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Assessing the Economic Value of Incorporating Family History in Risk Assessment and Primary Prevention of Coronary Heart Disease (CHD) Principles and Design

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Abstract

Aim. This paper sets out the principles, issues and method for an economic assessment of systematised family history tool in the primary prevention of CHD

Background. Family history is recognised as a risk factor for many chronic diseases (including CHD) and as a predictive tool can act in identifying those likely to be susceptible to disease. However, empirical evidence of its utility is missing. An economic assessment, which forms part of a wider study encompassing clinical utility, seeks to assess the cost and benefits of incorporating systematised family history information compared to current practice for CHD risk calculation in primary care.

Method. We propose using a decision analytic framework in assessing the economic value of the family history tool. To this end, a systematic review of the evidence supporting the incorporation of family history in risk assessment of CHD is being undertaken. We shall also develop the structure for a short-term decision model, setting out treatment pathways, identifying and discussing issues surrounding key parameters.

Results. There have been few economic evaluations of the use of family history in primary care. We will discuss issues raised in designing our short-term model, and present our model and systematic review results, at their current stage, to highlight the extent to which current evidence will be sufficient to populate the model.

Conclusion. In the longer term, the model will be populated using evidence from an RCT currently underway thus enabling us to assess the degree to which empirical data changes the results of the model.

Introduction

Incidence, Morbidity and Mortality

In the UK, Cardiovascular disease (CVD), the encompassing category for coronary heart disease (CHD), vascular disease and stroke, is a leading cause of illness and death responsible for almost 238,000 deaths a year representing 39% of all deaths with about half of these deaths attributable to CHD[1]. In 2002, it was estimated that CHD accounted for over 7 million deaths[2]. Apart from mortality, CHD is also responsible for significant morbidity within populations. In their 2002 paper, Liu et al[3], estimated 765,000 men and 698, 000 women had experienced at least one coronary event in the preceding year. The combination of morbidity and mortality translates to a significant burden on the economy. For instance, in 2004, it was estimated that CHD cost the UK economy £8.47 billion (29% of total cardiovascular related costs) of which £3.45 billion fell onto the NHS[4]. With the significant clinical and economic cost attributable to CHD, its prevention is increasingly a core activity in current UK policy and particularly in general practice[5].

Understanding Coronary Heart Disease Risk and its Prevention

In the literature, over 300 CHD risk factors have been cited, with 16 generally considered to be the most important[6]. Of these, 11 (high LDL cholesterol, high blood pressure, smoking, low HDL cholesterol, lack of exercise, diabetes (and glucose intolerance), left ventricular hypertrophy, central obesity, homocysteine, clotting factors, oral contraceptives) are termed *modifiable risk factors,* and 5 (age, sex, family history, genetic, birth weight) *non-modifiable risk factors.* In public health terms, the division of risk factors into these two categories may not be particularly useful as it denotes a degree of independence amongst risk factors that somewhat colours the various and complex interactions between them.

An alternative and arguably more useful way to understanding CHD risk is arrived at by posing the question – *Who dies from coronary heart disease?* The specific objectives of CHD prevention can then be defined more broadly in terms of (1) individuals with existing CHD and/or other heart disease and (2) individuals with hypertension, dyslipedaemia, diabetes and family history of premature CHD or a combination of these conditions[5]. From a clinical perspective, the former is at a high absolute risk of a further cardiac event necessitating the immediate management of contributory risk factors through clinical intervention without necessarily having to measure absolute risk. However, the latter group, who are asymptomatic for CHD may be at greater risk of the disease relative to a healthy population due to the presence of multiple pre disposing risk factors, necessitating a risk assessment before commencing clinical management.

This categorisation is useful in understanding the dichotomy between primary and secondary prevention. Essentially, it "reflects the reality of clinical practice because patients with symptomatic disease present to medical services and thus are already receiving care which should include secondary prevention, whereas high risk individuals in the general population have to be sought through screening, whether opportunistic or systematic to deliver primary prevention"[5].

Family History as a Predictive Tool

The use of family history enables the capture of information about an individual's genetic disposition to CHD, for instance, to *familial hyperlipidemia*, as well as susceptibility to cultural, behavioural and shared environmental factors. Its use in medicine is not a new concept - family history as been identified as a risk factor for CHD and for many other chronic diseases of public health significance[7], with the European prevention of CHD guidelines recommending that family history be used as a primary prevention approach for CHD[8].

