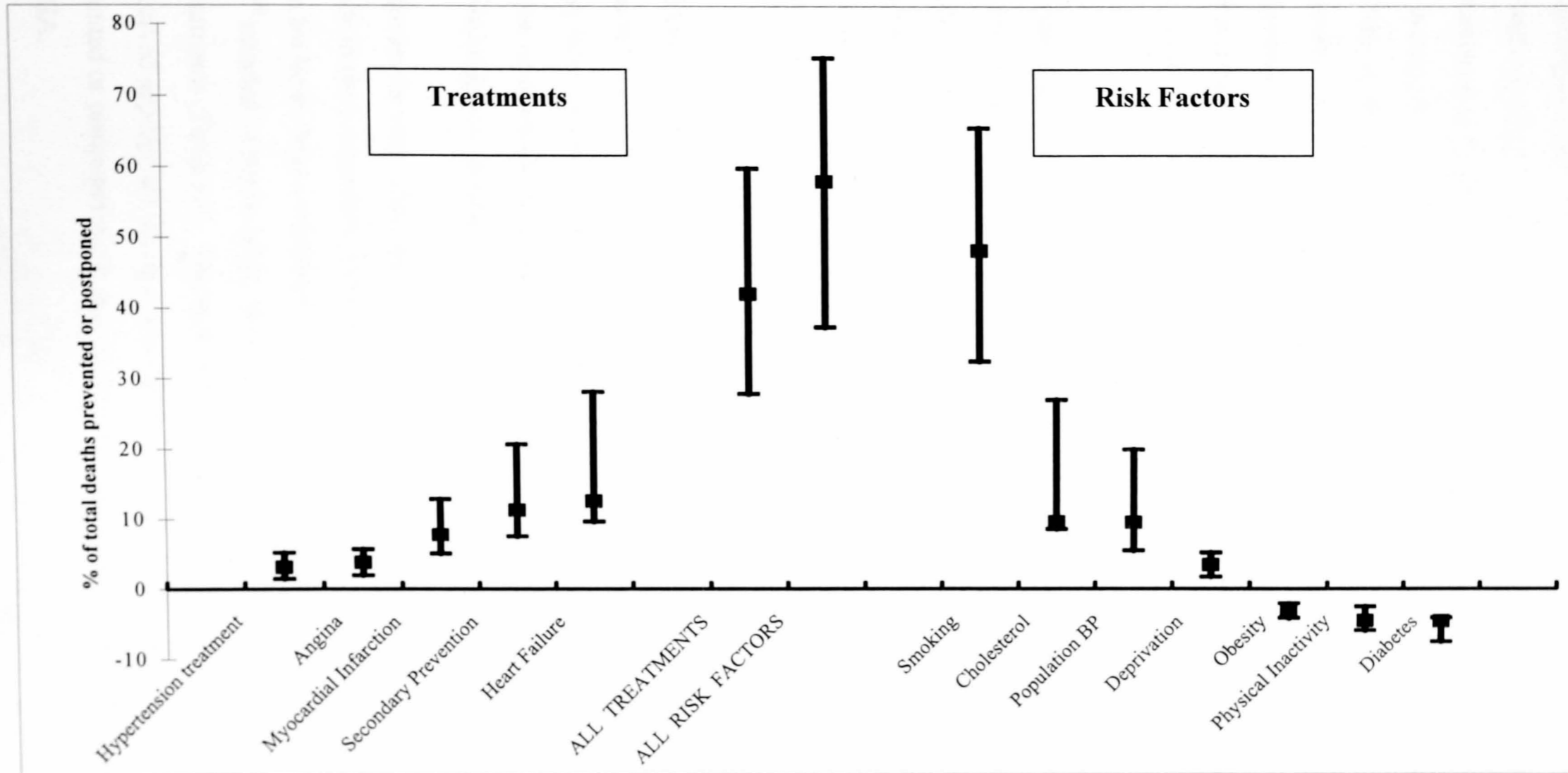
## 9.4 Interpretation

CHD mortality in England and Wales fell by more than half between 1981 and 2000. Approximately 40% of this fall was attributable to the combined effects of modern cardiological treatments and almost 60% to reduction in major risk factors, particularly smoking. This is consistent with the majority of other studies in the USA[193], Europe[251], Scotland[4], and New Zealand[5]. Although Hunink et al attributed 71% of the recent US decline to 'treatments', this exception was more apparent than real, and principally reflected a different categorisation of risk factor falls in individual patients with recognized CHD. In the entire US population, 50% of the CHD mortality decline was actually explained by risk factor reductions[233]. Furthermore, Hunink et al did not report on specific medical therapies[233].

Modern cardiological treatments together prevented or postponed approximately 26,000 deaths in 2000. Irrespective of whether best, minimum or maximum estimates were used, the most substantial contributions came from secondary prevention and heart failure treatments. Revascularisation from CABG surgery and angioplasty together accounted for only 4% of the total mortality fall, much as in the USA[375]. This is a disappointingly small contribution, particularly when considering the large financial and political resources being consumed[148;205].

Thrombolysis likewise only accounted for one quarter of the deaths prevented by initial treatments for acute myocardial infarction. This was much less than aspirin and cardiopulmonary resuscitation, as in other studies[159]. Furthermore, treating angina patients with aspirin in the community prevented almost twice as many deaths as treating unstable angina patients in hospitals, principally reflecting the larger numbers involved (Table 9.1).

Treatment uptake levels were often poor (Table 9.1). This was more apparent for heart failure treatments in the community. Even though there were approximately ten times more eligible patients for heart failure treatments in the community, low treatment levels and sub optimal doses[269] resulted in fewer deaths prevented or postponed compared with hospital heart failure treatments (Table 9.1). Earlier work suggested that if even 80% of eligible patients had received appropriate therapy, approximately 30,000 additional deaths might have been prevented or postponed each year in the UK[4], equivalent to 100,000 fewer deaths in the USA.

Reductions in the major risk factors between 1981 and 2000 accounted for approximately 36,000 fewer deaths in England and Wales in 2000. The biggest single contribution reflected a large fall in smoking prevalence, from 39% to 28% overall. In sensitivity analyses, the maximum estimate for smoking decline impact remained consistently greater than all treatment effects combined *(Figure 9.2)*. Almost 10% of the mortality fall came from a relatively small reduction (4.2%) in population total cholesterol level. This emphasises the large β coefficient of 1.9 –5.4[32], and highlights the potential gains from bigger reductions in population cholesterol. Other unquantified factors such as life-course effects, alcohol and other dietary improvements[55] accounted for approximately 10% of observed mortality reduction.

The adverse trends in obesity, diabetes and physical inactivity together contributed approximately 8,000 additional deaths in 2000. These cancelled out two decades of improvement in the fall of cholesterol levels. Furthermore, continuing deteriorations are expected[148;374;376].

Modelling studies have potential strengths and limitations. These points will be discussed in detail in the discussion section of this thesis.

In conclusion, over half the recent CHD mortality fall in England and Wales was attributed to reductions in major risk factors, and some forty percent to medical therapies.

In this chapter I focused on CHD mortality trends in England and Wales. In the next chapter, I will consider what these DPPs might mean in terms of the years of additional life gained.

# 10 LIFE-YEARS GAINED FROM CARDIOLOGICAL TREATMENTS AND POPULATION RISK FACTOR CHANGES IN ENGLAND AND WALES, BETWEEN 1981 AND 2000

In the last chapter, I focused on CHD mortality trends in England and Wales between 1981 and 2000. I will now attempt to estimate the years of additional life gained in 2000.

## 10.1 Introduction

Life expectancy at birth in England and Wales increased by 4.4 years in men and 3.2 years in women between 1981 and 2000[377]. Much of this has been attributed to reductions in CHD mortality rates, which have halved in two decades. Much of the CHD mortality decline is attributed to the widespread use of effective therapies such as thrombolysis, aspirin, ACE-inhibitors, statins and CABG[372]. However, reductions in major risk factors such as smoking, cholesterol and blood pressure[119] have also made substantial contributions[373].

As I presented in earlier chapters, the majority of studies consistently suggest that improvements in treatment explain less than half of the mortality decline[3-5;194;233;248]. However, most such analyses have simply concentrated on mortality rather than a gain in longevity. Therefore in this chapter I estimated the life-years gained (LYG) due to cardiological treatments and to changes in cardiovascular risk factor levels that occurred between 1981 and 2000 in England and Wales.

## 10.2 Methods

**Estimating the number of deaths prevented or postponed in England and Wales in 2000**

The number of DPPs in 2000 that could be attributed to improved cardiac treatment uptake and risk factor changes since 1981 was estimated using the IMPACT CHD mortality model[248]. The number of CHD DPPs by each treatment group and risk factor changes was estimated as described in methods section in *Chapter 8.*

# Median Survival Data

## *Medical and surgical treatments*

For each treatment category, median survival was obtained from the best available population-based data[143;144]. Most came from a retrospective cohort study of unselected patients. This is the only UK dataset routinely linking all hospital admission records and all mortality data for an entire population of 5.1 million since 1981[143;144]. Age-specific median survival values came principally from a large, unselected cohort of 117,718 patients admitted to hospital with a first acute myocardial infarction (AMI)[143] and all 66,547 patients with a first admission for heart failure[144]. The first study also provides long-term survival data in all AMI survivors, including those developing heart failure[143]. Case fatality in subsequent admissions was approximately twice that in first admissions [143]. Median survival estimates for patients with hypertension were based on the mortality (between 7% and 29% dependent on age and sex) observed in the Glasgow Blood Pressure Clinic Cohort[378]. Estimates of survival following CABG surgery were obtained from local sources[379], and a recent cohort study in Scotland[380]. Angioplasty for angina was assumed to have no additional survival benefit[152]. *Appendix 10 and 11* detail the estimates of median survival for each category and their sources.

## Deaths prevented or postponed by risk factor declines

Coronary atheroma generally begins early in life, symptomatic manifestations occur late and even then may go unrecognised. The deaths prevented by a risk factor reduction such as smoking cessation may therefore benefit an individual prior to or following the onset of symptomatic disease. Age-specific median survival in a patient with recognised CHD was assumed to be very similar to that in age-matched myocardial infarction survivors. Median survival in asymptomatic individuals was simply based on age specific life expectancy for the general population[377]. For the subjects with symptomatic but unrecognised CHD, median survival was assumed to lie midway between the values for myocardial infarction survivors[143] and the general population.

## Calculation of life-years gained

The number of LYG in 2000 in each ten-year age group, for men and women in each treatment category and for each risk factor change, was then estimated as the product of the

number of DPPs in England and Wales in 2000, and the estimated median survival for that group.

An example of calculation method is presented below:

*Men aged 65-74 given Beta-blockers for secondary prevention of myocardial infarction:*

In a meta analysis it was estimated that Beta-blockers reduced mortality in men with post myocardial infarction by 23%[166]. In England and Wales in 2000, 18,180 men aged 65-74 were eligible, 33% were given Beta-blockers[269] and compliance to treatment was assumed to be 65%[354]. One year case fatality in men aged 65-74 with post myocardial infarction was approximately 7%[143]. The DPPs for at least a year were therefore calculated as:

*Patient numbers x treatment uptake x compliance x relative mortality reduction x one-year case fatality = 18,180 x 33% x 65% x 23% x 7% = 63 DPPs.*

Median survival was estimated to be 5.5 years in this group[143]. The number of LYGs was then estimated as: *Deaths prevented or postponed x Median survival = 63 x 5.5 = 345 LYGs.*

Estimates of LYGs were adjusted to take into account the influence of 'competing causes of mortality[238;381]. This inflation was small, generally amounting to less than one extra year of life.

## Sensitivity analyses

A sensitivity analysis was performed using the analysis of extremes method[231]. This addressed the uncertainties surrounding the key variables (patient numbers, treatment uptake and efficacy, the overlap between different treatment categories and median survival). Minimum and maximum estimates of LYGs were generated using 95% confidence intervals where available, otherwise the minimum and maximum plausible values for each variable[231] were used*(Appendix 10 and 11).*

## 10.3  Results

In 2000, there were 68,230 fewer CHD deaths than expected from applying mortality rates in 1981, the baseline year. The age-specific model estimates for DPPs by all interventions were compared with the observed falls in mortality in each age and sex category. The model explained 61,595 fewer deaths, representing 90% of the observed CHD mortality fall *(Chapter 9, Table 9.5)*. These 61,595 fewer deaths resulted in a gain of approximately 925,415 life-years among people aged 25-84 *(minimum estimate 745,195, maximum estimate 1,138,655) (Table 10.1* and *Table 10.2)*.

### Life-years gained by medical and surgical treatments

Specific medical and surgical treatments for patients with CHD prevented or postponed approximately 25,745 deaths in England and Wales in year 2000[248]. They therefore gained approximately 194,145 life-years *(minimum 142,505, maximum 259,225)* in total *(Table 10.1)*. The largest contributions came from secondary prevention for patients following myocardial infarction or revascularisation (32%), heart failure treatments (13%) and hypertension treatments (9%). Coronary artery bypass surgery and angioplasty procedures together accounted for 17% of the LYGs by treatments *(Table 10.1)*.

**Table 10.1 Number of life-years gained by medical and surgical treatments of coronary heart disease in England and Wales in 2000.**

| INTERVENTION | Patients eligible | Number of DPPs* | Life-Years Gained* Best estimate (Minimum to Maximum) | % |
|---|---|---|---|---|
| Acute myocardial infarction | 66,195 | 5,750 | 38,330 (20,795 to 57,880) | 19.7% |
| Secondary prevention | | | | |
| *Post myocardial infarction* | 313,380 | 3,580 | 24,520 (11,900 to 37,140) | 12.6% |
| *Post CABG or PTCA* | 315,680 | 3,055 | 37,660 (35,360 to 39,960) | 19.4% |
| Angina | | | | |
| *CABG* | 187,415 | 1,935 | 25,805 (22,550 to 31,695) | 13.3% |
| *PTCA* | 112,405 | 560 | 7,905 (5,405 to 10,410) | 4.1% |
| *Unstable angina* | 72,600 | 910 | 5,530 (4,700 to 9,400) | 2.8% |
| *Aspirin in community* | 2,114,665 | 1,105 | 9,690 (4,845 to 14,535) | 5.0% |
| Heart failure | | | | |
| *Hospital treatment* | 41,385 | 4,755 | 6,120 (4,895 to 7,340) | 3.2% |
| *Community treatment* | 242,090 | 3,210 | 19,240 (7,605 to 21,140) | 9.9% |
| Hypertension treatments | 12,592,120 | 1,890 | 17,775 (15,290 to 25,485) | 9.2% |
| Statins for primary prevention | 7,630,760 | 145 | 1,570 (1,370 to 2,285) | 0.8% |
| **Total treatment effects in 2000** | | **25,765** | **194,145 (142,505 to 259,225)** | **100%** |

## Life-years gained by risk factor changes in the population

In England and Wales, approximately 35,830 deaths were prevented or postponed by risk factor changes in the population between 1981 and 2000. This accounted for some 731,270 LYGs *(minimum estimate 602,695, maximum estimate 879,430)*, and represented 79% of all LYGs we estimated in 2000. The largest contribution came from reductions in smoking (54%), blood pressure (28%) and cholesterol (22%) *(Table 10.2)*.

Adverse trends between 1981 and 2000 were seen for obesity, physical inactivity, and diabetes. They together caused approximately 7,650 additional CHD deaths. This resulted in a *loss* of approximately –92,640 life-years *(minimum -68,355, maximum -100,770)*, effectively halving the gain from population cholesterol reductions *(Table 10.2)*.

Table 10.2 Number of life-years gained by changes in population cardiovascular risk factors in England and Wales between 1981 and 2000.

| POPULATION RISK FACTORS | % Change in risk factor 1981-2000 | Number of DPPs* | Life-Years Gained* Best estimate (Minimum to Maximum) | % |
|---|---|---|---|---|
| Smoking | -34.0% | 29,715 | **398,080** (304,020 to 446,260) | **54.4%** |
| Blood pressure | -7.5% | 5,870 | **207,525** (197,870 to 288,445) | **28.4%** |
| Cholesterol | -5.6% | 7,900 | **164,305** (128,310 to 188,145) | **22.5%** |
| Deprivation | -6.6% | 2,125 | **53,995** (40,845 to 57,350) | **7.4%** |
| Obesity | +186.2% | -2,095 | **-10,690** (-8,565 to -13,470) | **-1.5%** |
| Physical activity | - 30.6% | -2,660 | **-37,055** (-27,245 to -39,450) | **-5.1%** |
| Diabetes | +65.6% | -2,890 | **-44,895** (-32,545 to -47,850) | **-6.1%** |
| **Total risk factor effects in 2000** | | **35,830** | **731,270 (602,695 to 879,430)** | **100.0%** |

Figure 10.1 Comparison of deaths prevented or postponed and life-years gained from risk factor changes and treatments given to CHD patients.
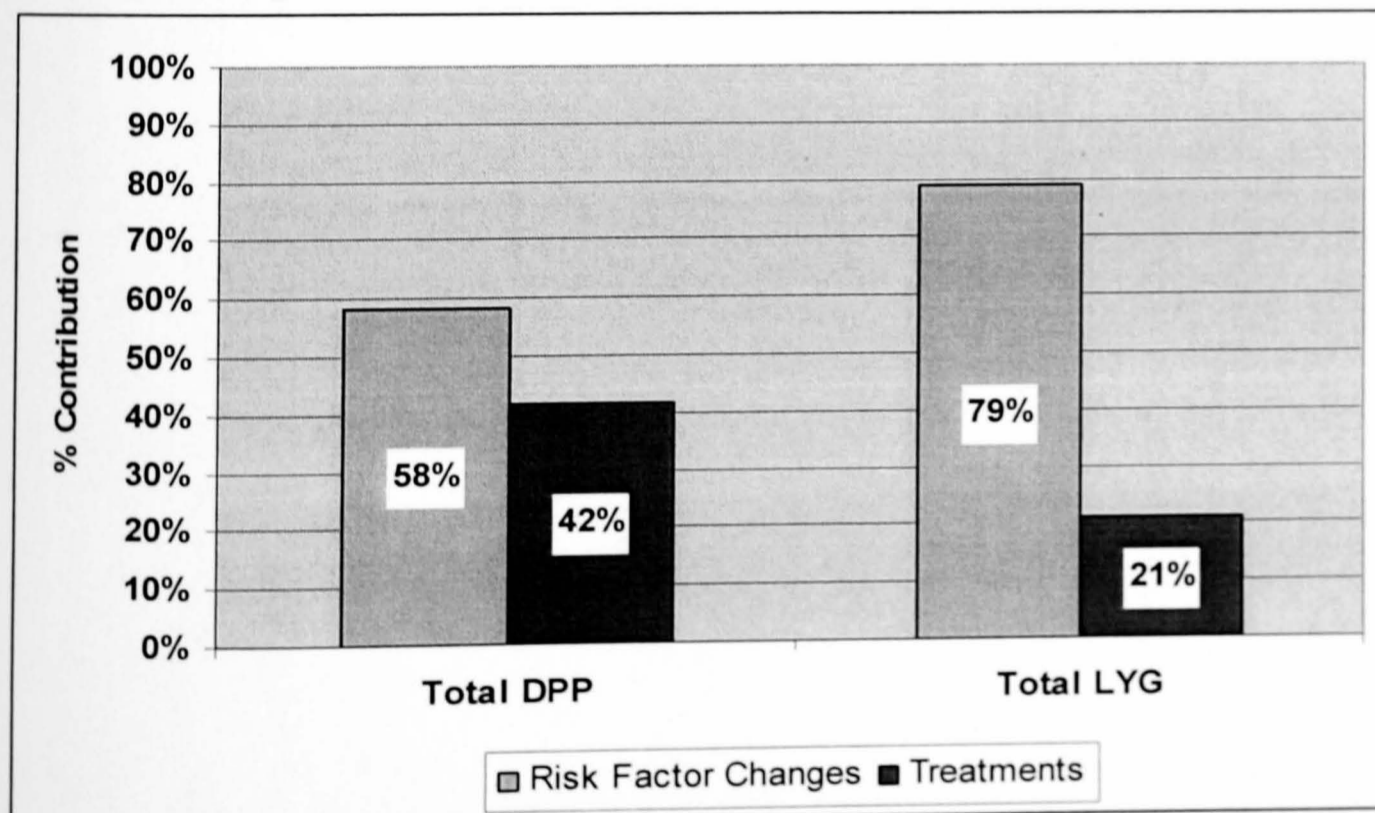
Although the numbers of DPPs from risk factor changes and treatments given to CHD patients were close to each other, number of LYGs was substantially higher from risk factor changes than treatments *(Figure 10.1)*.

## Age and sex distribution of life-years gained *(Figure 10.2)*

The majority of life-years were gained by individuals aged 55 to 74 years. More life-years were gained by men than women in all age groups; 68% (132,505 / 194,145) of the LYGs by medical and surgical treatments, and 69% (510,915 / 731,270) of the LYGs by risk factor reductions, *(Figure 10.2)*.

## Sensitivity analyses *(Figure 10.3)*

The relative contributions from treatments and risk factor reductions remained relatively constant, irrespective of whether best, maximum or minimum estimates were considered *(Figure 10.3)*.

Figure 10.2 Number of life-years gained from coronary heart disease treatments and population risk factor changes, in England and Wales between 1981 and 2000 by age and sex.
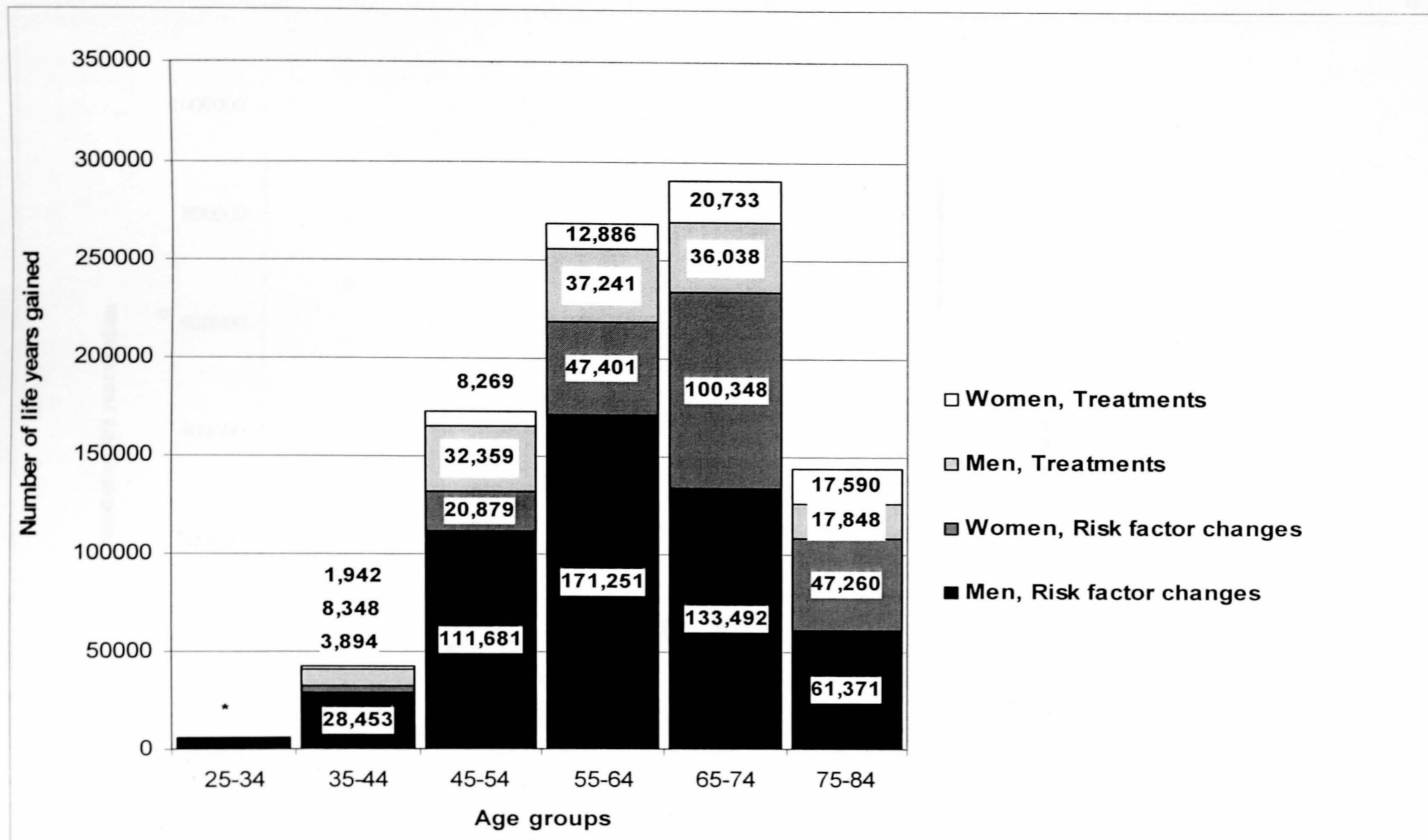
*Subjects aged 25-34: Changes in risk factors gained 4.665 life years in men. 574 in women; treatments gained 672 life-years in men. 219 in women.*

**Figure 10.3 Proportional contributions of specific treatments and risk factor changes to the total life-years gained from the CHD mortality decline in England and Wales, 1981-2000: Results of a sensitivity analysis.**

(■ Best estimate, - minimum and maximum estimates).
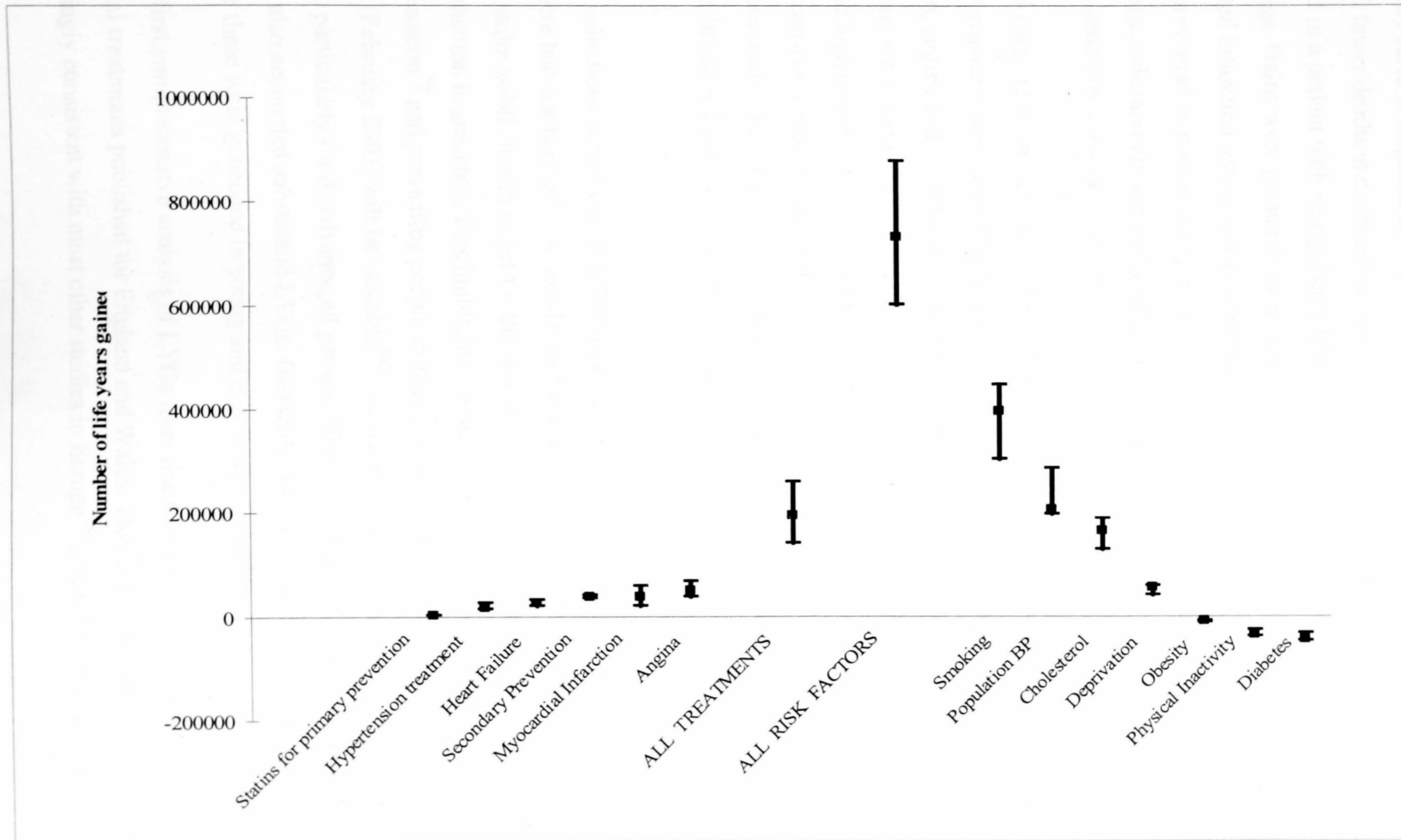
## 10.4    Interpretation

CHD mortality rates in England and Wales halved between 1981 and 2000. This resulted in some 70,000 fewer deaths and almost one million additional years of life. A death prevented or postponed in a patient with recognised CHD therefore gained an additional 7.5 years of life on average. Gains were greater in men, younger patients, or those surviving uncomplicated infarction, rather less in older patients or those with heart failure. In contrast, each death prevented or postponed by a risk factor reduction gained an additional 20 years of life on average, substantially more in younger individuals, rather less in older. These findings are generally consistent with previous studies[382].

