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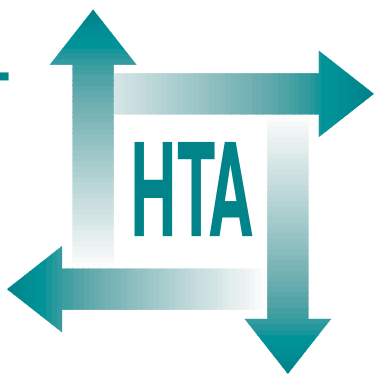
Review

Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis

D Marks
D Wonderling
M Thorogood
H Lambert
SE Humphries
HAW Neil

Health Technology Assessment
NHS R&D HTA Programme



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Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis

D Marks
D Wonderling
M Thorogood*
H Lambert
SE Humphries
HAW Neil

The London School of Hygiene and Tropical Medicine, Department of Public Health and Policy, Health Promotion Research Unit, London, UK

* Corresponding author

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This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Population Screening Panel and funded as project number 95/29/04.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

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Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
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Contents

List of abbreviations

4S	Scandinavian Simvastatin Survival Study
ABI	Association of British Insurers
AHA	American Heart Association
apoB	apolipoprotein B
CHD	coronary heart disease
DGGE	denaturing gradient gel electrophoresis
FH	familial hypercholesterolaemia
HDL	high-density lipoprotein
HMG CoA	hydroxymethylglutaryl-coenzyme A
ICD-9	International Classification of Diseases, 9th Edition
IHD	ischaemic heart disease*
LDL	low-density lipoprotein
LDLR	low-density lipoprotein receptor
LIPID	Long Term Intervention with Pravastatin in Ischaemic Disease
LYG	life-years gained
MI	myocardial infarction
ONS	Office of National Statistics
OXCHECK	Oxford and Collaborators' Health Check
PCR	polymerase chain reaction
RCT	randomised controlled trial
SSCP	single-strand conformational polymorphism
StOEH	Stichting Opsporing Erfelijke Hypercholesterolemie (National Foundation for Identification of Familial Hypercholesterolaemia)
TC	total cholesterol*
WOSCOP	West of Scotland Coronary Prevention Study

* Used only in tables and figures

Executive summary

Background

In the majority of people with familial hypercholesterolaemia (FH) the disorder is caused by a mutation of the low-density lipoprotein receptor gene that impairs its proper function, resulting in very high levels of plasma cholesterol. Such levels result in early and severe atherosclerosis, and hence substantial excess mortality from coronary heart disease.

Most people with FH are undiagnosed or only diagnosed after their first coronary event, but early detection and treatment with hydroxymethylglutaryl-coenzyme (HMG CoA) reductase inhibitors (statins) can reduce morbidity and mortality. The prevalence of FH in the UK population is estimated to be 1 in 500, which means that approximately 110,000 people are affected.

Objectives

- To evaluate whether screening for FH is appropriate.
- To determine which system of screening is most acceptable and cost-effective.
- To assess the deleterious psychosocial effects of genetic and clinical screening for an asymptomatic treatable inherited condition.
- To assess whether the risks of screening outweigh potential benefits.

Methods

Data sources

Relevant papers were identified through a search of the electronic databases. Additional papers referenced in the search material were identified and collected. Known researchers in the field were contacted and asked to supply information on unpublished or ongoing studies.

Inclusion/exclusion criteria

Screening and treatment

The review included studies of the mortality and morbidity associated with FH, the effectiveness and cost of treatment (ignoring pre-statin therapies in adults), and of the effectiveness or cost of possible screening strategies for FH.

Psychosocial effects of screening

The search for papers on the psychological and social effects of screening for a treatable inherited condition was limited to the last 5 years because recent developments in genetic testing have changed the nature and implications of such screening tests. Papers focusing on genetic testing for FH and breast cancer were included. Papers relating to the risk of coronary heart disease with similarly modifiable outcome (non-FH) were also included.

Data extraction and assessment of validity

A data assessment tool was designed to assess the quality and validity of the papers which reported primary data for the social and psychological effects of screening. Available guidelines for systematically reviewing papers concentrated on quantitative methods, and were of limited relevance. An algorithm was developed which could be used for both the qualitative and quantitative literature.

Modelling methods

A model was constructed to investigate the relative cost and effectiveness of various forms of population screening (universal or opportunistic) and case-finding screening (screening relatives of known FH cases). All strategies involved a two-stage process: first, identifying those people with cholesterol levels sufficiently elevated to be compatible with a diagnosis of FH, and then **either** making the diagnosis based on clinical signs and a family history of coronary disease **or** carrying out genetic tests. Cost-effectiveness has been measured in terms of incremental cost per year of life gained.

Results

Modelling cost-effectiveness

FH is a life-threatening condition with a long presymptomatic state. Diagnostic tests are reasonably reliable and acceptable, and treatment with statins substantially improves prognosis. Therefore,

it is appropriate to consider systematic screening for this condition.

Case finding amongst relatives of FH cases was the most cost-effective strategy, and universal systematic screening the least cost-effective. However, when targeted at young people (16 year olds) universal screening was also cost-effective. Screening patients admitted to hospital with premature myocardial infarction was also relatively cost-effective. Screening is least cost-effective in men aged over 35 years, because the gains in life expectancy are small. The modelling results would support a combination of strategies. For example, universal systematic screening at 16 years could be carried out alongside both opportunistic screening of patients with an early myocardial infarction (men aged 16–34 years, women aged 16–54 years) **and** case finding for family members of index cases (men aged 16–34 years, women aged 16–54 years).

Psychosocial effects of screening

Very few papers were found that addressed the psychosocial effects of screening for a treatable inherited condition, and the quality of the papers was generally disappointing. Problems with labelling and discrimination were hypothesised, but there were few data to support these hypotheses. There was no evidence of any deleterious effect on the mental health or social functioning of adults following a diagnosis of FH, although there was some weak evidence that diagnosis in childhood aroused anxiety and created tensions within families. It is possible that diagnosis in adults may make it more difficult for them to get life insurance. Fear of discrimination was reported as a barrier to screening. Many authors called for more counselling at the time of screening, but the nature of the counselling was poorly described and there were no data to support its effectiveness.

Conclusions: implications for healthcare and recommendations for future research

From the modelling exercise, it appears that a case-finding strategy (with a clinical or genetic diagnosis) to identify FH in the families of known FH patients would be cost-effective. Screening all 16 year olds using clinical methods of diagnosis appears to be similarly cost-effective, assuming that such screening is acceptable and that at least 55% of those invited for screening do attend.

There is a lack of qualitative or quantitative evidence on the psychosocial effects of screening for FH or other treatable inherited conditions, or on the effectiveness of educational and counselling interventions at the time of screening. Further research in these areas is needed.

The results of our model show that case finding in the relatives of known FH patients is probably cost-effective, as is a universal screening strategy in young people, and screening of patients admitted to hospital with premature myocardial infarction. However, primary data on the effectiveness and cost implications of screening strategies is lacking, so it is difficult to conclude with certainty that one strategy is more effective or less costly than another. Further research should concentrate on the systematic evaluation of each of these potential screening strategies.

Chapter 1

The nature and importance of familial hypercholesterolaemia

In the majority of people with familial hypercholesterolaemia (FH), the disorder is caused by a mutation within the low-density lipoprotein (LDL) receptor gene that impairs its proper function, resulting in very high levels of plasma cholesterol. Such levels result in early and severe atherosclerosis and hence substantial excess mortality from coronary heart disease (CHD).[1]

At present, the majority of patients with FH are undiagnosed or are only diagnosed after their first coronary event, but early detection and treatment with hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase inhibitors (commonly called statins) can reduce morbidity and mortality. Early work published in 1972 or before on FH estimated that 12.5% of hypercholesterolaemic men and women who survived a myocardial infarction (MI) below the age of 55 years had FH.[2] Other estimates are that 5% of middle-aged patients with coronary artery disease would have FH.[1] The prevalence of FH in the UK population is estimated to be 1 in 500,[1] which means that approximately 110,000 people are affected. An average primary care practice with 8000 registered patients would have between four and five FH families.[3]

Early detection is possible, and almost certainly beneficial to the individual. FH can be detected at any age from clinical and/or genetic testing plus family history. High levels of total and LDL cholesterol levels can be detected in babies, and these levels increase with age. This distinguishes FH from other forms of polygenic hypercholesterolaemia, and earlier treatment will be of more benefit than treatment at a later stage. The cumulative risk of fatal or non-fatal CHD in untreated men by the age of 50 years is over 50%.[4]

Criteria for population screening

Wilson and Jungner[5] have argued that there are ten criteria, which should be considered before population-wide screening is instituted. These are that:

1. the condition being screened for should be an important health problem
2. the natural history should be well understood
3. there should be a detectable early stage
4. treatment at an early stage should be of more benefit than at a later stage
5. there should be a suitable test for identifying people at the early stage
6. the test should be acceptable
7. intervals for repeating the test should be determined
8. there should be adequate health service provision for the extra clinical workload resulting from the screening
9. the risks of screening, both physical and psychological, should be less than the benefits
10. the costs should be balanced against the benefits.

A condition with a prevalence of 1 in 500 and a high risk of premature CHD can be described as an important health problem. The natural history of FH is well understood, and the condition can be detected early in life. There is strong evidence that early treatment is beneficial. The diagnosis of FH, whether by clinical or genetic testing, requires nothing more intrusive than venepuncture, and, once the diagnosis is made, there will be no need for further diagnostic tests.

In this review we consider the costs and benefits of screening for, and treatment of, FH at different ages in order to inform the development of a policy on screening. No recommended screening strategy currently exists in the UK.

Diagnostic criteria

Clinical

A diagnostic definition of FH, originally proposed by the Simon Broome Research Group and based on clinical signs and family history,[6] has become widely used. A definite diagnosis requires:

1. a total cholesterol level above 7.5 mmol/l (290 mg/dl) in adults or a total cholesterol level

above 6.7 mmol/l (260 mg/dl) in children under 16 years of age **or** LDL levels above 4.9 mmol/l (190 mg/dl) in adults (4.0 mmol/l in children)

plus

2. tendon xanthomas in patient or in first- or second-degree relatives.

A possible diagnosis of FH requires (1) above plus one of the following:

3. a family history of MI before the age of 50 years in second-degree relatives or before the age of 60 years in first-degree relatives
4. a family history of raised cholesterol above 7.5 mmol/l (290 mg/dl) in first- or second-degree relatives.

Genetic diagnosis

A genetic diagnosis depends on the identification of a mutation in the LDL receptor. There are several methods available for DNA-based rapid mutation screening (reviewed by Cotton[7]), although all have drawbacks, either with regard to use of toxic chemicals, radiolabel, sensitivity or specificity. New methods are being developed,[8] and techniques are likely to improve in the next few years. The single-strand conformational polymorphism (SSCP) technique is most widely used,[9] but denaturing gradient gel electrophoresis (DGGE) may be more sensitive.[10]

Once a blood sample (and family tree) is sent to the DNA laboratory, DNA extraction can be completed in one day, and apolipoprotein B (apoB) or specific mutation testing carried out in 2–3 days. Polymerase chain reaction (PCR) amplification of all exons, and the whole of the promoter and SSCP analysis, would take 4–6 days, and sequencing and confirmation of any detected SSCP 2–3 days. This procedure could be completed on four samples within 1–2 weeks, and is likely to detect more than 90% of the mutations present.[9,11,12] When the mutation is known for a proband (first known index case in that family), DNA tests in relatives will give an unequivocal result within 1–2 days, so that once a mutation has been identified, other family members can be diagnosed quickly and easily.

A cost of approximately £1000 has been estimated for the laboratory work for the first case in that FH family, but once a mutation has been found in the family, the cost of testing would fall to £185 for each subsequent member. Currently, a complete analysis takes between 8 to 10 weeks for a new kin group, as the majority of time is spent identifying the mutation. Quicker and cheaper detection methods would make large-scale screening possible.

It is still not certain what percentage of people with definite FH (based on clinical criteria) in the UK will have identifiable genetic mutations. It is estimated that 85% of mutations will be detectable as the technology improves, but, at present, between 45% and 55% of adults in the UK with clinically diagnosed FH have a detectable mutation. The figure for children is 75% (K Heath, personal communication). Worldwide, 680 different LDL receptor gene mutations have been identified (K Heath, personal communication) and this number is still increasing. In the UK, more than 40 different mutations have been reported, and there is a website that registers all identified mutations as they are discovered (http://www.ucl.ac.uk/fh). The heterogeneous composition of the UK population precludes the existence of any founder effect, so although some mutations occur in several families from different regions of the UK,[13] many are 'private', occurring in only one family. Recently, a clinical diagnostic service for FH has been established in the Regional DNA Diagnostic Laboratory at the Institute of Child Health, London (K Heath, personal communication).

A protocol for DNA testing of the mutation in the LDL receptor gene has been proposed.[3] The authors proposed that the contribution of a genetic diagnosis of FH can contribute towards a more effective screening procedure for FH. The cost-effectiveness of this procedure has yet to be ascertained.

Treatment options for FH

Treatment options for FH are, in order of effectiveness, HMG CoA reductase inhibitors (statins), resins and dietary advice.

Statins, which were first licensed in the UK in 1989, inhibit the hepatic biosynthesis of cholesterol. They are much more effective in lowering LDL cholesterol levels than previously available therapy (resins and fibrates). Large randomised placebo controlled trials have conclusively demonstrated that statins are effective in the primary and secondary prevention of CHD.[14–17] Although none of these trials specifically studied patients with FH, it is appropriate to extrapolate from these results.

Statins are now the first-line treatment for most patients with FH, and they are well tolerated. Only about 1% of patients experience side-effects and serious adverse reactions are very rare.[18] There are differences in efficacy between drugs in this class. A maximum reduction in LDL cholesterol levels of nearly 60% can be achieved with atorvastatin, 80 mg daily and about 40% with simvastatin 40 mg daily.[19] Other statins at currently licensed dosages achieve smaller reductions in LDL cholesterol levels. Statins result in a modest elevation in high-density lipoprotein (HDL) cholesterol levels of 6–10%, and a reduction in triglyceride levels of 10–15%, although larger reductions may be achieved in patients with hypertriglyceridaemia.[19]

Resins are bile acid sequestrants which act by interfering with hepato-enteric recirculation of bile acids. Resins are not systematically absorbed, and their long-term safety is well established. At high dosages resins can reduce LDL cholesterol levels by at least 25%. Unfortunately, compliance is often poor since they are not particularly palatable or convenient to take because the granules must be mixed with water. There is a high incidence of minor gastrointestinal side-effects such as abdominal bloating, fullness, diarrhoea or constipation. They may interfere with the absorption of other drugs and with lipid-soluble vitamins. However, because of their safety, they remain the usual drug treatment of choice in childhood.