Currently, family history is not systematically integrated into CHD risk assessment in the UK with recipients of primary prevention usually identified by utilising standard CHD risk assessment scores that incorporate age, gender, diabetes, smoking status and blood pressure[9,10]. The emphasis on a systematic nature is not an unimportant one if we consider the following points: 1) research has suggested that primary care professionals' lack the confidence to interpret family history information and have low baseline recording of family history information in general practice (GP) records[11,12] and 2) in the clinical genetics setting, disease susceptibility and inherited disorders are determined through interviews which assess medical conditions in each relative, including specific genetic disorders, mental retardation, age at diagnosis, current age or age of death, and questions relating to lifestyle, ethnicity and consanguinity[7]. In using a family history tool, a necessary consideration for use is the characteristic of the target population. For instance, in the UK, the population represents people from diverse cultural and ethnic backgrounds that may have differing ideas about the causes of CHD and the risk associated with a family history of the disease[13].

Usefully, the analytic framework for evaluating the family history tool can be adapted from the ACCE model, a project concerned with genetic testing conducted by the foundation of Blood Research funded by the Centre for Disease Control (CDC). The four relevant components are analytical validity, clinical validity, clinical utility and ethical, legal and social issues[14] Analytical validity is concerned with tool performance in a laboratory rather than clinical setting and are primarily concerned with how the test measures the property or characteristic that it is intended to measure. Clinical validity is concerned with measuring the accuracy of the tool in clinical practice, that is, a focus on the clinical sensitivity and specificity of the tool. Clinical utility is concerned with the degree to which the tool provides benefits following positive and negative results, before it's entry into

clinical practice. This stage would include some economic assessment of value for money. The final element, ethical, legal and social implications, is about issues arising from data collection and interpretation that might affect individuals and society negatively[7,14,15].

Economics of Primary Prevention

In the literature, there is overwhelming evidence of the link between risk factors – life style and biological, and CVD[16]. Correspondingly, a significant body of literature has evolved into interventions – pharmacological and otherwise, for the management of CHD and its associated risk. Thus, the prescription for clinical practice seems straightforward, that is, a determination of disease occurrence based on an assessment of risk followed by proven efficacious intervention. However, the reality for clinical practice is not so simple. In the UK, it has become increasingly important to assess interventions not only in terms of efficacy but also in terms of their economic effects. This means that the decision to treat is dependant on the cost of treatment, as well as the risk in the treated group of individuals[17], and the benefit of intervention in the context of life expectancy and quality of life[5].

Iunes[18] sees preventive medicine in developed countries as a form of intervention that in most cases (but not exclusively) aims to produce changes in behaviour. However, the identification, investigation and management of relevant individuals, particularly with the use of drug therapies, will be a considerable economic burden on the health service[5]. Therefore, it becomes imperative to identify those individuals in the population who are at a priority for intervention through effective population screening. We hypothesise that incorporating family history will increase the number of individuals identified as at high risk of CHD earlier, enabling preventive measures such as intensive lifestyle advice and/or drug therapy to be offered in a more timely fashion. Of course such information could lead to increased cost in the short term due to additional preventive interventions. However, in the long term, this may act to reduce costs and improve health benefits by reducing the morbidity and mortality associated with CHD. It is worth noting that the degree to which such reduction and/or improvement can be had is related to successful implementation of the intervention in terms of population participation and compliance to clinical advice.

Method

The economic assessment of incorporating systematised family history in the risk assessment of CHD is being undertaken in tandem with a clinical study. The study, through paired randomisation of 20 practices in Devon and in the East Midlands aims to evaluate the following outcomes:

1. To estimate the proportion of study population who are at a greater risk of CHD over a 10 year period, comparing current practice to systematic collection. For the study risk of CHD has been divided into three broad categories: low risk (less than 10% CHD risk), moderate risk (10% <20% CHD risk), and strong risk (20% or greater 10 year CHD risk)
2. Compare self-reported behaviour (smoking, exercise, diet), psychological impact (anxiety, fatalism) and social experience between patients who have undergone CHD risk assessment using (a) standard risk assessment complemented with systematic collection of family history (b) using standard risk assessment alone.
3. Assess their current practice of information recording, data storage, retrieval and ethical considerations with an assessment of the acceptability and feasibility of incorporating systematic family history into routine practice.

Recruitment of the study population is on-going, but it is estimated the sample will include 1000 (split equally between both arms) participants when complete. Participants would be patients offered CHD risk assessment as part of their normal care, aged between 30 and 65 years, without a previous history of atherosclerotic disease, not on statin therapy or considered inappropriate by their GP due to psycho-social reasons. The duration of the entire project is 28 months, 6 of which are dedicated to patient follow up.

Assessing the Value of FH – A Decision Analytic Approach

The economic question that arises from the clinical study can thus be stated – *in the primary prevention of CHD, is it cost-effective for general practitioners to incorporate family history systematically in disease risk assessment compared to the current practice where it is not systematically incorporated into risk assessment for CHD method of determining disease susceptibility and treatment?* In setting the answer to the question, we assume the viewpoint of the National Health Service.