Medical and surgical treatments in 2000 together gained approximately 195,000 life-years, a third from secondary prevention. Much of the remainder came from just three categories – hypertension, angina and heart failure. The LYGs from ACE inhibitors, beta-blockers and spironolactone were particularly impressive given the relatively low prescribing rates in 2000 and the high case fatality in heart failure patients[286]. This further emphasises that simple inexpensive treatments applied to all eligible patients can potentially produce huge gains[148]. Conversely, the substantial resources devoted to revascularisation in 2000 undoubtedly improved quality of life, however gains in life-years were relatively modest (Table 10.1).

Risk factor reductions accounted for a 79% of total LYGs. Gains would have been even greater if there had not been adverse trends in physical activity, obesity and diabetes. These represent a major public health target for the new millennium[374]. Substantial gains came from the reduction in smoking. This highlights the rapid and substantial benefits from smoking cessation[22] and preventing people to start smoking. The UK abolition of tobacco advertising (February 2003) will be valuable[383]. However, additional measures will remain essential[384], particularly for disadvantaged groups. Modest changes in blood pressure and cholesterol also accounted substantial LYGs. Generally risk factor changes accounted higher LYGs since these were generated in young and middle aged population.

This is the first comprehensive analysis of LYGs from risk factor reductions and cardiological treatments published for England and Wales. However, our mortality analyses are reassuringly consistent with most other studies in Europe[251], New Zealand[5] and the USA[193].

Bunker et al. examined the 7.1 years increase in life expectancy seen in the USA between 1950 and 1989[385]. Changes in coronary and cerebrovascular disease death rates accounted for 10%-20% of this increase[385]. This is consistent with our estimates for Scotland (1975-1981)[386] and for England and Wales.

Again in the USA, Tsevat et al attributed 1.0 to 1.2 years increase in population life expectancy by lowering blood pressure in men, (and 0.3 to 0.6 years in women), and 0.5 to 1.2 years by quitting smoking in 35-year old men (0.4 to 0.8 in women)[238]. Using similar assumptions, Grover et al estimated that reductions in CHD and stroke risk through blood pressure reduction would result in 0.9 to 1.2 years increase in life years in men and 0.6 to 1.3 years in women aged 40[382].

There are important implications for clinical and public health practice. In particular, the current UK government emphasis on treatments rather than risk factor reductions must be seriously questioned.

In conclusion, modern cardiological treatments in England and Wales in 2000 gained many thousands of life-years. However, four times as many life-years were generated by relatively modest reductions in major risk factors, principally smoking, cholesterol and blood pressure. Effective policies to promote healthy diets and physical activity, and reduce obesity, might therefore gain substantial numbers of additional life-years in England and Wales.

Having presented the impact of CHD treatment uptake and population risk factor changes in England and Wales, in the following two chapters, I will focus on the 'what if?' questions. What if treatments, or risk factor levels had been different?

# 11 IMPACT OF INCREASED TREATMENT UPTAKE ON CHD MORTALITY IN ENGLAND AND WALES IN 2000

In this chapter, I will explore the first "What if?" question:

**'What would have been the mortality impact of increasing the uptake of cardiological treatments in England and Wales, in 2000?'**

## 11.1 Introduction

In *Chapter 9*, I demonstrated that approximately 40% of the recent fall in CHD mortality rates can be attributed to the increasingly widespread use of effective therapies[248;373]. Furthermore, cardiology epitomises the evidence-based medicine paradigm. A wealth of evidence from randomised trials and meta-analyses underpins an expanding range of treatments including thrombolysis, aspirin, beta-blockers, statins, ACE-inhibitors, coronary bypass surgery and angioplasty[372].

However, benefit can only occur if the eligible patients actually receive the appropriate therapies[372]. Recent clinical audits and surveys suggest that treatment uptake rates remain disappointingly low for many groups of patients. For instance, following myocardial infarction, only about 25%, 44% and 56% of eligible patients receive statins, beta-blockers or aspirin respectively[269;289;349;387]. In the community, approximately 60% of angina patients are taking aspirin[289], yet barely 50% of heart failure patients receive ACE inhibitors[357]. Uptake rates are consistently worse in women, the elderly and the deprived[388].

Scope remains for substantial increases in treatment uptake; these would potentially result in large reductions in both morbidity and mortality. Recent NHS strategies including the National Service Framework for Coronary Heart Disease[148] are now beginning to address this issue. However, simultaneously tackling all these patient groups would require substantial additional resources[148;204].

I therefore examined the scale of the CHD mortality reduction potentially achievable from the increased uptake of specific medical and surgical treatments in England and Wales in 2000, in order to help identifying target groups for prioritisation.

## 11.2 Methods

The IMPACT mortality model was used to examine the consequences of increasing uptake of specific treatments in each category of patients. The IMPACT Model and the methods used to estimate DPPs were described in detail in *Chapter 8.*

All existing values contained within the model for the year 2000 were left unchanged (numbers of eligible patients, treatment compliance and effectiveness)[5]. The best available data on uptake of specific treatments in each category of patients. as detailed above, were used to calculate the baseline.

The potential mortality benefit if uptake was increased to reach 80% of all eligible patients, (the National Service Framework target)[148] was then calculated, assuming optimal dosing regimens. An uptake of 100% was considered unrealistic[321]. The corresponding calculation was performed for revascularisation, assuming that CABG surgery and PTCA procedures in 2000 were increased by 80%.

### Sensitivity analyses

Mortality effects were analysed by age and sex. The key parameters were all subject to imprecision and uncertainty. Multi-way sensitivity analyses were therefore performed using the analysis of extremes method[341]. Minimum and maximum mortality reductions were generated using 95% confidence intervals from meta-analyses for treatment efficacy, and minimum and maximum plausible values for patient numbers, treatment uptake and adherence[341]. Information sources for number of patients, treatment uptake, treatment efficacies in IMPACT Model were presented in *Chapter 8.*

## 11.3 Results

In 2000, specific medical and surgical treatments in England and Wales were estimated to prevent or postpone approximately 26,000 deaths for at least one year (minimum estimate 17,110, maximum estimate 49,040) *(Table 9.1)*. Some 19% of this fall was attributed to initial treatments for acute myocardial infarction, 26% for secondary prevention treatments, 31% for treatments for heart failure, and 7% for anti-hypertensive therapies *(Table 9.1)*. However, uptakes were generally poor. Uptake in MI survivors averaged 56% for aspirin, 34% for beta-blockers, and 25% for statins; and for heart failure patients in the community this averaged 56% for ACE inhibitors, 17% for statins and 15% for beta-blockers *(Table 9.1)*.

**Mortality benefit of increasing treatment uptake to 80%**

Increasing uptake to 80% of eligible patients would have prevented or postponed approximately 20,910 additional deaths at least one year (minimum estimate 11,030; maximum estimate 33,495). Of the 20,910 fewer deaths, 7,285 (35%) would have resulted from increasing heart failure treatments for community and hospital patients, and 4,680 (23%) fewer deaths from increases in secondary prevention therapies following AMI or revascularisation, *(Table 11.1)*.

Extending primary prevention statin therapy to 80% of the 7.6 million healthy individuals with total cholesterol levels above 6.2 mmol/l would have prevented approximately 3,295 deaths, representing 16% of the total gain, compared with 2,370 (11%) fewer deaths from initial treatments for acute MI; 2,680 (10%) from treatments for hypertension and 1,475 (7%) from increases in aspirin and statins for patients with angina in the community.

Only 400 (2%) additional deaths would have been prevented by an 80% increase in revascularisation procedures in 2000, and just 305 (1%) fewer deaths from increases in therapies for unstable angina *(Table 11.1 and Figure 11.1)*.

**Table 11.1 Coronary heart disease mortality reduction in England & Wales in 2000: Effect of increasing treatment uptake to 80%**

| TREATMENTS | Eligible Patients | Treatment uptake in 2000 | Treatment Efficacy (RRR*) | Deaths prevented or postponed In 2000 | Gain if 80% uptake | (% total gain) | Minimum estimate | Maximum estimate |
|---|---|---|---|---|---|---|---|---|
| **Acute Myocardial Infarction** | **66,195** | | | **4,740** | **2,370** | (11%) | *1329* | *3414* |
| Community Resuscitation | 3,045 | 0.48 | 0.11 | 800 | 380 | | | |
| Hospital Resuscitation | 7,280 | 0.99 | 0.21 | 1,455 | - | | | |
| Thrombolysis ** | | 0.47 | 0.21 | 1,320 | 50 | | | |
| Aspirin | | 0.94 | 0.15 | 1,950 | - | | | |
| Primary angioplasty*** | | 0.01 | 0.28 | 40 | 1,330 | | | |
| Beta-blockers | | 0.04 | 0.04 | 20 | 195 | | | |
| ACE inhibitors | | 0.19 | 0.07 | 170 | 410 | | | |
| | | | | | | | | |
| **2° prevention post infarction** | **313,380** | | | **3,845** | **3,695** | (18%) | *2741* | *4865* |
| Aspirin | | 0.56 | 0.15 | 1,240 | 65 | | | |
| Beta-blockers | | 0.34 | 0.23 | 970 | 720 | | | |
| ACE inhibitors | | 0.19 | 0.23 | 440 | 915 | | | |
| Statins | | 0.25 | 0.29 | 460 | 645 | | | |
| Warfarin**** | | 0.04 | 0.15 | 100 | 250 | | | |
| Rehabilitation | | 0.23 | 0.27 | 675 | 1055 | | | |
| | | | | | | | | |
| **2° prevention post revascularisation** | **157,840** | | | **3,055** | **985** | (5%) | *561* | *1638* |
| Aspirin | | 0.56 | 0.15 | 820 | 100 | | | |
| Beta-blockers | | 0.35 | 0.23 | 570 | 150 | | | |
| ACE inhibitors | | 0.22 | 0.23 | 350 | 270 | | | |
| Statins | | 0.34 | 0.29 | 675 | 205 | | | |
| Warfarin**** | | 0.04 | 0.15 | 54 | 115 | | | |
| Rehabilitation | | 0.35 | 0.27 | 585 | 150 | | | |

*RRR= relative risk reduction **60% Maximum uptake assumed ***40% Maximum uptake assumed if 60% for thrombolysis

**** 20% maximum uptake assumed for warfarin if 80% on aspirin

| TABLE 11.1 (continued) | Eligible Patients | Treatment uptake in 2000 | Treatment Efficacy (RRR) | Deaths prevented or postponed In 2000 | Gain if 80% uptake | (% total gain) | Minimum estimate | Maximum estimate |
|---|---|---|---|---|---|---|---|---|
| **Angina revascularisation** | | | | **2,495** | **400** | (2%) | *270* | *560* |
| CABG surgery | **187,415** | 1.00 | 0.31 | 1935 | 275 | | *233* | *381* |
| Angioplasty* | **112,405** | 1.00 | 0.08 | 560 | 125 | | *36* | *181* |
| **Unstable Angina** | **67,375** | | | **910** | **305** | (1%) | *224* | *419* |
| Aspirin & Heparin | | 0.59 | 0.27 | 465 | 165 | | | |
| Aspirin alone | | 0.30 | 0.15 | 235 | 0# | | | |
| IIB/IIIA Inhibitors & clopidogrel | | 0.48 | 0.09 | 210 | 140 | | | |
| **Chronic stable angina** | **2,114,670** | | | **1,105** | **1,475** | | | |
| Aspirin | | 0.58 | 0.15 | 995 | 370 | (2%) | *234* | *790* |
| Statins | | 0.07 | 0.29 | 110 | 1105 | (5%) | *958* | *1,471* |
| **Heart failure- in hospital** | **34,690** | | | **4,755** | **3,350** | (16%) | *2,178* | *6,206* |
| ACE inhibitors | | 0.62 | 0.26 | 1,845 | 595 | | | |
| Beta-blockers | | 0.31 | 0.37 | 1,280 | 1044 | | | |
| Spironolactone | | 0.10 | 0.30 | 350 | 990 | | | |
| Aspirin | | 0.50 | 0.15 | 870 | 119 | | | |
| Statins | | 0.21 | 0.29 | 410 | 700 | | | |
| **Community heart failure-** | **242,090** | | | **3,210** | **3,935** | (19%) | *1,020* | *3,048* |
| ACE inhibitors | | 0.56 | 0.26 | 1,535 | 34 | | | |
| Beta-blockers | | 0.15 | 0.37 | 550 | 1,595 | | | |
| Spironolactone | | 0.10 | 0.30 | 205 | 965 | | | |
| Aspirin | | 0.29 | 0.15 | 585 | 579 | | | |
| Statins | | 0.17 | 0.36 | 335 | 763 | | | |
| **Hypertension treatments** | **13,352,870** | **0.53** | **0.11** | **1,890** | **945** | (5%) | *438* | *1586* |
| **Statins for primary prevention** | **7,630,760** | **0.03** | **0.29** | **145** | **3,295** | (16%) | *1,078* | *5,493* |
| **TOTAL** | | | | **25,765** | **20,910** | 100% | *11,030* | *33,495* |

*Assuming relative risk reduction of 8%, equivalent to CABG for two vessel disease # If 80% get Heparin plus Aspirin, no option for increase in aspirin alone

**Figure 11.1 Estimated CHD mortality reductions in 2000, and potential gains IF specific treatment uptakes reached 80% of eligible patients**
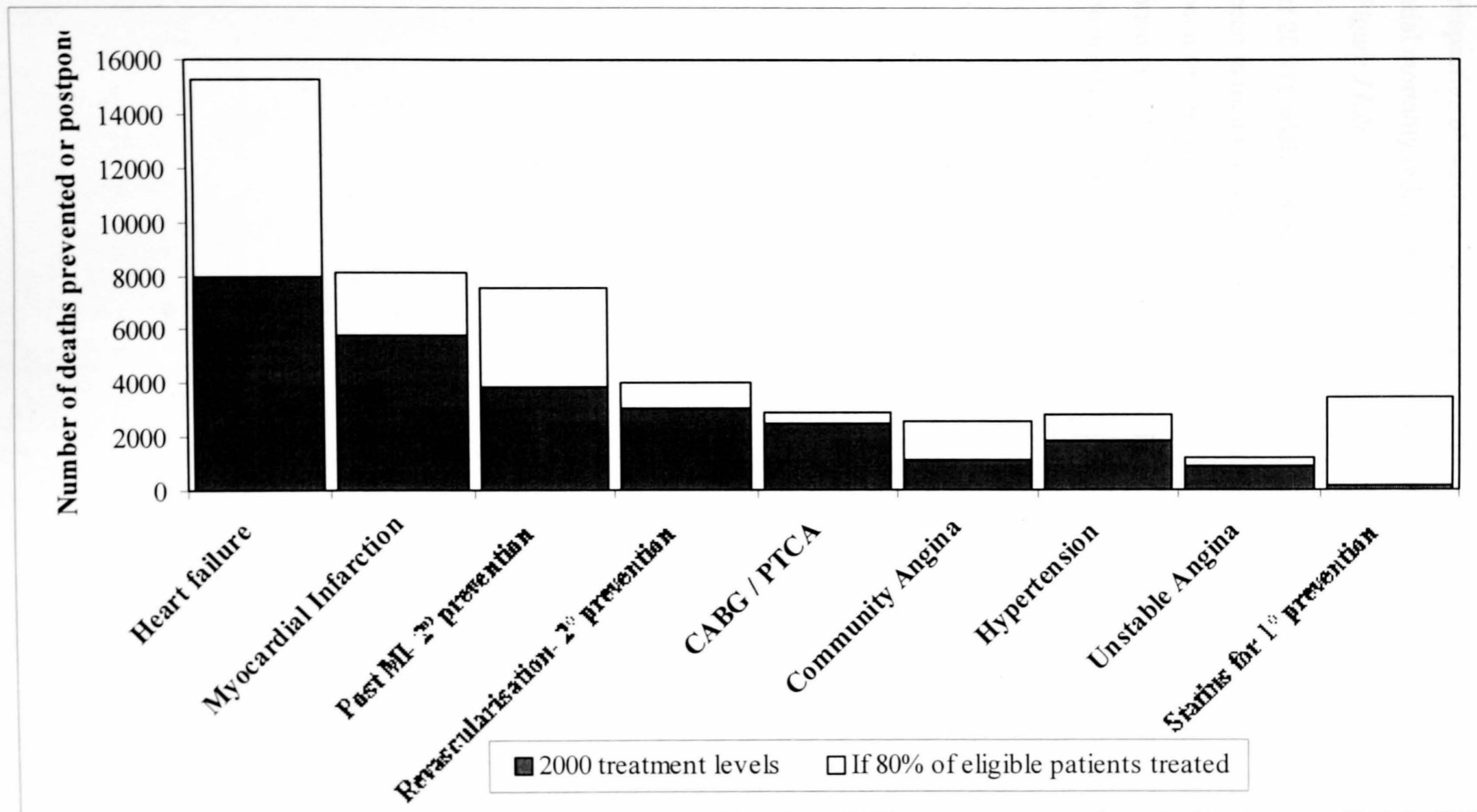
## Sensitivity analyses

The proportional contributions remained relatively consistent using an analysis of extremes approach. Irrespective of whether best, minimum or maximum values were used, the biggest potential mortality reductions came from treatments for heart failure and secondary prevention (*Figure 11.2*).

Of the total of 20,910 additional deaths potentially prevented or postponed, 12,895 (61.7 %) would have been in men and 8,015 (38.3%) in women. Two thirds of the fewer deaths would have occurred in older patients, with 7%, 15%, 22%, and 16% of the total reduction occurring in men aged 45-54, 55-64, 65-74, and 75-84 years respectively (and 2%, 6%, 14%, and 16% respectively in women, *Figure 11.3*).

**Figure 11.2 Sensitivity analysis showing best estimates for mortality reductions IF specific treatment uptakes reached 80% of eligible patients.**
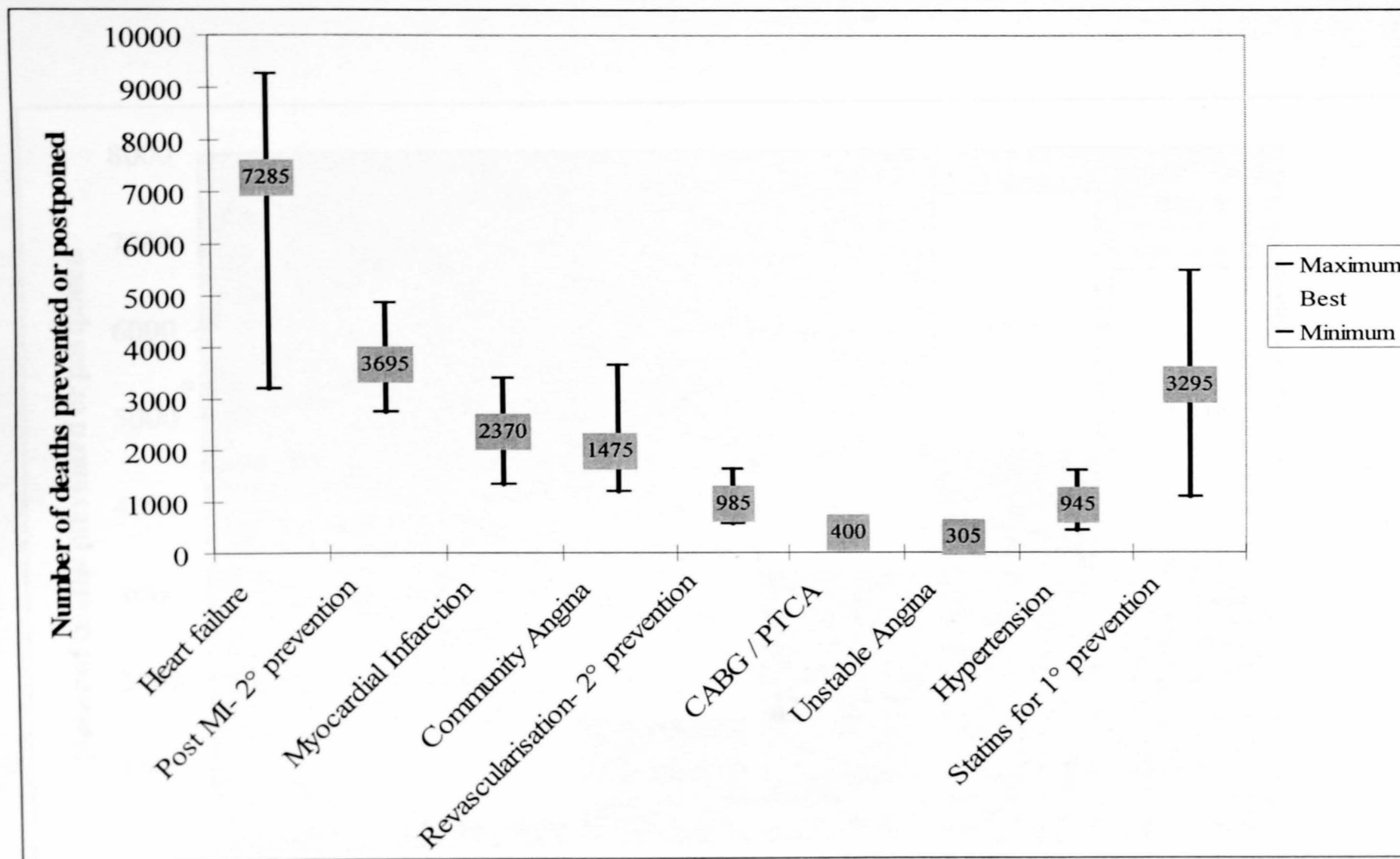
**Figure 11.3 Age and sex distribution of CHD mortality reductions IF appropriate specific treatment uptakes reached 80% of eligible patients.**
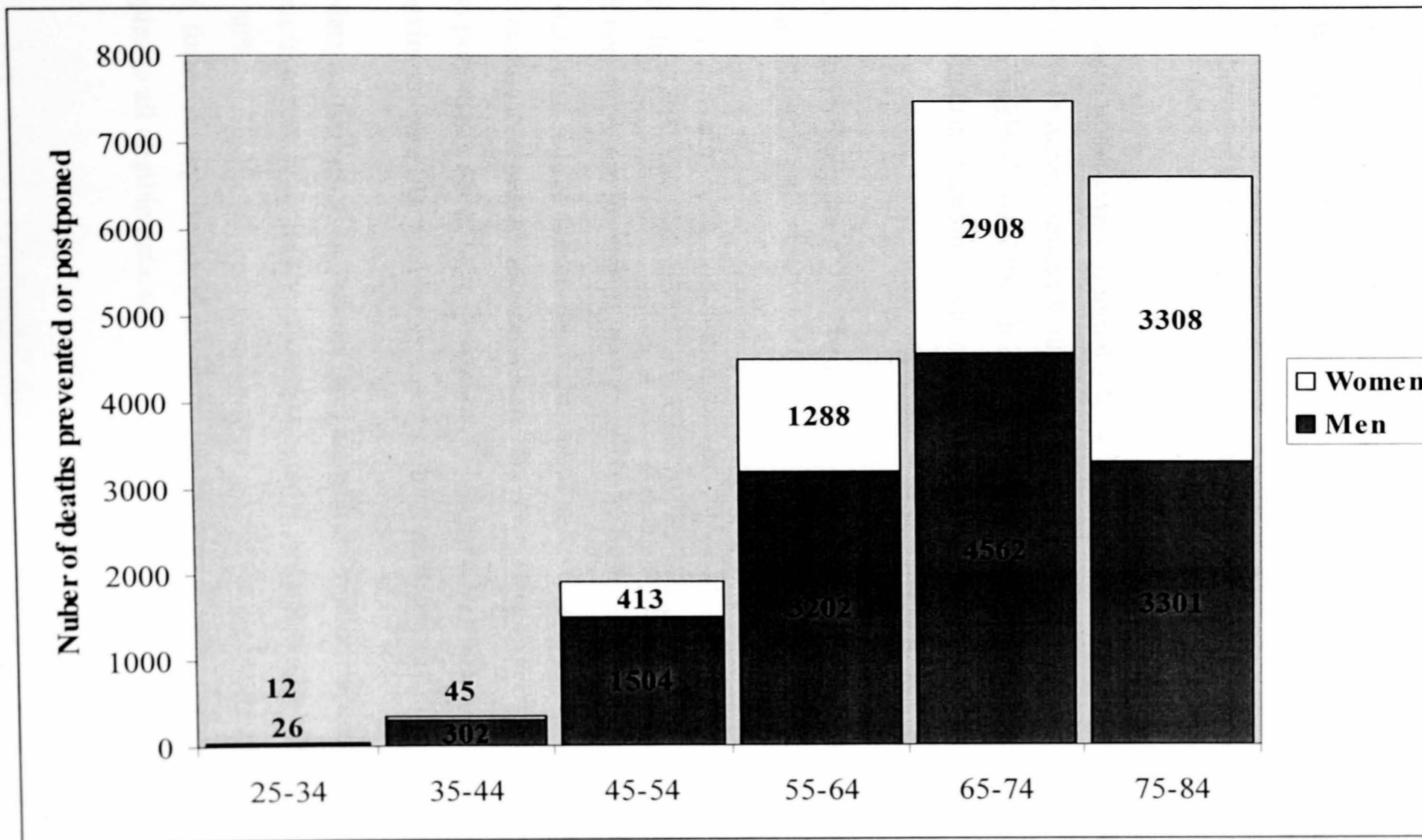
## 11.4 Interpretation

In 2000, barely half the patients with cardiac disease actually received the appropriate therapy [157;159;269;289;351;357]. If just 80% of eligible patients had received the cardiological treatment indicated, then over 20,000 extra deaths could have been prevented or postponed. This would have almost doubled the reduction in mortality achieved by treatment in England and Wales in 2000, and is consistent with other studies in Scotland and elsewhere [148;321].