Lipid lowering dietary advice (American Heart Association (AHA) Step 1 diet; total fat less than 30% of daily calories, saturated fat 10% or less of daily allowance and cholesterol less than 300 mg of daily calories) has been demonstrated in a recent meta-analysis of metabolic ward studies to reduce total cholesterol concentrations by 10–15%.[20] Compliance with dietary advice in free-living individuals is usually poor. A meta-analysis of lipid-lowering dietary trials of more than 6 months duration showed that the mean reduction in total cholesterol in response to an AHA Step 1 diet was only 3–5%, and increasing the intensity to an AHA Step 2 diet achieved about a further 2% reduction.[21] Clinical trial evidence suggests that dietary advice achieves a small additional reduction in total and LDL cholesterol for patients already prescribed a statin, which is of limited clinical value. Nevertheless, dietary advice remains important because mono- and polyunsaturated fats can be substituted for potentially atherogenic saturated fats. Encouraging consumption of fruits and vegetables is also important because increased plasma concentrations of lipid-soluble vitamins, vitamin C and flavonoids may reduce the atherogenicity of LDL cholesterol by rendering it less susceptible to oxidative modification.

Clinical trials have shown that sterol- and stanol-enriched margarines can reduce LDL levels by 10–15% in clinical trials,[22–24] but it is not clear how good compliance would be with an intake of 20–25 g per day. It is expensive to the individual, and since it cannot be prescribed it is unlikely that trial results can be replicated in the general population.

Objectives of this report

- To evaluate whether screening for FH is appropriate.
- To determine which system of screening is most acceptable and cost-effective.
- To assess the deleterious psychosocial effects of genetic and clinical screening for an asymptomatic, treatable inherited condition.
- To assess whether the risks of screening outweigh potential benefits.

Chapter 2

Systematic literature review methods

Questions addressed

1. What is already known about the morbidity and mortality related to treated and untreated FH patients?
2. What data are available to inform the process of modelling the cost-effectiveness of different screening options in the identification of FH?
3. What social and psychological effects of screening for a modifiable genetic condition have been demonstrated?

Data sources

Electronic searches and handsearches

A systematic search of electronic databases was conducted. This included MEDLINE, Ovid (EMBASE), BIDS, Psyclit, HealthSTAR and Health Management. Also, the Cochrane Library and the NHS Centre for Reviews and Dissemination databases were accessed. Keywords used in the search are provided in appendix 6. In addition, an Internet search was conducted using selected keywords from the electronic database searches. Papers that appeared to fit our inclusion criteria were collected and systematically evaluated according to a specific set of objectives decided at the outset. Additional papers referenced in the search material were identified and collected.

Search for 'grey' literature and contact with known workers in the FH field

In addition to the electronic searches, known workers in the field of FH were contacted by letter and asked to supply information on unpublished or ongoing studies. Twenty-three replies were received from 55 letters sent. Most replies did not provide any additional information, although we identified two ongoing studies on the psychological issues of FH screening where results were not yet available.

Study selection (inclusion and exclusion criteria)

Health effects of FH and resource implications of screening and treatment

Studies applicable to determining the feasibility of a national screening strategy were considered. Specifically, we included studies of the mortality and morbidity associated with FH, studies of the effectiveness and cost of treatment (ignoring pre-statin therapies in adults), and studies of the effectiveness or cost of possible screening strategies for FH. The treatment of FH has been radically changed and the effectiveness of treatment markedly increased since statins first became available in 1989, and the effectiveness of earlier (pre-statin) therapy has not been considered in this review. Therefore, the search for papers on the effectiveness of treatment in adults was restricted to papers published over the 10 years since statins became available. For other topics we extended the search back to 1966. Studies reporting on the epidemiology of FH before treatment was available were used to substitute the risks/health effects that unidentified FH patients face today. This is largely because since the introduction of effective cholesterol-lowering medication it is not ethical to conduct placebo-controlled trials on such a high-risk group.

We included a paper if the research question was still relevant to the screening and treatment strategies we were considering. For example, trials of resin therapy in adults would not be included, but a study comparing the effect of diagnosing FH at different ages would be. Papers on resin treatment in children were included because children are not usually prescribed statins in the UK (as they are not prescribed to patients under 18 years of age).

Psychosocial effects of genetic screening

As genetic testing becomes more widely available, a growing number of papers report the risks and benefits involved. Many of these papers focus on conditions that are not modifiable such as Huntingdon's disease, and because the risks associated with FH are modifiable with the use of statins, these are excluded from our review. We found few papers, and we have therefore included conditions related to risk of CHD with a similarly modifiable outcome (non-FH or hypertension) and one genetic screening test (for the breast cancer gene *BRCA1*) where a positive test has similar implications in terms of modification of risk (using tamoxifen) and of the impact on the patient and their family.

The search for papers on the psychological and social effects of screening for a treatable inherited condition was limited to the last 5 years because recent developments in genetic testing have changed the nature and implications of such screening tests. However, we included two earlier studies on the insurance and employment implications of genetic testing for asymptomatic conditions, because this is an important area, and we were able to find only one recent paper.

Search results

Morbidity and mortality associated with FH and resource implications

Five pretreatment FH papers (before the availability of statins) were identified which provided information on the mortality and morbidity from FH in the absence of effective treatment. Seventeen studies are included that are relevant for FH in adults. There are six studies that report on methods of identifying those with undiagnosed FH (either by population or targeted approaches), two papers on mortality in a cohort of FH patients that comment on the effects of the arrival of statins, and five papers that report on the resource implications of identifying and treating hypercholesterolaemic patients. Four other trials report on the effectiveness of cholesterol lowering with statins (but not in an FH population).

Eight papers examining FH in children have been included: three on diagnostic issues and five on treatment in FH children.

Psychosocial effects of genetic screening

Thirty-nine papers which fitted our inclusion criteria were identified by searching. Of these, 16 reported primary data and a further 23 were classified as opinion or review papers, which discussed issues but did not provide empirical evidence. For example, several papers claimed that counselling could assist in ameliorating the deleterious impact

TABLE 1 *First draft algorithm*

A	Study ID number
B	Questions addressed
C	Study design
D	Appropriateness of design Qualitative Quantitative
E	Type of population
F	Number of subjects
G	Setting
H	Methods of data collection (i) Qualitative (ii) Quantitative
I	Are these described in enough detail? (i) Qualitative (ii) Quantitative
J	Methods of data analysis
K	Was there any quality control? (Describe)
L	Results
M	Brief description of conclusions
N	Were they justified by the results?
O	Can the findings be transferred into other settings? Relevance to policy
P	General comments/problems

TABLE 2 *Final version of the algorithm*

A	Study ID number			
B	Questions addressed			
C	Type of population			
D	Number of subjects			
E	Setting			
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative			
	Quantitative			
G	Results			
H	Brief description of conclusions			
I	Were they justified by the results?			
J	Transferability of study/limitations/comments			
K	Relevance to policy			

of screening, but none of them reported any attempt to prove the efficacy of counselling by using experimental or observational data. The primary data literature was limited, and we have therefore also reviewed the secondary literature. Statements from the secondary literature should be treated with caution.

Data extraction and assessment of validity

Development of an algorithm to evaluate both qualitative and quantitative research papers

A data assessment tool was designed to assess the quality and validity of the papers which reported primary data for the social and psychological effects of screening. Available guidelines for systematically reviewing papers concentrated on quantitative methods, and were of limited relevance. We developed an algorithm which could be used for both the qualitative and quantitative literature in this review and ensures that the extracted information is concise but includes all relevant data. Greenhalgh's commentary on reading qualitative work was used as a starting point[25] for development of the algorithm.

The first algorithm drafted had a total of 17 cells that required information (*Table 1*). Data were entered into each cell independently by three of us (DM, HL, MT) before being discussed. The added value of information provided by completing that cell was analysed.

After reviewing our pilot responses, decisions were taken by consensus to merge, remove and redefine the contents of certain cells in order to improve the comprehension and interpretation of the algorithm (*Table 2*). Areas that required discussion and change were the study's design, the appropriateness of this design, methods of data collection, analysis and the presence or absence of quality control. The original algorithm had a separate cell for each of these questions but, after discussion, some were merged and others removed. The formulation of the 'appropriateness of design' category produced too great a range of subjective responses to be suitable for achieving consistent and objective assessment. Both descriptive responses and rankings using a 1 to 10 scale were attempted, but we found that an open question of this type relies excessively on the subjectivity of the assessor in determining whether and to what extent a particular study design is 'appropriate' to the questions being investigated. For example, a psychologist might consider the use of a particular instrument for measuring anxiety, administered in a clinic setting, entirely appropriate for determining whether screening has negative psychological effects, whereas a qualitative social scientist, concerned about the limitations of using predefined quantitative measures alone, might consider it inappropriate to answer such questions without using any qualitative, exploratory methods.

A matrix format was therefore designed to record whether a qualitative, quantitative or a combination method was used. Whether the chosen method was appropriate was then assessed on a 'yes/no' basis in relation to the original hypothesis (as recorded in the initial descriptive summary 'questions addressed') rather than as a global evaluation of the notional quality of the study. Thirdly, the matrix allows a 'yes/no' response to a question on whether the study design was adequately described.

Two other cells in the original data assessment tool (methods of data analysis and the presence or absence of quality control) were removed because not enough information was provided in most of the papers to answer these questions. Hence, the information from these cells did not add to the usefulness or comprehensiveness of the quality assessment.

In the pilot phase there was overlap between the responses entered into the cells on general comments/problems and transferability to other settings, so these were merged into a combined cell. In discussion, the purpose of and distinctions between the three cells for 'results', 'conclusions' and whether the latter were justified by the former were clarified so that these cells respectively record findings, interpretations and recommendations (usually presented in the discussion or conclusion section of a paper). The aim of these cells was to assess whether the interpretations and recommendations made were justified by, and commensurate with, the empirical results of the study.

The final version of the algorithm aimed to extract information in three areas:

1. The first section covered basic demographic factors (description of the questions asked, numbers of people studied and type of population).
2. The next section covered an assessment of the study design, its appropriateness and whether this was adequately described.
3. The final area was a commentary and interpretation of the results, and an assessment of whether the conclusions were justified by the results, whether the findings would be transferable to other settings and whether the findings were relevant to an FH screening policy.

Completed algorithms are provided in appendix 1.

Chapter 3

The natural history, diagnosis and treatment of FH

In this chapter we consider the evidence for the mortality and morbidity burden associated with FH before statins became available, and in patients treated with statins. We have used these data to estimate the benefits of identification and treatment of FH. In this chapter we also discuss the effect of different screening strategies, and issues in the initiation and evaluation of a screening programme. The costs associated with the screening and treatment of FH are discussed.

Morbidity and mortality associated with FH not treated with statins

Several early studies examined the risk of CHD associated with a diagnosis of FH. Unfortunately, the methodology used in most of these studies is weak, with previously diagnosed or deceased subjects included in risk calculations. However, very high risks of CHD and coronary death were also found in one cohort study that prospectively studied a small group of people with FH for 20 years.

An UK-based study published in 1969 compared the medical histories of 104 patients (44 index patients and 60 relatives) with type II hyperbetalipoproteinaemia (FH) with 41 patients (34 index patients and seven relatives) with hyperlipoproteinaemia associated with hypertriglyceridaemia (type III, IV and V hyperlipoproteinaemia). Follow-up of index patients ranged from 1 to 10 years, but some already deceased relatives were also included in the life table calculations. The authors calculated that the cumulative risk of a fatal or non-fatal MI in untreated FH patients by the age of 50 years was 51.4% in men and 12% in women. By the age of 60 years, men had an 85.4% risk, and women a 56.5% risk of a fatal or non-fatal event.[4]

A 1974 cross-sectional study reported the prevalence of coronary artery disease in 1023 adults, affected and unaffected, relatives of 116 FH index patients. Of the relatives, 738 were alive and 285 had already died. The authors used data from the relatives and from those index patients who had been referred to the lipid clinic **before** the onset of CHD to calculate cumulative probabilities of a coronary artery event. They estimated that, for FH-affected male relatives aged 40 years, the cumulative probability of non-fatal or fatal coronary artery disease was 16%, and by the age of 60 years the figure was 52% compared with 12.7% for unaffected male relatives.[26] Similarly, the authors estimated that women with FH aged 60 years had a 32.8% risk of fatal or non-fatal coronary artery disease compared with 9.1% of unaffected relatives.[26]

A Canadian cohort study in 1979, of 264 men and 311 women (mean age 29 years) with FH found that the manifestation of ischaemic heart disease was approximately 10 years earlier in the men than in the women; the mean age of occurrence was 40 years for men and 50 years for women.[27]

Similar findings came from a French study in 1976, which examined the prevalence of FH in a group of 158 men and 116 women who had been referred to a Paris hospital, 51% of them with pre-existing CHD. The authors commented that the prevalence of FH did not differ between men and women, but that the mean age of onset of ischaemic heart disease was 9 years earlier in men than in women (44.2 ± 10 years for men and 53.1 ± 10 years for women).[28]

Eleven Danish families with 181 members with hypercholesterolaemia and 'extrapalpebral xanthomatosis' and 150 normocholesterolaemic members were followed for 21 years, from 1944 to 1964.[29] CHD was detected in 59 (32.5%) of the members with hypercholesterolaemia compared with two (1.3%) of the normocholesterolaemic group. By the age of 50 years, 45.1% of the men in the hypercholesterolaemic group had their first CHD symptoms. For the 62 members of the hypercholesterolaemic group where the cause of death was known, the average age of death from CHD was 41 years for men and 58 years for women, compared with an average age of death from CHD of 70 years for men and 74 years for women in the normocholesterolaemic group.

Discussion and summary

We have discussed a series of early studies that indicate a high risk of early CHD and death in

people with FH. These studies are summarised in *Table 3*. Around 50% of men experienced adverse events by the age of 50 years, while women experienced adverse events approximately 10 years later. Pre-statin treatment, with resins and dietary advice, had little impact on reducing cholesterol levels, and, hence, risk of CHD in FH patients. For this reason, although some of the subjects in the early studies were being treated for their hypercholesterolaemia, we think it is reasonable to take the event rates reported as indicative of the natural history of the disease.

Mortality and morbidity in adults with FH treated with statins

A cohort of 526 patients with FH in the UK (the Simon Broome Register cohort) provides some information on the changes in mortality after the introduction of statins. The first paper published in 1991 showed that the risk of a fatal coronary event in people with FH was increased by nearly 100-fold between the ages of 20 and 39 years.[6] However, those surviving to age 60 years were not found to be at increased risk (*Table 4*). A more recent paper from the Simon Broome Register cohort includes a discussion of the effectiveness of statins. A decline in relative risk for coronary mortality was seen in patients aged 20–59 years, from being eightfold before 1992 to only 3.7-fold post-1992 when statin use became more widespread (*Table 5*).[30] The authors concluded that effective treatment of FH has been shown to reduce morbidity and mortality, and recommended drug therapy for all affected adult men and postmenopausal women.