We propose using a decision analytic framework in assessing the economic value of family history for CHD. "Decision analysis is a systematic method for making decisions when outcomes are uncertain"[19]. It enables the decision problem to be reduced to a logical structure of its component parts, informing the decision maker about the ordering of choices, information involved in making such decisions and the explicit identification of uncertainties and values of possible outcomes[20]. This approach offers one way of capturing patient level costs and outcomes, and importantly, understanding their variations based on decisions and/or behaviour of study participants.

A model will be developed in accordance with current health technology assessment guidelines[21] and will consist of seven broad stages: (1) identification of ways of incorporating family history in risk assessment for

CHD; (2) identification of all potential management pathways; (3) development/verification of model structure and identification of key input data (costs, outcomes and probabilities); (4) obtaining data from published literature and the clinical study; (5) obtaining expert opinion on key parameters for which no information is currently available and which is needed for the decision model; (6) run the model using a probabilistic sensitivity approach; (7) identification of the priorities for future research in the field. In the main, this paper is concerned with the development of stages 1 – 4. This model is termed a 'short-term' model. This is because it reflects the specific objectives and the timeframe of its associated clinical study. However, we anticipate developing a long term economic model thereafter to inform on the economic value of family history in risk assessment for life-long outcomes.

A first step in achieving our short term aim is the development of a model to be populated using data from published literature. Using its results as a comparator, we hope it will prove useful for model validation and in determining the value, if any, obtained through our empirical study.

The Decision Tree

An initial, and basic, decision tree is developed (see figure 1) from left to right, mirroring the decision sequence adopted in the clinical trial and current practice. It begins at the decision node (represented by the square). With the inclusion criteria of our study sample conferred, this point reflects the choice that has to be made in splitting our sample into the family history and current practice arm. Because a decision is chosen and does not arrive by chance no probability is attached to its branches. This is then followed by a chance node (represented by a circle). This reflects the probability of a patient being in either of the three risk categories dependant on CHD risk scores using standard risk prediction charts for the current practice arm and risk scores after incorporating familial CHD risk into the overall score for the family history arm. Having established a patient's risk status, a clinical consultation will ensue from those indicated to be at high risk of the disease. A clinical decision may then be made to offer statin therapy in addition to lifestyle advice on diet, exercise and smoking cessation. Those identified as average risk will be offered advice on lifestyle intervention, although for completeness, the model recreates drug therapy decision nodes for the other two other risk categories. Crucially, lifestyle intervention is modelled as a chance event underlying our hypothesis that uptake rate and the interventions' corresponding efficacy varies amongst patients. At the tip of the tree are the outcomes – cost per self-reported lifestyle changes which includes number of cigarettes smoked, adoption of exercise and diet change.

Issues arising – elements for decision analysis

Which Economic Perspective?

In evaluating the value of a family history tool the economic perspective adopted matters[19]. Importantly, a clearly stated perspective helps in understanding the applicability of the analysis to a decision making context. It is arguable that the societal perspective should be adopted for public health decisions in order to accurately capture all its attendant costs and consequences. In reality the limits of research design and feasibility are likely to reduce the analysis to a narrower one. In our study, we shall be adopting a national health care perspective but we hope to capture additional wider costs and benefits during the course of the study. This additional information will be presented separately from the base case analysis.

Outcomes and costs measures

An assessment of the value of the family history tool is predicated on the degree to which we accurately measure its impact on cost and outcomes (both positive and negative). For our study, costs attributable to family history depend on how the information is obtained and the intervention that consequently results. Examples of costs to be considered are the cost of collecting information (incorporating physician and administrative time), cost of communicating information, costs associated with testing/screening, costs of medication and lifestyle advice and the specific resource changes that results from lifestyle intervention, for example, increases in the number of GP appointments or longer consultations due to patient anxiety.

Important intermediate outcomes for our study are behaviour or behavioural risk factor changes and the uptake of statins by patients following identification of susceptibility to CHD from family history information. Although providing useful information, its sole use as a basis for an analysis is limiting as it obscures other important intermediate endpoints such as short-term health changes or the psycho-social consequences of a family history confirmation. Consequently, we hope to capture any health related quality of life/utility changes that may occur in health behaviour based on responses from questions of the SF-6D[22]**.** Whilst the consequences on health outcomes from the use of the family history tool can be determined, it still omits a consideration of non health outcomes for an analysis of the tool and long term beneficial impact of its use in primary prevention. By this, we refer to process attributes (waiting time or service location – primary or secondary care), the demand for information (individuals may gain value from information in its own right), non-use values or a caring externality element (the value relatives or others gain from the individual in need) and the impact on lifetime morbidity and mortality. Therefore, there is a strong case for adopting a willingness to pay approach (WTP) as an outcome measure to capture those benefits that go beyond health status