But how could treatment uptakes be increased? Focused clinical audit can be effective, and has already substantially increased thrombolysis uptake rates for AMI [389], and aspirin for secondary prevention [269]. Evidence -based clinical guidelines are now widely available [390], and strategies aiming to achieve treatment uptake levels of 80%-90% have been widely disseminated [148;390].

If a strategy for increased uptake were to initially focus only on heart failure and secondary prevention, then an 80% treatment uptake would be expected to result in approximately 12,000 fewer deaths in England and Wales in 2000 (almost two thirds of the total additional benefit). However, such prioritisation would mean focusing mainly on patients in the community.

All analytical models have limitations [3;233]. The strength and limitations of the models will be discussed in detail in *Chapter 13*.

This study focused on *mortality* reduction, rather than quality of life or symptom relief. Indeed, many cardiological treatments are given principally for symptomatic improvement, such as PTCA and beta-blockers for angina, and diuretics for heart failure [148]. Furthermore, increased therapy may also reduce serious morbidity, such as myocardial infarction, stroke or heart failure often leading to repeated hospitalisation. By preventing such events, these treatments can also potentially offset their own costs [205]. At present, many patients are under-dosed, whereas maximum benefits would only come with optimal dosing [148].

In conclusion, modern cardiological treatments have already contributed substantially to the observed reductions in coronary mortality. However, a more systematic application of proven therapies to reach 80% of eligible patients would almost double the DPPs. Because resources are always limited, future strategies should prioritise the delivery of secondary prevention and heart failure therapies to all eligible patients.

# 12 SMALL CHANGES IN UK CARDIOVASCULAR RISK FACTORS LEADING TO POTENTIALLY BIG REDUCTIONS IN CHD MORTALITY?

In *Chapter 9,* I described how population risk factor changes apparently explained approximately 60% of the CHD mortality fall between 1981 and 2000. In this chapter, I will now address the very important question:

**What is the potential benefit of further reductions in major risk factors?**

## 12.1   Introduction

As I have discussed in earlier chapters, CHD mortality rates have halved in most industrialised countries since the 1980s[2]. However, mortality has declined less in the UK, and CHD remains the single largest cause of death[2]. The UK government recently endorsed CVD as a top priority[148], and in 1999, the "Saving Lives" White Paper set the target of reducing the CHD and stroke death rate in people under 75 years by at least two fifths by 2010, in other words 28,000 fewer deaths in the year 2010[374].

In this chapter I have used the England and Wales IMPACT model[248], to estimate the number of additional CHD deaths that might potentially be prevented or postponed by 2010. Initially, by simply assuming that cardiovascular risk factors continued their recent trends, and then by assuming the additional small and eminently feasible reductions already seen in many other countries.

## 12.2 Methods

The IMPACT model has been described in the previous *Chapters 8 and 9* in detail. Here the IMPACT model was extended from 1981 through 2000 to 2010, using population projections and mortality data for men and women aged 25-84, from the Office for National Statistics[377]. The CHD deaths expected in 2010 were calculated a) by applying the age-specific death rates in 2000 to the 2010 population, and b) by extrapolating current CHD mortality trends to the year 2010[322].

**Risk factor projections**

**a) Assuming recent risk factor trends simply continue to 2010**

Recent trends in smoking prevalence using data from the General Household Survey[200] were projected to 2010. Recent trends in total cholesterol, blood pressure, body mass index, physical activity and diabetes were obtained from the Health Survey for England, British Regional Heart Study, Glasgow-Belfast MONICA, and other UK surveys[48;125;303]. Age specific trends were extrapolated to the England and Wales population in 2010.

**b) Assuming more substantial reductions in risk factors between 2000 and 2010**

More substantial but feasible risk reductions were chosen, based on data from comparable populations in Europe and USA. The calculations were then repeated assuming these greater risk factor reductions.

i) *Smoking* The UK target to reduce smoking prevalence from the current prevalence of 26% to 24% among adults by 2010 does not appear challenging, and may be achieved simply on the basis of current trends[200;374]. An eminently feasible 2010 prevalence of 17% in all adults aged under 65, as already achieved in California in 2000[119], was therefore chosen.

ii) *Cholesterol* Reductions in population mean total cholesterol levels between 1981-2000 have been modest in England and Wales, less than 5% in men and women aged 45-64[125]. The annual relative falls of 1.0% in men and 1.4% in women observed in Sweden[125] were therefore applied to the British population. The projected cholesterol levels for 2010, 5.2mmol/l overall, would then simply resemble those actually achieved in the 1990s in populations such as Gothenberg (Sweden), Stanford (USA) or Perth (Australia)[125].

iii) **Blood Pressure** Population mean diastolic blood pressure fell on average by almost 8% between 1981 and 2000[48]. A further 4% (3.7 mmHg) decrease in diastolic blood pressure between 2000 and 2010 was examined. Such falls have already been observed in several countries including Finland (5.2 mmHg), France (6.0 mmHg) and New Zealand (4.4 mmHg)[125].

iv) **Obesity** Community interventions to reduce obesity prevalence or mean BMI *in the general population* have mostly failed to achieve sustainable falls[391]. There are currently no UK obesity targets; however, a 15% reduction in obesity prevalence by 2010 was recently proposed in the USA[392]. I therefore examined the same target for England and Wales.

v) **Physical activity** Randomised controlled trials of rigorous, tailored interventions, generally focussed on *individual volunteers*, appear effective, with a 35% median net increase in time spent on physical activity and a net median energy expenditure increase of 64%[141]. Community interventions have generally failed to produce sustained increases in physical activity. However, a recent systematic review found that a variety of different interventions such as mass media communication and risk factor screening or counselling, increased the proportion of physically active people by 4.2%(-2.9 to 9.4) overall[141]. This may be compared with the 7%-9% increase reported in the Heart Beat Wales Programme[393]. I therefore examined the impact of a 5% potential increase in moderately active people in the England and Wales population by 2010.

vi) **Diabetes** Large Finnish and American studies in individuals with impaired glucose tolerance suggest that intensive individualised instructions on weight reduction, food intake and increasing physical activity can produce sustained lifestyle changes and reduce diabetes risk by 58%[394]. The main mechanisms for this risk reduction appeared to be moderate changes in body weight 3-4 kg (-5%), and moderate exercise for 150 minutes per week[394].

However these findings were from selected individuals in a high-risk group rather than the general population. In the absence of any published report of a successful reduction in diabetes prevalence in a community or population, I therefore examined the impact of 5% potential decrease in diabetes prevalence in England and Wales by 2010.

**Sensitivity Analysis**

Because of the uncertainties surrounding some of the estimates, a multi-way sensitivity analysis was performed using the analysis of extremes method[231]. Estimated mortality reductions were then generated using minimum and maximum plausible values for the main parameters[3-5;248].

## 12.3   Results

**Changes in CHD mortality in England and Wales**

**a)  Trends observed between 1981 and 2000**

Overall annual declines in CHD mortality rates were 3.1% in men and 2.3% in women, ranging from 3.2% in the younger men to 1.8% in men aged 75-84 *(Table 12.1)*.

**b)  Estimates between 2000 and 2010**

Assuming that recent trends in age-specific death rates continued to 2010, approximately 86,325 deaths would be expected in 2010 (56,565 among men, 29,760 in women). This would represent an overall reduction of 23% (23% and 22% respectively in men and women) from 2000 *(Table 12.1)*.

Table 12.1 Observed and projected CHD mortality rates and deaths in England and Wales, 2000-2010.

| | Population (thousands) | CHD Mortality Rates/100,000 | | Annual Change in CHD Mortality Rates (1981-2000) | Estimated CHD deaths in 2010 with current trend | Expected CHD deaths in 2010 applying 2000 rates | Fall in CHD Deaths 2000-2010 | |
|---|---|---|---|---|---|---|---|---|
| | a | b | c=b+(b*d*10) | d | e=a*c | f=a*b | g=e-f | g/f*100 |
| **MEN** | **2010** | **2000** | **2010** | **%** | **2010** | **2010** | **number** | **%** |
| 25-34 | 3,492 | 2.4 | 1.6 | -3.2 | 57 | 84 | -27 | -32 |
| 34-44 | 4,070 | 18.7 | 12.8 | -3.2 | 521 | 761 | -241 | -32 |
| 45-54 | 3,985 | 89.3 | 60.6 | -3.2 | 2,416 | 3,559 | -1,142 | -32 |
| 55-64 | 3,277 | 282.4 | 199.8 | -2.9 | 6,547 | 9,254 | -2,707 | -29 |
| 65-74 | 2,291 | 807.2 | 612.2 | -2.4 | 14,025 | 18,493 | -4,468 | -24 |
| 75-84 | 1,287 | 1896.9 | 1563.1 | -1.8 | 20,118 | 24,413 | -4,295 | -18 |
| **TOTAL** | **18,402** | **213.8** | **148.0** | **-3.1** | **43,683** | **56,565** | **-12,880** | **-23** |
| **WOMEN** | | | | | | | | |
| 25-34 | 3,358 | 0.6 | 0.4 | -2.7 | 15 | 20 | -5 | -27 |
| 35-44 | 3,855 | 4.5 | 3.4 | -2.4 | 133 | 173 | -41 | -24 |
| 45-54 | 3,885 | 18.7 | 13 | -3.0 | 506 | 726 | -220 | -30 |
| 55-64 | 3,342 | 78.4 | 55.3 | -2.9 | 1,849 | 2,620 | -771 | -29 |
| 65-74 | 2,480 | 335.2 | 252.8 | -2.5 | 6,270 | 8,313 | -2,042 | -25 |
| 75-84 | 1,700 | 1053.3 | 847.9 | -1.9 | 14,415 | 17,906 | -3,492 | -19 |
| **TOTAL** | **18,620** | **173.2** | **134.1** | **-2.3** | **23,188** | **29,760** | **-6,572** | **-22** |
| **TOTAL MEN & WOMEN** | **37,022** | **193.2** | **139.9** | **-2.7** | **66,830** | **86,325** | **-19,452** | **-23** |

## Cardiovascular risk factor changes

The risk factor levels in 2000, and the levels expected in 2010 on the basis of a) recent trends and b) more substantial reductions are detailed in *Table 12.2*.

**a)    Mortality reductions based on *recent trends* only *(Table 12.3)***

All three major risk factors showed declining trends between 1981 and 2000. Assuming that the same trends continued between 2000 and 2010, this would result in approximately 13,760 deaths prevented or postponed (DPPs) in 2010 (minimum estimate 9,540, maximum estimate 16,050- *Table 12.3*).

Approximately 8,880 fewer deaths would be attributable to a fall in smoking prevalence from (26% to 21%), with 2,525 attributable to a reduction in total cholesterol (from 5.8 mmol/l to 5.6 mmol/l) and 5,135 attributable to falls in population diastolic blood pressure (from 74.6 mmHg to 73.7 mmHg, *Tables 12.2 and 12.3*).

Obesity, diabetes prevalence and physical activity showed adverse trends between 1981 and 2000. Assuming the same adverse trends continued to 2010, these risk factors would cause approximately 6,980 additional CHD deaths (2,080 from obesity, 4,200 from diabetes and 705 from physical inactivity) *(Figure 12.1)*.

**b)    *More substantial reductions* in major risk factors *(Tables12.2 and 12.3)***

A total of approximately 50,410 deaths (minimum 37,210, maximum 75,435) could be prevented or postponed by additional but feasible reductions in cardiovascular risk factors.

i)      Approximately 17,060 fewer deaths assuming that the smoking prevalence fell from 26% to 17%;

ii)     24,945 fewer deaths assuming that population mean cholesterol levels declined to 5.2 mmol/l among men, and women;

iii)    6,505 fewer deaths assuming an average additional decrease in mean diastolic blood pressure of 3.7 mmHg across all age and sex groups (from 74.6 mmHg to 70.9 mmHg).

iv)     850 fewer deaths assuming a 15% decrease in obesity (a reduction from 21% to 18%o in men and women by 2010).

v)    485 fewer deaths assuming a 5% decrease in diabetes prevalence (from 3.0% to 2.9%
      in men and from 2.1% to 2.0% in women by 2010).

vi)   1,055 fewer deaths assuming a 5% increase in the prevalence of moderately active
      people (from 46% to 49% in men and from 37% to 39% in women).

The number of DPPs in 2010 due to these additional risk factor changes could thus be increased more than three fold, from 13,760 to 50,410; if relatively modest improvements in adverse risk factors were achieved *(Tables 12.2 and 12.3)*.

These estimates remained relatively stable when subjected to a rigorous sensitivity analysis *(Figure 12.1)*.

**Table 12.2** Risk factor levels in the 2000 base year and projections to 2010: a) simply continuing recent trends,  b) assuming more substantial reductions achieved elsewhere *(men and women aged 25-84 years).*

| Risk Factor Levels | Smoking % | | Cholesterol mmol/l | | Diastolic Blood Pressure mmHg | | Obesity % | | Diabetes % | | Physically Active* % | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Men* | *Women* | *Men* | *Women* | *Men* | *Women* | *Men* | *Women* | *Men* | *Women* | *Men* | *Women* |
| 2000 | 28 | 24 | 5.8 | 5.8 | 76.9 | 72.3 | 21 | 21 | 3.0 | 2.1 | 46 | 37 |
| a) 2010 recent trends | 22 | 21 | 5.7 | 5.7 | 76.4 | 71.1 | 33 | 24 | 4.7 | 3.0 | 43 | 34 |
| b) 2010 Additional reductions | 17 | 17 | 5.2 | 5.1 | 73.2 | 68.6 | 18 | 17 | 2.9 | 2.0 | 49 | 39 |

*: Moderate or strenuous activity ≥3 times/week for >20 minutes

**Table 12.3 The estimated reduction in CHD mortality in England and Wales between 2000 and 2010 on the basis of changes in specific risk factors: a) continuing recent trends, and b) with more substantial reductions.**

| RISK FACTORS | Change in Risk Factor Between 2000 & 2010 | | Deaths prevented or postponed in 2010 as a result of reductions in risk factors between 2000 and 2010 (maximum and minimum estimates) |
|---|---|---|---|
| | Men | Women | |
| **Smoking** | | | |
| Recent trend | -19% | -16% | 8,880 (6,115 to 13,610) |
| More substantial reduction | -40% | -36% | 17,060 (9,810 to 30,555) |
| **Total Cholesterol** | | | |
| Recent trend | -2% | -2% | 2,525 (1,530 to 4,735) |
| More substantial reduction | -10% | -13% | 24,945 (21,615 to 31,185) |
| **Population blood pressure** | | | |
| Recent trend | -1% | -2% | 5,135 (3,850 to 6,630) |
| More substantial reduction | -5% | -5% | 6,505 (4,875 to 8,265) |
| **Obesity** | | | |
| Recent trend | 57%* | 6%* | -2,080* (-1,610 to -8,010) |
| More substantial reduction | -15% | -15% | 850 (385 to 3,425) |
| **Diabetes** | | | |
| Recent trend | 48%* | 30%* | -4,200* (-1,945 to -5,915) |
| More substantial reduction | -5% | -5% | 485 (205 to 630) |
| **Physical activity** | | | |
| Recent trend | -2%* | -9%* | -705* (-350 to -915) |
| More substantial reduction | 5% | 5% | 1,055 (525 to 1,370) |
| **ALL RISK FACTORS** | | | |
| Recent trend | - | - | 13,760 (9,540 to 16,050) |
| More substantial reduction | - | - | 50,410 (37,210 to 75,435) |

\* *Worsening trend producing additional CHD deaths*

## Benefits stratified by age and sex, and comparison with UK targets

Overall, men would benefit more than women ('current trends' 72% of prevented deaths in men and 28% in women; 'additional reductions'60% in men and 40% in women). Approximately 24,000 fever deaths would occur in men and women aged under 75, the age group specified in the government target (Table 12.4).

## Deaths prevented or postponed by treatments

Medical and surgical treatments in 2000 together prevented or postponed approximately 25,765 deaths[248](Chapter 11). This figure might well rise to approximately 46,675 fever deaths by 2010, if the National Service Framework targets are achieved, with at least 80% of eligible patients receiving appropriate therapy[395]. This would therefore represent approximately 20,000 fewer deaths than in 2000.

## Sensitivity analyses

There is a consistently huge potential gain from cholesterol reductions in the population. Large DPPs can be achieved also from smoking reduction in the population. Furthermore, DPP gains from smoking can range from as little as 9,810 to very substantial higher values (30,555) (Figure 12.1).

**Table 12.4 Reductions in CHD mortality achievable in 2010, stratified by age and sex a) continuing recent risk factor trends and b) with more substantial risk factor reductions.**

| | Deaths prevented or postponed | | | |
| --- | --- | --- | --- | --- |
| | Men | | Women | |
| | Number | %* | Number | %* |
| **25-34 years** | | | | |
| Recent trends | 3 | 0% | 2 | 0% |
| More substantial reduction | 60 | 0% | 10 | 0% |
| **35-44 years** | | | | |
| Recent trends | 180 | 1% | 30 | 0% |
| More substantial reduction | 725 | 1% | 140 | 0% |
| **45-54 years** | | | | |
| Recent trends | 855 | 6% | 125 | 1% |
| More substantial reduction | 3,145 | 6% | 720 | 1% |
| **55-64 years** | | | | |
| Recent trends | 1,345 | 10% | 475 | 3% |
| More substantial reduction | 4,115 | 8% | 1,420 | 3% |
| **65-74 years** | | | | |
| Recent trends | 2,490 | 18% | 1,505 | 11% |
| More substantial reduction | 8,560 | 17% | 4,995 | 10% |
| **75-84 years** | | | | |
| Recent trends | 5,070 | 37% | 1,685 | 12% |
| More substantial reduction | 14,035 | 28% | 12,485 | 25% |
| **Total** | | | | |
| **Recent trends** | **9,935** | **72%** | **3,820** | **28%** |
| **More substantial reduction** | **30,635** | **60%** | **19,775** | **40%** |

* Over total DPPs gain from recent trends (13,760) and more substantial reductions (50,410).

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**Figure 12.1 Potential change in CHD mortality in England and Wales between 2000 and 2010 if risk factors a) continue recent trends b) undergo more substantial reductions.**
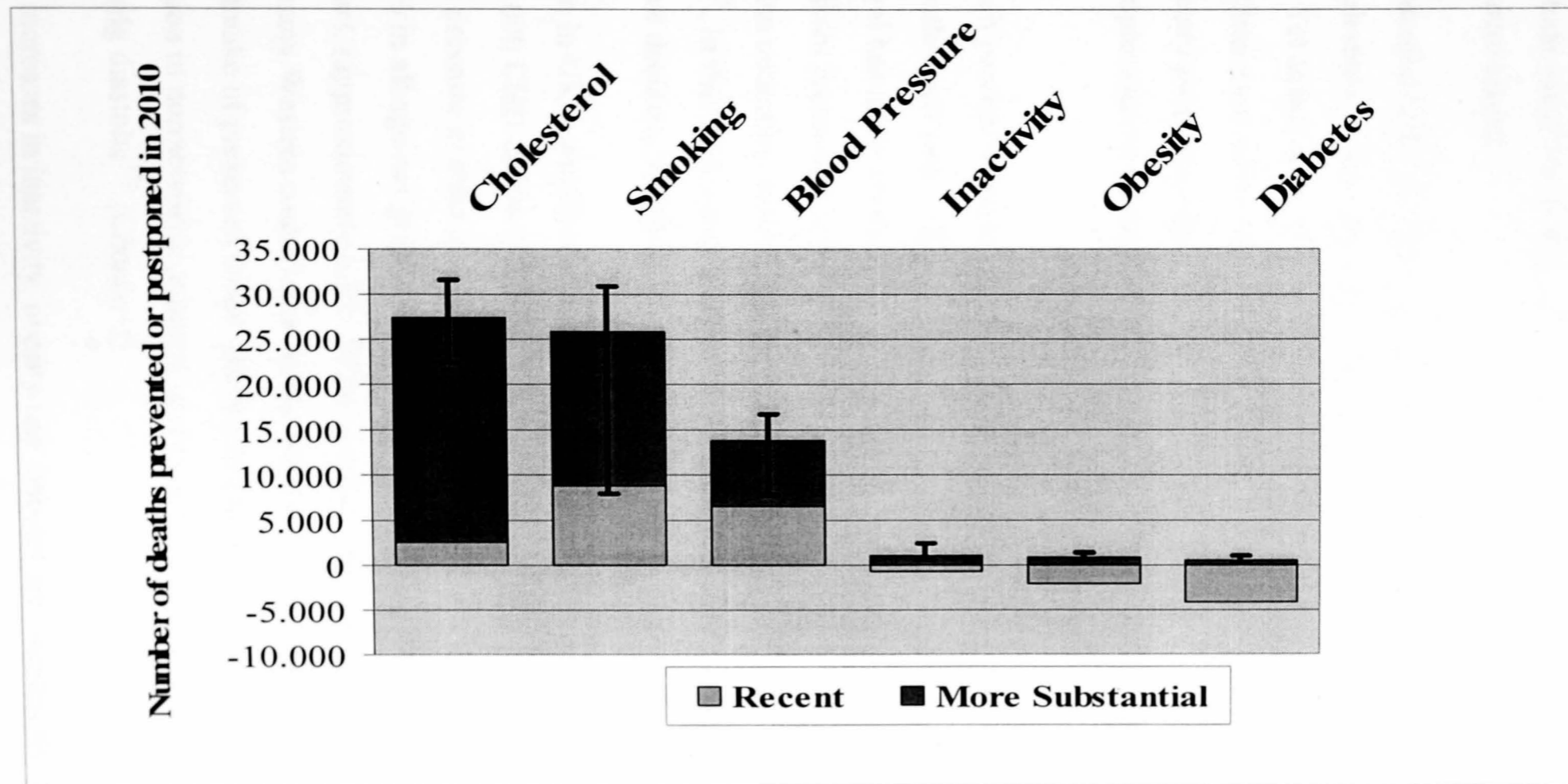


(Bars indicate maximum and minimum estimates from the sensitivity analysis).

## 12.4 Interpretation

Surprisingly modest risk factor reductions could prevent or postpone over 50,000 CHD deaths in 2010 in the UK. This would represent half the 100,000 current annual coronary deaths[2], and would include some 24,000 fewer premature deaths (aged under 75), as specified in recent government targets.

The biggest potential CHD mortality reductions in the UK would come from decreases in blood total cholesterol: with a 2% - 4% mortality reduction for every 1% decrease in cholesterol[32]. Yet actual falls in UK total cholesterol have been modest, and current levels remain higher than most of the other Western countries[2]. This is not surprising given the lack of coherent dietary policies in the UK. As I have previously emphasised in *Chapter 3*, elsewhere, complementary national and local programmes have achieved substantial dietary changes[123;124].

I found that each percent reduction in UK smoking prevalence would result in some 2000 fewer CHD deaths each year. The recently approved WHO Framework Convention for Tobacco Control has again emphasised the two essential comprehensive strategies: preventing young people from commencing to smoke, and promoting cessation in smokers[396]. In most of the Scandinavian countries, advertising bans were found to be effective in lowering tobacco consumption[117]. In the USA intensive health promotion and taxing programmes resulted in more impressive declines, which slowed visibly when these programmes were suspended[119].

A 1% reduction in UK population diastolic blood pressure, continuing recent trends, would prevent over 5,000 CHD deaths in 2010. This is because recent relative changes in mean diastolic blood pressure in older age groups were substantial, up to 8%. Thus, assuming a reduction of 5% in **all** age-sex groups, as seen in Scandinavia, would have surprisingly little additional impact, (approximately 6,505 DPPs overall). Population blood pressure has been decreasing in many Western countries in recent decades[125]. Much of this has been attributed to the reduced intake of preserved foods. Dietary salt restriction clearly achieves a small blood pressure reduction in normotensive subjects, and even more in hypertensives, about 4 mmHg systolic / 2 mmHg diastolic[126] *(Chapter 3)*.

The recent UK increases in inactivity, obesity and diabetes are responsible for over 7,000 CHD deaths each year. Effective interventions to change these risk factors in the population

are discussed in *Chapter 3*. Systematic reviews of mostly US studies suggest that *in individuals*, exercise interventions promoting walking are more successful than those requiring attendance at a facility[142]. The most effective intervention for *obese individuals* is apparently a combination of advice on diet and exercise, supported by behavioural therapy[138]. In the *population*, obesity reduction appears challenging whereas several interventions clearly increase physical activity. These include community wide campaigns, school based interventions and individually adapted health behaviour change programmes[141]. Furthermore, transport policies that promote walking and cycling may play a major role. No government obesity targets have yet been set. The recommendations by the ongoing Health Select Committee enquiry are eagerly awaited.

The strengths and limitations of the model are discussed in detail in *Chapter 13*. In addition a number of further assumptions were made to estimate the number of deaths that could be prevented with additional risk factor reductions. For example, I assumed that major risk factors might continue to change at similar annual rates until 2010, and that coronary mortality would continue to decline at current rates. Extensive sensitivity analyses were therefore required to consider higher and lower values for each estimate[231]. These modestly influenced the number of DPPs, but did not alter the relative contribution of each risk factor *(Figure 12.1)*.

Furthermore, our findings are generally consistent with a recent report on monitoring the 2010 CHD target[336]. This report suggested that reducing mean population cholesterol level to 5 mmol/l or less would prevent approximately 50% of CHD deaths. An (optimistic) 25% reduction in the prevalence of obesity or inactivity might prevent 2% and 1% of CHD deaths respectively[336].

In conclusion, the government's "Saving Lives" target therefore appears eminently achievable and distinctly unchallenging. However, Britain lags behind many other counties and CHD will remain the biggest cause of death for the foreseeable future. Furthermore, continuation of current trends cannot be assumed, particularly given the 'levelling off' in CHD mortality recently seen in the USA[397].

The policy implications of these findings will be discussed in the next chapter.

# 13 DISCUSSION

## 13.1  Main findings

In my thesis, I first evaluated the data sources available for CHD in the UK. Data were varied in quality. Population and patient data were usually available and accessible from official statistics. Risk factor data were limited for the early 1980s  but more extensive by 2000. Data on hospital interventions were not routinely available, but limited prescribing and uptake data for primary and secondary care were available.  In general, data for women and the elderly (over 65) were particularly scarce and variable in quality.

Using these available data, I then explored the CHD burden in England and Wales. In 2000, an iceberg of disease was apparent in the England and Wales population of 51 million, with approximately 60,000 patients undergoing revascularisation, over 2.5 million patients living with CHD and over 32 million possessing one or more elevated risk factors *(Chapter 4)*.