An unpublished further analysis with almost 13,000 person-years of observation (an increase of almost 50% since the previous analysis) confirms that the relative risk of all causes of mortality in patients over 60 years old is similar for FH patients and the general population (HAW Neil, personal communication).

Trials of statin use in non-FH patients with elevated cholesterol levels

The safety and efficacy of statin use has been tested in four large double-blind placebo-controlled randomised trials which are summarised in *Table 6*. The (4S) study of 4444 Scandinavian patients with pre-existing CHD and cholesterol levels between 5.5 and 8.0 mmol/l were given up to 40 mg of simvastatin or placebo equivalent.[15] After a mean follow-up time of 5.4 years, a reduction of 25% in total cholesterol and 35% in LDL cholesterol levels between baseline and follow-up was seen in the treatment group as compared with the placebo group. Moreover, there was a 42% reduction in the risk of coronary mortality and a 30% reduction in overall mortality in the treatment group.

The Care study, a double-blind randomised placebo controlled trial, included 4159 patients

TABLE 3 *Morbidity and mortality in FH men and women not treated with statins*

Reference	No. of subjects	Country of study	Risk of CHD in men	Risk of CHD in women
Slack, 1969[4]	104 (44 index and 60 relatives)	UK	51.4% by age 50 years and 85.4% by 60 years	12% by age 50 years and 56.5% by age 60 years
Stone *et al.*, 1974[26]	1023 relatives of 116 index patients	UK	**Affected relatives:** 16% by 40 years and 52% by aged 60 years **Unaffected relatives:** 12.7% by age 60 years	**Affected relatives:** 32.8% by 60 years **Unaffected relatives:** 9.1% by age 60 years
Gagne *et al.*, 1979[27]	264 men and 311 women	Canada	Mean age of onset – 40 years	Mean age of onset – 50 years
Beaumont *et al.*, 1976[28]	158 men and 116 women	France	Mean age of onset – 44.2 years	Mean age of onset – 53.1 years
Jensen *et al.*, 1967[29]	11 families – 181 hyper- and 150 normocholesterolaemic patients	Denmark	45.1% by 50 years. Average age of death in affected – 41 and 70 years in the unaffected	Average age of death in affected was 58 years and 74 years in the unaffected

who had a history of MI with a total cholesterol level below 6.2 mmol/l and LDL cholesterol between 3.0 and 4.5 mmol/l and tested the effectiveness of 40 mg pravastatin versus placebo. The median follow-up period was 5 years. A 20% total cholesterol and 28% LDL cholesterol reduction between the baseline and follow-up was reported for the treatment group as compared with the placebo group.[14] There was a 24% reduction in fatal or non-fatal coronary events in the treated group compared with the placebo group during the last year of follow-up.[14]

TABLE 4 *Simon Broome Cohort data, 1980–89: CHD mortality in FH patients*[6]

Age (years)	Person-years	Standardised mortality ratio	Observed deaths (total mortality)	No. of observed CHD deaths
Men				
20–39	439	8,975**	5	5
40–59	653	312	6	4
60–74	133	75	4	1
20–74	1,226	374***	15	10
Women				
20–39	335	16,039*	1	1
40–59	447	1,538***	7	4
60–74	225	–	1	0
20–74	1,008	413*	9	5
Both men and women				
20–39	774	9,686***	6	6
40–59	1,110	519***	13	8
60–74	358	44	5	1
20–74	2,234	386***	24	15

*$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

TABLE 5 *Simon Broome Cohort data, 1980–95: CHD mortality in FH patients*[27]

Age (years)	Person-years	Relative risk	Observed deaths (total mortality)	No. of observed CHD deaths
Men				
20–39	1318	48.4****	7	6
40–59	2189	3.5***	19	13
60–79	627	1.1	12	7
0–79	4613	2.6****	38	26
Women				
20–39	1190	125.0***	2	2
40–59	1544	8.4***	12	6
60–79	1049	2.6**	21	12
0–79	4159	3.7****	35	20

Both men and women

Age (years)	1980–91		1992–95	
	Relative risk	No. of observed CHD deaths	Relative risk	No. of observed CHD deaths
20–39	84.3****	7	17.5	1
40–59	5.3****	12	3.3*	7
60–79	1.2	5	2.1*	14
0–79	3.6****	24	2.5**	22

*$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$

TABLE 6 *Evidence from cholesterol-lowering trials*

Trial	No. of subjects	Inclusion criteria	Reduction in total cholesterol (TC) (%)	Reduction in LDL cholesterol (%)	Mean follow-up time (years)	Reduction in CHD mortality (%)	Reduction in total mortality (%)
Scandinavian Simvastin Survival Study (4S)[15] Simvastatin/placebo	4444	Pre-existing CHD and TC 5.5–8.0 mmol/l	25	35	5.4	42	30
Care[14] Pravastatin/placebo	4159	Post-MI; TC below 6.2 mmol/l LDL cholesterol 3–4.5 mmol/l	20	28	5	24	Not reported
West of Scotland Coronary Prevention (WOSCOP) study[17] Pravastatin/placebo	6595	No evidence of coronary artery disease; mean TC 7.0 mmol/l	20	26	4.9	31	22
Long Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study[16] Pravastatin/placebo	9014	History of MI/unstable angina – cholesterol levels between 4.0 and 7.0 mmol/l	18	25	6.1	24	22

TABLE 7 *Trials of cholesterol lowering through diet and/or drugs in children*

Study	No. and age of children	Type of intervention	Country study set in	Compliance	Reduction	Follow-up time
Vuorio *et al.*, 1997[31]	35	Cholestyramine vs placebo	UK	55% after 6 years and 48% after 8 years	26–44% in TC (30% mean)	8 years
Kwiterovich *et al.*, 1973[32]	72, 6–10 years	Cholestyramine vs placebo	Norway	66%	16.9% in LDL cholesterol	1 year
Leonard *et al.*, 1977[33]	76, 10–16 years	Colestipol granules vs placebo	Norway	66%	19.5% in LDL cholesterol	1 year
West *et al.*, 1980[34]	71, 0.1–20.6 years (median age 9.1 years)	Diet alone vs diet and cholestyramine	Germany	Not stated	Diet = 7.4% in TC and 9.9% in LDL cholesterol; diet and drug = 29.7% in TC and 25.9% in LDL cholesterol	2–74 months
Tonstad *et al.*, 1996[35]	132 boys, 10–17 years	Lovastatin vs placebo	USA and Finland	92% in phase 1 and 83% in phase 2	17, 24 and 27% in LDL on doses of 10, 20 and 40 mg/day	1 year

A double-blind, randomised control trial in Australia and New Zealand (the LIPID study), compared 40 mg of pravastatin with placebo.[16] There were 9014 patients aged between 31 and 75 years who had a history of MI or who had been hospitalised with unstable angina. A mean follow-up time of 6.1 years showed a 24% relative reduction in risk in death from CHD or non-fatal MI in the treatment group compared with the placebo group, and a 22% relative risk reduction in overall mortality. Total cholesterol levels were reduced by 18% and LDL cholesterol levels were reduced by 25% in the treatment group.

The WOSCOP study of primary prevention of coronary disease included 6595 Scottish men with no evidence of coronary disease and with a mean cholesterol level of 7.0 mmol/l. After 4.9 years of follow-up, the total cholesterol level was reduced by 20% and the LDL cholesterol level was reduced by 26% in the active treatment group as compared with the placebo group, and there was a 31% reduction in the risk of non-fatal MI or death in the treated group.[17] A 22% reduction in the relative risk of death from any cause was observed between the groups.

Summary of morbidity, mortality and treatment of FH in adults

These trials demonstrate the effectiveness of statin therapy in populations with elevated cholesterol levels, but not in patients with FH. No such trial has been conducted, and is unlikely ever to be conducted for ethical reasons. However, the evidence of falling mortality rates in the Simon Broome Register cohort, and the strong evidence for the effectiveness of statins in lowering cholesterol levels and reducing the risk of CHD, indicate that treatment with statins reduces coronary risk in patients with FH. The Simon Broome Register group data suggest that while patients aged under 60 years experience an increased mortality risk, this increase in risk is not apparent in older patients.

Issues in the detection and management of FH in children

Diagnosis of FH in children

In a Finnish study, 25 new-born babies with a parent with DNA-confirmed FH had their cholesterol levels tested at birth and at 1 year old and the presence of a DNA mutation confirmed, to determine whether serum lipid levels could be used to diagnose FH at these ages. Both total and LDL cholesterol levels were measured. Cholesterol levels overlapped more in the babies with FH than in 1 year old children, and the authors concluded that lipid levels tested at 1 year old produced a more reliable diagnosis of FH.[31]

These findings confirm a study conducted in the USA in 1973. Of the 29 children tested at birth (from 23 FH families), 16 had elevated cholesterol levels compatible with FH diagnosis. However, three had levels below the 95th percentile of total cholesterol levels in healthy control children indicating that up to 20% of FH children would be wrongly diagnosed if tested for total cholesterol levels only.[32] At follow-up, between 1 and $2\frac{1}{2}$ years later, all but one child were still hypercholesterolaemic, and this child with reduced levels had been on a strict low-fat diet.

A 1977 study in the UK measured the cholesterol of 134 children aged between 1 and 16 years, who had at least one first-degree relative considered to have FH (from 57 kin groups). Hypercholesterolaemia in adult parents was defined as two standard deviations above the mean. Of the surviving 49 parents, coronary artery disease was evident in 23 of them. The mean total cholesterol levels for the FH children were 8.9 mmol/l and 4.9 mmol/l for non-FH children. The distribution curves of the two groups intersected at 6.77 mmol/l. The authors conclude that at this cut-off point 4.25% of subjects would receive an incorrect diagnosis. Five per cent of unaffected cases would be diagnosed with FH (false positives) as their levels were above 6.77 mmol/l and 3.5% of FH heterozygotes had cholesterol levels below this point (false negatives) but they would be diagnosed as unaffected.[33] In addition, boys had a lower mean cholesterol level (6.75 mmol/l) than girls (7.8 mmol/L), indicating that more boys might be misdiagnosed.

Evidence of effectiveness of treatment in FH children

Resin therapy in children is modestly effective, but compliance is poor. The medication is unpalatable, and there is a high drop out rate in the trials which would probably be higher in a non-trial setting. There is a risk that by putting children on to a drug regimen that they cannot easily tolerate they may be less willing to present for treatment when they are adults.

Studies of the effectiveness of cholesterol-lowering therapy in children are summarised in *Table 7*. Data on adherence to dietary changes in the long term are sparse and the psychological effects of screening for an asymptomatic condition should be

taken into consideration (see chapter 4 on psychosocial effects of FH screening).

If resin therapy is prescribed in the long term, there is evidence that compliance reduces over time. In a UK study, of 35 children who were prescribed cholestyramine, only 55% remained on treatment after 6 years, and 48% after 8 years.[34] The age that the child starts treatment will have a significant effect on long-term compliance. Compliance was significantly better for the 25 children who started treatment before the age of 10 years (67%), whereas only one of the ten who started treatment over the age of 10 years was still taking the medication by the end of the study. In addition, those with a first- or second-degree relative with CHD showed slightly better compliance than those without. Overall, total cholesterol levels were reduced by between 26 and 44% (30% mean reduction) with cholestyramine therapy. The cholesterol-lowering effects were dose-dependent. The children were not on any special diet.

A randomised double-blind placebo controlled trial of cholestyramine (resin) was conducted in Norway on 72 boys and girls aged between 6 and 10 years. A 16.9% reduction in LDL cholesterol levels was achieved in the group assigned to active treatment[35] compared with a 1.4% reduction in the placebo group. Twenty-two of the 36 children in the cholestyramine group completed the 1 year study versus 26 out of 66 in the placebo group. Most withdrawals were related to unpalatability of cholestyramine or the placebo. These children had been on a low-fat and low-cholesterol diet for a year leading up to the drug intervention. Growth in the children was not adversely affected in the intervention group.

An 8 week double-blind, placebo-controlled study in Norway measured the effects of colestipol granules (10 g/day) in 76 FH children aged between 10 and 16 years. In addition, all the children were on a low-fat diet. A 19.5% reduction in LDL cholesterol levels was achieved in the colestipol group versus a 1% reduction in the placebo group.[36] After a year, two-thirds remained in the study.

A trial of 71 children with FH in Germany measured the effect of diet alone or diet plus resins (15 children on cholestyramine and two on colestipol).[37] The group assigned to receive medication had been on a low-fat diet for at least 6 months prior to receiving treatment. Observation of this group ranged from a mean of 14.5 months (2–46 month range). The second group, assigned to both diet and medication, were followed for a mean of 10.6 months for the dietary component and 24.9 months (range: 3–74 months) for the drug component. Diet alone reduced total cholesterol level by a mean of 7.4% and the LDL cholesterol level by 9.9%. With diet and drug therapy, the median total cholesterol level was reduced by 29.7%, and the LDL cholesterol level was reduced by 25.9%.

A 1 year double-blind placebo-controlled trial was conducted in 14 outpatient clinics in the USA and Finland.[38] The aim was to examine the effect of statins (lovastatin) on a group of 122 10–17 year old adolescent boys with FH (63 on intervention and 59 on placebo) in terms of efficacy of treatment, sexual maturation, growth and biochemical safety. LDL cholesterol levels were reduced by 17, 24 and 27% on doses of 10, 20 and 40 mg of lovastatin per day. Initial results indicated that there did not appear to be a negative impact on growth, sexual maturation, hormonal or nutritional status. The authors concluded that further examination is required to support these findings.

Recommendations for the management of FH in children

There is widespread debate about screening children. The recommendations of the British Hyperlipidaemia Association[39] are that children with FH should not be screened before the age of 2 years but the aim should be to identify them before the age of 10 years. The recommendations for the management of FH in children are to try initially to reduce cholesterol levels by dietary and lifestyle advice.[39–43] Diets should be low in cholesterol (200 mg/day), with fat intake no more than 30% and saturated fat intake no more than 10% of total calories.[44] Dietary treatment should not begin before the age of 2 years. Statins are not usually prescribed until the age of 18 years, and are not licensed for use in children.[43] Resins (cholestyramine and colestipol) are the recommended drug of choice in hyperlipidaemic children. The British Hyperlipidaemia Association recommends that boys with cholesterol levels above 7.8 mmol/l should be treated with drugs.