Other considerations

The explicit identification of the time horizon over which costs and benefits are to be collected for analysis is important. So our emphasis on the preventive value of the use of family history would likely lead to assessment of cost savings or treatment benefits (if any) over a 6 months. An equally important consideration is the need for discounting of costs and benefits to reflect society's time preference. Future Cost and outcomes will be discounted using a discount rate of 3.5% as used by the National Institute for Health and Clinical Excellence (NICE)[23] and recommended in the Treasury Green book[24

The parameters for our decision model - costs, outcomes, probabilities and indeed the structuring of the tree are characterised by a degree of uncertainty that may influence the cost-effectiveness for family history use, for example, uncertainty surrounding the efficacy of statins, the rate of adherence to lifestyle interventions or the incidence of patients with a family history. We propose using a probabilistic sensitivity analysis for our model but recognise the importance of our baseline data to reflect reality as far as possible.

As a first step to achieving our study aim is a systematic review of the current literature on prevention and CHD. Our tentative findings are reported below.

Literature Review

Search strategy

A computerised search strategy was developed and run in the Medline electronic database on 24th November 2006. The search sought to identify papers that examined the economics consequences of primary intervention to prevent CHD with a particular focus on the use family history use. The following key words were used to identify relevant papers through their titles and abstracts: 'economics', 'costs', 'coronary heart disease' and 'primary prevention'. The search identified a total of 87 papers with all records imported to reference manager. Two reviewers were involved in checking the title and abstract for economic evaluation terms (including modelling), with 46 papers selected for a full study review.

Assessment of quality and data extraction

A checklist was developed and used for data extraction. The extraction form was adapted for our needs from one developed by Unal et al[25]. Papers were evaluated for the following variables: Author, study setting and population, Risk factors considered, Type of model (where relevant), Disease Group and Treatment considered, outcomes, sensitivity analysis, model validation (where relevant), costs elements and data sources, effectiveness

data sources, Time horizon, discount rate, comparators. Following data extraction, papers were quality assessed using a check list developed by Drummond[26].

Inclusion and exclusion Criteria

Any study reporting on a key outcome (treatment cost, treatment uptake rates) or/and using modelling methods in the evaluation were selected. All reviews, effectiveness studies that have little or no impact for an assessment of cost, survey of utilisation and description of methods studies were excluded. In total 30 papers were excluded with 16 selected. The search was limited to papers that were abstracted on Medline and in English. As a result 18 abstracted foreign language papers were excluded from our analysis.

Results

Table 1 shows the summaries of the methodological aspects of papers undertaking an economic evaluation of the primary prevention of CHD. A wide range of interventions were considered, including, but not limited to, different types of statins, dieting and exercise. However, a noticeable feature is the absence of either family history as a focus of intervention or as a risk factor for CHD. Of the studies that reported on gender of the study population only 3 papers were based on a single sex. A wide range of ages were considered in the studies with the majority using a middle aged to aging population. Half of these populations were North American (6 US, 2 Canadian)[27,28,29,30,31,35] with only one study on a UK population (Scotland)[41].

1 paper[33] was identified as economic evaluation conducted along a clinical trial. The remaining studies were based on data obtained from secondary sources. 9 these included indirect cost components in their analysis[17,27,29,30,33,34,37,38,40], 5 papers reported Quality Adjusted Life Years (QALYs) as an outcome measure[27,29,34,35,40], 5 used life years gained/saved[28,32,33,38,39], and 3 used both[17,36,37]. Other outcomes measures used included cost per reduction on cholesterol level, costs per cardiac event prevented or death from CHD. None used a WTP measure. While all papers reported the use of an 'economic model' only 3 papers were identified as having used Markov modelling[17,29.36], 1 used a Monte-Carlo model[35],1 a simulation[17], 3 used mathematical or logistic models[30,38,39] and 1 used a life table analysis[32]. The remaining papers did not state clearly the methodological methods used.

Discussion and Conclusion

The overall aim of our study is a determination of the economic value of incorporating a systematic family history tool in CHD risk assessment. We believe adopting a decision analytic approach facilitates an analysis within a framework that captures the parameters (especially relating to patient behaviour) and values that ultimately dictate the degree of its cost effectiveness. Crucially, the predictive power of our model rests upon our ability to structure the decision problem accurately and populate it with appropriate data. Given this context, our accumulated evidence thus far presents some issues and challenges for implementation.

There have been a few studies using a decision analytic framework in assessing interventions in the primary prevention of CHD but none considered family history as an intervention. There were wide differences in the selection criteria adopted including, but not limited to, different cholesterol levels for participation and in defining presence or absence of co-morbidities. Also, there were a range of interventions considered, with different drug therapies or lifestyle interventions investigated. Disappointingly, only 1 paper considered the effects on uptake from lifestyle combinations – an important parameter in our model. Importantly, all the studies were based on populations in geographic and health settings which limit our ability to use their results and estimates in our model without numerous caveats and/or assumptions. Whilst we find the use of decision modelling encouraging, with the exception of one evaluation conducted along a RCT, sourced their data from secondary sources that were mainly population based for, example the Framingham study, that provides little insight into individual behaviour.