CHD mortality fell by more than half between 1981 and 2000 in England and Wales.  In my thesis, I therefore transformed and developed the IMPACT model to explore this decline. Approximately 40% of the fall was attributable to the combined effects of modern cardiological treatments, whereas almost 60% was attributable to reductions in major risk factors *(Chapter 9)*.  These findings were consistent with the majority of other studies that used  diverse methodologies in the USA[193], Europe[251], Scotland[4], and New Zealand[5]. Thus in the US population, for instance, 50% of the recent CHD mortality decline was actually explained by risk factor reductions[233].

Modern cardiological treatments prevented or postponed approximately 26,000 deaths in 2000 in England and Wales.  The most substantial contributions came from secondary prevention therapies and heart failure treatments. This is not surprising, because improvements in survival after acute coronary events in the last decade have been documented in many countries, including England and Wales[249] , thus potentially increasing  the number of patients eligible for secondary prevention.

Reductions in the major risk factors between 1981 and 2000 accounted for approximately 36,000 fewer deaths in England and Wales in 2000.  The biggest single contribution reflected a large fall in smoking prevalence, from 39% to 28% overall.  Almost 10% of the mortality fall came from a relatively small reduction (4.2%) in population total cholesterol level.  This

emphasises the potential gains from bigger reductions in population cholesterol, with a 2% - 4% mortality reduction for every 1% decrease in cholesterol[32].

In my thesis, I then estimated life-years gained (LYGs) from cardiovascular risk factor reductions and cardiological treatments. This is the first comprehensive analysis of life years gained from risk factor reductions and cardiological treatments published for England and Wales. The fall of 69,000 DPPs corresponded to almost one million additional LYGs in the same period. Surprisingly, cardiological treatments explained only 21% of this gain, mostly from secondary prevention and angina treatments. Although heart failure treatments resulted in over 7,700 DPPs, because of the short life expectancy in these patients, only 25,360 LYGs (or 2% of overall LYGs gained by cardiological treatments and population risk factor changes in England and Wales, in 2000) might actually be gained[248;264]. Almost 79% of the LYGs came from changes in population risk factors, principally smoking, but also cholesterol and blood pressure *(Chapter 10)*.

A death prevented or postponed in a patient with recognised CHD gained an additional 7.5 years of life on average. Gains were greater in men, younger patients, or those surviving uncomplicated infarction, rather less in older patients or those with heart failure. In contrast, each death prevented or postponed by a risk factor reduction gained an additional 20 years of life on average, substantially more in younger individuals, rather less in older people. These findings are generally consistent with previous studies[382]. However these LYGs occurred in people whose deaths due to CHD was prevented or postponed, rather than in the whole population. However, population life expectancy might also be increased. Bunker et al. examined the 7.1 years increase in life expectancy observed in the USA between 1950 and 1989. Changes in coronary and cerebrovascular disease death rates accounted for 10%-20% of this increase[385]. This is consistent with estimates for Scotland (1975-1981)[386]. Again in the USA, Tsevat et al attributed 1.0 to 1.2 years increase in population life expectancy by lowering blood pressure in men, (and 0.3 to 0.6 years in women), and 0.5 to 1.2 years by quitting smoking in 35-year old men (0.4 to 0.8 in women)[238]. Using similar assumptions, Grover et al estimated that reductions in CHD and stroke risk through blood pressure reduction would result in 0.9 to 1.2 years increase in life years in men aged 40, and 0.6 to 1.3 years in women[382].

In 2000, barely half the patients with CHD actually received the appropriate therapy in England and Wales. I therefore further explored potential benefits from increasing treatment

uptake levels. If just 80% of eligible CHD patients had received the cardiological treatment indicated for them in evidence-based guidelines, then a further 20,500 deaths could have been prevented or postponed. This would have almost doubled the reduction in mortality actually achieved by treatments in England and Wales in 2000(Chapter 11). The largest contributions would come from increasing heart failure and secondary prevention treatments to 80%. Furthermore, such prioritisation would mean focusing principally on patients in the community. These findings were consistent with previous studies[321]. Furthermore, as discussed in Chapter 11, they highlighted the need to identify effective strategies for increasing treatment uptake.

In Chapter 12, I considered the number of additional CHD deaths that might potentially be prevented or postponed by further reductions in major cardiovascular risk factors. Firstly assuming that cardiovascular risk factors simply continued their recent trends to 2010, and then by assuming the additional small and feasible reductions already seen in several other countries. The modest additional risk factor reductions already achieved in Scandinavia and the USA could potentially prevent or postpone over 50,000 CHD deaths in 2010 in the UK. This would halve the 100,000 current annual coronary deaths. However, I only estimated the impact of population risk factor change without considering in detail how these levels could be achieved. There is ongoing debate about whether to target high-risk people or the whole population for risk factor interventions. Kottke et al modelled these two interventions to compare the expected benefits from high-risk and population strategies, using Monte Carlo simulation[398]. They used actually achieved cholesterol and blood pressure changes without drug treatment in North Karelia between 1972 and 1977[399]. They found that a 4% reduction in cholesterol, 3% reduction in DBP and 15% reduction in smoking prevalence in the whole population would lead to 12% decrease in nonfatal MI, and 18% decrease in CHD deaths in the US[398]. However, just targeting people who have 3 risk factors with high levels and reducing their cholesterol to 180 mg/dl (or 4.7 mmol/l), diastolic blood pressure to 80 mmHg and eliminating smoking would reduce nonfatal MI by 2% and CHD death by only 5% in the US[398]. Their findings were similar for Finnish North Karelia cohorts[398]. It has been consistently suggested by Rose and others that in populations with a relatively high incidence of CHD, such as England and Wales, targeting entire population would produce larger effects than focusing on high-risk populations[188;398].

## 13.2 Strengths of the IMPACT Model

This study used a cell-based mortality model, which has been tested and refined over a number of years in several different populations[4;5;321;322;386]. It was extensively developed over the three years of my PhD studentship. The IMPACT Model can now generate estimates for DPPs and life years gained for England and Wales population. Furthermore it can estimate potential gains from further treatment increases[320] or risk factor reductions[322].

In this thesis, I have described the further development of the original IMPACT Model to include new treatment options and risk factors. This has made the IMPACT Model quite comprehensive. Despite its size, the IMPACT Model is user friendly, as it is based in a common spreadsheet package, Excel, and therefore easy to update with new data or to add new treatment options or risk factors.

The IMPACT Model is the first comprehensive CHD mortality model for whole population of England and Wales. In this thesis, I used the model to consider questions relevant to public health policy and CHD NSF[148].

The model incorporated large amounts of data from various selected best available sources. Data quality was assessed first, and missing or incomplete data were dealt with by extrapolation or explicit assumptions. The assumptions used in IMPACT Model were documented and tested. Comprehensive sensitivity analyses were then carried out to explore these limitations.

Comparing with other major models in *Table6.2*, the IMPACT model satisfies most of the quality criteria recommended in the ISPOR Guideline[216]. The IMPACT model considers risk factors and categories of CHD and treatment options in a coherent model. Few of the models reviewed in *Chapter 6* considered risk factors and treatments together. Furthermore, IMPACT's internal validity was extensively checked by two other researchers (SC, JC).

The IMPACT Model estimates were then validated by comparison with the observed reductions in CHD deaths in England and Wales, stratified by age and sex. This method appears acceptable since IMPACT is a descriptive model. External validity or predictive validity may be considered desirable but not be essential for this kind of model[215,216].

The validity of this model could be further evaluated using different models for the same question[215], such as PREVENT or CHD Policy Model (corroboration). However this might well require considerable time and effort.

All modelling studies include a number of assumptions, which need to be clear and well documented for the users. The assumptions used in IMPACT Model were tested and documented.

## 13.3 Limitations of the IMPACT Model

### CHD Data input

All modelling studies have limitations. Models are based on large amounts of data from many sources. However available data may be mixed in quality and lacking in quantity. In case of the IMPACT model, UK CHD data sources lacked precise data for some of the risk factor changes and patient numbers. However, to a certain extent it was possible to extrapolate some of the missing data. This was the case for diabetes and cholesterol trends since data were not available for the beginning of 1980s.

I also needed to make a number of explicit assumptions to cover deficiencies in the UK data on CHD[206]. This was essential for age specific treatment uptake levels for hospital CHD care, and some of the risk factors in the early 1980s such as blood pressure and cholesterol. Furthermore, different sources reported slightly different uptake levels or risk factor levels. In such cases, I choose the most "reasonable" source after critical consideration of all alternative sources. In modelling studies uncertainties in some data are unavoidable. However, sensitivity analyses are extremely useful to quantify the degree of uncertainty and hence the potential bias. I therefore used rigorous 'analysis of extremes' sensitivity analysis methodology to examine these uncertainties in data[231]. Reassuringly, the relative contribution of each risk factor and treatment to the overall CHD mortality decline was little changed whether considering best, minimum or maximum estimates *(Figure 9.2)*.

When I started to build the IMPACT Model for England and Wales, I aimed to include all age groups over 25. However, risk factor and treatment data for people over 85 years were very limited. Therefore, my final model only included the age groups 25-84. The model fit was also not so good in older women, aged 75-84 years. This probably reflects less satisfactory data quality, particularly less accurate coding for cause of death *(Table 9.5)*[157, 183]. The elderly

population is increasing, and as they will have higher health care needs. it is very important that modelling studies in the future should explicitly include these groups. Fortunately. in the UK and other comparable countries more data have become available for elderly people in 1990s[400].

## Model Outcomes

At the moment, the IMPACT Model focuses only on mortality and LYGs. A recent attempt was made to include cost and cost-effectiveness of the treatments for CHD in England and Wales in 2000[401]. Future work should also focus on converting LYGs in to quality adjusted life years (QALYs), and estimating the cost-effectiveness of interventions for primary and secondary prevention strategies. It would also be desirable to include outcomes such as the incidence of CHD or symptomatic relief. Some CHD policy models have included a wider range of outcomes. For instance, the CHD Policy Model can generate estimates for many outcomes such as incidence of CHD events, CHD prevalence, CHD mortality, life years gained, cost per life year and all cause mortality[222]. However that model does not include all individual CHD treatment effects.

The IMPACT model was confined to CHD, and did not explicitly consider patients with other CVD such as stroke or peripheral arterial disease. Neither does IMPACT consider the development of other diseases or "competing causes" such as cancer[373]. However, since many cancers share some CHD risk factors such as smoking, interventions for reducing smoking would actually decrease deaths from lung cancer and other cancers[2;119;156].

The original Scottish IMPACT Model only included three major risk factors - smoking, cholesterol and blood pressure. I therefore introduced new risk factors including diabetes, obesity, physical inactivity and deprivation to the IMPACT Model for England and Wales. This improved the model fit substantially and now IMPACT Model explains 89% of the mortality fall. Furthermore, it has been estimated that these major risk factors explain approximately 85% of the UK variation in CHD risk [333]. However, other independent risk factors, such as dietary antioxidants, homocysteine and the birth weight, could be included to increase comprehensiveness.

## Methodology

Certain methodological issues merit further attention in the IMPACT Model. Risk factor lag times were not explicitly considered. For many carcinogens, the delay between exposure to a carcinogen and overt disease may be decades, however, lag times for CVD are much shorter[366]. Lag times may therefore be relatively unimportant over a 20-year analysis of CHD, because mortality reduction occurs relatively quickly, within 1-5 years of quitting smoking or reducing cholesterol[22;32].

## Assumptions

The IMPACT Model used β coefficients to estimate impact of risk factor changes on CHD mortality. Assumptions were made that benefits from concomitant risk factor reductions are "independent" therefore DPPs from each risk factor could be summed. All the beta coefficients and relative risk values were obtained from multivariate logistic regression analyses and therefore adjusted for potential confounding from the major risk factors. However 'residual confounding' from other potentially important risk factors for CHD, including diet (such as consumption of fish oils anti-oxidants and alcohol), and life-course factors and some novel risk factors may remain. These estimates may therefore still overestimate, because most multivariate regression models, of necessity, included data on only a limited range of risk factors. For the MONICA study, for instance, these were smoking (yes or no), systolic blood pressure, total cholesterol, and body mass index[125]. Further development work is clearly needed[3].

The IMPACT model also assumes that efficacy, the mortality benefits reported in randomised controlled trial patients can be generalised to effectiveness in unselected patients in clinical practice. Though not ideal, this appears acceptable[402]. A consistent treatment effect independent of the level of risk is also assumed, again, perhaps not unreasonably[402].

Sensitivity analyses were essential to examine the effect of varying these underlying assumptions, and hence test the robustness of the model[231]. Maximum and minimum estimates were sometimes wide. However, the relative contribution of each individual intervention remained remarkably consistent. Thus the major potential gains from *treatments* generally came from heart failure and secondary prevention, followed by initial treatments for myocardial infarction and statins. Correspondingly, the largest risk factor impacts always came from smoking and cholesterol, *(Figure 9.2, Figure 10.3, Figure 12.1)*.

## 13.4  How can CHD modelling be improved?

Modelling is potentially very useful for health policy decision-making. However not all the models are equally suitable for this purpose. Modelling in health is a relatively new scientific field. As model users and developers increase and become more experienced, so modelling standards should also improve as validation becomes routine.

First comes internal validity. The technical accuracy of models must be verified to ensure that the model performs all the calculations correctly. Data entry errors, logical inconsistencies can all be detected during verification[218].

External validation is also becoming more straightforward. Recently published guidelines now provide basic principles for modelling[216;220;226]. Furthermore, such guidelines are not prescriptive; they simply attempt to systematize the components of the model and the information needed for model development. Clearly, different circumstances may lead to deviations from these guidelines, depending on the purpose of the model and on resources available (time, data, money). However, promoting and publicising 'best practice principles for managing models, (whether based on spread sheets or on other methodologies) is likely to increase their user friendliness, acceptability and credibility [226].

### How can we improve the IMPACT model?

A number of improvements should be considered:

- Including different outcomes, such as the QALY. This could be achieved by applying published QALY weights to specific patient groups.

- Including CHD events (incidence) or 'number of surgical interventions such as CABG and PTCA avoided' as outcome. This could be done with more reliable data on these outcomes as they become available

- Including new treatments and risk factors. The model can then be updated as new effective treatments become available. It could also be updated with trend data on new risk factors as these become available, for instance low birth weight, or specific dietary factors.

- Consultations between the developers, the potential users of the IMPACT Model and one or more IT specialists could improve the user friendliness of the model. For instance, a more user-friendly "front end". The IMPACT Model could start with a brief introduction, portfolio of exercises, and options to test and compare different policy options. This could

perhaps be achieved by incorporating macros, which could save some columns in the currently large model spreadsheet.

- The original Operational Manual for the IMPACT Model was created by our team (SC, JC, BU) and used by collaborating researchers. A revised and updated manual would potentially be very useful to introduce new users to the basic methodology of the model.

## 13.5   Implications for public health practice

The National Service Framework for Coronary Heart Disease now requires primary care disease registers in every practice. Such registers will certainly help to identify eligible patients, but will require substantial resources[148]. Furthermore, it is unclear whether registers alone will substantially increase treatment uptakes[403]. The National Service Framework for Coronary Heart Disease also requires practices to establish 'cardiac prevention clinics' run by trained nurses and supported by a doctor. Structured care should be provided in these clinics for the patients with CHD. It is recommended that by April 2002, the use of effective medicines after heart attack (especially use of aspirin, beta-blockers and statins) should be improved so that 80-90% of people discharged from hospital following a heart attack will be prescribed these drugs. However, no clear milestones were set for patient care in the population[148]. These recent government targets, combined with financial incentives in the new GP contract, may also have positive effects[404]. Greater patient empowerment may also be required[148].

## 13.6   Policy implications for decision makers

This modelling work provided potentially very useful information for health policy makers. It demonstrates that risk factor changes consistently prevented more deaths and saved more life-years in the general population than treatments. This is mainly because the number of individuals eligible for each treatment was much smaller compared than the number of subjects potentially eligible for risk factor changes using the 'population approach'. Some interventions offer only small benefits to individual patients however, when applied to large numbers of people they produce significant health gains for the population and this is known as *prevention paradox*[188]. This emphasises the importance and potential of primary prevention strategies. Interventions should therefore target the whole population, and should be comprehensive. Tobacco taxation plus legislation on smoking restrictions in public places, green transport policies and diet interventions can all be particularly valuable. Such policies

could produce further substantial reductions in coronary mortality, as already achieved elsewhere[119;125;192]. Periodic risk factor evaluation for the individuals recommended and interventions directed to the high-risk people rather than the whole population[148]. However in the CHD NSF this population approach was rather overshadowed by the individual patient care perspective.

## 13.7 Clinical implications

This thesis also produced potential useful findings for the clinical management of CHD. Treatments for the secondary prevention of CHD prevented or postponed more deaths than any other intervention in CHD patients. Heart failure therapies also had a major effect, particularly surprising given the often poor prognosis of heart failure in many patients.

Revascularisation from CABG surgery and angioplasty surprisingly accounted for only a very small part of the mortality fall and gains in life-years. Similar findings have been reported from other countries such as USA too[375]. This is a disappointingly small contribution, considering the large financial and political resources being consumed to promote revascularisation[148;205]. However, it is important to remember that this thesis has considered only mortality and life years gained as outcomes. Revascularisation might be more effective at relieving anginal symptoms than medical treatments such as beta-blockers, nitrates and calcium channel antagonists[151].

The LYGs from ACE inhibitors, beta-blockers and spironolactone were relatively large, given the relatively low prescribing rates in 2000 and the high case fatality in heart failure patients[286]. This further emphasises that simple inexpensive treatments applied to all eligible patients can potentially produce huge gains[148].

## 13.8 Research implications and future research questions

1) One of the future research questions is related to the modelling methodology. At present I assume that risk factor reductions are independent, as discussed above. It would be worthwhile to explore how much difference does clustering of risk factors make and whether the reductions occur in those with many or only one risk factor.

2) CHD mortality did not fall equally in all social classes. It would therefore be desirable to evaluate the risk factor trends in these groups and explore their impact on mortality change.

3) More effective methods are needed for changing risk factor distributions in the whole population. There is currently a lack of evidence for some factors, including physical activity, diabetes, and obesity.

4) This thesis emphasised effective strategies to reduce CHD mortality in England and Wales. Liaison with local and national policy makers to increase the utility of the model is therefore very important. Several people and groups who worked in various levels of NHS have consulted us to use the model to answer different questions in their practice. We offered training and collaboration, because the model was not sufficiently user friendly to let them use it unaided. Future work should therefore involve efforts to increase the user friendliness of the IMPACT Model, as described above.

## 13.9 Lessons I have learned

- While building a model, it is very useful to keep a diary, because modelling is an iterative process.

- A list of data and the sources used in the model should be prepared and updated frequently with evaluation, strengths and weaknesses of the sources.

- Building the model involves a lot of teamwork. Good cooperation and communication between the team members is crucial. Regular meetings and supervision can be very helpful.

- There should be also some agreement between the team members on the ways of working on the model. These may involve more practical actions for example writing the formulas in a certain way, not putting the same data source in the spreadsheet more than once but linking it if it is necessary or using the same colour code for some estimates. A 'best practice points' list was suggested by Edwards et al[226] *(Appendix 12).*

- Teamwork is also important for model verification to check the model for erroneous data entries and formulas.

- While building a model, it is important always to keep electronic back-ups on different computers, since a virus attack or a technical problem can destroy the product of long and painstaking work.

## 13.10 Conclusions

CHD represents a massive burden of disease in England and Wales. Yet information on CHD is quite patchy and poor. Future CHD disease monitoring and evaluation therefore will require more comprehensive and accurate population-based information on trends in patient numbers, treatment uptake and risk factors. This will require adequate resources to improve existing information systems. Regular and comprehensive surveys (including women and elderly people), using standardised methodology will also be essential.

CHD mortality in England and Wales fell by more than half between 1981 and 2000. Over half this fall was attributed to reductions in major risk factors, and some forty percent to medical therapies. This fall in CHD mortality resulted in almost one million additional years of life. Modern cardiological treatments in England and Wales in 2000 gained many thousands of life-years. However, three times as many life-years were generated by relatively modest reductions in major risk factors, mainly smoking, cholesterol and blood pressure.

In the year 2000, treatment uptake levels were generally poor. Increasing uptake levels to reach 80% in all eligible patients would have almost doubled the deaths actually prevented or postponed. The largest benefits would have come from heart failure and secondary prevention treatments. Furthermore, if the UK managed the modest additional risk factor reductions already achieved in the USA and Scandinavia, this could prevent or postpone substantial numbers of deaths, potentially halving the current coronary mortality by 2010. Cholesterol and smoking reductions would provide the largest gains.

These findings therefore emphasise the importance of a comprehensive strategy which actively promotes primary prevention, particularly for tobacco and diet, and which maximises population coverage of effective treatments, especially for secondary prevention and heart failure.

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# 15 APPENDICES

# LIST OF APPENDICES

# 15 APPENDICES

## Appendix 1 Search strategy for CHD policy models review

1. exp Cardiovascular Diseases/

2. (coronary adj10 (disease$ or event$ or atherosclero$ or arteriosclero$ or thrombS)).tw.

3. (heart adj10 (attack$ or isch?emi$ or arrest or disease$)).tw.

4. (myocardial adj10 (infarct$ or isch?emi$)).tw.

5. angina$.tw.

6. (CHD or IHD or CAD).mp.

7. (CHD or IHD or CAD).tw.

8.(sudden$ adj10 cardiac).tw.

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. coronary.tw.

11. exp Myocardial Infarction/

12. exp Coronary Disease/

13. exp Coronary Arteriosclerosis/

14. *Arteriosclerosis/

15. exp Arteriosclerosis Obliterans/

16. exp Coronary Thrombosis/

17. exp Myocardial Ischemia/

18. Heart Failure.tw.

19. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. model$.tw.

21. simulat$.tw.

22. prevent$.tw.

23. treat$.tw.

24. 20 or 21

25. 22 or 23

26. 19 and 24 and 25

27. POHEM.tw.

28. CRISPERS.tw.
29. exp Decision Making/ or decision making.mp.
30. exp Health Care Policy/ or health policy.mp.
31. exp Public Health/ or public health.mp.
32. 26 or 27 or 28
33. 29 or 30 or 31
34. 32 and 33
35. limit 34 to human

# Appendix 2 Data extraction form for the eview of CHD Models

**Paper:** (Author, Year)
**Ref ID:**
**Reviewer:**          **Date:**

|  | Please tick one of the options | | |
|---|---|---|---|
|  | Yes | No | Unclear |
| Do the study refer to modelling*? |  |  |  |
| 2- Does the study deal with the population rather than the individual? |  |  |  |

Does the study report on one or more of the following health outcomes?
*(Please tick)*

| | |
|---|---|
| CHD deaths prevented |  |
| CHD disease prevented |  |
| CHD mortality |  |
| CHD prevalence |  |
| CHD incidence |  |
| CHD prevention OR treatment cost |  |
| Life years gained |  |
| Disability |  |
| Hospital admission for CHD |  |

## Final decision about a paper:

| Tick | | |
|---|---|---|
|  | 'In' | 'yes' to questions 1-2 **and** includes at least one of the outcomes in question 4 |
|  | 'Pending' | if any of the sections are 'unclear' |
|  | 'Out', | if any of the sections are 'no' ** |

*: for the purpose of this review, modelling is defined as attempts to create tools which help predicting outcome of interventions or explain observed trends (by risk factor change or specific treatment effect or implementation a new strategy) on population level.

**: If 2 reviewers disagree, they can then discuss

# DATA EXTRACTION FORM FOR CHD MODELS REVIEW

**Paper:** (Author, Year)
**Ref ID:**
Reviewer:                Date:

## A) MODEL DETAILS

**Name of the Model:** .....................

**Author of the model:** .....................

**Purpose of the model:** .....................

Model Setting
Country / Area:

Study Population
General description of population (Age, sex structure)

**Time period which the model covers**
Baseline modelling period:
Prediction period:

| Type of model | Please tick every method |
|---|---|
| Simulation | |
| Micro simulation | |
| Spread sheet | |
| Life table analysis | |
| Markov model | |
| Monte-Carlo model | |
| Others .......... | |

**Model Description:**

| RISK FACTORS INCLUDED | Tick please | Form* | Intervention *(describe)* |
|---|---|---|---|
| Primary prevention | | | |
| Smoking | | | |
| Cholesterol | | | |
| HDL-C | | | |
| LDL-C | | | |
| Triglycerides | | | |
| Drug therapy (ie statins for prim prev?) | | | |
| Blood pressure DBP/SBP | | | |
| Diabetes | | | |
| Physical activity | | | |
| Deprivation | | | |
| Obesity or BMI | | | |
| Diet-nutrition | | | |
| Other | | | |

| Secondary prevention (*Please specify the TX*) | | | |
|---|---|---|---|
| Tx1: ...... | | | |
| Tx2: ...... | | | |
| Tx3: ...... | | | |
| Tx4: ...... | | | |
| Rehabilitation | | | |
| Smoking cessation | | | |
| Diet | | | |
| Other | | | |

| Disease categories included | *Please tick* |
|---|---|
| Angina | |
| AMI | |
| Sudden cardiac death/Arrest | |
| Post MI | |
| Heart failure | |
| CABG | |
| PTCA | |

> * If the variable was modelled as continuous use 'Con' if it was categorical use 'Cat'

| DATA SOURCES USED: | Source | Comments on quality (Please consider sample size and response rates for surveys/ national data etc) | Limitations |
|---|---|---|---|
| Population data | | | |
| Mortality number/rate | | | |
| Morbidity number/rate | | | |
| Treatment uptake | | | |
| Risk factor Prevalence/ trends | | | |
| Treatment effectiveness | | | |
| Risk factor change effectiveness/ Betas | | | |
| Others | | | |

## TYPE OF OUTCOMES STUDIED          *Tick please*

| | |
|---|---|
| Number of deaths prevented | |
| Number of morbidity (MI/ HF/ etc?) prevented | |
| CHD mortality | |
| Prevalence | |
| Incidence | |
| Cost (per life year, per death prevented..) | |
| Life years gained | |
| Hospital admission for CHD | |
| Others (please describe) | |

**Please describe 'main' outcome of the study in the author's words:**

_____

_____

| SENSITIVITY ANALYSIS | No | Yes |
|---|---|---|
| Any sensitivity analyses carried out? | | |
| Were 95% CIs for RRs used for sensitivity analyses? | | |

Which sensitivity analyses were carried out? *(Analysis of extremes, One- Multi way, other?)*

..................................................................................

| | Poor | Reasonable | Good |
|---|---|---|---|
| Were sensitivity analyses discussed? | | | |

| CALIBRATION | No | Yes |
|---|---|---|
| Was the model calibrated? | | |

How was the model calibrated? *Describe........*

| PREDICTIVE VALIDITY | No | Yes |
|---|---|---|
| Was the validity of the model tested? | | |

How was the validity of the model checked? *Describe........*

How was the validity quantified? *(eg % explained)...............*

| TRANSPARENCY | Not available | Yes (Available) |
|---|---|---|
| Illustrations/ examples | | |
| Assumptions | | |
| Model availability for reader | | |

| POTENTIAL LIMITATIONS | Not Reported | Reported | Discussed | Method refined |
|---|---|---|---|---|
| Assumptions | | | | |
| Confounding | | | | |
| Lag times | | | | |
| Competing causes | | | | |

**Other comments on the study:**

# Appendix 3. Summaries of CHD policy models

## Coronary Heart Disease Policy (CHDP) Model

The CHDP Model was developed in 1980s by Weinstein et al as a state-transition, cell based model[1]. Its aim was to project the future mortality, morbidity and cost of CHD in the US[1]. CHDP Model was used to examine trends in CHD mortality[2;3] and expected gains in life expectancy from risk factor modifications[4]. It was also used to evaluate the cost effectiveness of medical interventions for primary and secondary prevention of CHD[5-8] and health promotion activities[9].