An Oslo lipid clinic has developed a classification of risk for children and adolescents depending on their risk profile. The use of statins is not recommended until after the age of 18 years unless the patient is considered high risk (defined as having a cholesterol level above 10.0 mmol/l, male, and no early CHD in the family, or a cholesterol level above 7.0 mmol/l and early CHD in the family).[45] For this group, resins can be used as early as 7 years

TABLE 8 *Evidence from cost-effectiveness analyses of statin treatment*

Study	Hypothesis	Data sources	Results
Johanneson *et al.*, 1997[47]	Cost-effectiveness of simvastatin in relation to age, sex and cholesterol levels	Direct and indirect costs of intervention and CHD morbidity	Cost/LYG (direct costs only) TC of 8 mmol/l: Men aged 35 years, US $6700 (women, US $13,200); men aged 59 years, US $4200 (women, US $7100)
Jonsson *et al.*, 1996[46]	Cost-effectiveness of simvastatin in relation to avoided hospitalisation due to treatment on statins – secondary prevention	Swedish hospital data, mortality data from the 4S. Direct costs only	32% reduction in hospitalisation between placebo and treatment group estimated. Cost per discounted LYG: £5502 (0.24 LYG from 5.5 years of treatment)
Caro *et al.*, 1997[48]	Cost consequences of pravastatin treatment in avoiding transition from health to CHD and cost per LYG – primary prevention	Effectiveness data from the WOSCOP study built into model of transition to CHD event. Direct costs (discounted at 6%) from local hospitals' estimates and WOSCOP admission data	For 40% men at highest risk, cost per LYG is £5601 (benefits undiscounted); all men, cost per LYG is £8121. With benefits discounted, £13,995 for 40% high risk and £20,375 for all men. Number needed to treat to avoid transition is 22.5 in high-risk group, and 31.4 for all
Morris *et al.*, 1997[49]	Systematic review of the cost-effectiveness of cholesterol management	Only studies reporting outcomes data and at least direct costs were included	Secondary prevention more cost-effective than primary prevention; universal screening and statin treatment in younger age groups least cost-effective
WHO report, 1997[51]	Cost per LYG of treatment of FH	Mortality data from published studies built into CHD policy model (from 1993 paper). Minimal explanation of how assumptions and estimates of LYG and treatment effectiveness reached	Cost per LYG at 50% effectiveness: men aged 20–75 years, US $5500/LYG; women aged 20–75 years, US $16,500. If cost of treatment if halved, the estimates also halve

old in males (12 years old in females) and statins from the age of 15 years (18 years in females).

Summary of issues for FH children

Diagnosis of FH is difficult in new-born babies and is best postponed until children are at least 1 year old. Statins are not normally prescribed in children because they are not licensed for children in the UK and the safety of statins in children is less certain than in adults. The main concern is that growth and sexual maturation could be affected. Resins can be used to treat children, but they are unpalatable and compliance is poor. Some authorities have recommended that adolescent boys at high risk of CHD should be treated with statins.

Resource implications of treatment

Studies on resource implications of treatment for hypercholesterolaemia are summarised in *Table 8*.

Two papers have examined the cost-effectiveness of cholesterol lowering using the survival and cost

data from the 4S randomised controlled trial (RCT).[46,47] One paper estimated a 32% reduction in the total cost of hospitalisation for acute cardiovascular events and procedures between the placebo group and the simvastatin group.[46] Simvastatin treatment saved an estimated 0.377 undiscounted life-year per treated subject (0.24 life-year with discounting at 5% per annum). The cost of statin therapy per discounted life-year saved was estimated to be £5502 (combined age groups). The UK comparison (using UK costs with 4S hospitalisation data) was £6983. These estimates are based on Scandinavian hospital costings, so should be transferred with caution.

The second paper using 4S data measured the cost per life-year gained (LYG) with simvastatin therapy for three age groups (35, 59 and 70 years) and for three pretreatment cholesterol levels (5.5, 6.75 and 8 mmol/l).[47] Calculations were carried out for direct costs only and for direct and indirect costs (to include lost labour productivity). All costs and LYGs were discounted at 5%. Statin treatment in men aged 70 years, with a cholesterol level of 8 mmol/l, had a cost per LYG of US $3800 when calculating direct costs only (women US $6200). Statin treatment in men aged 35 years with the same cholesterol level would cost $6700 per LYG, and in men aged 59 years, US $4200 per LYG (women aged 35 years, US $13,200; women aged 59 years, US $7100). The group in which treatment was estimated to be least cost-effective was women aged 35 years with a pretreatment cholesterol level of 5.5 mmol/l with a cost per LYG of US $27,400. When indirect costs were included (losses in productivity), savings were anticipated for men and women in the 35 year old group. The older age group did not 'save' when indirect costs were included, as the calculations for lost productivity had an upper age limit of 64 years old.

A cost-effectiveness analysis of the WOSCOP RCT[48] (6595 men with no previous MI) also concluded that the 40% of men with the highest risk profiles (20% CHD risk over 10 years) have the most favourable cost-effectiveness ratio: £5601 per LYG (undiscounted) and £13,995 per LYG with benefits discounted.[48] This can be compared with an undiscounted cost per LYG of £8121 (£20,375 per LYG with discounted benefits) if all risk groups are included in the analysis. Costs only included direct costs, and were discounted at 6%. If these data are transferred into a number needed to treat figure, 1 in 31.4 men started on pravastatin therapy would avoid developing CHD over a 5 year period. If only the 40% highest-risk men were treated, this would be reduced to 1 in 22.5 men needing pravastatin.

A systematic review of the cost-effectiveness literature for the management of hypercholesterolaemia included 38 papers, and concluded that statins are more cost-effective when targeted at high-risk groups.[49] Only studies with outcomes and at least direct cost data of cholesterol management were included. Thirty-seven out of 74 papers identified filled these criteria. From the limited evidence available, the authors concluded that secondary prevention with medication is more cost-effective than primary prevention with medication. In addition, it appears that it is least cost-effective to treat the young. However, when initial levels of risk are considered, treating those patients with pre-existing CHD with statins is 80% more cost-effective than treating those without pre-existing CHD.

A cost-effectiveness analysis was conducted using US cost data and adaptation of the Coronary Heart Disease Policy Model using pretreatment FH morbidity and mortality data.[50] The results presented are based on 25 year simulations of the effects of different doses of lovastatin. The incremental cost per life-year saved (comparing 20 mg lovastatin with 40 mg daily) was under $50,000 in men with one other risk factor and in women with two other risk factors. The cost-effectiveness ratios were similar for the primary prevention in FH patients to the secondary prevention of CHD in non-FH patients. The costs are measured in US dollars at their 1993 value.

A recent cost-effectiveness evaluation of the treatment of people with heterozygous FH[51] made estimates ranging from $3375 per LYG for men aged 20–65 years (based on a 100% ideal effectiveness) to $6750 per LYG assuming 50% effectiveness. It is not clear how the cost-effectiveness analyses were performed. The mortality data are based on published literature. The value of cost-effectiveness data are limited when the calculations are not linked to actual trial data.[52] Data are presented in this analysis for wide age bands (men and women aged 20–65 years), so the effects of the age of identification and subsequent years of treatment are averaged out over a 45 year period. The options for the effectiveness of treatment are presented as 100% 'ideal scenario', 50% 'realistic' and 'pessimistic' 10% effectiveness. It is not clear what the effectiveness refers to. One scenario presented adds 10 years of life due to the effects of statin treatment, but no data are provided to support this large estimated benefit. As the methods of the analysis are not explained, it is not possible to reproduce the modelling assumptions.

TABLE 9 *Total cholesterol levels expected to diagnose FH with 98% specificity*

Age (years)	Total cholesterol level (mmol/l)	
	First-degree relatives	General population (Utah)
< 18	5.7	7.0
20	6.2	7.5
30	7.0	8.8
≥ 40	7.5	9.3

Conclusion and summary

Cost-effectiveness analyses vary widely in their conclusions. Methodological shortcomings are evident in many studies, as they rely on published literature for evidence of effectiveness. It has been suggested that the reliability of the data could be improved if more cost-effectiveness studies linked economic analysis with clinical trials data.[49] In addition, not all studies explain in sufficient detail their methodology and assumptions taken. This severely limits the transferability.

In a meta-analysis of the data from RCTs of cholesterol lowering, the authors conclude that lipid-lowering drugs have the greatest overall benefit in reducing CHD, and all cause mortality in those with high initial cholesterol levels.[53] Net benefits for total mortality from cholesterol lowering was only seen for the very high initial risk patients. The greater the risk of CHD, the greater the benefit seen.

These results are verified by the large RCTs reported in this review. Although there are not RCTs of statin treatment in FH patients, the clear message that can be drawn is that statins are effective in reducing cholesterol levels and CHD mortality, and therefore would be most cost-effective in the highest CHD risk groups.

Detecting undiagnosed FH

Comparing clinical and genetic diagnosis

Elevated cholesterol levels are the primary diagnostic criterion for FH, and therefore accurate measurement of the plasma cholesterol concentration is a key requirement for diagnosis. However, there is a certain amount of variation in blood cholesterol levels, and laboratory measurements of levels are not completely accurate.[54] It is important therefore, that at least two blood cholesterol measurements are performed before hypercholesterolaemia is diagnosed.

Total or LDL cholesterol levels alone cannot always detect FH (since cholesterol levels in FH are not always sufficiently elevated). Genetic mutation screening can give a definitive diagnosis in some cases. A DNA test can result in the diagnosis of FH being made in approximately 15–20% of known FH family members where measurement of cholesterol levels alone would not have established the diagnosis.[55,56]

A US paper reported a modelling exercise which compared the sensitivity and specificity of using differing cut-offs of total serum cholesterol levels for diagnosing FH in both a general population sample and in close relatives of confirmed FH cases. The authors estimated the cut-offs of total cholesterol required to achieve 98% specificity in screening programmes of first-degree relatives of an index case and in the general population at differing ages (*Table 9*).

The sensitivities would vary with the population screened, and were estimated to be 88% for screening first-degree relatives and 54% for screening the general Utah population. The results of the modelling were validated in a group of 207 first-degree relatives from five FH families, in whom FH status had been established with a DNA test. Seventy-five individuals had a DNA marker. Using the proposed 98% specificity cholesterol cut-offs correctly identified 129 of the 132 subjects who were DNA-marker-negative and 65 of the 75 who were DNA-marker-positive.[57]

The UK's Simon Broome Register criteria for diagnosis of FH uses a cut-off of 7.5 mmol/l of total cholesterol for adults and 6.7 mmol/l of total cholesterol for children aged under 16 years, but require the additional feature of the presence of xanthomas in the index patient or a first-degree relative.[6]

Data from the Health Survey for England in 1994 indicate that 5% of men aged 35–44 years would have a total cholesterol level above 8 mmol/l.[58]

Although blood cholesterol levels are generally much higher in people with FH, the range of blood cholesterol values overlaps with that of the general population. Therefore, screening for FH using cholesterol measurements alone would not be sufficiently specific; report of a family history of FH, or of premature CHD, or of the presence of xanthomas would improve specificity.

The advantage of DNA testing is that an unequivocal FH diagnosis can be achieved. The diagnostic problem caused by the overlap between population and FH subjects could be eradicated. A single test, once in a lifetime, will be able to ascertain FH status. Early diagnosis in children would also be possible. One early study indicated that it would not be possible to make an unequivocal diagnosis in 5–10% of children through cholesterol measurement alone.[33]

It is possible that different mutations have different effects on the LDL receptor function, which may result in more severe clinical consequences. As the sophistication of testing improves, so too should the accuracy of assessing risk in those genetically predisposed to CHD. If genetic testing is used for diagnosis, it will be necessary to provide adequate education for those testing negative, as patients must be made aware that this does not preclude them from developing CHD in the future from non-LDL receptor mutation causes.

One problem with genetic testing is the possibility of discrimination for life insurance, although discrimination as a result of genetic tests has been ruled out for policies under £100,000.[59] There is a concern that an individual could be discriminated against simply because they had a genetic test (irrespective of the outcome of the test). This could have repercussions for both index patients and their relatives.[60–63]

Discussion

There are no clear reliably agreed definitions of what the clinical diagnostic criteria for FH should be, or what the most sensitive cholesterol cut-off levels (ability to identify affected individuals) should be, to avoid getting a high number of false-negative or false-positive cholesterol measurements. Genetic confirmation can overcome the uncertainties of relying on cholesterol measurements alone in identifying a possible FH individual, who would be referred to a specialist for closer investigation. In addition, in the UK, due to the heterogeneous composition of the population, it is more difficult (and costly) to identify a genetic mutation in a population group.

We had to decide what cholesterol cut-off point to use in the screening strategies for both high-risk and population groups. Having considered the data above, it is apparent that there is no clear set of guidelines to follow. We have used the Simon Broome Register criteria for targeted screening and the 95th percentile for population screening. To achieve a high sensitivity and specificity rate and avoid biological and analytical variability, our protocol includes two blood cholesterol tests, to be taken at least 1 month apart.

Screening options for undiagnosed FH

Possible strategies for detecting undiagnosed FH include universal or targeted screening, and opportunistic or systematic identification strategies. Universal screening would imply that everyone is tested, regardless of their apparent risk of having FH, while targeted screening would involve the selective screening of people at high risk, for example first-degree relatives of index cases, or people who develop heart disease below the age of 55 years. Identification of individuals for screening can be either opportunistic, when people come into contact with the health services for other reasons, or it can be systematic, for example systematically screening all school leavers.

Population screening

A pilot study in Denmark measured the concentrations of apolipoproteins a-1 and B in capillary blood from the ear. Children starting their first year (aged 6–8 years old) in the Copenhagen school system were identified, and their families were offered the chance to participate in the study to detect FH in a community.[64] Parents of 2166 of the 3025 children gave permission for samples to be taken, and 2085 samples were provided. Seventeen children had persistently high levels of total cholesterol, and these children plus all available first- and second-degree relatives were offered a full, fasting lipid test. Twelve children from ten families were diagnosed with FH after a full family history had been taken. One of the ten families was known to have FH. Twenty-nine relatives (aged 1–59 years) were found to be hypercholesterolaemic. Only five of the 12 newly diagnosed children had a positive family history of premature ischaemic heart disease, and the authors concluded that measurement of

apolipoproteins in capillary blood is more efficient than screening for FH by first identifying children with a positive family history.

A study conducted in the USA in Utah sought to establish how much benefit could be attained from what the authors describe as limited resources (two full-time secretaries, a part-time nurse, a part-time program analyst and consulting physicians) in terms of identifying new FH cases.[65] Apart from known FH patients who had been identified through lipid clinic attendance, the effectiveness of a number of sources for finding new index patients was compared. The sources were:

- Local and state computer records of health department screening for people with elevated cholesterol levels (above 7.8 mmol/l). One-hundred and fifty-three people were identified; 30% responded to the questionnaire. Nine cases were identified by this method, after examining the records of 75,000 people.
- Letters were sent to persons discharged from hospital who had an MI before the age of 55 years. Five new index patients were identified from the records of 2769 people with premature MI.
- Family history records collected from the parents of 50,000 high-school children in an earlier 'health family tree project'. This identified 178 families with both early heart attacks and high cholesterol levels. The response rate was not reported. Twenty cases were identified by this method.
- Letters sent to 720 local family practitioners, which identified 14 cases (out of 35 responses).
- Shopping mall cholesterol testing of over 7000 people, which identified two new cases.

The final result was that 101 cases were identified, of which 50 were previously undiagnosed. The details of the remaining 51 had already been registered at the local cardiovascular genetics clinic.