Given the background, outline of the wider project and the discussion thus far, we would welcome feedback on any of the aspects or issues raised. In particular:

1. Given the sparse evidence how do we determine uptake rates (including joint probabilities) for lifestyle interventions?
2. Given no evidence of the use of family history as a preventive tool in CHD how do elicit and synthesis expert opinion to populate our model?
3. In view of the primary setting, should we be adopting a wider analytical perspective?
4. Is a modelling approach appropriate for this study? Any suggestions on alternative approaches?

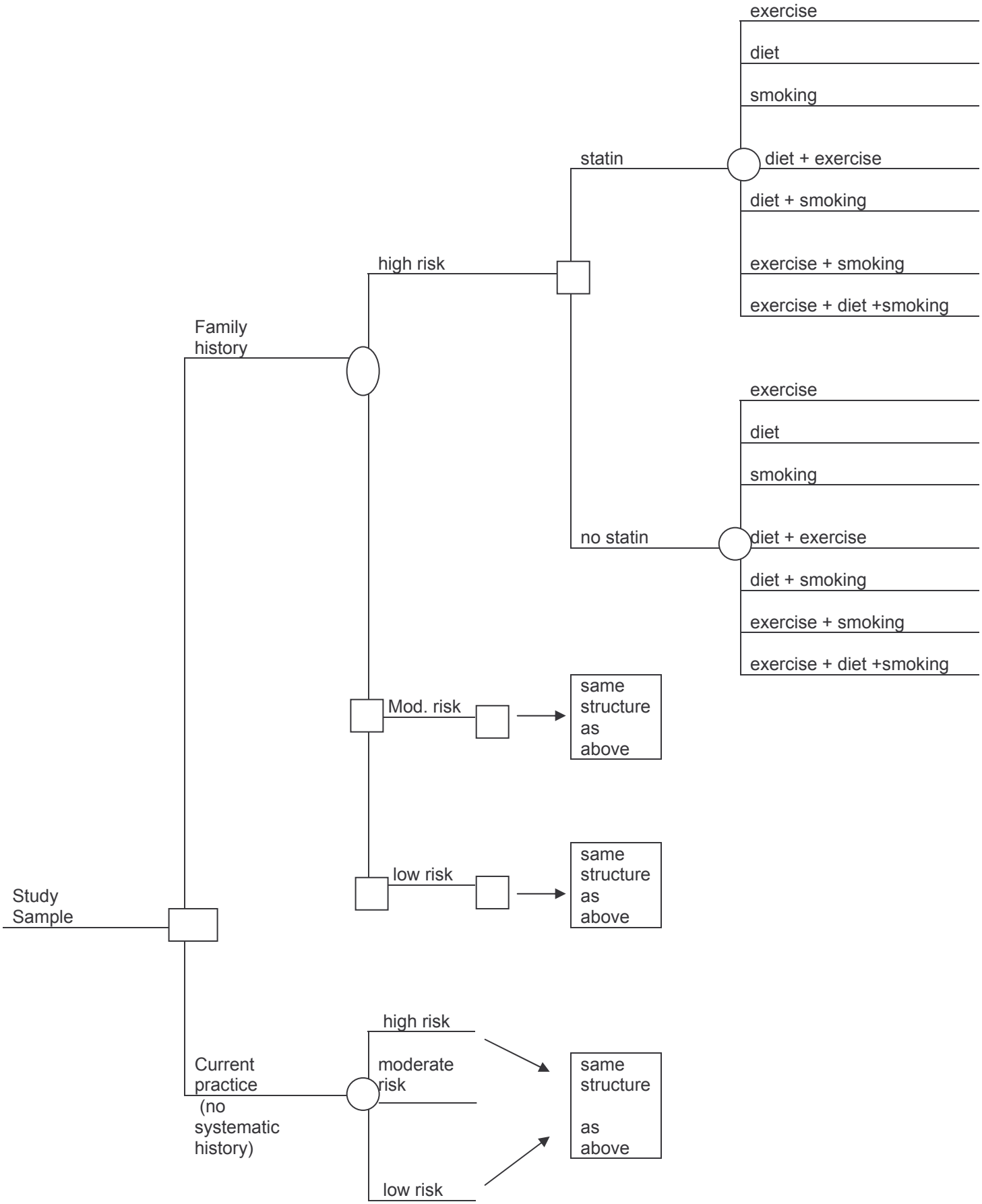
Further Development Work

Publication bias is likely to be an issue as the search was based entirely on Medline. Future work will be undertaken to extend the search to other computer databases (CINAHL, Social Sciences Citation index, NHS EED, DARE and HTA Database). Further, the review and quality assessment will be done by two reviewers as

current summaries have for the most part been undertaken by only reviewer (a small percentage of papers – 6.5%, were double reviewed). Also, in the longer term, the model will be populated using evidence from an RCT currently underway which will enable an assessment of the degree to which empirical data changes our results.