This model was based on 1980 population and mortality statistics. The methods, assumptions and limitations of the model were discussed in the published papers. When it was first developed it was not possible to check its validity. After few years it was calibrated using actual CHD mortality data of 1986.

- This model consists of three sub-models:

- A *demographical/ epidemiological* model, which represents the disease– free population aged 35-84. Here the population is stratified by sex, age groups and cardiovascular risk factors. This model includes risk factors as categorical variables, therefore in total over 5,000 cells are required. It then uses a logistic risk function based on the Framingham equation to calculate the annual incidence rates of CHD events for each cohort.

- A *bridge* model, which covers subjects for the first 30 days after they develop coronary disease. Using a CHD incidence data from Minnesota, the model first determines whether the first event is angina, myocardial infarction or cardiac arrest[1].

- A *disease history model*, which includes the survivors of the first 30 days, places them in 12 CHD states by age and sex, and then follows them through treatment pathways.

The CHDP model allows the user to simulate the effects of an intervention (either preventive, by risk factor modification, or therapeutic) by changing case fatality rates and observing the effect on mortality, morbidity and cost for up to a 30-year period.

### Risk factors included

Smoking, diastolic blood pressure, serum cholesterol and obesity (relative weight).

### Diseases considered

Angina, myocardial infarction, and cardiac arrest.

*Outcomes*

The number and rates of all cause and CHD deaths, number and rates of CHD events, number of persons surviving to age 85 with or without CHD, and costs for treatment and preventive interventions for CHD.

*Strengths of the model*

- Has been progressively refined since 1980s
- Relatively comprehensive model. Includes major risk factors and major CHD categories

- The model was validated by comparing CHD incidence and death estimates with 1986 US vital statistics and hospital discharge data

*Potential limitations of the CHDP model*

- Numbers of strata can get very large with addition of new risk factors

- It assumes that risk factors are distributed independently in the population rather than clustered as they are in the real world. This may overestimate the effects of multiple risk factor interventions.
- Congestive heart failure and angioplasty are not included

- The Framingham equations may not be entirely appropriate for cardiovascular risk factors in populations in Europe or elsewhere

## PREVENT

This is a cell based simulation model developed by Gunning-Schepers (1989) in the Netherlands[10]. It can be used to estimate the health benefits for a population of changes in risk factor prevalence comparing i) continuation of existing trends with ii) alteration of proportions of the population with given risk factors. The model allows one risk factor to be associated with more than one disease and one disease to be associated with more than one risk factor. Demographic evaluation is also taken into account in simulations[10].

The Prevent Model was used in many countries including Netherlands[10,11], Denmark[12-14] and the UK[15-17], to explore different health promotion interventions for CHD. Its validity was evaluated by applying it into a synthetic population generated by microsimulation. It was found that the estimates from Prevent Model were higher than the microsimulation

estimations therefore Prevent model slightly overestimated the health benefits of preventions[13]. However, depending on the calculation methods used, the Prevent Model slightly underestimated the smoking attributable deaths in Denmark[14] compared with the method defined by Peto et al[18].

The Prevent Model was adapted to the England and Wales population and used to explore effects of increased physical activity levels for CHD mortality[16]. The first strategy was to increase the proportion of moderate activity by 25% and the second strategy was a 25% increase in vigorously activity. Estimates for these two strategies showed useful policy directions in terms of effectiveness of physical activity. The greatest health gain could be achieved by concentrating the health promotion activities on sedentary people, on older people and on men[16]. However the model only focused on CHD mortality rather than morbidity or quality of life, despite physical activity having much bigger effect on prevalence of non-fatal diseases[16].

Data can be incorporated on present state and projections for: population structure, total mortality, disease specific mortality and risk factor exposures.

*Risk factors included*: Smoking, hypertension, cholesterol, lack of physical activity, obesity, and alcohol.

*The diseases considered*: CHD, stroke, chronic obstructive lung disease, lung cancer, liver cirrhosis, breast cancer, traffic accidents and accidental falls.

*Outcomes:* Changes in disease-specific mortality and total mortality, and life expectancy.

*Strengths*
- Has been progressively refined more than a decade
- Has been used to examine a variety of scenarios in different populations
- User friendly
- Does not need huge data input
- The simulations take into account the fact that an increased risk of a disease will not stop immediately after exposure stops but will reduce gradually (lag time)

*Potential limitations*
- Does not include specific treatments
- Benefits are measured only in terms of mortality, not morbidity or quality of life

- Originally ignores lead time (the length of time between first exposure to a risk factor and full-blown risk) but in later versions of the model this weakness was adressed[16].
- The model assumes that risk factors are independent of each other.
- Does not consider socio-economic variables explicitly
- Includes only population between 15 and 64 years old
- The code is not well documented
- The way risk factors can be described and changed is limited
- It includes risk factors as categorical variables (as prevalence rates) it is not possible to include risk factors as continuous variables

PREVENT PLUS is a more recent but less used version, which covers disease specific hospital days, costs and unhealthy person years[19].

## Cardiovascular Life Expectancy Model

This model was developed by Grover et al (1992) in Canada to examine cost-effectiveness of different treatment options for CHD. The model includes primary and secondary CHD prevention model parts. The primary CHD part calculates the annual probability of dying from CHD or other causes and annual risk of CHD events (with or without intervention) for a person without symptomatic CHD at entry to the model. The annual risk of developing specific CHD endpoints is based on data published for the Framingham Heart Study and depends on age, sex, diastolic blood pressure, total cholesterol, HDL cholesterol level and presence of left ventricular hypertrophy, the presence or absence of glucose intolerance and smoking status. The risk of 'all cause death' is based on 1986 Canadian Life Tables after adjustment for the diastolic blood pressure, smoking and glucose intolerance.

Once a person develops CHD then he moves to the secondary CHD model. This part of the model calculates the risk of dying during the 12 months following a nonfatal myocardial infarction. The risk estimations are again based on the Framingham logistic equations for primary events but this time after adjustment for the presence of CHD[20].

The predicted annual cumulative mortality difference with vs without intervention over the total life expectancy represents the total years of life saved after intervention.

*Risk factors included*
Age, smoking, diastolic blood pressure, serum cholesterol and glucose intolerance.

*Diseases considered*

Angina, myocardial infarction, coronary insufficiency

*Outcomes*

Life-years gained and years of life free from CHD symptom

*Strengths of the model*

- They used multivariate logistic coefficients for risk factors
- The model was validated using clinical trials (Helsinki Heart Study, Lipid Research Clinics Study and MRFIT Study).

*Potential limitations of the model*

- The validation of model only included middle-aged men; it is unclear how the model is validated for other age and sex groups.
- Initially no sensitivity analyses were performed but in recent papers based on the same model, sensitivity analyses were reported.
- The age range and population on which the model focused is not clear in any papers published

## CHD Policy Analysis Model

This model was developed for the Department of Health by the London School of Hygiene and Tropical Medicine and Universities of Southampton and Birmingham[21,22]. The primary prevention component of the model simulates the impact on benefits and costs of different primary prevention strategies[21]. The treatment component of the model evaluates the impact of different treatments given to different groups of CHD patients[22].

Both components are micro-simulation models and simulate the experience of individual members of the population in terms of discrete times of events.

The primary prevention component of the model includes risk factors such as age, sex, systolic blood pressure, total cholesterol, and smoking[21]. The disease events included are stable angina, unstable angina, myocardial infarction, sudden cardiac death, stroke death, other cardiovascular death, cancer death and death from other known and unknown cause[21]. Once an individual has had stable or unstable angina or myocardial infarction then he enters into the CHD part of the model[22].

The main data sources include the Health Survey for England for population characteristics. and the Framingham Study, which is used to provide data on CHD natural history. in the form of time-to-disease-event distributions conditional on the attributes of the individual concerned. However the Framingham risk estimates may not be easily generalisable to the UK population. The British Regional Heart Study was used to calibrate the baseline risk to the English level. Much of the incidence data were taken from the Bromley Study (in Kent) and the UK Heart Attack Study (based in Oxford). These may not be representative for the UK population. This model is still under development[21;22] and therefore validity has not been formally tested[21;22].

### Strengths

- When it is completed it will be comprehensive (will include major risk factors and treatments)
- Discrete event simulation gives advantages

### Potential limitations

- Framingham equations may not be generalisable to the UK population
- Does not include heart failure as a state
- At the moment does not include treatments for CHD
- Sensitivity analyses not done
- Not ready for extensive use yet

## IMPACT CHD Mortality Model

The IMPACT model is a cell-based model developed by Capewell et al in 1996. The methods, data sources used and assumptions will be described in detail in *Chapters 7, 8, 9.* In this model, principal age groups are from 25 to 84 since the data for over 85s is limited. The model focuses only on mortality and LYGs, not incidence or symptomatic relief. The number of risk factors included into the model is limited; dietary antioxidants are not yet included. Methodological issues merit further attention e.g. lag times, potential interactions between treatment effect and risk factor effects. IMPACT Model assumes that the efficacy in randomised trials can be generalised to effectiveness in clinical practice. It also assumes that DPP benefits from 'concomitant risk factor reductions are independent'. IMPACT does not consider the development of other diseases such as cancer and it is thus restricted when assessing the longer-term implications of different policy options.

## The Global Burden of Disease Model

This model was developed at WHO by Alan Lopez and Chris Murray as part of the Global Burden of Disease (GBD) Study in 1992 at the request of the World Bank. The three primary goals of the model were (i) to provide information for debates on international health policy and on international non-fatal health outcomes, (ii) to develop unbiased epidemiological assessments for major disorders, (ii) and to quantify the burden of disease with a measure that could also be used for cost-effectiveness analyses[23]. The ten major risk factors included in the model were malnutrition, poor water quality, unsafe sex, alcohol, occupation, tobacco use, hypertension, physical inactivity, illicit use of drugs, and air pollution[24].

The model can calculate the attributable burden of disease for a specific risk factor, population and time, which is defined as 'the difference between currently observed burden and the burden that would be observed if past levels of exposure had been equal to a specific reference distribution of exposure'. The reference distribution of exposure is defined as the risk factor exposures with lowest relative risk [24].

Global Burden of Disease Model has five components; causes of death, descriptive epidemiology of disabling sequel, burden attributed to selected risk factors, projections of burden for future and sensitivity analyses. Cause of death data is obtained from vital registrations or other sources. Data on 107 disorders and number of selected disabling sequels were investigated regarding average age of onset, duration, incidence and prevalence. Case fatality rates by age and sex and region were also estimated. Burden of disease and injury attributable to ten major risk factors were calculated. The model uses attributable fractions, taken from reviews and meta-analyses, applied to the population of a region to calculate the burden of disease of these risk factors[24].

Burden of disease is measured using disability adjusted life years (DALYs) calculated as the sum of years lost and years lived with disability [25].

CHD is included in the model, and is modelled as being caused by tobacco use, hypertension and physical inactivity, and reduced by alcohol at all levels of consumption.

### Strengths

- Comprehensive and global
- Well documented and described

## Potential limitations

- Does not provide information about specific health problems, specific forms of CHD, nor specific CHD treatments.

## Other models

A number of other CHD policy models were developed, mostly for rather narrow purposes, such as assessing cost effectiveness of a single treatment, or health care planning. Some aimed to explore impact of interventions in the whole population versus high-risk groups. However few papers were published using these models. I systematically reviewed all these papers and summarise them below. (Details are presented in *Appendix 1*).

### Cardiovascular Disease Policy Model

This microsimulation model was developed in 1999 by Mui et al[26] in Australia, to project the incidence rates for CHD, and the number of hospitalised incident CHD cases and hospital costs, for men and women, aged 45-69, up to 2014. The model has many similarities with Weinstien's CHD Policy Model[1] but the main difference is microsimulation method and inclusion of stroke, beside CHD.

The Cardiovascular Disease Policy Model is based on four integrated submodels:
- *Incidence submodel* conditional to each individuals risk status this model predicts CHD and stroke incidence using Framingham equations.
- *Bridge submodel* intends to determine the outcome of first CHD event
- *Prevalence submodel for CHD and Prevalence submodel for stroke* simulates subsequent CVD in people with CVD history.

This model's validity was checked by comparing the estimates of CHD and stroke incidences with MONICA data for the same years. The model overestimated incidence of CHD by 50% to 110% in men and underestimated in women by 50% to 70%. Therefore age and sex specific adjustment factors were incorporated to the model[26]. Currently the model focuses on prevention rather than treatment.

### Risk factors included
Smoking, systolic blood pressure, serum cholesterol and relative weight.

### Diseases considered

CHD events (angina, myocardial infarction, coronary insufficiency) and stroke

*Outcomes*

CHD and stroke incidence, hospital admissions

*Strengths of the model*

- Includes CHD and stroke
- Validity was checked and methods refined
- Changes in risk factors with ageing was considered in the model

*Limitations*

- Framingham equations are used for CHD and stroke incidence estimates however these equations may not be generalisable to the Australian population
- No sensitivity analyses were performed
- Does not estimate treatment effects

## POHEM - The Population Health Model

This model was developed by Wolfson et al at Statistics Canada in Ottawa[27]. In contrast to the cell-based approach used by Weinstein, it used microsimulation to model the dynamics of a number of risk factors and major diseases including CHD, lung cancer and breast cancer. The CHD component of the model used Coronary Heart Disease Policy Model, transformed to POHEM architecture and uses Canadian risk factor distributions and treatment protocols. Little work using this model has been published[27]. It concentrated on prevention aspects of CHD rather than treatment.

## Pathways of Care

This model was developed by David Bensley et al[28] in 1995 to address the health care needs for CHD in Yorkshire Health Authority Region in the UK. It was a spreadsheet model and focused on treatment side of the CHD care rather than disease prevention. The objective of developing this model was to answer 'what if' questions such as 'what if the effect of a 10% reduction in the incidence of angina on number of deaths, angiograms, angioplasties and CABGs?'

*Outputs* are numbers of angiograms, CABGs, angioplasties and deaths each year over a ten-year period.

*Strengths*

- Model was developed by a team including cardiologists, cardiac surgeons, public health specialists, statisticians and operational research analyst.
- It was based on a health authority population
- Estimates from the model were validated against observed events
- User friendly, provides visual graphs
- Described clearly

*Potential limitations*

- Did not include risk factors
- Prevention strategies could only be addressed by directly altering attack rates rather than risk factors
- Did not include specific medical treatments for CHD patients
- Restricted to the age range 35-74

## CRISPERS

This model was developed by Dr Park and Dr Zhuo at the University of Minneapolis for their PhDs, submitted in 1987 and 1991 respectively[29-32]. The model uses Monte Carlo simulation method and it was designed to simulate morbidity and mortality from a disease within a structured population. It can also simulate intervention strategies designed to reduce disease effects in the population. Simulation outcomes such as total or age specific incident or prevalent rates of morbidity or mortality can be reported on a yearly basis. Model includes only three major risk factors; smoking, cholesterol and diastolic blood pressure as continuous variables[30]. These models mainly simulated the impact of population based vs high-risk interventions for risk factors using data from North Karelia Project.

### Augustovski 1998

This model was developed as a Markov decision model with a relatively narrow purpose of evaluating the effects of aspirin use for primary prevention in patients with different cardiovascular risk levels. Seven hypothetical cohorts were created for men and women, aged 55 and 65, and with risk categories defined by high cholesterol, high blood pressure, low HDL and smoking status. Framingham equations and incidence were used for CHD events and stroke probabilities[33]. The strategy of giving 75-375 mg aspirin for primary prevention

was evaluated. The model was run for 10 years. Validity of the model was checked by comparing the model estimates with Cox parametric regression models. One-way sensitivity analyses were performed. It was concluded that by taking aspirin the lowest risk cohort would lose 1.8 quality adjusted life days and the highest risk cohort would gain 11.3 quality adjusted life days. Therefore the decision for aspirin use for primary prevention depends on patient risk.

## Hjort 1986

This model was a simple cost model developed in 1980s in Norway to examine potential benefits of secondary prevention after myocardial infarction. It included post MI patients between 20 and 75 years old. It estimated the benefits of beta-blocker use and smoking cessation in terms of deaths prevented and LYGs. Direct and indirect costs in post MI patients were also estimated. The basic methodology of these estimations, data sources, assumptions, and validity of this model was poorly described. The number of post MI patients for Norway was estimated by extrapolating figures from Norwegian Timolol Study. It was concluded that beta-blocker use increased life years by 0.25-1.6 years in post MI patients. Smoking cessation had a similar effect. Furthermore it was concluded that secondary prevention would increase health services expenses and pensions but the cost seemed modest.

# Appendix 4. Summary tables for systematic review of CHD policy models

## App4. Table 1. Summary table for CHD Policy Model papers

| Author (year) | Purpose of the model | Setting, Time period & Population | Risk factors & interventions included | Disease categories & Treatments included | Outcomes | Key Results | Sensitivity analysis or validation | Transparency | Data Quality & Strengths and Limitations | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Goldman 1984[34] | To analyse potential effect of medical interventions and changes in life style | USA, 1968-1976, general USA population | Smoking, cholesterol, blood pressure, obesity | AMI, Angina, Sudden death, post MI<br><br>β Blockers, antihypertensive, CABG surgery | Number of deaths prevented | More than half the CHD decline 1968-1976 was related to changes in lifestyle (cholesterol, smoking). About 40% could be directly attributable to specific medical interventions, mainly CCU, medical treatments of CHD and hypertension | None | Assumptions discussed.<br><br>Model not available.<br><br>No illustrations, no discussion of confounding, lag times or competing causes. | Data sources adequate. The first published attempt to explain CHD mortality fall in terms of treatments and risk factor changes. Clear estimates and assumptions. Admits limitations. | Poor (2) |
| Weinstein 1987[1] | To project future mortality, morbidity, and cost of CHD | USA, 1980-2010 M-F, aged 35-85 | Smoking, cholesterol, blood pressure, obesity (relative weight) | Angina, AMI, Sudden death, CABG<br><br>No specific treatments included | Number and rate of<br>- CHD events (Arrest, angina, AMI)<br>- CHD deaths<br>- CHD prevalence, incidence<br>- Resource cost of interventions<br>-All cause mortality | Predicted by 2010:<br>10% decline in CHD incidence rates<br>38% increase in CHD events<br>50% prevalence increase<br>46% increase in deaths | None | Assumptions discussed.<br><br>Model not available.<br><br>No illustrations, nor discussion of confounding, lag times or competing causes. | First Policy Model, rather basic, steadily refined since then. Data sources adequate. | Poor (2) |

| Author (year) | Purpose of the model | Setting, Time period & Population | Risk factors & interventions included | Disease categories & Treatments included | Outcomes | Key Results | Sensitivity analysis or validation | Transparency | Data Quality & Strengths and Limitations | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Goldman 1989[35] | To evaluate long term national effects of lowering cholesterol | USA, 1990-2015 all 35-84, M-F | Smoking, cholesterol, blood pressure, obesity (relative weight) *Interventions:* 1-To reduce high cholesterol (>250 mg/d) to 250 mg/dl in all people, in 1990. 2- population wide cholesterol reductions to reach the same benefit | No disease categories No specific treatments included | Number of disease cases prevented | Targeted programme would reduce CHD incidence by 8-10% in men 35-54 and by 1-4% in men 55-74. 10mg/dl reduction in men pop mean cholesterol and 23% red in women pop would achieve similar result. Relying on targeted cholesterol reduction would be inadvisable to reduce national CHD. | One-Way sensitivity analysis Model was calibrated but predictive validity notchecked | Illustrations: Yes Assumptions discussed. Model not available. Confounding & lag times discussed, but not competing causes | Data sources adequate. | Adequate (7) |
| Tsevat 1991[4] | To determine potential gains in life expectancy from risk factor modifications | USA, 1990, people who turned to 35 in 1990 | Smoking, cholesterol, dbp, relative weight | No disease categories included No treatments included | Gains in life expectancy | Pop gain in life expectancy (Years in Men/ Women) IF); a) 10mg/l red in cholesterol- (0.2-0.2 years); 20 mg/l (0.4-0.3yr), all high cholesterol reduced to 240mg/dl (0.3-0.5yr) b) smok halved (0.4-0.4 yr) c) DBP below 88 (1.1-1.1 yr) d) weight ideal (0.6-0.4 yr) e) eliminate all CVD (3.1-3.3 yr) | One-Way sensitivity analysis Calibrated- life years estimated compared with US life expectancy from 1980 national vital statistics | Model not available. No illustrations. Discussed assumptions, lag times & competing causes but not confounding | Risk factors assumed to be independent therefore coefficients might cause underestimation. Data sources adequate. | Adequate (6) |
| Goldman 1991 | To determine cost effectiveness of HMG-CoA reductase inhibitor in primary and secondary prevention | USA, 1989, 35-84 M-F | Smoking, cholesterol, dbp, relative weight | No other treatments included | Cost per life year saved | Lovastatin 20 mg/d save lives and costs in young men with cholesterol >250mg/dl and have favourable cost effectiveness ratio regardless of cholesterol level except in young women with cholesterol<250mg/dl. Doses of | Different scenarios examined. Calibrated- life years estimated compared with US life expectancy from | Model not available. No illustrations. Discussed assumptions, lag times & competing causes but not confounding | Restricted focus Data sources adequate. | Adequate (5) |

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| Author (year) | Purpose of the model | Setting, Time period & Population | Risk factors & interventions included | Disease categories & Treatments included | Outcomes | Key Results | Sensitivity analysis or validation | Transparency | Data Quality & Strengths and Limitations | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 40 mg/dl had favourable cost effectiveness ratio in men with cholesterol>250mg/dl. By comparison primary prevention with lovastatin had favourable cost effectiveness ratio only in selected groups based on cholesterol levels and other established risk factors. | 1980 national vital statistics | | | |
| Hunink 1997[2] | To examine effect of secular trends in risk factor levels and improvements in treatments on CHD mortality decline in USA, 1980-1990. | USA, 1980-1990 35-84 M-F | Smoking, cholesterol, HDL, LDL, DBP | Angina, sudden death, post MI, CABG, PTCA<br><br>Specific treatments not included | Number of deaths prevented | Model explained 92% of the observed decline. 43% of the fall was attributed to treatments and 25% to primary prevention | One-way sensitivity analysis- 95%CIs from case fatalities and Beta coefs. Model calibrated with 1986 mortality data- 98% Validity: (model estimates compared with 1990 observed)- | No illustrations, model is not available. Assumptions discussed and method refined.<br><br>Discussed Confounding, lag times & competing causes. | Data sources well explained- However model excluded over 85 people, did not consider specific treatments and excluded heart failure. | Adequate (7) |
| Tosteson 1997[9] | To estimate cost effectiveness of population wide approaches to reduce cholesterol in US adult pop. | USA, 1995-2020, 35-84 M-F, free of CHD | Smoking, cholesterol, HDL, DBP | No disease categories included<br><br>No treatments included | CHD incidence, LYG, cost per LYG, CE ratio | A population wide programme with the cost (4.95 per person per year) and cholesterol lowering effects (an avr. 2% reduction) would prolong life at an estimated cost of $3200 per life year saved. | One-Way sensitivity analysis<br><br>Model calibrated (in previous papers), predictive validity –not checked | No Illustrations Model not available<br><br>Discussed competing causes but not assumptions, confounding or lag times | Data sources adequate | Adequate (4) |

| Author (year) | Purpose of the model | Setting, Time period & Population | Risk factors & interventions included | Disease categories & Treatments included | Outcomes | Key Results | Sensitivity analysis or validation | Transparency | Data Quality & Strengths and Limitations | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Goldman 1999[36] | To project the population wide effect of full implementation of ATP II guidelines in the USA | USA, 2000-2020, 35-84 M-F | Smoking, cholesterol, HDL, LDL, DBP<br><br>Primary /secondary prevention in high risk persons and primary prevention in moderate risk persons. | Angina, AMI, sudden death, post MI, CABG, PTCA<br><br>No treatments included | Number of deaths prevented, LYG, QALY | ATP implementation means 500 million person years on lipid lowering treatment (2/3 primary prevention and 1/3 on secondary prevention) with 2 million fewer AMIs, 1.7 million fewer CHD deaths, PLUS 14 million LYGs and 13.5 million QALYS | One-Way sensitivity analysis<br><br>In previous papers model calibrated<br><br>Predictive validity –not checked | Assumptions presented.<br><br>Model not available, no illustrations.<br><br>No discussion of confounding, lag times or competing causes | Data sources adequate | Adequate (4) |
| Phillips 2000[6] | To examine the potential health and economic impact of increase use of beta-blockers in AMI survivors | USA, 2000-2020;<br><br>AMI Survivors in 2000 aged 35-84, followed up for 20 years PLUS successive survivors of first MI from 2000 to 2020 | None | Post MI<br><br>Treatment: beta blocker use after AMI | Number of deaths prevented, cost per life years, QALY | Increase of beta-blocker uptake from 44% to 92%.<br><br>Implementing this strategy in MI survivors in 2000: would lead to 4,300 fewer CHD deaths and 3,500 AMIs PLUS 45000 LYGs. Cost per QALY=$4,500.<br><br>All first MI survivors annually over 20 years: 72,000 fewer CHD deaths, 62,000 fewer AMIs PLUS 447,000 LYGs. Would save $118 million during. 20 years | One way sensitivity analysis- different scenarios were explored<br><br>No validation or calibration in here | No Illustrations. Model not available.<br><br>Discussed assumptions but not confounding, lag times or competing causes. | Model described well but the purpose was very narrow<br><br>Data sources adequate | Poor (3) |

| Author (year) | Purpose of the model | Setting, Time period & Population | Risk factors & interventions included | Disease categories & Treatments included | Outcomes | Key Results | Sensitivity analysis or validation | Transparency | Data Quality & Strengths and Limitations | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Prosser 2000**[8] | To evaluate cost effectiveness of primary and secondary prevention with cholesterol lowering drugs in separate risk groups | USA, from 1987 for 30 years M-F aged 35-84 | HDL, LDL | Angina, post MI <br><br> Treatment: Statins Step 1 diet | Number of deaths prevented, QALY, cost effectiveness ratio | Cost per QALY for step 1 diet generally <$100 k if subjects had more than 1 RF. -Primary prevention with statins expensive varied $54k- 240 k in men, $62 k to 1400 k in women. -Secondary prevention with statins $3800- $9900 per QALY in men and $8100-4000 per QALY in women. | One-Way and multi-way sensitivity analysis done <br><br> Calibrated and predictive validity checked | No Illustrations provided. Model not available. <br><br> Discussed assumptions, but not confounding, lag times or competing causes. | Useful. <br><br> Data sources adequately reported | Adequate (5) |
| **Goldman 2001**[3] | To estimate impact and cost effectiveness of risk factor reductions between 1981 and 1990. | USA, 1981-1990 and 1991-2015; 35-84 M-F | Smoking, cholesterol, DBP, obesity | Angina, AMI, sudden death, pot MI, CABG, PTCA <br><br> No treatments included | Number of deaths prevented, incidence, cost per death prevented | RF changes between 1981-1990 resulted in 7-11% reduction in CHD incidence rates- 430,000 fewer CHD deaths. 55% of this reduction was from DBP, 38% cholesterol, 7% smoking. Overall RF changes gained 1.9 million QALYs | One-Way sensitivity analysis <br><br> Calibrated- in other papers | No Illustrations. Model not available. <br><br> Discussed assumptions, lag times & competing causes but not confounding | Ambitious paper, difficult to understand and cost estimations slightly confusing. <br><br> Data sources adequately reported | Adequate (6) |
| **Tice 2001**[37] | To examine the potential effect of grain fortification with folic acid and vitamin therapy i.e. cyanocobalamine, on CHD events in the US. | USA, 2001-2010; 35-84 M-F | Smoking, cholesterol, HDL, DBP, diet (folic acid fortification) | Angina, AMI, heart failure, QALYs <br><br> No other treatments included | Number of deaths prevented, number of CHD events prevented, QALYs | Grain fortification would decrease AMI in men and women by 13% and 8% respectively. <br><br> 310, 000 fewer deaths and lower costs if all known CHD patients treated with folic acid and cyanocobalamin over 10 years Providing all men over 45 without CHD would save 300,000 QALYs and would save $2 billion | Multi-Way sensitivity analysis By incorporating homocysteine level distribution from NHANES III. <br><br> This version of the model apparently predicts CHD mortality within 2% of the 1990 US vital statistics. | No illustrations and model not available. <br><br> Discussed assumptions, Lag times & competing causes but not confounding | Assumed 100% compliance- Same RR assumed for primary and secondary prevention- no negative effect of rx, - lack of completed RCT evidence <br><br> Data sources adequately reported | Adequate (6) |

| Author (year) | Purpose of the model | Setting, Time period & Population | Risk factors & interventions included | Disease categories & Treatments included | Outcomes | Key Results | Sensitivity analysis or validation | Transparency | Data Quality & Strengths and Limitations | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Gaspoz 2003[7] | To estimate cost effectiveness of aspirin, clopidogrel or both for secondary prevention | USA, 2003-2027; 35-84 M-F | No risk factors included | Two treatments for secondary prevention of CHD Aspirin, Clopidogrel | Number of deaths prevented, cost per LYG and QALY | Cost per QALY results: Aspirin for all eligible patients =$11,000- Aspirin all and clopid for others: =$31,000- Clopidogrel for all =$250,000 | One-Way sensitivity analysis Using cholesterol changes in 4S Study the model estimated almost perfectly the observed CHD events in the trial. | No illustrations, model not available. Discussed assumptions, lag times & competing causes but NOT confounding or compliance | Narrow focus. Data sources adequately reported | Adequate (6) |