The authors estimated that the various methods of population screening combined had cost US $1600 per new case identified, while tracing relatives of identified index cases had cost US $400 per new case identified. They went on to calculate that it would cost US $5000 per new case detected if a large-scale cholesterol-screening operation were launched. Their conclusion was that targeted screening of relatives of identified cases was more efficient (by which they seem to mean more cost-effective) than universal screening. However, very little information is given about the methods of costing the different screening techniques, and it is difficult to know how to interpret these data.

Family tracing (cascade screening)

From index patients in a lipid clinic

A pilot project to estimate the effectiveness of family tracing was conducted at the Manchester Royal Infirmary and the University Hospital of South Manchester. Two-hundred and fifty-nine known FH patients were contacted and asked to provide details of their relatives. One-hundred and fifty-seven of them provided information on 205 relatives, out of which 121 were identified with FH.[66] Of the affected relatives, 62% were women, which may indicate that a number of men had already died prematurely. The ratio of men to women in the group of unaffected relatives was around one. Twelve of the newly diagnosed relatives were aged under 16 years (*Figure 1*).

Unfortunately, largely due to the fact that the research nurse assigned to the project changed a number of times within the life of the project, details of the number of relatives approached, the procedures for approaching them, and reasons for not participating were not recorded using a standardised procedure throughout. The problems with changes of research nurse as well as funding insecurity may have reduced the potential yield of relatives available. Cost estimates from this pilot are that the nurse spent an hour with each relative, and half an hour with each proband. These time estimates include contacting the relative by phone and taking family histories.[66]

The Dutch National Foundation for Identification of Familial Hypercholesterolaemia (Stichting Opsporing Erfelijke Hypercholesterolemie) (StOEH)

A genetic case-finding screening has been set up in The Netherlands: StOEH (for details, email stoeh@wxs.nl). Index patients were identified as having FH only if they had a known genetic mutation. Therefore this case-finding approach set out to identify family members of index patients who have an identified genetic mutation. There was a 34.4% prevalence of the genetic mutation for FH in the men, and 33.7% in the women (first- and second-degree relatives). A cost-effectiveness evaluation of the StOEH programme has been undertaken (unpublished data from the evaluation study were kindly provided for this review by AHA ten Asbroek and PJ Marang van de Mheen, University of Amsterdam). An analysis has been undertaken on the data collected by the StOEH programme between 1994 and 1998. Data were

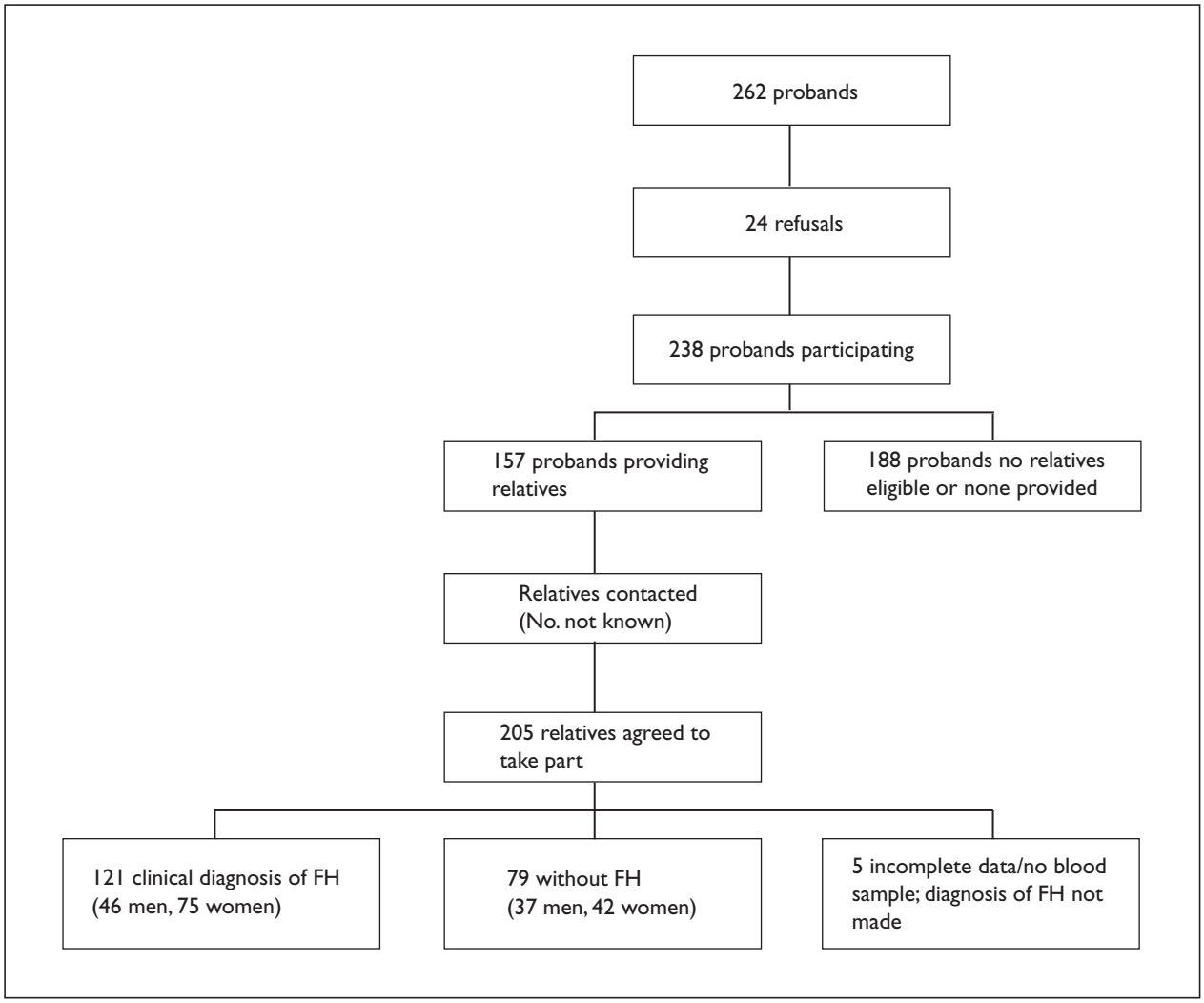

FIGURE 1 *The Manchester case-finding study*

analysed on persons aged 20–60 years with test results for both DNA analysis and lipid profiles. These data do not represent all the available data from the StOEH programme. Cholesterol testing is not part of the StOEH. Blood samples on 1037 first- and second-degree relatives (491 men and 546 women) aged between 20 and 60 years were analysed for the purpose of the cost-effectiveness evaluation. Hypercholesterolaemia (cholesterol levels above the 95th percentile) was evident in 107 of the 169 FH-positive men (63.3%) and in 122 of the 184 FH-positive women (66.3%). Of these, 70% of men and 66.4% of women were not receiving statin treatment at the time of identification. Of those relatives in which the genetic mutation was not identified, 46 men and 49 women were classified as hypercholesterolaemic. Thus, genetic testing identified about 70% of the adults with hypercholesterolaemia. About two-thirds of adults with a genetic mutation would have been identified by cholesterol testing alone. The distribution of hypercholesterolaemia in the UK and The Netherlands is not the same, so these results may not reflect a similar programme based in the UK.

Other targeted strategies

From post-mortem examinations

A UK-based study of 485 consecutive autopsies identified 11 'high-risk' cases, that is, cases aged less than 45 years with evidence of significant atheroma, in good health with no known risk factors for hyperlipidaemia.[67] Three cases were found to have considerably elevated cholesterol levels resulting in one confirmed FH diagnosis. Testing of surviving family members of this case found that two of the six surviving siblings had an elevated cholesterol level, as did the mother. The authors concluded that cholesterol levels should be routinely checked in high-risk patients' deaths, and relatives of diagnosed hypercholesterolaemic individuals should then be screened.

In children of high-risk individuals

A pilot study in the UK evaluated a method of identifying FH children in one geographic location.[68] The authors calculated that only ten of the estimated 300 children with FH in the area had been identified. High-risk patients were defined as men aged under 50 years and women aged below 55 years who had an MI or angina. Index patients were identified through hospital and general practitioner (GP) records, referrals from lipid clinics, and scrutiny of death certificates. The children in the families of high-risk patients had their cholesterol level measured by a health visitor. Family histories were obtained prior to testing, and those with hypercholesterolaemia associated with other conditions were excluded. Out of the 200 children identified from the first search phase (from 120 families), 12 (6%) new cases of FH were identified in the first 9 months of the study.

Discussion and summary

In the UK, population levels of total cholesterol are high, and population screening for FH using the diagnostic criteria of a total cholesterol level above 7.5 mmol/l will result in poor specificity (a high proportion of false positives). Diagnostic confirmation can be made either by genetic screening or a combination of measuring lipid subfractions, clinical examination and family history. In the UK population, genetic screening will detect mutations in about 50% of people with FH identified by clinical methods (see chapter 1). Dutch experience suggests that cholesterol measurement may fail to detect as much as one-third of patients with a genetic mutation.

There are few studies that have examined the costs and effectiveness of FH identification and treatment. In Denmark, population screening of school entrants was shown to be acceptable. However, the prevalence of FH in this population was higher (about 1 in 300) than estimated for the UK (about 1 in 500). Population screening in a study in the USA was not considered effective. Methods of targeted screening have been tried, particularly family tracing. Most studies conclude that a case-finding strategy will be an effective and least costly option of identifying undiagnosed FH. However, much of the data is poorly described. The paucity of studies makes it difficult to reach firm conclusions about relative effectiveness or cost of different strategies.

Chapter 4

Social and psychological effects of screening for FH and similar conditions

As described in chapter 2, we developed an algorithm to evaluate both qualitative and quantitative research papers. The completed algorithms for the papers in *Table 10* resulting from this procedure are given in appendix 1.

The number and content of the papers identified was disappointing. Although a great deal has been written, most of it is opinion, unsubstantiated by any data. There appears to have been very little research on the possible consequences of screening and diagnosis of a treatable inheritable condition such as FH. The lack of any qualitative work, exploring what may be some very complex issues, is particularly striking. Almost all the measures of adverse effects rely on psychological scales in which the issues are predetermined and not necessarily related to FH.

The papers which contain primary data are summarised in *Table 10*, followed by a discussion of the opinion papers, which are summarised in *Table 11*.

Studies containing primary data

Sixteen studies reporting primary data were identified. Six of them considered cholesterol screening in general (two specifically looking at the effects on children). Two studies (three papers) focused on responses to genetic screening for FH (one on the effects of FH screening in children). Five papers considered screening for the breast cancer gene, and three others considered discrimination (one on cholesterol screening and two on genetic testing).

A range of effects of screening was investigated. This included labelling,[69,70] the impact of screening on self-perceived health and well-being,[70–72] the impact on family relationships,[73] and the behavioural effects in children who underwent screening for hyperlipidaemia.[74,75] Attitudes to genetic screening were examined by assessing the psychological impact of those testing positive versus those testing negative[76] and whether there is a relationship between psychological distress and genetic test use.[77] Only one paper set out to gain a better understanding of patients' knowledge, perceived benefits, risks and concerns over genetic testing, using small-scale focus groups to elicit the scope of issues concerning the patients.[78] Two studies specifically examining FH discuss psychological reactions to screening relating to family conflict, diet, social and emotional difficulties, and fear of CHD.[71,73]

Perceived advantages and disadvantages of screening

A Danish cross-sectional postal survey of 162 people with FH aged between 16 and 72 years examined attitudes to genetic screening and the impact on well-being of having a diagnosis of FH.[71] The questionnaire was sent to 62 index patients and 108 of their relatives with diagnosed FH, who had previously given a blood sample. The response rate was 88%. In responders, the mean time since the clinical diagnosis of FH was 9.4 years, but 61% of index patients and 54% of their relatives were also given a molecular diagnosis at this time. Anxiety about having FH and fear of developing CHD were reported by 44 and 36% of respondents, respectively, but 83% of respondents said that they did not regret having been given the diagnosis. Most respondents (84%) were in favour of family screening, and less than 3% disapproved. The authors concluded that psychological reactions were not a problem in initiating a screening programme for FH.

A study in Sweden followed a group of 12 men, all 40 years old, who had been diagnosed as hypercholesterolaemic (total cholesterol level above 6.5 mmol/l) following a voluntary health check.[72] The men were followed-up weekly over the course of a year, with visits including less formal discussions and more structured interviews. The study attempted to show how the boundaries between health and ill-health were formed, reformed and adjusted. The relationship between the medical profession and the men was also considered in attempting to see how the preventive health message was conveyed and understood. Five men still had high cholesterol levels several months after the first test, and four of these had attempted

TABLE 10 *Summary of the primary data studies of the psychological aspects of screening*

Study	Key issues addressed	Design	Brief description of conclusions	No. and type of subjects	Comments/ problems	Relevance to FH screening policy
Andersen, 1997[71]	1. Attitudes to disease detection 2. Present well-being in persons at risk of disease with a modifiable outcome	Quantitative cross-sectional	1. Majority in favour of screening for relatives (84%) 2. Anxiety and fear of FH and related CHD 3. Increased knowledge of disease and higher education more likely to support screening	150 FH family members (aged 16–76 years)	1. 80% already aware of hypercholesterolaemic state 2. Attendees only; psychological problems probably not so severe 3. Only one open-ended question	Psychological reactions were not severe enough to warrant not initiating a screening programme – data could be more severe in general population who have less knowledge of disease and consequences
Billings *et al.*, 1992[85]	Whether genetic discrimination occurs in the workplace, in access to social services, in insurance underwriting and in the delivery of healthcare	Qualitative case history study	Discrimination does occur. Misunderstanding of implications of positive results. Promise and burden of genetic testing – detect early **but** suffer stigmatisation	41 cases	Very small number of cases. Will be difficult to assess scope of problem due to reluctance of individuals to formalise problems	Possible discrimination of FH patients. Might affect uptake of genetic testing
Croyle *et al.*, 1997[76]	To compare levels of psychological distress in women who tested positive for the *BRCA1* mutation versus those who tested negative	Quantitative cross-sectional	Greatest distress in carriers – declined by 20% at follow-up (worst for carriers without experience of cancer). Learning carrier status alleviated anxiety	60 high-risk women aged 19–83 years	Increased health and cancer awareness. Genetic and psychological counselling given. Small sample. Preliminary results – 2 week follow-up	Population screening would not have same awareness of disease implications
Irvine and Logan, 1994[69]	Negative psychosocial consequences of being labelled as hypercholesterolaemic and if this can be can be mitigated by management of hypercholesterolaemia in the workplace	Quantitative RCT	Hypercholesterolaemia detection and treatment not associated with adverse changes in perceptions of psychological or physical health, social/leisure activities or global measure of life satisfaction	477 male factory workers	Hypertension and hypercholesterolaemia labelling different. Perceived control over risk factor likely to influence labelling effects	Looking at moderately high cholesterol levels, so not wholly relevant to FH. Tested labelling, not what effects may be
Kash *et al.*, 1995[79]	To compare the effect of education and counselling on reducing distress and perceived vulnerability	RCT	80% overestimated risk – can be a major barrier to screening. Cancer anxiety and psychological distress were significant predictors of poor adherence. Intervention reduces perception of risk, and increases adherence	40 women	Poorly described, small trial. Conclusions not supported by data	If overestimation of risk and disease misbeliefs contribute to poor adherence, then educational intervention might improve acceptance of screening

continued

TABLE 10 contd *Summary of the primary data studies of the psychological aspects of screening*