Figure 1

Schema of a decision analytic model to assess the costs and benefits of incorporating systematic family history information in CHD risk assessment



Summary of reviewed papers

Table 1a

Authors	Prosser et al[27]	Morris S and[28] Godber E	Gavin J Blake et al[29]	Perreault S et al[30]
Study setting and Population	Men & women 35 – 84 year [primary & secondary]	Individuals without CHD but with LDL cholesterol level > 190mg/dl. [primary]	Hypothetical cohort of men & women (35-85 yrs) with no overt hyperlipidemia [primary]	Hypothetical cohort of men and women [primary]
Publication year + country and currency year	(2000), USA, US$ 1998 values	(1999), CAN$ constant 1997 to 1998 prices ($US1 = $CAN 1.31)	(2003), US$ 2000	(1998), CAN$ 1992 prices. Adjustment details not specified.
Alternatives considered	**Primary**: diet, statin, no treatment **Secondary**: statin, no treatment	Cholesterol modifying pharmacotherapy's – atorvastatin, cholestyramine, fluvastatin, lovastatin, pravastatin	C-reactive screening + targeted statin therapy, diet counselling	Comparison of 3 different doses of statin – 20, 40 and 80 mg/d
Outcomes	Take up rate, QALYs, lipid levels	Life years gained, cost per 1% reduction in LDL-C level, least cost agent to achieve LDL-C of 160mg/dl	QALYs	Relative risk based on cholesterol level, cost, life year saved
Disease	CHD	CHD	CVD – myocardial infaction (MI), stroke	CHD – myocardial infaction (fatal & non fatal), arrhythmia, congestive heart failure, coronary insufficiency
Risk Factors considered	Smoking, age, sex, blood pressure, low-density lipoprotein level	Cholesterol	Drug therapy, age, sex	Drug therapy
Cost elements	**Primary Prev.** physician visit for diet therapy , medication costs, patient time, HDL measurement costs **Secondary prev.** statin patient time, cost of hospitalization cost of associated procedures (CABG, angioplasty, catheterization), physician visit	Initiation to therapy costs, drug therapy, monitory of therapy costs, costs from treatment of CHD events.	Projected lifetime cost of myocardial infaction, acute cost of stroke, annual cost after stroke, annual cost of statin, cost of C-reactive protein test, cost of two office visits & liver function test;	Patient visit cost to physician, collection of blood for testing, lipid profile, biochemical profiles.
Data sources	**Effectiveness:** literature **Cost:** literature	**Effectiveness:** literature **Cost:** literature	**Effectiveness:** Literature, Trial data **Cost:** published data, trial data	**Effectiveness:** Literature **Cost:** wholesale prices, reimbursement fees
Type of Model	Simulation	Not stated	Markov model	Mathematical model
Model validation	Implicit. Estimates of costs and effects based on previously validated model	Not stated	Not stated	Implicit. Estimates of costs and effects based on previously validated model
Time horizon + discount rate	30 years; 3%	Not stated – appears to be lifetime, 6%	Lifetime, 3%	Not stated
Sensitivity analysis	Not clear - probably 1,2 & 3 way – drug price, diet, HRQL weights, effectiveness of diet	Implicit – Not stated explicitly	1 and 3 way –annual risk of MI, cost of statin therapy, efficacy of statin therapy, utility (after MI, MI/stroke, stroke) increased risk associated with C-reactive protein level, discount rate, yearly mortality post MI, annual risk of stroke, fatal MI rate, cost of screening test.	Not clear – appears to be one way