# App4. Table 2. Summary table for PREVENT Model

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Buck, 1996[15] | To simulate the health outcomes associated with health promotion and prevention and relative costs of associated with different health promotion | England, 2000-2029, M-F under 65 | Smoking, cholesterol, blood pressure | None | Number of deaths prevented, cost | Reducing smoking by 2.5% over 1 yr in the population; would reduce CHD death numbers by 2,378 in 2000, 31,602 in 2029. Reducing cholesterol 5% over 3 yrs; would avert 67,598 CHD deaths in 2000, 438,396 CHD deaths in 2029 | Different scenarios explored  Validity not checked | Illustrations& assumptions provided. Model not available. Discussed confounding & competing causes but not lag times. | Ignore socioeconomic variables  Data sources adequate | Adequate (6) |
| Naidoo, 1997[16] | To evaluate effect of physical activity in reducing CHD deaths | England and Wales, Baseyear: 1991 Intervention 1994-2005 then 14 years prediction (to 2019), M-F aged 15-64 | Smoking, cholesterol, blood pressure, physical activity, obesity | No treatments | Number of deaths prevented, LYG | Increasing physical activity would result in small reduction in CHD death rates (0.15% in men & 0.06% in women). Greatest health gain can be achieved by concentrating on sedentary people, on older people and on men Much bigger potential gains from smoking reduction | One-Way sensitivity analysis  Validity not checked | Illustrations & model not available  Discussed assumptions, lag times, competing causes but not confounding. | Physical activity included here in the PREVENT Model. Assumed complete reversal of prior risk from being sedentary.  Data adequate, RR: 1.9 from Berlin et al still reflects cohorts not interventions, probably a big overestimation. | Adequate (5) |
| Bronnum-Hansen, 2000[14] | To estimate smoking attributable mortality from lung cancer, chronic bronchitis, emphysema, CHD, and stroke, by using PREVENT Model and the method proposed by Peto et al. | Denmark, 1993, M-F | Not reported | None | CHD mortality | In 1993 PREVENT model estimated 33% of the deaths in men and 23% in women could be attributable to smoking. The Peto et al method estimated 35% of deaths in men and 25% in women attributable to smoking. | No sensitivity analysis  Validity thus checked | Illustrations & model not available  Discussed assumptions, lag times, competing causes but not confounding. | Data sources poorly reported and discussed | Adequate (4) |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Mooy, 2000[11] | To evaluate three policy options (anti tobacco, cycling, high fruit-vegetable consumption) using PREVENT Model | Netherlands, 1993-2003, M-F under 65 | Smoking, physical activity (cycling), diet | None | Life years gained (LYG) | Anti-tobacco policy had greatest impact, a cycling policy resulted in substantial health gain, increased fruit-vegetable consumption had little effect | Different scenarios explored<br><br>Validity not checked | Illustrations & assumptions provided. Model not available. Discussed lag times but not confounding or competing causes. | Superficial paper lacks detail. Rather brave and optimistic assumptions??<br><br>Data sources reported poorly | Adequate (4) |
| Bronnum-Hansen, 2002[12] | To predict effect of reducing prevalence of hypertension, high cholesterol, smoking and increasing physical activity | Denmark, 1999-2008, M-F aged 20-64 | Smoking, cholesterol, hypertension, physical activity | None included | Number of deaths prevented | Reducing smoking by 1/3 over 10 yrs would reduce CHD deaths 10% for men and 15% for women < 65. If % of heavy smokers or hypertensive reduced by 25% the CHD mortality would be 5% lower for men (6-7% lower women.) Reducing number with cholesterol (>8mmol/l) by 25% would lower CHD mortality by 3% in men (6% in women) after 15 yrs. | One-Way sensitivity analysis<br><br>Validity not checked | Illustrations & model not available<br><br>Discussed assumptions & competing causes but not lag times or confounding. | Data sources reported poorly | Poor (3) |

## App4. Table 3. Summary table for Cardiovascular Life Expectancy Model

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations & Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Grover, 1992[20] | To evaluate life-time benefits of reducing total cholesterol levels to prevent CHD | Canada, (time not clear), Low risk and high risk M-F | Smoking, total cholesterol, diastolic blood pressure, glucose intolerance, age | No disease categories  No other treatments | Years of life saved,  Years of life without CHD symptoms  Increased life expectancy | In low risk and high risk men and women reducing serum cholesterol levels by 5% to 33% would increase the average life expectancy by 0.03 - 3.16 years. Onset of symptomatic CHD would be delayed among these patient groups by 0.06 - 4.98 years, on average | None  Validation only checked for middle age men Not clear about model fit for other age and sex groups. | Illustrations &: assumptions provided Model not available.  Discussed lag times but not confounding or competing causes | Fairly clear &, detailed paper.  This model used multivariate logistic regression coefficients.  Data sources adequate | Adequate (5) |
| Hamilton, 1995[38] | To evaluate life-time cost effectiveness of statins for treating high cholesterol levels | Canada,1993??, (not clear) M-F aged 30-70 free of CHD | Smoking, total cholesterol, HDL-C, LDL-C, diastolic blood pressure, glucose intolerance | No disease categories  No other treatments | Years of life saved, Cost per life years saved (LYS) | Treatment of hypercholesterolemia relatively cost-effective for men (as low as $20,882 per LYS at age 50) & women ($36,627 per LYS at age 60). | One-Way sensitivity analysis  Validation reported in previous papers | Illustrations& model not available. Assumptions& competing causes discussed but not confounding or lag times. | Assumed 100% compliance to treatment (!). Treatment effectiveness data from only one RCT, no meta-analysis. Data sources adequate | Adequate (5) |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Grover, 1998[39] | To compare potential years of life saved associated with risk factor modification in the primary and secondary prevention of CVD | Canada, ??, (not clear) Lipid Research Clinics Cohort over 30 M-F | 1992 paper *not clear* | No disease categories<br><br>No other treatments | Number of CHD, stroke cases prevented, life years saved (LYS) | In hyperlipidemic men and women without CVD lipid therapy benefits greater in high-risk vs low-risk groups (4.74-0.78 vs 2.50-0.25 LYS, respectively). Similar forecasted benefits among people with CVD. Hypertension therapy benefits also greater for high-risk vs low risk (1.34-0.29 vs. 0.85-0.13 LYS respectively) | No sensitivity analysis<br><br>Predictive validity checked by using data from primary and secondary prevention trials. | Illustrations and model not available.<br><br>Discussed assumptions, confounding, lag times but not competing causes. | Method explained well.<br><br>Data sources explained | Adequate (5) |
| Perreault, 1998[40] | To compare average and marginal life-time cost-effectiveness of increasing dosages of statins for primary prevention of CHD | Canada, 1992?, (not clear) Hypothetical high risk (smoker, DBP>100mmHg) and low risk (non-smoker, DBP<80mmHg) men and women | Age, sex, cholesterol, HDL-C, diastolic blood pressure, left ventricular hypertrophy, glucose intolerance, smoking | No disease categories<br><br>No other treatments | Years of life saved, Cost per life years saved | Treatment with lovastatin at a dosage of 20mg/d apparently cost-effective in middle-aged men and women with baseline total cholesterol >6.67mmol/L. Treatments with 40mg/d is also cost-effective for total cholesterol >7.84mmol/L. However 80mg/d not cost-effective for primary prevention. | None<br><br>Validation was reported in previous papers | Illustrations& model not available.<br><br>Discussed assumptions, confounding, lag times & competing causes. | Narrow focus. Not based on a real population.<br><br>Data sources adequate | Adequate (5) |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Grover 1999[41] | To estimate cost-effectiveness of statin therapy in secondary prevention, using 4S study published results | Canada, (Not clear) M-F 40-70 yrs 15% random sample of LRC program | Mean BP, LDL/HDL, smoking, glucose intolerance | No disease categories  No other treatments | Recurrent CHD events  Cost per life year saved (LYS) | Suggested benefits of long-term statin therapy generally cost effective. Costs for low risk patients with LDL/HDL>5 $5424 - $9548 per LYS in men and $8339-13747 in women. In high-risk patients $4487 to 8532 in men and $5138 to 8389 in women. | One-Way sensitivity analysis  Model estimates were compared with events observed in 4S trial- predicted and observed rates were quite similar | Illustrations& model not available.  Discussed assumptions but not confounding, lag times or competing causes. | Limited to a very narrow focus Little exploration beyond 4S trial  Data sources adequate | Adequate (4) |
| Perreault, 1999[42] | To estimate the potential effect of primary prevention treatment of hyperlipidemia or hypertension to reduce the risk of CHD death | Canada, Years unclear 1986? 1992?,  M-F aged 35-74 (Canadian Heart Health Survey Population.) | Smoking, Cholesterol/HDL-C ratio, blood pressure | No disease categories  No other treatments | Number of CHD cases prevented | The clustering of modifiable risk factors in hypertensive patients demonstrated the need for comprehensive RF screening | No SA  Validation of the model checked previously | Illustrations& model not available.  Discussed assumptions, lag times, but not confounding or competing causes. | Adequate data quality for population, risk factors &treatment uptake. But data on treatment effectiveness relatively poor, ignored a meta-analysis. | Adequate (4) |
| Lowensteyn 2000[43] | To evaluate potential long term cost effectiveness of exercise training for cardiovascular disease risk factors | Canada, 1992, M-F aged 35-54, 55-64, 65-74 | Age, sex, HDL/LDL ratio, blood pressure, CVD presence, glucose intolerance, smoking | No disease categories  No other treatments | Years of life saved, Cost per life years saved | Assuming 100% lifetime adherence, exercise training gained 0.7 life-years in men aged 35-54. Gains smaller in older men and women without CVD, but larger in those with CVD. Still cost effective. Assuming 50% adherence | One-Way sensitivity analysis  Validation of the model was checked previously (Grover 1998) | Illustrations& model not available.  Discussed assumptions & competing causes, but not confounding or lag times. | Clearly written paper. Data adequate. Sensitivity analyses well described | Adequate (5) |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Grover, 2001[44] | To estimate long term cost effectiveness of lipid therapy among diabetic patients without CHD versus results in CVD patients without DM | Canada, USA, Italy, Spain, Germany France, 1998, M-F | Smoking, HDL-C, LDL-C, diastolic blood pressure, diabetes,<br><br>Diagnosed CVD at baseline | No disease categories<br><br>No other treatments | Years of life saved, Cost per life years saved | Among diabetic men and women who do not have CVD, lipid therapy is likely to be as cost-effective as treating nondiabetic individuals with CVD | No sensitivity analysis<br><br>Calibration yes | Illustrations& model not available.<br><br>Discussed assumptions but not competing causes, confounding or lag times. | Assumed all subject were non-smokers!<br><br>Data sources presented but lacked RCT data on primary prevention in diabetes patients | Poor (3) |
| Grover 2003[45] | To compare cost/effectiveness of lipid modification in primary prevention of CVD (with and without indirect costs) | Canada Restricted to hypothetical cohort of 1000 participants reflecting baseline risk factor levels of the population | Smoking, LDL-C/HDL-C, mean blood pressure, glucose intolerance, age, sex | No specific disease categories, 10 mg daily Atorvastatin for CVD-free people at baseline. People categorised as: low risk: (Normal BP, non smoker) or -High risk: (High BP, smokers). | Direct and indirect cost per life year saved | Lipid therapy with statins can reduce CVD morbidity and mortality.<br><br>Adding indirect costs associated with productivity losses can result in cost savings to society. | One-Way sensitivity analysis | Illustrations& model not available.<br><br>Discussed assumptions, confounding & lag times but not competing causes | Data sources poorly explained | Adequate (4) |

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# App4. Table 4. Summary table for CHD Policy Analysis Model

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Babad 2002**[21] | To evaluate the impact of different primary prevention strategies on health care costs | England and Wales, time? (not clear), 45-84 ? M-F | Smoking, cholesterol, systolic blood pressure, age, sex | No disease categories / No other treatments | Stable angina, unstable angina, MI, Sudden death, stroke death, other CV death, cancer death, other death | None reported | No SA / No validation | Confounding: No Lag times: No Competing causes: No Illustrations& model not available. Discussed assumptions but not confounding, lag times or competing causes | Considers treatment adherence, compliance, treatment delay and effectiveness for risk factors. However limited number of risk factors. Data quality adequate. National survey used to populate the model. However Framingham equations greatly over-estimate risk for English population | Poor (2) This model is on the developing stage still |
| **Cooper 2002**[22] | To explore treatment, survival, and subsequent CHD event experience of CHD patients | England and Wales, time ?? (not clear), ...-85 M-F | No risk factors included | Angina (stable/unstable), AMI, post MI, CABG, & PTCA only, no specific medical therapies | Number of deaths prevented, morbidity prevented, CHD mortality, unstable angina admissions, patient investigations, angiograms, PTCA, CABG, noncardiac deaths | CABG: 19 deaths postponed/prevented per million population | No sensitivity analysis Cardiac deaths estimated by the model were validated against data from ONS-model 12% underestimates. Angina prevalence estimate of the model compared with HSE 94 prevalence. Discrepancies ranged from 1% to 20% | Illustrations & model not available. Discussed assumptions but not confounding, lag times or competing causes | Uncritical and rather arbitrary approach to selection of data sources. Data quality often poor. No attempt to quantify or manage uncertainties. Future model versions to include secondary prevention? Model fit is better for men than women. | Poor (3) This model is on the developing stage still |

# App4. Table 5. Summary table for IMPACT CHD Mortality Model

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Capewell 1999[46]** | To estimate proportion of CHD mortality fall in Scotland 1975-1994 attributable to treatments and to risk factor changes | Scotland, 1975-1994, Population 5.1 million M-F aged 45-64,65-74, >74 | Smoking, cholesterol, blood pressure, deprivation | Comprehensive *See footnote | Deaths prevented or postponed (DPP) | 6205 fewer deaths observed in 1994 compared with 1975 base year. Treatments together explained 40% of the mortality fall. 2722 DPPs (min 1373- max 5986); Major Risk factors explained 51% of the fall: 4025 DPPs (3412-4679); 9% attributed to other, unmeasured factors | SA: Multi way sensitivity analysis using - Analysis of extremes method Validation: Estimated falls in CHD mortality were compared with observed falls in CHD mortality | Illustrations available & model available on request. Discussed assumptions & confounding but not lag times or competing causes | Aims to include ALL effective CHD treatments given in 1994. Mortality the only outcome. (Not non-fatal events) Omits diabetes, BMI, Physical activity, diet, antioxidants, Barker. Data quality adequate (Census, MONICA, National population statistics, results from representative studies) | **Adequate (7)** |
| **Capewell 1999[47]** | To determine the extent to which increases in the uptake of effective treatments could further reduce CHD mortality in Scotland in 1994 | Scotland, 1994, all adults 45+ | No risk factors considered, apart from medications for hypertension | Comprehensive *See footnote | Deaths prevented or postponed | 2722 DPPs between 1975 and 1994, attributable to treatments. (Min1373-max5986) Increasing uptakes to 80% of eligible patients would have prevented or postponed approx 4078 DPPs (1886-6702). 39% from 2'prevention, 29% from Heart failure, 13% from initial treatments for AMI, 10% from HT and 8% from angina treatments. | Multi way sensitivity analysis using Analysis of extremes Previously validated: comparison of estimated and observed falls in CHD mortality | Illustrations available & model available on request. Discussed assumptions, confounding & lag times. Competing causes not relevant. | Considers a wide range of effective treatments available for CHD. Outcome is mortality only (not nonfatal events). Data quality adequate | **Good (8)** |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall gradin (Score |
|---|---|---|---|---|---|---|---|---|---|---|
| Capewell 2000[48] | To determine how much of the recent CHD mortality fall in New Zealand can be attributed to treatments or to risk factor changes | Auckland 1982-1993, Population 996,000 M-F | Smoking, cholesterol, blood pressure, statins for primary prevention, | Comprehensive *See footnote | Deaths prevented or postponed | 558 fewer deaths observed in 1993 than expected from 1982 rate. Medical and surgical treatments estimated to prevent or postponed 310 deaths (101-920), risk factor changes 361(204-596) DPPs [Smoking 204, cholesterol 79 Diastolic BP 97 other factors 28] | Multi way sensitivity analysis- Analysis of extremes Estimated falls in CHD mortality were compared with observed falls in CHD mortality | Illustrations available & model available on request. Discussed assumptions, confounding, lag times& competing causes. | Considered a wide range of effective treatments for CHD. Outcome is mortality only. Nonfatal events not included. Omitted diabetes, BMI, Physical activity, diet, antioxidants, Barker Data quality adequate | Good (9) |
| Critchley 2003[49] | To examine potential for risk factor changes to reduce CHD deaths in Scotland | Scotland, 1994-2010, M-F aged 45-84 | Smoking, cholesterol, blood pressure | Treatments not considered | Deaths prevented or postponed (DPPs) | 2169 DPPs if recent risk factor trends simply continued to 2010. Additional, modest RF reductions would prevent 4749 deaths. [2167 cholesterol, 1168 smoking, 914 Diastolic BP reductions respectively]. Extrapolation to UK pop suggested approx. 53,000 lives could be saved in 2010. | Multi way sensitivity analysis- Analysis of extremes - Estimated falls in CHD mortality were compared with observed falls in CHD mortality | Illustrations available & model available on request. -Discussed assumptions, confounding, lag times& competing causes. | Considers major risk factors only, omits diabetes, BMI, Physical activity, diet, antioxidants, Barker. Data quality adequate | Good (9) |
| Critchley 2003[50] | To estimate life years gained due to risk factor changes and improved treatments in Scotland between 1975-1994 | Scotland, 1975-1994, M-F aged 45-84 | Smoking, cholesterol, blood pressure | Comprehensive *See footnote | Life years gained (LYGs) | Treatments together prevented or postponed 1862 deaths. This resulted in 12025 LYGs (8689-14,461). Risk factor reductions prevented or postponed 2674 deaths resulting in 35991 LYGs (25782-40750). 50% from smoking. 70% of LYGs were in men. | Multi way sensitivity analysis- Analysis of extremes Estimated falls in CHD mortality were compared with observed falls in CHD mortality | Illustrations available & model available on request. Discussed assumptions, confounding, lag times& competing causes. | Considers a wide range of effective treatments for CHD. Mortality only. Nonfatal events not included. Omits diabetes, BMI, Physical activity, diet, antioxidants, & Barker. Data quality adequate | Good (9) |

*AMI: Cardiopulmonary resuscitation, thrombolysis, aspirin, PTCA, Beta blockers, ACE inhibitors; Secondary prevention (post MI/CABG/PTCA): Aspirin, Beta blockers, ACE inhibitors, Statins, Warfarin, Rehabilitation; Chronic angina: CABG surgery, Angioplasty, Aspirin, Statins; Unstable angina: Aspirin, Aspirin & Heparin; Heart failure: ACE inhibitors; Hypertension treatment

# App4. Table 6. Summary table for The Global Burden of Disease Project

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations & Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Murray 1997[24] | To provide a standardised approach to epidemiological assessments and use a standard unit, the DALY to aid comparisons. | World, 1990 | Smoking, blood pressure, physical activity | None None | DALYs | Developed regions experience 12% of the burden and spend 90% of health care. CVD explain 10% of the total DALYs (20% in developed world, 23% in USSR & Eastern Block), 8% in developing countries. | None None | Illustrations & model not available. Discussed assumptions & competing causes but not confounding or lag times. | Large and ambitious. Data quality: Adequate for this model | Poor (3) |
| Murray 1997[23] | To compare three scenarios of future mortality and disability for different causes and 8 regions of the world | World, 1990-2020 | Smoking | None None | Deaths, DALYs, years of life lost | In established market economies life expectancy will be 88 for women and 78 for men. CVD will remain top cause of death globally. In 2020 CHD will account 20% of DALYs in EME counties and 15% in the world. | Different scenarios (optimistic vs pessimistic) explored. Calibration, Validity – not checked | Illustrations & model not available. Discussed assumptions & competing causes but not confounding or lag times. | Useful for WHO and strategies. Includes trends for CHD and CVD however does not provide information on specific interventions. Data sources adequate | Adequate (4) |
| Ezzati 2002[51] | To estimate contributions of selected risk factors to global and regional disease burden | World, 2000 | High blood pressure, high cholesterol, high BMI and smoking besides other 22 selected risk factors | None None | DALY | Maternal and childhood underweight accounted 15% ; high blood pressure 4.4% (64 million), tobacco 4.1% (59 million), high cholesterol % 2.7 (40 million) of the global DALYs. | None None | Illustrations & model not available. Discussed assumptions & competing causes but not confoundingor lag times. | Data sources adequate | Poor (3) |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories& Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Murray 2003**[52] | To estimate health effects and costs of selected interventions to reduce the risks associated with high cholesterol and high blood pressure in different parts of the world | Three WHO regions (South east Asia, Latin America and Europe), 2000, Whole population | Cholesterol, SBO, smoking, BMI | None<br><br>Treatments? | Cost per DALY averted | All personal and non-personal interventions explored in this work were cost-effective over all three WHO regions. In low resource settings population intervention strategies to lower salt intake, cholesterol concentration or both would be purchased first. Decision makers would next move to combined strategy of legislated reductions in salt content of processed foods with mass-media campaigns, and then add the absolute-risk approach to management of blood pressure and cholesterol concentration. | Multi-way sensitivity analysis<br><br>Validity was not checked | Illustrations & model not available.<br><br>Discussed assumptions & competing causes but not confounding or lag times. | Useful primary prevention model. Focuses on effective interventions.<br><br>Detailed paper supported with web-tables to explain the method used.<br><br>Does not include effect of specific treatments.<br><br>Adherence omitted. Limitations discussed briefly. Data sources adequate | Adequate (4) |