Study	Key issues addressed	Design	Brief description of conclusions	No. and type of subjects	Comments/ problems	Relevance to FH screening policy
Lerman *et al.*, 1997[77]	Relationship between psychological distress and requests for *BRCA1* test results in high-risk individals – psychological predictors of test use	Quantitative cross-sectional	Absence of psychological distress, which may be a reflection of emotional habituation or adaptation to persistent stresses of living in a family with hereditary breast–ovarian cancer. 58% requested *BRCA1* results. Cancer-specific distress was significantly and positively associated with requests for test results	149 male and female members of a cancer registry aged 18 years or over	24% refused baseline interview – high distress could provoke avoidance of receiving test results Subjects mainly white, high school educated, with health insurance and increased knowledge of the disease	Education and counselling for all – but members of a cancer registry, not representative of population group. Highly selected
Lerman *et al.*, 1997[80]	To evaluate the impact of alternative strategies for pretest education and counselling on decision-making regarding *BRCA1* testing	Quantitative RCT	Education alone as effective as education and counselling in increasing knowledge. Intention to have test not affected	400 women aged 18–75 years with low to moderate risk	Subjects were white, well educated and above average income	No evidence that education or counselling affects decision to have a genetic test
Low *et al.*, 1998[60]	To gather empirical evidence on reactions of families with genetic conditions to insurers, the medical profession, employers and social services	Quantitative cross-sectional	33.4% of family members experienced problems in applying for life insurance, and 5% of population sample had problems	7000 members from seven support groups and 1033 members of the general public	Some respondents' health is affected by genetic disorder, while others are not affected, so difficult to ascertain if problems are from genetic discrimination or are health related	Inconsistency of insurers could affect FH patients too, especially if actuarial risk is not based on epidemiological evidence
Marteau, 1996[81]	If population-based cardiovascular screening programme raises concerns of health or undermines belief in ability to reduce risk of CHD	Quantitative RCT	No negative effects from participation in screening. It is reassuring rather than threatening. Reduction in perceived ability to reduce own risk of future heart attack	6560 randomly selected men and women aged 40–59 years	Patient-centred approach with nurses aware of potential negative consequences of screening	Focus is population screening, so for a target approach may not be transferable. No adverse reaction in men or women or at different levels of intervention intensity so results could be generalisable

continued

TABLE 10 contd *Summary of the primary data studies of the psychological aspects of screening*

Study	Key issues addressed	Design	Brief description of conclusions	No. and type of subjects	Comments/ problems	Relevance to FH screening policy
Meland *et al.*, 1996[70]	If high-risk groups are adversely affected by opportunistic CHD screening and labelling effects. Psychological well-being measured in high CHD risk subjects in a 1 year intervention	Quantitative cross-sectional screening	No significant differences between reference and intervention groups. No adverse effects on satisfaction with life from labelling	127 male GP attendees aged 30–59 years	Measuring labelling through a single question: "I found it unpleasant to be reminded of the risk of heart disease". Results could not be used to confirm the authors' original hypothesis. Heavy reliance on literature	No adverse effects of labelling were found
Neil and Mant, 1991[83]	How insurers assess proposals for life assurance from raised cholesterol applicants and to determine excess rating applied	Quantitative cross-sectional	Wide variation in excess	49 companies	Excess rating depends on type and term of policy, and the presence of risk factors	FH patients will have to pay higher premiums. May deter asymptomatic people from being screened
Rosenberg, 1997[74]	To assess the behavioural and psychological effects of screening asymptomatic children at high risk of hyperlipidaemia	Quantitative prospective and cross-sectional	Do not screen children at moderately high risk of hyperlipidaemia. Higher percentage of diagnosed children had behavioural problems after diagnosis than controls	52 (prospective), 58 (cross-sectional) aged 4–17 years	Unable to separate effects of screening to that of diagnosis to that of family history. Controls also high risk. Selection bias	Do not screen moderate high risk children
Rosenthal, 1993[75]	Relationship between family functioning, impact of diagnosis of hypercholesterolaemia and dietary habits. Do children experience psychological distress (behaviour problems, self-esteem or depressive symptoms)?	Quantitative cross-sectional	No difference in psychological functioning between groups. Cohesive and organised families more likely to implement diets. Reinforces importance of family in the treatment of chronically ill children	36 children (19 affected and 17 controls)	Sample bias (white suburban families). Small sample. No assessment of child's understanding of own condition	Conventional practice is to 'treat' FH children by changing dietary behaviour rather than providing statins

continued

TABLE 10 contd *Summary of the primary data studies of the psychological aspects of screening*

Study	Key issues addressed	Design	Brief description of conclusions	No. and type of subjects	Comments/ problems	Relevance to FH screening policy
Sachs, 1996[72]	To examine how the boundaries between health/ ill-health were formed, reformed and adjusted. To consider the relationship between the medical profession and patients in relaying information	Qualitative interviews	Anxiety, stress and worry about taking the medication, lack of social support, isolation and difficulty in adjusting to the diet	12 , 40 year old men with cholesterol > 6.5 mmol/l	Small sample, but men were followed up weekly over a year	There was a range of adverse effects to screening. Sense of blame and responsibility allayed from nurses to patients, especially after unsuccessfully reducing cholesterol levels. There is a need for more studies like this with larger number of participants
Tessaro *et al.*, 1997[78]	To understand women's knowledge, perceived benefits, risks and concerns about testing and potential influences, and support needs in decision to have a genetic test for breast cancer	Qualitative focus groups	Balanced information about screening needed. Involve doctors in women's decision. Consider family relationships. Provide public education about genetic testing	66 women (affected and unaffected)	Subjects were a better educated group than the general populace	Main advantages: information to reduce uncertainty and future decision-making. Main disadvantages: confidentiality and loss of insurance, lack of proven options post-screening and stress of being a mutation carrier
Tonstad, 1996[73]	To assess the psychological concerns of families with FH. Parental concerns over diet, family and social relationships and emotional difficulties	Quantitative cross-sectional	1. 11% of parents felt quality of life would have been better without FH diagnosis 2. Majority felt advantages of treatment outweighed disadvantages 3. Familial conflict in 20% 4. Do not postpone treatment. Be aware of individual vulnerabilities and provide counselling	154 parents; 154 children aged 6–16 years with one FH parent	Only included those who attended a clinic at least twice before. Non-attendance may reflect psychosocial problems which may be more frequent than the study suggests	Psychological problems should not be a barrier to implementing an FH screening programme

Table 11 *Content of opinion papers on social and psychological aspects of screening*

Study	Main points	Potential benefits	Potential disadvantages	Recommendations and comments
Alderman, 1990[97]	Hypertension labelling. Assesses usefulness of hypertension diagnosis		'Sick role'. Absenteeism. Loss of productivity – majority labelled but will not benefit from diagnosis and treatment. Impact on employment status, and marital problems	Studies of labelling required to assess the link between diagnosis and medical care. Establish criteria for assigning a diagnostic label related to the likely useful intervention
Alper, 1993[103]	Is genetic information different to any other medical information? Answer impacts on whether insurers should have access		Genetic test for a multifactorial condition, provides less predictive information than is assumed	A moratorium on the use of genetic test results for insurance where underwriting is based on medical risk
Biesecker, 1995[90]	Counselling at pretest, notification and follow-up outlined. Educate the public. Genetic services available for all. Provide genetic information. Consumers to have a role in the development of testing programmes			Useful, concise overview. Outlines aspects of pretest education and counselling, risk notification and surveillance
Brett, 1991[98]	Distinction between disease and illness. Accurate risk assessment important		Labelling – individuals consider themselves 'unhealthy' rather than on a continuum of 'at risk'	Counselling. Outlines steps that doctors and counsellors could take to reduce anxiety
Davison *et al*., 1994[93]	Social and cultural impact of risk information for hyperlipidaemia, hypertension and cancer screening. Screening indicates vulnerability/predisposition, **not** definite or inescapable onset		Labelling and fatalism after positive test	Accurate education/information and distinction between lay and medical understanding of disease needed to aid better counselling
Fost, 1992[61]	Genetic disorders are heterogeneous. Cost–benefit analyses of screening vary between individuals		Heterogeneity, confusion (so education/information important) and stigmatisation	Informed decision-making is important
Glanz and Gilboy, 1995[82]	Labelling, psychological distress, memory and knowledge of disease, follow-up referral adherence and behavioural change	Possible positive changes in perceptions of health at follow-up	Absenteeism, poorer health and psychological distress after positive test. Negative test results in no change in lifestyle or worse habits being adopted	Labelling is not a problem with hypercholesterolaemic diagnosis
Holtzman and Shapiro, 1998[102]	Validity and benefit of genetic tests need establishing before widespread use. Discrimination and breaches of confidentiality are barriers to testing		Discrimination, breached confidence and inaccurate interpretation of results	Policies to minimise potential barriers needed

continued

Table 11 contd *Content of opinion papers on social and psychological aspects of screening*

Study	Main points	Potential benefits	Potential disadvantages	Recommendations and comments
Lefebvre *et al*., 1988[97]	Evaluation of quality, accuracy and efficacy of screening in detecting disease and reducing risk factors (see Koivisto *et al.*[56])		Labelling	Detrimental effects can be ameliorated by counselling
Lerman and Croyle, 1995[63]	Potential barriers due to psychological distress. Counselling important	Children's risk status can provide reassurance	Stigmatisation. Insurance discrimination. Adverse effects on family relationships	Education and counselling can aid decision-making and improve adherence. Caution is required for studies with reduced effects, as in controlled environments
Lerman and Croyle, 1996[95]	Adverse responses to learning test results	Reduction of uncertainty	Anxiety, guilt and depression if positive test. Negative test leads to less healthy lifestyle	Counselling time and resource implications. Need empirical not anecdotal evidence
Lerman, 1997[87]	Introduction to special issue of empirical work assessing psychological aspects of genetic screening	Awareness of genetic risk can facilitate informed medical decision-making and promote risk-reducing behaviour	Live with uncertainty and knowledge of heightened risk. Also, guilt and fear of transmission to children	
Marshall, 1996[89]	Brief overview – no in-depth investigation or discussion of issues		Psychological, physical, social or ethical reactions. Excessive awareness of health, anxiety, labelling, and false negatives lead to clean bill of health	
Marteau, 1990[96]	How to reduce the adverse effects. Protocol with education and counselling		Anxiety, negative test implying a 'clean bill of health', and false positives and negatives	Avoid distress by awareness of needs at each stage of the screening process with written protocol. Information can increase attendance. Perceived control can influence labelling
Marteau and Croyle, 1998[92]	Factors influencing decision to be screened, how tests are conducted, and impact on families/society. Presentation of risk information affects how its perceived and responded to. See Humphries *et al.*[3]	Research suggests adverse reactions are uncommon if set up with 'best practice' protocol	Popular assumption that genetic predisposition means that disease is not preventable or treatable. This is a predictor of compliance	Counselling and support can reduce distress. Research for most effective counselling strategies needed
Murray, 1993[105]	Adverse selection and insurance issues discussed		Access to life and disability insurance can be affected	

continued

Table 11 contd *Content of opinion papers on social and psychological aspects of screening*

Study	Main points	Potential benefits	Potential disadvantages	Recommendations and comments
Quaid, 1993[106]	Effective transmission of risk information stressed		Misunderstanding of results, misdiagnosis, labelling, stigmatisation and reduced psychological well-being. Insurance implications	Informed consent to protect privacy. Follow-up counselling and surveillance needed.
Richards, 1993[94]	Social aspects of genetic disease detection. Atendance rates depend on disease. Role of fatalism. Religious and cultural differences	Reassurance of negative carrier status.	Refusal due to implied risk for children, lack of effective treatment, loss of health insurance, and completion of child bearing	Be aware of social differences when designing education and counselling protocol
Rothstein, 1995[104]	Insurance implications and employability		Employment discrimination, compromise of privacy and confidentiality and fear of discrimination may prevent high-risk groups from having a test	Must address concerns to prevent discrimination and stigmatisation or will discourage testing. Also do not want to coerce individuals into being tested. Maintain confidentiality
Tijmstra, 1990[88]	Labelling, uncertainty, costs and 'clean bill of health' effect. Absolute and relative risk		Inconsistent and variable findings in the literature. Anxiety. 'Certificate of health' effect	
Wardle and Pope, 1992	Evaluation of psychological impact of screening. Attention paid to economic costs and medical risk. Psychological costs little attention. Education on disease important to increase participation and reduce anxiety	Progression can be slowed/halted by early intervention	Trauma of identification of disease in asymptomatic individuals. Stress of false positives on quality of life	Information/counselling. How issues are explained is important. Be aware of psychological costs and identification of the most vulnerable to reduce costs and increase benefits of screening

to change their lifestyle (traditionally a high saturated fat diet). They became more aware of their heightened risk of CHD, which caused anxiety and stress. One man felt he had a 'bomb of fat' in his body, and another felt his veins were 'clogged up'. This same individual was nervous about taking drugs to lower his cholesterol level as he did not understand the way the drugs would react in his body. The men experienced isolation from their social network and lack of support from friends, in part caused by attempts to adopt a healthier lifestyle that was different from their peer group. They had difficulty adjusting to a low-fat diet, and felt increased pressure, which was heightened by the nurse's reaction at the follow-up test when their cholesterol levels remained elevated. It appears from this study that the health information promotes increased anxiety and implies individual responsibility and blame for an individual's condition.

A study of 60 members of a large Mormon kindred with a high risk of breast and ovarian cancer compared the psychological distress in women who tested positive for the *BRCA1* mutation versus those testing negative. Results were reported for psychological distress at the baseline, when the genetic results were given to the women and 2 weeks later. The greatest distress was in carriers of the mutation, although amongst these women there was a 20% decline in distress between the baseline and follow-up 2 weeks later,[76] suggesting that distress may be short term. Carriers of the mutation who had no experience of cancer either personally or in a close family member showed significantly greater distress, suggesting that prior

experience of cancer reduces the negative effects of learning that one is carrying the gene mutation.

A randomised trial of a psycho-educational intervention in 40 women at high risk of developing breast cancer assessed the effect of counselling on reducing emotional distress and decreasing perceived vulnerability.[79] Misbeliefs and lack of knowledge were considered to contribute to poor screening adherence and poor quality of life. Eighty per cent of the women overestimated their risk of developing breast cancer. Results indicated that a 6 week psycho-educational intervention reduced perceptions of risk and increased knowledge (of the disease and of risk factors). This conclusion was based on inadequately described results. It is strong on opinion but very weak on analysis or presentation of conclusions relating to the results.