Table 1b

Authors	Michael Brandle et al[31]	Van Hout B.A. and[32] Simoons M.L.	Johannesson et al[33]	Johannesson M[34]
Study setting and Population	472 diabetic subjects without history of myocardial infaction or chest pain from NHANES study [primary]	Mainly male subjects, middle aged, with & without heart disease. AFCAPs-TEXCAPS 45-73yrs for men, 55-73 for women. Age distribution for other studies not detailed [Primary & secondary]	384 , 30 – 59 years, with at least one cardiovascular risk factor in addition to moderate primary hyperlipidemia [primary]	Hypothetical cohort of men and women without a history of CHD at 8 different ages: 35,40,45, 50,55,60,65 and 70 years [primary]
Publication year + country and currency year	(2003), USA, US$ adjusted to 2002 prices (details not specified)	(2001), Netherlands, NLG & Euro. Conversion rate or price year not detailed.	(31996), Sweden, SEK 1991 prices converted to US$ using 1991 exchange rate	(2001),Sweden, SEK converted to US$ 1999 ($1 = SEK 8.50)
Alternatives considered	Not clear – appears to be statin treatment, no additional statin therapy	Not clear	Usual advice only, usual advice + drug therapy, intensive advice only, intensive advice + drug therapy	Drug therapy, no treatment
Outcomes	Cardiac events prevented per year, decrease in LDL cholesterol	Life year gained, event free survival	life year gained	QALYs
Disease Group	CHD – myocardial infaction, angina	CVD – CHD, stroke (fatal & non fatal), myocardial infaction (fatal & non fatal) PTCA and CABG	CHD – sudden death, acute myocardial infaction, silent myocardial infaction, coronary insufficiency	CHD – myocardial infaction, angina pectoris, unstable angina pectoris
Risk Factors considered	LDL Cholesterol, drug therapy	Drug therapy	Age, sex, diastolic blood pressure, drug therapy, smoking, cholesterol	Drug therapy
Cost elements	Lipid lowering medication, drug monitoring and adverse experience, cost of major coronary events.	Medication costs, cost of myocardial infaction, cost of death	Consultation cost, drug cost, laboratory test, group meetings, patient time, patient travel cost	Drug cost, cost of laboratory test, physician visit, morbidity associated costs (health care cost, productivity cost); retail prices, literature
Data sources	**Effectiveness:** literature **Cost:** published data, literature	**Effectiveness:** literature – 4S, CARE, WOSCOPS, LIPID and AFCAPS-TEXCAPS **Cost:** literature	**Effectiveness:** Trial, Framingham **Cost:** literature	Published data, literature
Type of Model	Not stated	Life table analysis	Not clear – appears to be a mathematical model	Markov model
Model validation	Not stated	Not stated	Not stated	Not stated
Time horizon + discount rate	Not stated, not stated	5 years, not stated	Not clear – appears to be 18months	Not stated – appears to be 5 years, 3%
Sensitivity analysis	+/-25% on cost of statin, cost of coronary event, incidence of coronary events with statin treatment, incidence of coronary events without statin	Univariate analysis +/- 25% on risk reduction, medication, death, non fatal MI/stroke, other events	Yes - Change in serum cholesterol, regression dilution bias, intervention cost, morbidity cost, cost concept (no indirect cost, health care budget), mortality risk after CHD, age, discounting	Yes – threshold analysis ($40,000, $60,000 and $100,000 per QALY) and what appears to be one way analysis on reduction in risk, increase in mortality risk after CHD, intervention costs, morbidity associated cost after CHD, cost concept (excl. future cost, future and morbidity cost), quality of life with CHD, discount rates

Table 1c

Authors	Lindgren P et al[17]	Pignone P et al[35]	Lamotte M et al[36]	Silvia M. Ess and Thomas D. Szucs[37]
Study setting and Population	60-year-old cohort based on a randomised study of 160 men aged 35-60 years with no previous history of CVD, diabetes or other severe illness [primary]	45 year old men with no history of cardiovascular events and with various levels of CHD risk [primary]	Meta-analysis. Four discrete populations – UK, Germany, Spain, Italy	**Primary:** hypothetical cohort of 300,000 apparently healthy men 33 – 64 years. **Secondary:** cohort of 10,000 patients (appears to be men and women) with total cholesterol < 4.52mmol/I and a history of myocardial infaction and unstable angina – Germany & Italy
Publication year + country and currency year	(2003), Sweden, no price date stated although an adjustment was made to 2000 year price using CPI	2006, USA, US$ 1999 prices converted to 2003 price using CPI factor of 1.195	(2006), Belgium, Euro	2001, Switzerland, price year not stated
Alternatives considered	Dietary advice, exercise, dietary advice + exercise	Aspirin, statin, aspirin + statin	Not clear – intervention is low dose aspirin	**Primary:** CRP testing vs. no testing followed by aspirin and/or stain use **Secondary:** CRP testing vs. no testing followed by statin use
Outcomes	Life years gained, QALYs	QALYs	Life-years, QALYs	**Primary:** life years saved **Secondary:** QALYs
Disease Group	CHD	CVD – CHD, myocardial infaction, haemorrhagic stroke, angina, other stroke	CVD	CVD - death from CHD, myocardial infaction (fatal & non fatal), fatal ischemic stroke
Risk Factors considered	Diastolic blood pressure, total cholesterol, smoking status, LVH (%), Glucose intolerance, age, sex	Age, drug therapy	Drug therapy	age, sex, LDL level and two other risk factors (risk factor implied but not stated explicitly)
Cost elements	Group session costs, cost of new shoes, physician time, cost of in and out patient care, cost of pharmaceuticals, cost of dietician, productivity cost	Drug costs, myocardial infaction, stroke, angina, gastro intestinal bleed, myopathy related death, physician visit, serum lipid level test, hepatic function test, day institutionalised	Aspirin, MI, Ishaemic/haemorrhagic stroke, GI bleed, Fatal MI, Fatal stroke, in-hospital follow-up per year; official tariffs	Cost of CRP testing, cost of aspirin, cost of statin treatment. Published and expert opinion
Data sources	**Effectiveness:** Published data, literature, Framingham **Cost:** literature	**Effectiveness:** Literature **Cost:** literature and national databases	**Effectiveness:** Literature **Cost:** Published data, literature	published data, literature
Type of Model	Markov model	Monte-Carlo	Markov model	Not specified
Model validation	Yes. Survival years for an "average" Swedish patient aged 50, 60, and 65 were predicted and compared to life tables from Swedish statistics.	Not stated	Yes. Compared the number of CHD events avoided as reported by a study (Hayden et al) with the number calculated in the model	Not stated
Time horizon + discount rate	lifetime	Lifetime, not stated	10 years, 3.5% (UK), 5% (Germany), 3% (Spain and Italy)	Appears to be 5 years, not stated
Sensitivity analysis	Probabilistic analysis – Declining effect (Diet + exercise, exercise, diet), remaining effect (diet + exercise, exercise, diet)	One way – drug costs, incidence of gastrointestinal bleeding, risk of hemorrhagic stroke, disutility of taking medication, treatment efficacy, risk of myopathy or death after initial event, and, probabilistic	Probabilistic (Monte Carlo)	Type of sensitivity not stated. Variable examined: price of the test, cost of the cardiovascular event