# App4. Table 7. Summary table for other CHD policy models

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Kottke 1985[53] | To compare expected benefit of high-risk and population strategies on the basis of Risk Factor distributions of the male population of Eastern Finland | North Karelia, Finland, 1992, Men aged 25-59 in 1972 | Cholesterol Diastolic BP | None Targeting Cholesterol and DBP in NK men. | Number of deaths prevented | Three strategies explored. -**Achieved** (reducing cholesterol 10% and reducing DBP below 95mmHg) -**Good** (reducing cholesterol 20% and reducing DBP below 90 mmHg) -**Ideal** (reducing cholesterol below 190, and reducing DBP below 80). Implementing these 3 (achieved/ good/ ideal). Interventions in **a)** **High-risk** people would reduce population CVD by 16%, 28% and 33% respectively **b)** **Population level** would reduce population CVD by 31%, 52% and 70%. | None Calibration: used actual mortality rates for NK cohort | Illustrations & model not available. Discussed assumptions & competing causes but not confounding or lag times. | Did not acknowledge any limitations Data quality good However study limited to men aged 25-59 years | Adequate (4) |
| Nissinen 1986[54] | To estimate costs and effects of North Karelia Project hypertension control program during the first 5 yrs | Finland, North Karelia, 1972-1977 M-F 35-64 yrs | Hypertension | None, No other treatments | Life years gained life expectancy, & costs | 1239 MI deaths and 327 stroke deaths observed between 1972 and1977. 288 fewer than expected: 134 were attributable to BP treatment. Thus 2143 life years saved; cost per QALY was $3612 (excluding earnings) and $322 (including earnings). | None None | Illustrations & model not available. Discussed assumptions & competing causes but not confounding or lag times. | Rather old paper Data sources adequate | Poor (3) |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score |
|---|---|---|---|---|---|---|---|---|---|---|
| **Browner 1986**[55] | To estimate the overall impact of a risk factor modification programme | USA, 1964-1974 and 1972-1983, men only aged 35-59 | Cholesterol | None, No specific treatments | Incidence | With optimistic assumptions about the impact of cholestyramine Rx at various cholesterol. levels about 5% of CHD cases in middle-aged men could be prevented. More realistic assumptions reduced that estimate by half. | None<br><br>None | Illustrations & model not available.<br><br>Discussed assumptions but not competing causes, confounding or lag times. | Simplistic model. Model details not clear. Focused only on cholesterol.<br><br>Model mostly used data from a small trial therefore issues of generalisability poor | **Poor (** |
| **Hjort 1986**[56] | To examine potential benefits of secondary prevention after AMI | Norway, 1980? (Not clear),<br><br>MI survivors aged 20-75 yrs | None | Post MI<br><br>Bet-blocker | Life years gained | Beta-blockers gained 0.25-1.6yrs in post MI patients.<br><br>But Smoking cessation has similar effect and lasts longer: Smoking prevalence 50%, If all quit, 5120 extra survivors and 3.3 LYG gained per quitter. | None<br><br>None | Illustrations & model not available.<br><br>Discussed assumptions but not competing causes, confounding or lag times. | Very simple modelling methodology<br><br>Data: Main data source was Timolol RCT hence generalisability poor | **Poor (1)** |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall gradi (Scor |
|---|---|---|---|---|---|---|---|---|---|---|
| Kottke 1988[57] | To examine the magnitude of risk factor clustering within individuals and to examine the implications of risk factor clustering for CHD prevention policy | US railroad (USRR) cohort and Finnish North Karelia cohort -USRR-1959-'64, NK: 1972-78 -US railroad cohort- 2571 men aged 40-59 (1959). -North Karelia 3022 men aged 40-59 | Smoking, cholesterol, blood pressure | No specific treatments No groups | Number of deaths, number of morbidity, non fatal AMIs | Reducing cholesterol 10%, smok 20% and DBP 5% in general population would lower CHD death by 33%-38% & nonfatal AMIs by 21% -23% (US-NK) -Reducing cholesterol 4%, smok 15% and DBP 3% in general population would lower deaths by 22-18%. & nonfatal AMIs by 12-13% -Single interventions in high-risk groups were less effective i.e. max of 8% reduction in MI or CHD death. | None None | Illustrations & model not available. Not discussed assumptions, competing causes, and confounding or lag times. | Limitations in data sources. -US railroad cohort: Selected-healthy worker effect? Generalisibility to US population is questionable. -North Karelia results more generalisable. | Poor ( |
| Park 1989[29] | To compare high risk versus population approach to primary prevention in North Karelia | North Karelia, Finland, 1972-77 | Cholesterol: simulated reduction to 180mg/dl a) in high risk b) in whole pop. Blood pressure | None, None | Number of deaths prevented | Reducing cholesterol below 180 in top quartile would lead to 34% reduction in CHD deaths. Reducing cholesterol 30mg/dl across pop would lead 24% reduction in CHD deaths. | None None | Illustrations & model not available. -Discussed assumptions & competing causes but not confounding or lag times. | Poor-early model. Lacks detail. Data quality is adequate. North Karelia data were used. | Poor (3) |
| Martens 1990[58] | To assess cost effectiveness of cholesterol reduction with simvastatin or cholesteramine | Holland, 1988, Dutch pop aged 35-70 | Cholesterol | None, None | Number of CHD events prevented, life expectancy, cost per life years gained | Simvastatin increased the life expectancy in men and women more than 3 times those with cholestyramine. Simvastatin therapy for men cholesterol>8 mmol/dl increased life expectancy by 1.75 yrs whereas cholestyramine increased 0.48 yr. For men with initial cholesterol >8 mmol/l the cost of life years saved of cholestyramine ranged $104,000 to $241,500. For simvastatin cost effectiveness ranged by $23,000 to $49,000. | One-way sensitivity analysis None | Illustrations & model not available. Discussed assumptions but not competing causes, confounding or lag times. | Poor- very narrow. Only simvastatin or cholestyramine . Focused mainly on extremely high chol levels 7,8,9. Data sources poor | Poor (2) |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Zhuo 1991 CRISPERS** | To investigate the relationship between the risk coefficients and simulation outcomes using CRISPERS model | Model was developed in Canada using North Karelia population, 1972-1979, 3022 men aged 40-59 | Cholesterol, number of cigarettes, DBP | None, None | CHD mortality, MI incidence, deaths due to other causes | All population approaches are better than high-risk approaches. | Multi-way-discussed  Yes- | Illustrations & model not available.  Discussed assumptions & competing causes, but not confounding or lag times. | Early modelling study. Includes only young men  Data: Adequate | **Adequate (4)** |
| **Johannesso n 1991[59]** | To estimate cost-effectiveness of CVD prevention | Sweden, 35-74 yr M-F free of CVD | Smoking, cholesterol, blood pressure, glucose intolerance, LVH | Angina, AMI, sudden death,  None | Life years gained, cost | In this paper they described the model only no results were reported | None  None- but planned | Illustrations available but model not available. - Discussed assumptions but not competing causes, confounding or lag times. | Data: Adequate | **Poor (** |
| **Macksikak 1992** | To predict disease rates in cohorts and to estimate effect of interventions | New South Wales? Australia, Hypothetic cohort of 100,000 men aged 40-64 | None | AMI, sudden death, CHD death, death from other causes (7 CHD states were described)  No treatment | CHD incidence, AMI | | Sensitivity None  Validity None | Illustrations & model not available.  Not discussed assumptions, competing causes, lag times or confounding. | Relatively narrow age group. Only men included. Arbitrary chosen changes in management and natural history of CHD. -Data sources adequate; national surveys and MONICA were used. | **Poor (1)** |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Jones 1994** | To quantify cost-benefit relationship of walking to prevent CHD | USA, time? hypothetical cohort of M-F aged 35-74. | Physical activity (Assumed RR=1.9, 95%CI 1.5 to 2.4) | None | Net cost | At a RR of 1.9 for heart disease associated with sedentary behaviour, $5.6 billion would be saved annually if 10% of adults began regular walking program. If all currently sedentary people (40%) start to walk 5-hours/per week then this would save annually $4.3 billion, mostly in men. Walking is beneficial for men aged 35 to 64 yrs and for women aged 55 to 64 yrs. | One-way SA, None | Illustrations & model not available. Not discussed assumptions, competing causes, confounding or lag times | A poor study. No details of methods on calculating the reductions of events or deaths. -Data sources described poorly | **Poor (** |
| **Doliszny 1994**[60] | To assess the possible contribution of CABG o the decline in CHD mortality between 1970 and 1984 in Minneapolis | Minneapolis St Paul, USA, 1970-1984, 30-74 M-F | Smoking, BP, DM | Angina, AMI, post MI, heart failure, CABG  CABG surgery | Number of deaths prevented | CABG contributed modestly to the decline in CHD mortality 1970-84. By 1984, the estimated contribution had increased to 6.6%. Adjustment 'attenuate but does not eliminate' this contribution. It is questionable whether contribution increased 1980s and 1990s because of competition from other therapeutic approaches. | None  Split 2/3 and compared predicted number of deaths with observed deaths- there was a good agreement | Illustrations available but model not available.  Discussed assumptions but not competing causes, confounding or lag times | Clear well written paper. However very narrow, only looked a CABG. Used entirely different method. Useful method for validation. -Data quality adequate | **Adequate (4)** |
| **Silagy 1994**[61] | Modelling workload from different servicing options in primary care, in order to avert future CHD events. | South of England, 1992,  5,727 M-F, aged 35-64 registered with GPs | Smoking, cholesterol, HDL, blood pressure, diabetes, LVH | None, None | CHD events | 517 of the population predicted to get CV event within 10 years (242 in men, 189 in women). a) No screening: 5035 patients need intervention to avert 73/517 CVD events b) limited screening would avert 29/73 events c) extended screening would avert 48/73 events | None  None | Illustrations & model not available.  Discussed assumptions but not competing causes, confounding or lag times | This model looks at CHD events not deaths. Includes GP registered patients not the real population. Theoretical interventions not real. | **Poor (2)** |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall gradin (Score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Data quality adequate | |
| **Bonneux 1994**[62] | To make quantitative analysis of the dynamics of the heart disease epidemic to explore future of heart disease morbidity in the Netherlands | Netherlands, 1985-2010, Dutch population | None | Angina, AMI, post MI, HF<br><br>None | CHD incidence, prevalence, mortality | Prevalence rates of CHD will decrease among the young and middle aged but increase among elderly by 2010 | Extreme scenarios -Model estimates on hospital admission and hospital deaths due to CHD were compared with observed figures in 1985. Looks suspiciously good. | Illustrations & model not available.<br><br>Discussed assumptions & competing causes, nut not confounding or lag times | Omits sudden deaths. Only looked at hypothetical changes in incidence and survival rates to 2010. Did not consider RFs or Rx.<br><br>Data: National statistics were used, adequate | **Adequ** (5) |
| **Bensley 1995**[28] | To quantify the potential health gain in terms of a fall in mortality from prevention and treatment policies | Yorkshire- UK, 1989, M-F 35-74 | None | Angina, AMI, sudden death, CABG, PTCA, post MI<br><br>None | Number of CHD deaths, number of CABG, PTCA and angiograms, and costs associated with them /GP referrals | 1-Model can be used to examine sensitivity of outputs (deaths) to parameters: attack rate, referral rate, and incidence. 2-Forecasting effects on future deaths of hypothetical reductions in attack rates, SVD rate, hospital death rate and episode rate e.g.. | One way sensitivity analysis - discussed reasonably but without examples -Numbers predicted by model was compared observed figures in Yorkshire but no further detail provided | Illustrations available but model not available.<br><br>Discussed assumptions but not competing causes, confounding or lag times | Simple tool to communicate with decision makers, model was built with consulting practising clinicians. However does not include risk factors, data sources rather old and needs to be updated. Model focuses on revascularisati on only; other CHD | **Adequate** (5) |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | treatments overlooked i.e. statins. Model does not include heart failure. | |
| Pharoah 1996[63] | To estimate cost-effectiveness of statins in lowering serum cholesterol in people with varying CVD death risk | UK, Cambridge and Huntington, 10 years period, M-F 45-64 | Cholesterol (fifths), | None<br><br>Statins for primary prevention | Number of CHD deaths prevented, number of CHD cases prevented, and costs per life year saved | The average cost effectiveness for statin therapy for 10 years, in men aged 45-64 with no history of CHD but cholesterol>6.5 mmol/L was £136,000 per life years saved. It was £32,000 with pre-existing CHD and cholesterol>5.4 mmol/L. Cost effectiveness change widely with existing CHD history and cholesterol levels. In women aged 45-54 with angina and cholesterol 5.5-6.0 mmol/l CE: £361,000 | Multi-way? - Different scenarios explored<br><br>None | Illustrations available but model not available.<br><br>Not discussed assumptions, competing causes, confounding or lag times | It was assumed a typical treatment cost for statins for patients. So the compliance would be the same as reported in studies<br><br>Data quality adequate | Poor ( ) |
| Oster 1996[64] | To estimate the effects of reducing dietary saturated fat intake on the incidence and economic cost of CHD | USA, 1990-2000, 35-69 yrs persons with cholesterol level of 5.17 mmol/l or higher, free of CHD | Cholesterol, saturated fat intake (Strategy: reducing saturated fat intake by 1 or 3% | None, None | Incidence (CHD) lifetime direct and indirect costs | Reducing dietary saturated fat intake by 1 or 3% in people with high cholesterol levels would reduce CHD incidence by 32,000 and 199,700 respectively and would save $4.1 and $12.7 billion over 10 years. | None<br><br>None | Illustrations& model not available.<br><br>Discussed assumptions but not competing causes, confounding or lag times | Estimates direct and indirect costs. However it just evaluated impact of diet-saturated fat change through cholesterol, other factors ignored. Data sources adequate | Poor (2) |
| Bots, 1996[65] | To study relative contributions of medical care and | Netherlands, 1978-1985, Dutch pop- age- | Smoking, cholesterol, blood pressure | AMI, Post MI | Number of deaths prevented | Treatments accounted 46% and risk factor changes 44% of the CHD mortality decline in | None<br><br>Estimated | Illustrations available but model not | Estimates are crude, not age-sex specific- | Adequate (6) |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| | changes in CVD risk factors to decline in CHD mortality in Netherlands between 1978 and 1985 | sex not clear | | Beta blockers, anticoagulants, ant platelets, CABG, CCU care | | Netherlands between 1978-85 | figures compared with observed deaths prevented- 90% explained | available. Discussed assumptions, confounding, lag times but not competing causes. | overlaps between treatments and risk factors not accounted/ mean blood pressure change not considered- PAR method was used Overestimation ?? Data sources adequate | |
| Lightwood, 1997[66] | To estimate short term benefit of smoking cessation | USA, 1990, 35-64 yrs M-F | Smoking 1% absolute reduction in smoking prevalence | None, None | Number of deaths prevented, hospital admission for CHD and CVD | A national programme that would reduce smoking prevalence by 1% per year would prevent 98 100 hospitalisations for AMIs and strokes (and 1300 deaths of AMI outside the hospital) and eliminate the need to spend ~$3.2 billion on the treatment of MI and strokes for 7 years. | None None | Illustrations& model available. Discussed assumptions, lag times but not confounding or competing causes. | Very narrow- smoking cessation in prim prevention. - No sensitivity analysis Data sources adequate | Adequate (5) |
| Kellet 1997[67] | To estimate likely gains in life expectancy of patients with CAD treated with statins | CHD patients who had 2, 3 vessel and left main stem coronary artery disease, aged 40-80 | None | CHD patients who had 2, 3 vessel and left main stem coronary artery disease Two treatment options were possible: medically or surgically | Quality adjusted life expectancy | Statins were estimated to provide a gain in life expectancy for medically managed patients of all ages with CHD, ranging from 4.6 to 10.1 QALY | None None | Illustrations& model available. Discussed assumptions but not lag times, confounding or competing causes. | Very narrow purpose, decision tree analysis. Data sources adequate | Adequate (4) |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Riviere 1997[68] | To determine the cost effectiveness of simvastatin in the secondary prevention of CHD in Canada | Canada, …. Average 59.4 years old M-F | | None, None | Cost per life year saved | Premise A: no benefit beyond 5.4 yrs and survival curves continue parallel for 15 yrs. Premise B: The benefit from statins is cumulative, survival curves diverge to 10 yrs then continue parallel until 15 yrs. Premise C: The benefits of statins are assumed to continue for 15 yrs, survival curve would diverge for 15 yrs. For Premises B and C cost effectiveness ratios estimated were $9,867 and $6,108 respectively. | One-way sensitivity analysis<br><br>None | Illustrations& model available.<br><br>Discussed assumptions, but not lag times, confounding or competing causes. | Clear plausible consistent with other studies however includes just one disease and one treatment<br><br>Data: Adequate However treatment effectiveness was based only on 4S study. | Adequate (4) |
| Bonneux, 1998[69] | To examine whether elimination of fatal diseases will increase health care costs | Netherlands, 1986-1990, Dutch population | None | None<br><br>None | Life expectancy and life time health care cost | Elimination of CHD would increase life expectancy by 1.9 yrs proportion of CHD in lifetime health costs increase from 2.5% to 6%. The medical cost of added life years would be about £890 to £1400 per life year. | None None | Illustrations available but not model. Discussed assumptions& confounding but not lag times or competing causes. | Data Sources: Based on old data for life expectancy. Poor. Only medical costs estimated. | Poor (3) |
| Galgali 1998[70] | To calculate the potential for prevention by limiting the pop exposure to common risk factors | New Zealand, 1992-97, M-F 55+ yrs | Smoking, cholesterol, hypertension, physical activity, obesity | None, None | Number of CHD deaths reduced | 3% reduction in smoking, 3% reduction in hypertension, 6% decrease in physical inactivity, and 3%reduction in high cholesterol (in next 5yrs) would result in 1,228 fewer deaths per year (in next 5 yrs). | None<br><br>None | Illustrations available but not model.<br><br>Not discussed assumptions, confounding, lag times or competing causes. | Population and mortality data is national-adequate. However RRs based international studies. Could be a limitation. | Poor (2) |

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| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall gradin (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Augustovski 1998[71] | To evaluate the effects of aspirin in primary prevention of CVD patients with different risk profiles | ? 10 years period (cohorts follow up), - 7 hypothetical cohorts, M-F, age 55-65 with different CVD risk levels | None (but cholesterol, HDL, SBP, smoking, DM, LVH were used to divide the subjects in risk categories) | None  Aspirin 75-375 mg | QALY (end point: CHD or stroke event | Lowest risk cohort (just high cholesterol) would have a loss of 1.8 days QALY. High risk cohort (all rfs +) would achieve 11.3 days QALY | One-Way sensitivity analysis  ?? Cox regression analyses for validity | Illustrations & the model not available.  Discussed assumptions but not confounding, lag times or competing causes. | Aspirin effectiveness is assumed to be same in women. Compliance ignored, generalisability ? For which pop?  Data: Adequate | Adeq (4) |
| Bonneux 1999[72]  (Incidence-prevalence-mortality model) | To estimate changing prevalence of CHD as a consequence of the changing disease history. | Life table population is used for estimations. 10 yrs period- Dutch M-F aged 40-80 in 1980-83 / 1990-93. | None | ACE, recurrent MI, CHD death, CVD deaths, deaths other than CHD | Incidence, prevalence, CHD deaths, hospital discharges | Incidence of first ACE changed little between 1980-83 and 1990-93 among men<60 incidences decreased by 10% among women incidence increased by 9%. Average prevalence of survivors increased sharply, predominantly among elderly: from 12% in 1980s to 16% in 1990s in men >60 and 3.3% to 5.5% in women >60. | One-way sensitivity analysis- using plausible recurrence probabilities . | Illustrations & the model not available.  Discussed assumptions but not confounding, lag times or competing causes. | Quite broad CHD definition- no detail. Details available from a web page. Data sources reported. Administrative data were used. | Poor (3) |
| Mui 1999[26] | To project the incidence rates for CHD, and the number of CHD cases, hospital costs for M/F aged 45-69 up to 2014 | Australia, 1989-2014, M-F aged 45-69 | Smoking, cholesterol, TC/HDL ratio, blood pressure | None, None | Incidence (CHD and stroke) | If current CHD risk factor distributions change only by a location shift and the treatment availability stays the same CHD incidence will decline 13% in M and 24% in W by 2014 | None  Model CHD incidence estimates were compared with MONICA data for the same year. | Illustrations & the model not available.  Discussed assumptions but not confounding, lag times or competing causes. | Model takes into account changes in risk factors with aging, change in smoking status. Model validity was improved with regressing the rates. | Poor (3) |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| Naidoo 2000 | To assess effects of achieving two targets of reducing smoking in terms of AMI and stroke | England, 1996-2015, M-F aged 15-64 | Smoking, Target? reducing smoking | Male | Number of AMI and stroke | Targets would result in fall in AMI and stroke events... | Model 50% overestimates in M and 110% underestimates for W | | Estimates hospitalisation costs. Data: Adequate | |
| Thompson 1999[73] | To explore lifetime health and economic consequences of obesity using a lifetime model. | USA, ?, M-F aged 35-64 | Smoking, cholesterol, DBP, diabetes, obesity, age, sex | None None | Number of CHD, stroke event, life expectancy | Lifetime risk of HT, high cholesterolemia, DM, stroke and CHD in men 45-54 increases with BMI. Life expectancy reduced by 1 year in men and women with BMI over 37.5. Lifetime medical care costs for treatment of (High cholesterol, HT, DM, CHD, stroke) are estimated to differ by $10,000 ($29,600 vs $19,600). | None None | Illustrations & the model not available. Discussed assumptions but not confounding, lag times or competing causes. | Data sources reported poorly | Poor (???) |
| Lindholm 1999[74] | To estimate C/E calculation within a defined budget for CHD primary prevention options BP, Cholesterol, treatments and community interventions | Vaterbotten, Sweden, 1996?, M-F 30-69 | Smoking, cholesterol, BP, community based interventions (education and screening) | None, None | Cost per life year saved | Hypertension treatment cost depends on cost of drug used. Marginal C/E ratios 17,000-500,000 ECU/life years saved (mean 55,000 Ecu). Cholesterol lowering drugs 53,000-800,000 Ecu/LYS (mean 83,000 Ecu). Community programme 4,000-23,000 Ecu/ LYS (mean 12,000 Ecu). Optimal division of resources would require lowering budget for hypertension treatment but increasing cholesterol treatment and community interventions. | One-way sensitivity analysis Based on actual budget of 6.2million ecu | Illustrations & the model not available. Discussed assumptions but not confounding, lag times or competing causes. | Basic model. Assumed no benefits from statins Data: Adequate | Adequate (4) |

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| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Naidoo 2000**[75] | To simulate effects of achieving two targets of reducing smoking in terms of AMI and stroke hospitalisation numbers prevented | England, 1996-2010, M-F aged 35-64 | Smoking Target1: reducing smoking prevalence from 28%(1996) to 26% (2005) and to 24%(2010) Target2: More ambitious reductions- from 28%(1996) to 22%(2005) and to 17% (2010) | None | Number of AMI and stroke hospitalisations prevented | Target1 would result in 347 AMIs and 214-stroke hospitalisation prevented in 2000 and 6386 AMIs; 4964 strokes in year 2010. Achieving target 2 would result in 739 AMI and 11,304 strokes in 2010. Target 1 would save £524 million and Target 2 would save 1.14 billion NHS costs. | One way sensitivity analysis <br><br> None | Illustrations & the model not available. <br><br> Not discussed assumptions, confounding, lag times or competing causes. | Data: Adequate | Poor ( |
| **Kuulasma 2000**[76] | To explain the extent to which risk factor changes explain the variation in CHD events rate trends across 38 populations | 38 populations over 30 countries, mid 1980s- mid 1990s, M-F aged 35-64 | Smoking, total cholesterol, SBP, BMI) | In another paper they considered immediate treatments for AMI and secondary treatment for post AMI patients. | Change in CHD event rates | During the study period risk scores and CHD event rates decreased. Trend model showed a poor fit, but after considering 4 years lag improved. The explanatory power of the analyses was limited (46% in M and 19% in W) by imprecision of the estimates and homogeneity of trends in the study populations. | One-way sensitivity analysis -Validity was checked by comparing estimated falls with observed falls in event and deaths. | Illustrations available but the model not. <br><br> Discussed assumptions, confounding, lag times but not competing causes. | Weak study design (ecological) <br><br> Data: From real populations and quality checked therefore adequate. | Adequate (7) |
| **Fichtenberg 2000**[77] | To estimate whether California Tobacco Control Programme was associated with lower rates of CHD deaths | USA, California, 1977-1997, US California, CHD death rates | Smoking | None, None | CHD mortality | Between 1989 and 1992 per capita cigarette consumption declined faster in California by 2.72 pack per year. IHD mortality also declined faster by 2.93/10000 per year. Programme was associated with 33,000 fewer CHD deaths 1989-1997. Effectiveness diminished after | None <br><br> None | Illustrations & the model not available. -Discussed assumptions & method refined for confounding and lag times. Not discussed | Quite simple model looked at all heart disease mortality. <br><br> Data: Adequate | Adequate (4) |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1992 associated with 8,300 more deaths. A large aggressive tobacco control programme was associated with a substantial reduction in deaths from heart disease. | | competing causes. | | |
| **McNeil 2000**[78] | To model life time risk of fatal or nonfatal CHD in different risk percentiles | Australia, 1993-1995, Men aged 20-69 Australia | Cholesterol | None, None | Number of CHD deaths prevented | Top decile of individuals contained 23% of CHD risk, top 30% contained over 50%. Survival curves separate after age 45 in men, 55 in women | None -Predicted individual risk event compared with observed rate in AFCAPS and TEXCAPS primary prevention trials | Illustrations available but the model not. Discussed assumptions but not confounding, lag times or competing causes. | Poor- lots of assumptions- risk at 69 extrapolated to 84 Data: Adequate | **Adequ** (4) |
| **Baker 2000**[79] | To estimate the impact of using thresholds based on absolute risk of CVD to target drug treatment to lower blood pressure in the community | Auckland/ New Zealand, ??, 2158 M-F aged 35-79 sampled from general population | Smoking, cholesterol/HDL, SBP, diabetes, age and sex | No disease categories included. Antihypertensive treatments | Number of CVD prevented (angina, MI, CHD death, stroke, TIA, congestive HF, peripheral vascular disease) | 46,374 (12%) Auckland residents aged 35-79 receive antihypertensive treatment. It was estimated that 1689 disease over 5 yrs would be averted. Restricting treatments to individuals with >170/100mm/hg and BP between 150/90-169/99 mmHg who have 5 yrs disease risk >10% would avert 19,401. Implementing guidelines and use treatment thresholds based on absolute risk could significantly improve efficiency of antihypertensive treatments. | None None | Illustrations & model not available. Discussed assumptions but not confounding, lag times or competing causes. | Risk factor information was available from a national population study. Excluded Maori& Pacific Islander population. Confined to BP only. Assumed 25% of relative risk reduction, might be a high efficacy. | **Poor (2)** |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations &Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Data sources adequate | |
| **Selmer 2000**[80] | To estimate health and social consequence of reducing daily salt intake by 6 gr per person | Norway, 1995-2020, over 40 M-F | Blood pressure | None, None | Cost | A 2 mmHg reduction in SBP would reduce stroke by 4.2%, MI by 3.8%. Implies overall 1-2% reduction in total mortality, Life expectancy in 40-year-old men increase 1.8 months, in women 1.4 months. *25 year benefit:* 7000 lower MI deaths, 4500 lower stroke deaths, 87000 LYG (6000 lives saved at year 25) on average 10 LYGs each.  Total 150000 LYG (discounted 52000). Net saving $270 million- 120 million discounted) | One-way sensitivity analysis  None | Illustrations & model not available.  Discussed assumptions & competing causes but not confounding or lag times. | Narrow Data quality adequate with limitations on generalisability of FINMARK Study to Norwegian pop. | **Poor** |
| **Malik 2001**[81] | To assess cost effectiveness of ramipril in patients with low, medium, high risk | UK, 1998, men average age 66 from HOPE Trial | None | Highest risk, high risk and low risk patients.  Treated with ramipril | LYG, cost per LYG | Cost effectiveness of ramipril was £36600 £13600 and £4000 per life year gained at five years and £5300, £1900, and £100 per life year gained at 20 yrs in low, medium and high risk groups respectively.  Treatment of medium risk HOPE population would cost UK NHS £360 million but would prevent 12 000 deaths. | One-way sensitivity analysis  None | Illustrations & model not available.  Discussed assumptions but not competing causes, confounding or lag times. | Data: Adequate | **Poor (3)** |
| **Peeters 2002**[82] | To measure CVD burden of disease in Framingham cohort, by generating years of life lost or lived with the disease | USA, 1941-1991, M-F, aged 18-62 years at onset | None | Angina, AMI, heart failure, stroke, TIA, intermittent claudication | Life expectancy and lives lived with disability | 5,070 individuals without CVD at the beginning, 50% developed CVD and 60% died over 40 years. 34% developed CHD, 20% AMI, 14% stroke, and 14% heart failure. Using life tables it is estimated that at age 50 20% (6.3 yrs for men and 5.7 yrs for women) of a | None  None | Illustrations available but model not.  Discussed assumptions & competing causes but not confounding or lag times. | Disease states are not mutually exclusive.  Data: Quite few event numbers for women. | **Poor (3)** |

| Author (year) | Purpose of the model | Model setting, Time period & Population | Risk factors included | Disease categories & Treatments included | Outcomes studied | Key Results | Sensitivity analysis & Validity | Transparency | Strengths / Limitations & Data Quality | Overall grading (Score) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | populations residual life expectancy is spent with CVD. Much of this (4.7 yrs male, 3.7 yrs females) spent on CHD. | | | | |
| Marshall 2002[83] | To develop a model to evaluate costs and health benefits of implementing guidelines for prevention of CVD prevention--6 strategies (2 from joint British recommendations) | England, ?1998, Hypothetical cohort of 2000 patients aged 30-74 | Smoking, cholesterol, HDL, blood pressure, diabetes, age, sex, LVH. | None, Aspirin, thiazid, Beta blocker, ACE inhibitor, statin | Cardiovascular event prevented | Novel strategies prevent more CVD at lower cost than traditional strategies | One-way sensitivity analysis None | Illustrations & model not available. Discussed assumptions & competing causes but not confounding or lag times. | Lacks detail on model, not very relevant on explaining risk factor or treatment effects on CVD in the population Data sources adequate | Adequate (4) |

# App4. Table 8. List of excluded studies

| EXCLUDED STUDIES (Alphabetical order) | Reason for Exclusion |
|---|---|
| Assman 1990[84] | This is an individual data based statistical model. It is simply a validation study of PROCAM equations using Helsinki Heart Study. |
| Avins 1998[85] | This is a general evaluation of interventions used in North Karelia and Minnesota Heart Health Programmes. No CHD outcomes reported. |
| Beard 1989[86] | Not a modelling study. It is a case control study, which uses PAR estimations. |
| Bronnum-Hansen 1999[13] | No CHD outcomes reported |
| Cleland 1998[87] | This is an individual based statistical model not a population based CHD health policy model. |
| Cowen 1996[88] | CHD is not an outcome in this model, it is an input |
| Glick 1992[89] | Not a population based model. |
| Grover 1994[90] | Review, not an original model paper. |
| Gunning-Schepers 1999[91] | General editorial, not an original paper |
| Gunning-Schepers 1987[92] | General review, not an original paper |
| Hatziandreu 1988[93] | Decision analysis of hypothetical cohort of 1000 men aged 35 years followed up for 30 years. Not population based model. |
| Hinzpeter 2000[94] | German language. Abstract checked. Cost estimates only. |
| Kaplan 1988[95] | This study used logistic regression analysis and compared two cohort studies. It is not a population CHD health policy model. |
| Kawachi 1990[96] | Outcome is not CHD |
| Kaplan 2001[97] | No CHD outcome reported |
| Liew 2002[98] | This is a general review paper not an original paper |
| Murray 1994[99] | This not a CHD health policy model. This paper aims to explore ways of comparison between intervention and control communities in community intervention trials |
| Murray 1994[100] | This paper presents the distribution of DALYs by cause, age, sex and region. However provides very little detail on CVD. |
| Murray 1994[25] | This paper simply defines the cause of mortality by eight regions of the world, it does not model CHD. |
| Nissinen 1992[101] | Duplicate paper of Nissinen 1986[54] |
| Peeters 2003[102] | This is not a population CHD health policy model. It is an individual based statistical model |
| Petersen 1982[103] | Just reports on RF distributions and individual risk of developing CHD risk. This is not a population CHD health policy model. |
| Salonen 1986[104] | General evaluation of community based CHD control programmes |
| Wolfson 1994 | The Population Health Model (POHEM) was developed for chronic diseases but then never used for CHD policy analyses. This paper provides a framework to understand the POHEM Model. |

# Appendix 5. CHD data sources in the UK: Conference proceedings, audit reports, official web sites and personal correspondence used for.