An RCT in the USA evaluated the effects of different education and counselling approaches for *BRCA1* testing.[80] Participants were randomised to three arms. The first group received an 'education-only' intervention which included information about risk factors, inheritance of cancer susceptibility, benefits, risks and limitations of genetic testing. The second group received education plus counselling which included a discussion about cancer experiences in the family and the potential psychological and social impacts of testing. The third group was a waiting list control group with neither intervention offered at the 1 month follow-up stage. An increase in knowledge (about modes of transmission, and facts relating to the *BRCA1* gene) of approximately 30% was attained in the intervention groups but there was no difference between the three groups in intention to have a *BRCA1* genetic test.

An intervention study without a control group in the USA explored the relationship between psychological distress and requests for genetic testing of the *BRCA1* gene in high-risk families.[77] The researchers contacted 196 people belonging to 11 families taken from a register of families with known hereditary breast cancer. At the baseline, 149 (76%) agreed to a structured telephone interview, and were then given an educational genetic counselling session. Immediately after the counselling session, participants were offered the chance to receive their *BRCA1* test results. This was possible because blood samples taken earlier for other research purposes were available. Fifty-eight per cent of participants asked for the results. Cancer-specific distress (but not global distress) was significantly and positively related to requests for test results. Of these participants in the lowest tertile of cancer-specific distress, only 39% requested their test results. The authors concluded that the distress prompted behaviour that offered the potential for risk reduction, and contrasted this with the results of offering screening for Huntingdon's disease, where distress seems to inhibit requests for test results and there is no potential for risk reduction.

One study used focus groups to explore women's knowledge, perceived benefits, risks and concerns about genetic testing for breast cancer.[78] Eight focus groups (five groups of women diagnosed with breast cancer and three groups of their unaffected relatives) were held to determine what issues affected women's decisions to undergo screening. The findings showed a general lack of knowledge about genetic testing and a strong sense of altruism about being tested to help both family members and other women. The main problems identified were concerns over confidentiality and loss of insurance, a lack of proven options postscreening and the effects on family relationships. Some women perceived the advantages of genetic testing as reducing uncertainty and aiding future decision-making over treatment, surveillance and lifestyle modifications.

A population-based RCT considered the extent to which participation in a cardiovascular screening programme raised health concerns. A group of 2984 middle-aged men and women undergoing cardiovascular risk factor screening was compared with a group of 3576 patients registered with the same general practice who were not offered the screening.[81] In the intervention group, at the 1 year follow-up, 26% had become more positive about their current health; and these changes were strongly related to reductions in the Dundee Risk score. Individuals who felt more positive were those who had lessened their risk of CHD. There was no evidence that participation in screening for hypercholesterolaemia raised concerns about current health or the risk of suffering a heart attack. Participation was seen as reassuring rather than threatening, and perceptions of current health tended to be more optimistic.

Labelling

A Canadian RCT examined the psychosocial consequences of being given a diagnosis of hypercholesterolaemia through a workplace screening programme.[69] Two-hundred and eighty-seven male factory workers with a diagnosis of hypercholesterolaemia and 236 randomly selected

controls without hypercholesterolaemia were studied to test whether there are negative psychological consequences of receiving a diagnosis of hypercholesterolaemia (a labelling effect). Hypercholesterolaemia detection and treatment were not associated with adverse changes in perceptions of psychological or physical health, participation in social or leisure activities or on a global measure of life satisfaction. At 1 year, only about half of the men with hypercholesterolaemia at the baseline considered themselves to have high cholesterol levels. The group whose members did not describe themselves as hypercholesterolaemic had better mental health but a more negative attitude to dietary changes or changes in cholesterol levels than those who accepted the label. The authors concluded that 'denial' was harmful to health although no follow-up cholesterol levels were reported so it is impossible to judge whether these levels had fallen in either group. No discussion of the relative importance of mental health and compliance with dietary advice was provided.

A Norwegian cross-sectional screening study looked at the effect of screening for hypercholesterolaemia in general practice.[70] The authors used a scale questionnaire to measure satisfaction with life but also asked for level of agreement with the statement "I found it unpleasant to be reminded of the risk of heart disease". Over 50% of the subjects agreed with the statement, but no adverse effects on satisfaction with life were evident.

A systematic review considered studies published since 1985. Topics included in the review covered the impact of cholesterol screening, notification of test results and education in terms of psychological distress caused, awareness and knowledge of the disease, and subsequent behaviour change or risk factor reduction.[82] The authors concluded that labelling is not a problem in hypercholesterolaemia screening. They postulate that this could be because, following the earlier experience with hypertension screening, the guidelines for screening providers to incorporate feedback, education and follow-up into the hypercholesterolaemia screenings helped to minimise any negative consequences.

Discrimination/stigmatisation

A UK study examined how insurance companies assess proposals for life insurance from applicants with high cholesterol levels.[83] Forty-nine insurance companies were asked to assess four fictional men, aged 30 years, who wished to apply for life insurance. Two subjects had differing elevated total cholesterol levels, but no other risk factors for CHD, while a third subject had high cholesterol levels, and was an overweight, mildly hypertensive smoker. Another subject had a family history of premature CHD and a presumptive diagnosis of FH. The underwriters offered wide-ranging variations in the excess mortality ratings, but these were mainly restricted to patients with severe hypercholesterolaemia. Some companies applied either no excess or a small excess for the possible FH subject, despite the high cumulative probability of CHD associated with FH.

The Human Genetics Advisory Commission has investigated the issue of genetic discrimination, particularly with respect to life insurance.[84] The commission noted a lack of empirical evidence to support anecdotal reports of discrimination, but concluded that some people were not presenting for a genetic test of a preventable disease due to fear of discrimination, and were thus not benefiting from early detection and treatment. The commission reported that insurers did not use records of one family member in assessing applications from other family members unless it was a joint application.[84] The commission concluded that until the relevant epidemiological and medical data to estimate health and life span are available, insurance companies should respect a moratorium on requiring disclosure of results of genetic tests. The Association of British Insurers (ABI) have adopted a temporary moratorium on the use of genetic tests on policies under £100,000:[59]

> All life insurance members of the ABI have agreed that genetic test results need not be shown in new applications for life insurance up to £100,000 that are directly linked with a new mortgage.

They will, however, continue to expect people to report the results of relevant genetic tests which may result in higher premiums for increased risk:[59]

> Applicants will not be asked to take a genetic test to get insurance. However, when applying for insurance any existing genetic test result must be given to the insurer unless the insurer has said that such information is not required and as long as the application form asks a relevant question.

A cross-sectional survey conducted in the UK sought to gather information on how families in the UK felt that they had been treated by the insurance sector, the medical profession, employers and social services in terms of genetic discrimination.[60] This paper did not attempt to provide an objective measure of genetic discrimination; it obtained perceptions of discrimination. Seven thousand members of seven support groups and 1033

members of the public (the omnibus component) were sent a structured postal questionnaire. Of a response rate of 53%, a third of the members of support groups had experienced problems when applying for life insurance, and 5% of the omnibus group also reported problems. Further analysis was reported on subgroups whose genetic disorder does not affect their health (healthy carriers of a recessive disorder, sex-linked conditions or non-carriers of late-onset disorders). Thirteen per cent of the subgroup study felt that they had been unfairly discriminated against due to a family member's genetic risk, as they did not consider their health to be affected by the condition and they did not present any adverse actuarial risk on genetic grounds.

A case history study in the USA and Canada sought to establish whether genetic discrimination exists and, if so, where this is manifested (for example in health/life insurance or employment restrictions).[85] The aim of the study was to discover whether incidents of genetic discrimination were occurring rather than provide statistically significant data on the extent of discrimination. The authors contacted 1119 professionals who worked in clinical genetics, the social services, disability medicine, paediatrics and genetic counselling, and also placed an advertisement in a genetics journal. The authors describe genetic discrimination as "discrimination against an individual or against members of that individual's family solely because of real or perceived differences from the 'normal' genome of that individual". Forty-two responses were received, of which 29 fitted the authors' criteria for genetic discrimination. A total of 41 incidents of possible discrimination were reported, all but two of which involved insurance or employment issues. Labelling the asymptomatic as 'ill' was a concern, as was the dilemma of whether to present for genetic testing or not due to fear of discrimination. The authors conclude that genetic screening programmes should ensure that confidentiality and privacy are not breached. Legal protection and changes in social attitudes (possibly through effective education and accurate risk assessment) will be needed to ensure that genetic discrimination does not affect people who have a genetic test.

Screening children

While it is clear that adults will benefit in terms of CHD risk reduction from the detection and treatment of FH, the case for screening children is debatable because it is still unknown if the benefit in CHD risk reduction may be outweighed by the long-term risk of drug taking (statins). There are four papers looking at the effects of screening on children.

One Canadian paper reports two observational studies of children with a diagnosis of FH.[74] Fifty-two children aged between 4 and 17 years who attended for diagnostic tests were followed for 1 year. Thirty-four of the children were diagnosed with FH, and 18 were not. The response rate at 12 months was 67%, and at 12 months those children with a diagnosis of FH had significantly higher (worse) scores on the Child Behaviour Checklist (completed by the parents), although these scores had fallen since the first follow-up at 1 month postdiagnosis. The parents of 58 children, who attended a lipid clinic, and had been diagnosed with FH between 2 and 5 years previously, were invited to participate in a cross-sectional interview survey. The response rate was 83%. Children in the cross-sectional survey had a mean Child Behaviour Checklist score that was similar to those of other children with chronic disease, but higher than those of healthy children. The Child Behaviour Checklist scores in both studies were correlated with the mothers' depression and anxiety scores, but not with children's self-report of problems. The authors speculate that it may be that mothers had come to see their children as more vulnerable, and raise a question about where the problem lies: "in the child or in the parent's perception of the child". However, the authors conclude that identification of hyperlipidaemia in children may have harmful psychological effects in the families involved, and that screening children at moderately high risk for hypercholesterolaemia should not be undertaken.

Two papers report studies of children attending a lipid clinic in Oslo. In the first study,[86] reports from teachers and self-reports from young people, together with a semi-structured interview, were administered to 152 children who were aged 7–16 years and had attended the lipid clinic at least once, and to a random population sample of 62 children. Psychosocial scores were similar in the children with FH and the population sample.

Another cross-sectional study from the same lipid clinic considered the psychological concerns of parents and children with FH, and included children who had attended a lipid clinic at least twice.[73] No attempt was made to contact children who failed to keep a second appointment at the lipid clinic. Although it is not stated by the authors, there is probably a large overlap in the subjects of this study and the one described previously.

Parents of 154 high-risk children aged 6–16 years filled in a questionnaire on the psychosocial functioning of the child, including experiences of conflict in the family. One child per family was asked to complete a semi-structured interview on knowledge of FH, reaction to the diagnosis of FH and other related worries. Twenty per cent of the parents felt that FH caused family conflict, and 11% thought that their quality of life would have been improved if the diagnosis had not been made. The authors concluded that most parents do not report psychosocial problems in children with FH and screening should not be postponed due to fears of such problems but, rather, that counselling should be provided to allay concerns. However, the exclusion of children who did not attend two clinic appointments may have excluded some children with more severe problems.

A cross-sectional study in the USA included 36 children (18 with hypercholesterolaemia and 14 with normal cholesterol levels) aged between 8 and 11 years, and focused on the relationship between family functioning, the impact of a diagnosis of hypercholesterolaemia and the family's dietary habits.[75] Respondents were from a largely white, suburban area, and were recruited at their paediatrician's office. Parents and children filled in questionnaires with standard psychological scale questions. The authors concluded that children with hypercholesterolaemia and their families did not differ from their peers on measures of psychological functioning. Concern over negative psychological consequences of cholesterol screening were considered unfounded. There was no attempt to assess the children's understanding of their condition.

Issues raised in the opinion papers

Many papers discuss the potential adverse social and psychological consequences of conventional and genetic screening. The latter in particular is described as raising specific psychological issues:

- Genetic information on FH and similar conditions is probabilistic – it does not provide information about when the disease will occur or to what degree of severity an individual will be affected.
- A positive test indicates a risk of a disease where symptoms may occur only some time in the future, so an individual does not have to cope with immediate stresses of treatment but rather with uncertainty and knowledge of heightened risk.
- Genetic susceptibility is transmitted within families. The impact of genetic screening can go beyond the individual, inducing feelings of guilt, relief and fear of transmission to children.[87]

In most of the reviewed studies it is assumed that as genetic testing for disease susceptibility becomes more widely available, education about risk and meaning of test results will become more important. The specific issues raised by such testing are in addition to other possible adverse psychological consequences of conventional screening such as labelling, excessive awareness of health, anxiety and adopting a more unhealthy lifestyle after a positive test due to feelings of fatalism. Conversely, a negative test can result in a person assuming that they have a 'clean bill of health' and can risk a less healthy lifestyle. This is referred to as the 'certificate of health' effect.[88,89]

Knowledge, information, education and counselling

'Counselling' as referred to in these papers in fact encompassed three types of contact with the patient: educational (informing patients of the prevalence and natural history of a disease), post-test notification (giving the results) and surveillance (monitoring the patient after the results are given).[90] It is assumed in these papers that the more a person knows about the disease and the impact of the screening process, the less the psychological distress will be, but this is not supported by evidence, and remains to be proven.

Education is seen as a way to facilitate decision-making, allowing individuals to understand potential risks and benefits, with the expectation that this will improve adherence. Pretest counselling is recommended to address emotional responses that may impair decision-making about presenting for a genetic test. Many authors assume that counselling and education can provide the patient with accurate risk assessment that would lead to a lesser degree of adverse psychological reactions. One author states that this could increase participation and reduce anxiety.[91] It has been suggested that the way risk information is conveyed can affect psychological distress and, consequently, screening adherence, especially when presenting numerical estimates of the risk,[92] and that health beliefs of individuals or groups must be allowed for when designing an educational programme.[63,93,94]

The need for counselling of patients who receive a negative test result has been suggested in order to reduce paradoxical increases in risk behaviour.[95] It

has been suggested that there is a risk that patients with a positive test will have a sense of fatalism, believing that a positive test implies certain early morbidity and mortality; hence education about the efficacy of treatment is required.[92] It is also suggested that educating the insurance sector may be necessary, as discrimination against an individual with FH is unfounded because of the efficacy of available medication.[84]

According to several papers, many of the undesirable adverse reactions to screening can be avoided or ameliorated by careful attention to patients' needs at each stage of the screening process. This could be ensured by the availability of a written protocol before implementing a screening programme.[96,97] Another paper outlines steps that doctors or counsellors could take in alleviating patient anxiety when notifying patients of their results.[98]

Labelling

Labelling has been described as a problem, most notably in the hypertension-screening studies reported in the 1980s[97,99–101] in which it was shown that screening asymptomatic individuals for hypertension could lead to a range of negative reactions including greater work absenteeism, poorer self-perceived health, depression and psychological distress. These papers describe the putative effects of labelling in two categories. The first is self-stigmatisation or self-labelling, whereby the individual patient will adopt the 'sick role' and impose restrictions on his or her lifestyle now that he or she is aware of their genetic risk.[61,88] The second is labelling by others that can present itself in the form of insurance or employment discrimination or stigmatisation.