Table 1d

Authors	Plans-Rubio P[38]	Martens LL and Gilbert R[39]	Hay JW and Sterling KL[40]	Caro J et al[41]
Study setting and Population	Smokers and Individuals with hypercholesterolaemia (total cholesterol >7.24 mmol/L[>270 mg/dL]) [primary]	Cohort of 45 year old men who smoke and have pre-treatment LDL cholesterol levels of 4.5mmol [primary]	Hypothetical cohort of men and women aged 45 – 74 years with low levels of HDL-cholesterol and no prior history of CHD	Men aged 45-64 years with a mean cholesterol concentration of 7.0 mmol/l and no evidence of previous MI, to either placebo or pravastatin 40 mg/day, both in addition to dietary advice, [primary]
Publication year + country and currency year	(2004), Spain, US$ 1998	(1994), Canada, price year (not stated) adjusted to 1993 US$ values using Canadian CPI	(2005), US, price year not stated	(1997), Scotland, £UK 1996
Alternatives considered	Medical advice, medical advice and smoking cessation therapy, lovastatin use for hypercholesterolaemia	HMG-CoA reductase inhibitors (Pravastatin, Lovastattin, Simvastatin, fluvastatin), no treatment	Gemfibrozil, fenofibrate, lovastatin	Treatment with pravastatin, no primary intervention, normal dietary advice
Outcomes	Life years gained	Years of life saved	QALYs	Deaths from CHD or CVD causes
Disease Group	CHD	CHD	CHD	CHD
Risk Factors considered	Smoking, cholesterol	Smoking, diabetes mellitus, blood pressure, cholesterol level (LDL and HDL), left ventricular hypertrophy	Cholesterol level (LDL and HDL), blood pressure, hypertension, smoking, diabetes mellitus, no evidence of ECG-detectable left ventricular hypertrophy	Not stated
Cost elements	Cost of lovastatin, cost of nicotine, cost of laboratory monitoring, cost of medical visits and health tests	Cost of monitoring cholesterol-lowering therapy (physician visits and laboratory tests), drug costs	Medication acquisition, monitoring and adverse event costs, time spent attending physician visits	Cost of monitoring each type of event, cost of pravastatin
Data sources	**Effectiveness:** literature **Costs:** literature	**Costs:** interviews with 4 GPs, literature, published data **Effectiveness:** published data, literature	**Costs:** published data **Effectiveness:** published data, literature	**Cost:** published data, trial data **Effectiveness:** national data, trial data
Type of Model	Logistic regression modelling	Mathematical model	Not stated	Not stated
Model validation	Not clear	Not stated	Not stated	Not stated
Time horizon + discount rate	Not stated, appears to be no discounting	Not clear, 5%	5 years, not stated although it appears there was discounting	5 years, 6%
Sensitivity analysis	Not clear	Yes – changes to the lipid lowering effect of Fluvastsatin.	Appears to be one way – smoking/diabetes mellitus, CHD risk reduction, CHD treatment costs, Gemfibrozil total costs, utility of MI and	Monte Carlo - - discount rates, initial risk of CVD, the price of the drug, cost of monitoring, cost of subsequent care, efficacy of prevention, age of subjects

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