## Conference proceedings

- British Cardiac Society
- Congresses of European Society of Cardiology
- Society for Social Medicine Meetings 1990- 2003

## Audit Reports

- Audit commission http://www.audit-commission.gov.uk
- Dr. Liddy Goyder (Sheffield) for diabetes sources

## Official web sites

- British Cardiac Intervention Society http://www.bcis.org.uk/audit/oct01.html
- Health Development Agency http://www.hda-online.org.uk/
- Heart Start Scotland http://www.heartstart.org/
- National Heart Forum http://www.heartforum.org.uk/nationalheartforum.html
- Ambulance Service Association http://www.asancep.org.uk/

## Personal correspondence

- David Cunningham
- Julia Critchley
- John Mc Murray
- Gary Smith

## Appendix 6. CHD Mortality fall in England and Wales between 1981 and 2000: Numbers of deaths prevented or postponed by risk factor changes and treatments in individuals with CHD, categorised into specific CHD patient groups.

| CHD patient groups | Number of DPPs | Minimum and Maximum Estimates | % |
|---|---|---|---|
| **2' Prev Post MI** | **3,844** | **(2,850 -5,059)** | **100%** |
| Treatments | 1,964 | 1,691 - 2,073 | 51% |
| *Cholesterol reduction* | 333 | 249-561 | 9% |
| *Smoking cessation* | 1,451 | 878-2,317 | 38% |
| *Blood pressure reduction* | 96 | 32-108 | 2% |
| | | | |
| **2' Prev Post CABG/PTCA** | **3,055** | **(1,737- 7,610)** | **100%** |
| Treatments | 1,784 | 1,056- 5,800 | 58% |
| *Cholesterol reduction* | 194 | 66 -319 | 6% |
| *Smoking cessation* | 818 | 510- 1,148 | 27% |
| *Blood pressure reduction* | 259 | 105-343 | 8% |
| | | | |
| **Chronic Angina** | **3,424** | **(1,907- 5,889)** | **100%** |
| Treatments | 2,032 | 1,045-3,706 | 59% |
| *Cholesterol reduction* | 198 | 96-460 | 6% |
| *Smoking cessation* | 1,114 | 713-1,605 | 33% |
| *Blood pressure reduction* | 80 | 53-118 | 2% |
| | | | |
| **Hospital Heart Failure** | **4,756** | **(2,296-7,682)** | **100%** |
| Treatments | 3,985 | 1,832-6,326 | 84% |
| *Cholesterol reduction* | 131 | 55-265 | 3% |
| *Smoking cessation* | 597 | 399-1,025 | 13% |
| *Blood pressure reduction* | 43 | 10-66 | 1% |
| | | | |
| **Community Heart Failure** | **3,211** | **(1,938-6,318)** | **100%** |
| Treatments | 1,710 | 1,102-3,096 | 53% |
| *Cholesterol reduction* | 348 | 176-847 | 11% |
| *Smoking cessation* | 1,055 | 600 -2,160 | 33% |
| *Blood pressure reduction* | 98 | 60-215 | 3% |

## Appendix 7. Trends in CHD mortality in England and Wales 1981 – 2000.

| | Population (000s) | | CHD Mortality Rates (/100,000) | | Change in CHD mortality rate | CHD Deaths observed | | Expected CHD deaths in 2000 if 1981 rates persisted | Fall in CHD deaths in 2000 |
|---|---|---|---|---|---|---|---|---|---|
| **MEN** | 1981 | 2000 | 1981 | 2000 | 1981-2000 | 1981 | 2000 | | |
| AGE | a | b | c | d | % | e | f | (bxc) | (bc-f) |
| 25-34 | 3,533 | 4,059 | 7 | 2 | -63 | 231 | 97 | 265 | 168 |
| 34-44 | 3,041 | 4,049 | 51 | 19 | -63 | 1,546 | 744 | 2,058 | 1,314 |
| 45-54 | 2,788 | 3,479 | 249 | 89 | -64 | 6,953 | 3,105 | 8,676 | 5,571 |
| 55-64 | 2,682 | 2,685 | 681 | 282 | -59 | 18,255 | 7,590 | 18,275 | 10,685 |
| 65-74 | 2,025 | 2,036 | 1,562 | 807 | -48 | 31,632 | 16,462 | 31,804 | 15,342 |
| 75-84 | 827 | 1,145 | 2,927 | 1,897 | -35 | 24,205 | 21,772 | 33,512 | 11,740 |
| **Total** | **14,896** | **17,453** | **556** | **214** | **-62** | **82,822** | **49,770** | **94,592** | **44,822** |
| | | | | | | | | | |
| **WOMEN** | a | b | c | d | | e | f | (bx c) | (bc-f) |
| 25-34 | 3,482 | 3,837 | 1 | 1 | -54 | 45 | 22 | 50 | 28 |
| 35-44 | 2,994 | 3,920 | 9 | 5 | -47 | 255 | 179 | 334 | 155 |
| 45-54 | 2,713 | 3,483 | 47 | 19 | -61 | 1,287 | 654 | 1,652 | 998 |
| 55-64 | 2,914 | 2,752 | 191 | 78 | -59 | 5,555 | 2,192 | 5,246 | 3,054 |
| 65-74 | 2,621 | 2,320 | 659 | 335 | -49 | 17,274 | 7,811 | 15,290 | 7,479 |
| 75-84 | 1,563 | 1,753 | 1,727 | 1,053 | -39 | 26,988 | 18,574 | 30,269 | 11,695 |
| **Total** | **16,287** | **18,065** | **316** | **173** | **-45** | **51,404** | **29,432** | **52,841** | **23,409** |
| | | | | | | | | | |
| **MEN & WOMEN** | | | | | | | | | |
| AGE | a | b | c | d | | e | f | (bx c) | (bc-f) |
| 25-34 | 7,015 | 7,896 | 4 | 2 | -61 | 276 | 119 | 315 | 196 |
| 35-44 | 6,035 | 7,969 | 69 | 40 | -49 | 1,801 | 923 | 2,392 | 1,469 |
| 45-54 | 5,501 | 6,962 | 150 | 54 | -64 | 8,240 | 3,759 | 10,329 | 6,570 |
| 55-64 | 5,596 | 5,437 | 425 | 179 | -58 | 23,810 | 9,782 | 23,522 | 13,740 |
| 65-74 | 4,646 | 4,356 | 1,053 | 556 | -47 | 48,906 | 24,273 | 47,094 | 22,821 |
| 75-84 | 2,390 | 2,898 | 2,142 | 1,387 | -35 | 51,193 | 40,346 | 63,781 | 23,435 |
| **TOTAL** | **31,183** | **35,518** | **430** | **193** | **-55** | **134,226** | **79,202** | **147,433** | **68,231** |

## Appendix 8. One year case fatality rates (per 1000) for unselected patients on usual treatment.

| Men and Women | Post AMI | CABG | PTCA | Unstable Angina | Community Angina |
|---|---|---|---|---|---|
| 25-34 | 14 | 12 | 12 | 21 | 2 |
| 35-44 | 14 | 12 | 12 | 30 | 2 |
| 45-54 | 29 | 25 | 12 | 43 | 4 |
| 55-64 | 52 | 41 | 25 | 72 | 7 |
| 65-74 | 77 | 62 | 38 | 90 | 11 |
| 75-84 | 97 | 92 | 56 | 117 | 13 |
| 85+ | 106 | 138 | 84 | 152 | 15 |

- In SLiDE Study median AMI age was 68 and 75 year for men and for women respectively[105;106].
- Case fatality halved in younger decades and doubled in older decades.
- Case fatalities essentially the same in men and women.

# Appendix 9. Adjustment for poly-pharmacy in individual CHD patients.

Individual CHD patients may take a number of different medications. However, RCT data on the efficacy of treatment combinations are sparse. Mant and Hicks[107] suggested a method to estimate case-fatality reduction by polypharmacy. This was subsequently also used by Wald and Law[108].

If we take the example **of secondary prevention following acute myocardial infarction**, good meta-analysis evidence (Appendix 2) suggests that, for each intervention, the relative reduction in case fatality is approximately:

Aspirin 15%, beta-blockers 23%, ACE inhibitors 23%, statins 29% and rehabilitation 27%. The Mant and Hicks[107] approach suggests that in individual patients receiving all these interventions, case-fatality reduction is very unlikely to be simply additive ie not **117%** (15% + 23%+ 23% + 29% + 27%). Indeed, 117% is clearly absurd, implying immortality. Instead, having considered the 15% case fatality reduction achieved by aspirin, the next medication, in this case a beta-blocker, can only reduce the **residual** case fatality (1-15%). Likewise, the subsequent addition of an ACE inhibitor can then only decrease the **remaining** case fatality, which will be 1 - [(1- 0.15) X (1-0.23)].

The Mant and Hicks approach therefore suggests that a **cumulative relative benefit** can be estimated as follows:

*Relative Benefit = 1 - [(1 -Treatment A) X (1-Treatment B) X (1 -Treatment C) X (1 - Treatment D) X (1 -Treatment E)]*

In considering appropriate treatments for AMI survivors, applying relative reductions for aspirin, beta-blockers ACE inhibitors statins and rehabilitation then gives:

*Relative Benefit = 1 - [(1 -aspirin) X (1 - beta-blockers) X (1 - ACE inhibitors) X (1- statins) X (1- rehabilitation)]*

$$= 1 - [(1- 0.15) X (1-0.23) X (1-0.23) X (1- 0.29) X (1- 0.27)]$$
$$= 1 - [(0.85) X (0.77) X (0.77) X (0.71) X (0.73)]$$
$$= 0.74 \quad \text{ie a 74\% lower case fatality}$$

This represents a **37%** relative reduction (74/117) compared with the simple additive value of **117%.**

**Following AMI secondary prevention patients** are eligible for rehabilitation plus secondary prevention with aspirin, beta-blocker, ACE inhibitor and a statins.

**The uptake of medications** in 2000 in eligible patients surviving AMI was approximately: Aspirin 56%, beta blockers 34% ACE inhibitors 19%, statins 25%, and rehabilitation 23%. **Assuming** approximately **10%** of total patients received all five interventions, case fatality would be reduced by 37% in this group. This represents **142** fewer DPPs out of a total of 3,844 DPPs. Knowing the uptake of each medication; a matrix approach then can be used to calculate the maximum proportion of patients on four, three and two drug combinations respectively. Assuming that some 5% of total patients received four medications, case fatality would be reduced by 29% in this group. This represents a **55** fewer DPPs out of a total of 3,844 DPPs.

Assuming 1% of total patients received three medications aspirin, ACE inhibitor and a statins, case fatality would be reduced by 19% in this group. This represents a **7** fewer DPPs out of a total of 3,844 DPPs.

The same exercise can then be repeated for the (few) remaining patients receiving any **pair** of aspirin / beta blocker/ ACE inhibitor or statins treatment. Having removed the 10% on quintiple, 5% on quadruple, and the 2% on triple therapy, that leaves approximately 31% patients on these medication pairs. Using the same methodology, **181** fewer DPPs out of a total of 3,844 DPPs were estimated for those combination therapies.

Therefore, after summing these adjustments for polypharmacy in secondary prevention in AMI survivors, the total deaths prevented or postponed might be reduced by approximately **393** (=142+55+7+181). **This adjustment represents a reduction of about 15% of the 3,844 DPP total.**

The same approach was used to estimate the potential reduction in efficacy with combined therapy for all other patient groups. This suggested that deaths prevented or postponed might be reduced by a total of **2,118** (395 for initial treatment of acute myocardial infarction, 393 for secondary prevention treatments post AMI, 530 for secondary prevention treatments post CABG or PTCA, 562 for heart failure treatments in hospital and 238 for heart failure treatments in the community).

This 2,188 total would represented an approximately 8% reduction of the 25,805 estimated deaths prevented or postponed by treatments, or 3% of the total mortality fall of 68,231 between 1981 and 2000.

## Appendix 10. Estimates of median survival used in sensitivity analyses: for men and women stratified by age groups and by each category of treatment.

| Treatment category or Risk factor change | Improvements in treatment uptake and efficacy | | | | | | Reference / assumption |
|---|---|---|---|---|---|---|---|
| | Best estimate | | Minimum estimate | | Maximum estimate | | |
| Post-Myocardial Infarction patients | Men | Women | Men | Women | Men | Women | |
| 25-34 | 25.0 | 25.0 | 18.4 | 16.2 | 31.6 | 33.8 | Capewell et al. 2000[105]. Maximum value is survival reported in those with first admission only, minimum value is difference between 'best' estimate and 'maximum' estimates |
| 35-44 | 20.0 | 20.0 | 14.8 | 12.7 | 25.2 | 27.3 | |
| 45-54 | 14.0 | 14.0 | 9.4 | 7.4 | 18.6 | 20.6 | |
| 55-64 | 7.0 | 7.0 | 2.0 | 0.2 | 12.0 | 13.8 | |
| 65-74 | 5.5 | 5.5 | 3.1 | 1.7 | 7.9 | 9.3 | |
| 75-84 | 4.2 | 4.2 | 3.5 | 2.7 | 4.9 | 5.8 | |
| Post-CABG patients | | | | | | | |
| 25-34 | 35.8 | 35.8 | 18.5 | 18.5 | 53.1 | 55.6 | Astbury[109] and Pell[110] |
| 35-44 | 28.6 | 28.6 | 18.5 | 18.5 | 38.6 | 41.1 | |
| 45-54 | 20.0 | 20.0 | 17.0 | 17.0 | 23.0 | 24.0 | |
| 55-64 | 12.0 | 12.0 | 12.5 | 12.5 | 11.5 | 12.5 | |
| 65-74 | 8.5 | 8.5 | 9.0 | 9.0 | 8.0 | 7.5 | |
| 75-84 | 6.0 | 6.0 | 4.5 | 4.5 | 7.5 | 7.3 | |
| Heart Failure | | | | | | | |
| 25-34 | 3.5 | 3.5 | 2.8 | 2.8 | 4.2 | 4.2 | MacIntyre et al. 2000[106]. 'Maximum' is survival reported for first admissions only, minimum is difference between 'best' estimate and 'maximum' estimates |
| 35-44 | 2.5 | 2.5 | 2.0 | 2.0 | 3.0 | 3.0 | |
| 45-54 | 2.0 | 2.0 | 1.6 | 1.6 | 2.4 | 2.4 | |
| 55-64 | 1.5 | 1.5 | 1.2 | 1.2 | 1.8 | 1.8 | |
| 65-74 | 1.3 | 1.3 | 1.0 | 1.0 | 1.6 | 1.6 | |
| 75-84 | 1.1 | 1.1 | 0.9 | 0.9 | 1.3 | 1.3 | |

| Heart Failure treated in the community | | | | | | | |
|---|---|---|---|---|---|---|---|
| 25-34 | **15.0** | **15.0** | 12.0 | 12.0 | 18.0 | 18.0 | Median survival |
| 35-44 | **13.0** | **13.0** | 10.4 | 10.4 | 15.6 | 15.6 | assumed to be double |
| 45-54 | **9.0** | **9.0** | 7.2 | 7.2 | 10.8 | 10.8 | that of severe heart |
| 55-64 | **6.4** | **6.4** | 5.1 | 5.1 | 7.7 | 7.7 | failure treated in |
| 65-74 | **6.2** | **6.2** | 5.0 | 5.0 | 7.4 | 7.4 | hospital (above) |
| 75-84 | **5.5** | **5.5** | 4.4 | 4.4 | 6.6 | 6.6 | |
| **Hypertension** | | | | | | | Maximum estimate is same as Registrar |
| 25-34 | **36.9** | **39.1** | 29.3 | 32.0 | 48.8 | 53.3 | General's general population life table |
| 35-44 | **28.6** | **31.9** | 22.3 | 26.3 | 37.1 | 43.9 | (2000), 'best' is based on mortality observed |
| 45-54 | **22.0** | **24.1** | 18.0 | 20.5 | 30.1 | 34.1 | at Glasgow blood |
| 55-64 | **14.3** | **16.1** | 12.9 | 15.2 | 21.5 | 25.3 | pressure clinic, |
| 65-74 | **9.8** | **11.2** | 8.4 | 10.2 | 14.0 | 17.0 | 'minimum' is 50% |
| 75- 84 | **6.3** | **7.3** | 5.1 | 6.3 | 8.5 | 10.4 | reduction in survival compared with the population life table. |
| **Angina-CABG and community angina** | Same as post-CABG. | | | | | | Astbury[109] Pell[110] |
| **Angina - unstable** | | | | | | | |
| 25-34 | **25.0** | **25.0** | 21.3 | 21.3 | 42.5 | 42.5 | Chalmers (2001)[111] |
| 35-44 | **16.0** | **16.0** | 13.6 | 13.6 | 27.2 | 27.2 | |
| 45-54 | **12.0** | **12.0** | 10.2 | 10.2 | 20.4 | 20.4 | |
| 55-64 | **7.0** | **7.0** | 6.0 | 6.0 | 11.9 | 11.9 | |
| 65-74 | **5.0** | **5.0** | 4.3 | 4.3 | 8.5 | 8.5 | |
| 75-84 | **4.0** | **4.0** | 3.4 | 3.4 | 6.8 | 6.8 | |

# Appendix 11. Estimates of median survival used in sensitivity analysis for deaths prevented or postponed in men and women by risk factor reductions.

For those with **recognised CHD**, survival was assumed to be the same as that among post AMI patients. For those with **unrecognised CHD**, survival was assumed to be midway between those with recognised CHD and those without symptomatic CHD.

For those with **no symptomatic CHD**, the estimates below apply. 'Best estimates' are those of the Registrar General's life table, minimum estimates are midway between normal expectation of life and expectation for those post-AMI, maximum estimates are inflated to account for estimates of the life-years gained by eliminating 'competing risks'.

| Median Survival | | | | | | | Source |
|---|---|---|---|---|---|---|---|
| | *Best estimate* | | Minimum Estimate | | Maximum Estimate | | |
| | Men | Women | Men | Women | Men | Women | |
| **Reduction in smoking prevalence** | | | | | | | Grover *et al. 1994* [112] |
| 25-34 | 42.8 | 46.1 | 34.8 | 36.7 | 47.4 | 51.3 | |
| 35-44 | 32.8 | 33.3 | 26.7 | 29.9 | 36.2 | 36.5 | |
| 45-54 | 26.0 | 29.0 | 20.4 | 22.1 | 28.9 | 32.4 | |
| 55-64 | 17.8 | 20.6 | 13.2 | 14.8 | 20.1 | 23.4 | |
| 65-74 | 11.9 | 14.1 | 9.1 | 10.4 | 13.3 | 15.9 | |
| 75- 84 | 7.4 | 8.8 | 6.0 | 6.8 | 8.2 | 9.9 | |
| **Reduction in population blood pressure** | | | | | | | Tsevat *et al.*1991[4] |
| 25-34 | 45.3 | 49.1 | 35.7 | 37.7 | 48.0 | 52.1 | |
| 35-44 | 34.6 | 40.0 | 27.6 | 30.8 | 36.6 | 42.8 | |
| 45-54 | 27.7 | 31.1 | 21.2 | 22.9 | 29.4 | 33.1 | |
| 55-64 | 19.4 | 22.9 | 13.6 | 15.4 | 20.7 | 24.2 | |
| 65-74 | 12.8 | 15.3 | 9.4 | 10.7 | 13.6 | 16.4 | |
| 75- 84 | 7.9 | 9.5 | 6.1 | 7.0 | 8.3 | 10.1 | |
| **Reduction in population cholesterol levels (Diabetes, Obesity, Deprivation, Physical Activity)** | | | | | | | Grover *et al.* 1994 [112] |
| 25-34 | 41.4 | 44.4 | 34.3 | 36.1 | 46.8 | 50.5 | |
| 35-44 | 31.7 | 32.5 | 26.3 | 29.4 | 35.8 | 36.3 | |
| 45-54 | 25.0 | 27.8 | 20.1 | 21.6 | 28.5 | 31.8 | |
| 55-64 | 17.0 | 19.6 | 12.9 | 14.5 | 19.6 | 22.7 | |
| 65-74 | 11.4 | 13.4 | 8.9 | 10.2 | 13.0 | 15.4 | |
| 75-84 | 7.1 | 8.5 | 5.9 | 6.7 | 8.1 | 9.7 | |

# Appendix 12. Good practice in spread sheet modelling *(Edwards et al, 2000)*

1. Keep all the major components of each area of organisational responsibility together and make each component a different module in the spreadsheet.

2. Within each module segregate the data model from the logic model.

3. Incorporate information about the major assumptions and modelling conventions underpinning the whole of the spreadsheet explicitly **in** the spreadsheet.

4. Specify the range of application of the spreadsheet – either of the whole spreadsheet or of parts of it.

5. Put the name of the file that holds the spreadsheet permanently into the summary model section of the spreadsheet.

6. Arrange for the time and date when the results were produced to be automatically printed with the results, linked to the current date of the underlying model.

7. Write an information flow diagram to support the SS development.

8. Subdivide the logic model modules into logically integrated sub-units.

9. For each relationship, check: its 'shape', its dimensions, the units used and its range of application.

10. Use factor names rather than cell references.

11. Assign titles to the top left hand corner of each of the spreadsheet modules.

12. Protect or lock some of the entries in a spreadsheet.

13. Never include the values of any coefficients and parameters within formulae: make these factors part of the data model.

14. Never input the same piece of data more than once.

15. Add notes to data values to indicate their source and any associated confidence level.

16. Choose cell widths and appropriate formats to give visual clues as to anomalies in the data.

17. Use limit-checking formulae to ensure that the data values are sensible.

18. Link graphs to the data to bring attention to less obvious errors.

19. Put in reminders that you need to consider (or must change) particular values.

20. In organisational databases understand just what the data values refer to so as to avoid 'translation' errors.

21. Use macros to help navigate around the system and ensure things are done as intended.

*By Edwards et al, 2000*[113]

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# Appendix 14. Published or submitted papers resulting from this thesis

## *Published papers*

1. Unal B, Critchley J, Capewell S. Missing, mediocre or merely obsolete? An evaluation of UK data sources for coronary heart disease. Journal of Epidemiology and Community Medicine.2003; 57:530-535.

2. Unal B, Critchley J, Capewell S. Impact of smoking reduction on coronary heart disease mortality trends during 1981-2000 in England and Wales. Journal of Tobacco Induced Diseases. 2003;1(3):185-196.

3. Unal B, Critchley J, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales, 1981-2000. *Circulation* 2004;109:1101-7.

## *Papers in press*

2. Unal B, Critchley J, Fidan D, Capewell S. Life-years gained from modern cardiological treatments and population risk factor changes in England and Wales, 1981-2000. American Journal of Public Health 2003;(In press).

## *Papers submitted for publication*

1. Unal B, Critchley J, Capewell S. Small changes in UK cardiovascular risk factors leading to potentially big reductions in coronary heart disease mortality? Journal of Clinical Epidemiology (2004).

2. Capewell S, Unal B, Critchley J, McMurray J. 20,000 avoidable coronary deaths in England and Wales in 2000: the failure to give effective treatments to eligible patients. Annals of Internal Medicine (2004).

## *Conference proceedings*

1. Unal B, Critchley J, Fidan D, Capewell S. Life-years gained from modern cardiological treatments and population risk factor changes in England and Wales, 1981-2000. Society of Social Medicine 47th Annual Scientific Meeting. September 2003, Edinburgh, UK.

2. Fidan D, Unal B, Critchley J, Miners A, Capewell S. Economic analysis of treatments contributing to the recent coronary heart disease mortality decline in England and Wales. Journal of Epidemiology & Community Health 2003;57:A14.

3. Taylor RS, Unal B, Critchley J, Capewell S. Reductions in cardiac mortality with exercise-based cardiac rehabilitation: How much can be attributed to improvements in cardiovascular risk factors? British Cardiac Society Meeting 2003. Heart 2003; 89(Suppl 1): A23.

4. Aslan BU, Critchley J, Capewell S. Impact of smoking reduction on coronary heart disease mortality trends during 1981-2000 in England and Wales. First Annual Meeting of International Society for the Prevention of Tobacco Induced Diseases. Conference book, pg 6. University of Essen, Germany, 2002.

5. Aslan BU, Critchley J, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales, 1981-2000. J Epidemiol Community Health.2002;56(Suppl 2):A9. (Abst)

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7. Aslan BU, Critchley J, Capewell S. Reducing coronary heart disease mortality in England and Wales by increasing the uptake of cardiological treatments. J Epidemiol Community Health. 2002;56(Suppl 2): A9 (Abst).