Discrimination/stigmatisation

Many authors express fears that if insurance companies obtain an individual's test results, the company might discriminate against the individual and his or her family.[61,84,102,103] This could have cost implications in terms of psychological distress as well as monetary costs of higher insurance premiums.[61,63,104,105] One of the four most common reasons for refusing to undergo a genetic test, according to one paper, is the potential loss of health insurance as a result of a positive test.[94] The potential denial of insurance to high-risk groups leads to a paradox in screening. It is ironic that a programme set up to identify high-risk groups in order to reduce morbidity and mortality may deny those people the healthcare they need.[106] In the UK this would fail to identify those who are likely to be at high risk (e.g. due to awareness of family history), and may apply to private health insurance, life insurance or employment discrimination.

Discussion

We found very few studies which have examined the psychological or social effects of either a clinical or genetic diagnosis of FH. Moreover, there were methodological weaknesses in many of the studies we did find. Problems with labelling and discrimination have been hypothesised, but few data are available to support the existence of such problems. Many authors have called for counselling to be provided at the time of screening, but the nature of the counselling is not specified and no data are available to support the value of counselling.

The generalisability of many of the results of the studies we found is limited by the nature of the populations studied. Subjects were often already being seen regularly by a specialist clinic, or were part of a register specific to their disease, and their knowledge of their disorder would be higher than for other people. This could have affected their psychological reactions.[76] Non-attendance at clinics or for research might be due to distress over the screening process or the diagnosis. This information is missing.

In many studies the follow-up period was short; longer periods of follow-up would allow longer-term psychosocial consequences to be assessed. Almost all the studies were narrowly focused on a limited, and predetermined, range of adverse effects. Relatively few studies explored the issue more widely by giving study participants the chance to describe what they felt the range of negative effects of screening were.[72,78,85] More qualitative work may help reveal a wider and unexpected range of adverse effects of screening.

In the screening programmes studied, pretest education and post-test notification were included in written protocols, but the contents of these sessions were poorly described, and there was variability in what was included. It is not possible to draw conclusions about the value of these 'counselling' sessions. It is important to have research that systematically explores different kinds of educational and counselling interventions and their effects in reducing any deleterious effects from the screening process.

There is an urgent need for qualitative studies to explore potential social and psychosocial effects of

FH screening and quantitative studies of screening uptake and outcomes of screening for treatable inherited disorders such as FH. As genetic screening becomes more widespread, the possible impact of discrimination and stigmatisation will become more important. Low response rates may suggest that discrimination is relatively unimportant but, on the other hand, the low response may reflect patients' reluctance formally to reveal problems incurred, rather than a non-existence of discrimination.

The potential for genetic discrimination requires research. Fear of discrimination has been reported as a barrier to screening, and to maximise uptake and safeguard those taking part, guidelines need to be established that will protect participants' privacy. Further research should be undertaken on whether insurance underwriters would apply excess ratings to a patient with FH who is being successfully treated with statins.

Relevance to FH screening policy

As there was such a scarcity of papers looking specifically at the social and psychological effects of FH screening, the review extended its search to include conventional hypercholesterolaemia screening and genetic breast cancer screening. Many of the papers on cholesterol screening had few or no subjects with a risk of CHD as high as that of people with FH. Conclusions drawn from screening population samples with moderate risk levels cannot necessarily be extrapolated to the very high levels found in FH patients.

Screening for asymptomatic FH is an attractive option because early treatment with statins before symptoms appear would be of benefit. Adverse psychological effects have been reported, but most studies conclude that screening should not be delayed due to these effects since these appear to be relatively minor. Identification of the vulnerable group could facilitate targeting effective and appropriate education and possible counselling to ameliorate deleterious effects, but the utility of this strategy has not been evaluated. Educating the public and insurance sector may also be necessary to avoid unnecessary stigmatisation and discrimination of those testing positive, but, again, the evidence for the existence of stigmatisation and discrimination is weak.

Our review has shown that to date there has not been sufficient sound research undertaken to assess whether or not longer-term and broader social or psychological negative consequences result from screening or from diagnosis. It is important to note, however, that evidence on these effects are weak, not necessarily because thorough investigation has indicated that effects are lacking but rather because little adequate investigation has been undertaken, so that evidence in either direction is very limited.

Summary

The search for data on the adverse psychosocial effects of screening has been disappointing. We found very few data to support the adverse effects of labelling or to support the advantageous effects of providing education and counselling before screening for an inheritable disease, such as FH. Research in this area is urgently needed, but a provisional conclusion based on the weak data is that a diagnosis of FH does not adversely affect the health of adults, although it may affect them financially if insurance companies discriminate against them. There is some (weak) data to support the hypothesis that a diagnosis of FH in childhood arouses adverse anxieties and tensions within families. Unless new and more effective treatments for children become available, there is, at present, little justification for screening before they are old enough to be treated with statins.

Chapter 5

Modelling the cost-effectiveness of screening for FH: methods

A model was constructed to investigate the relative cost and effectiveness of a number of different FH screening strategies. We addressed the following questions:

1. What is the most cost-effective method of detection and treatment of FH? To address this we considered the following alternative methods of detection according to sex and age of identification:
   a. universal population screening
   b. opportunistic (through GPs)
   c. opportunistic (patients suffering an early MI)
   d. case finding though already identified FH patients.
2. Which is more cost-effective: a genetic diagnosis or a clinical diagnosis?

Effectiveness was considered in terms of the number of life-years that would be gained due to identification of FH through one of the screening strategies. The costs of each strategy considered were the screening costs, or programme costs (laboratory costs, staff time, letters, overheads) and the treatment costs (statin treatment and one GP appointment per year until 60 years of age). Expected future cost savings due to reduced incidence of coronary events are also included. Cost-effectiveness is measured in terms of incremental cost (net of cost savings) per year of life gained.

Costs, effects and cost-effectiveness were calculated for each of eight age–sex groups. Overall figures were calculated for each strategy by weighting the result of each age–sex group by the proportion that group would be with respect to the entire target group of the strategy.

Strategies

The strategies that are considered in this report are:

- Universal screening of school leavers at the age of 16 years (referred to as 'universal (16)').
- Universal screening at the ages of 16–55 years (referred to as 'universal').
- Opportunistic screening of people aged 16–55 years who visit their GP for another reason (referred to as 'opportunistic (GP)').
- Opportunistic screening of people who have been admitted to hospital with an early MI (aged 16–55 years) (referred to as 'opportunistic (MI)').
- Case finding of family members of an 'index' patient who has been identified with FH and is attending a lipid clinic (referred to as 'case finding')

The opportunistic (MI) strategy benefits from targeting a group with a higher prevalence of FH. The case-finding approach is even more targeted, but it has additional costs associated with approaching the proband. The universal (16) strategy has the advantage of targeting younger people such that the health benefits are maximised. The opportunistic (GP) strategy benefits from not having any associated invitation costs.

In addition, for each strategy the cost-effectiveness of receiving a clinical or a genetic diagnosis is considered (see the different criteria for FH diagnosis, in chapter 1). So, effectively, ten screening strategies are evaluated.

The protocol

The protocol is very similar for all strategies. It is inevitably less complicated than a real-world screening programme. Confirmation of an FH diagnosis will come at stage 5 (see below), after an individual has had two elevated cholesterol measurements: the first a non-fasting test, and the second a fasting, full lipid profile.

I. Individuals will have a sample of blood taken at their general practice. Ten minutes has been allocated for the initial test. The sample is then sent to a laboratory for a cholesterol test. The universal, opportunistic (MI) and case-finding strategies will incur a cost for invitations to attend a screening.
II. Results letters will be sent to everybody who attended. Those with a high cholesterol level at

the first test will be invited to return to their GP's surgery to give a second blood sample. At this appointment the nurse will interview them about their family history. The appointment lasts half an hour. The blood sample is given for either (a) a fasting, full lipid test that will measure HDL and LDL cholesterol and triglyceride levels or (b) a molecular genetic test to look for FH mutations.

III. All those who attended the second appointment return for an outpatient appointment. Either (a) a lipidologist will make a diagnosis on the basis of the family history, lipid test results and clinical symptoms or (b) a cardiovascular geneticist will make a diagnosis on the basis of the molecular genetic test results.

For the case-finding approach, we have developed an additional protocol for approaching the index patient (proband) and his or her relatives. A practice nurse will invite the proband to a half-hour clinic appointment to explain the aim of the screening programme and ask for the names and contact details of his or her first-degree relatives. The proband will be given an invitation letter to hand to his or her relatives. The relatives are asked to visit their local GP or lipid clinic (whichever is the more convenient) to provide a blood sample for a cholesterol test to be done. In the genetic diagnosis strategy, the proband gives a blood sample to be genetically tested. Only if a mutation is found will that patient's relatives be invited for screening.

The decision model

Figure 2 shows the decision tree on which the computer model is based. The probability of endpoints A, B, C, D, E and F add up to 1. The probabilities at each stage are as follows:

- **Stage 1.** The probability of the person not attending the first round of cholesterol testing. This differs by strategy because attendance will vary according to setting and perceived risk.
- **Stage 2.** The probability of the person attending but receiving a negative result (cholesterol concentration below the cut-off level). This differs by strategy mainly because FH prevalence varies.
- **Stage 3.** The probability of attending stage 1 cholesterol testing, getting a high total cholesterol level but then not attending for stage 2 confirmation testing. Again this differs by strategy because attendance will vary according to setting and perceived risk.
- **Stage 4.** The probability of attending for a second cholesterol test and receiving a negative result (cholesterol concentration below the cut-off level). This is due to biological variation and does not vary by strategy.
- **Stage 5.** The probability of having two cholesterol measurements above the cut-off point but not fulfilling the clinical or genetic diagnostic criteria for FH.
- **Stage 6.** The probability of having two cholesterol measurements above the cut-off point and having FH. This is the probability that a person goes on to treatment for FH.

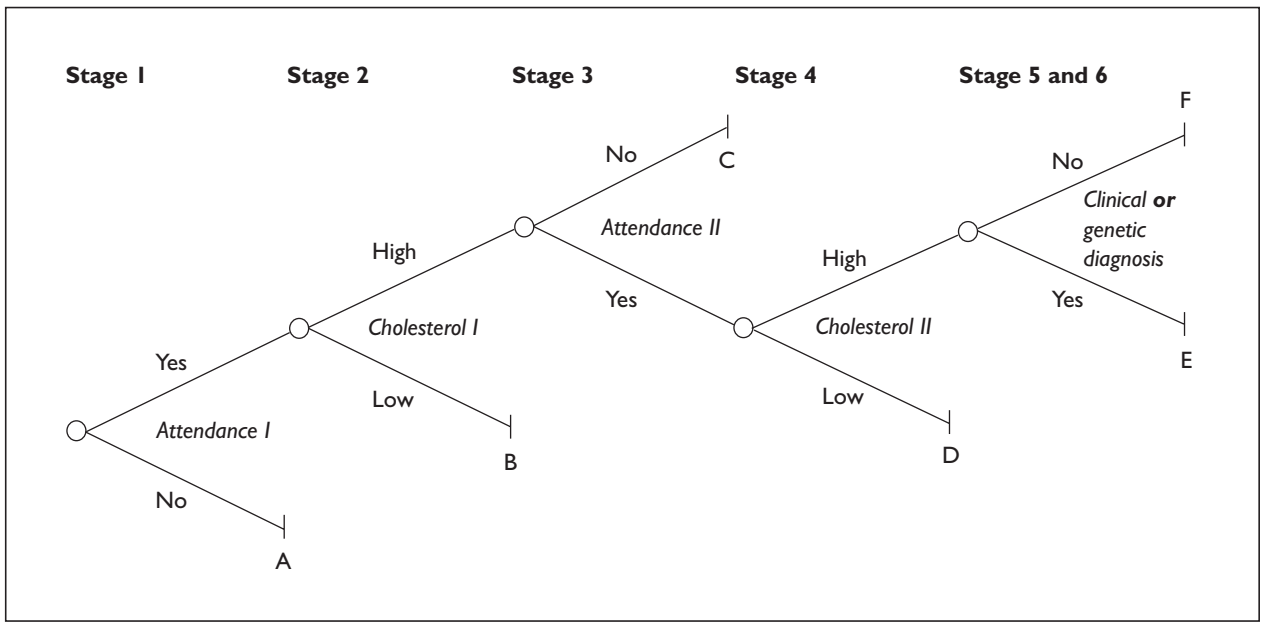

FIGURE 2 *Decision tree used in the modelling*

TABLE 12 *Summary of probabilities (assumed and derived)*

Row	Description	Strategy				
		Notation	**Universal**	**Opportunistic (GP)**	**Opportunistic (MI)**	**Case finding**
1	Prevalence of FH	P(FH)	0.002	0.002	0.05	0.5
2	Probability an individual does not have FH	P(¢FH)	1 – P(FH) = 0.998	1 – P(FH) = 0.998	1 – P(FH) = 0.95	1 – P(FH) = 0.5
3	Probability of a high cholesterol result for a person with FH	P(HC|FH)	0.95	0.95	0.95	0.95
4	Probability of a high cholesterol result for a person without FH	P(HC|′FH)	(P(HC) – P(HC|FH)P(FH))/P(′FH) = 0.0482	(P(HC) – P(HC|FH)P(FH))/P(′FH) = 0.0482	(P(HC) – P(HC|FH)P(FH))/P(′FH) = 0.2563	0.0482
5	Probability of finding a genetic mutation in an FH case	P(M)	0.5	0.5	0.5	1
6	Probability of attending the first appointment (stage 1)		0.55	0.8	0.6	0.95
7	Probability of a high cholesterol result (stage 2)	P(HC)	0.05	0.05	0.291	P(HC|FH).P(FH) + P(HC|′FH).P(′FH) = 0.4991
8	Probability of attending the second appointment (stage 3)		0.75	0.75	0.9	0.9
9	Probability of a low cholesterol result after a high result the first time (stage 4)		0.065	0.065	0.065	0.065
10	Probability of FH given a high cholesterol level (stage 5)	P(FH|HC)	P(HC|FH).P(FH)/P(HC) = 0.038	P(HC|FH).P(FH)/P(HC) = 0.038	P(HC|FH).P(FH)/P(HC) = 0.1632	P(HC|FH).P(FH)/P(HC) = 0.9517
11	Probability of a genetic diagnosis of FH given a high cholesterol level (stage 5)		P(FH|HC)*P(M) = 0.019	P(FH|HC)*P(M) = 0.019	P(FH|HC)*P(M) = 0.0816	P(FH|HC)*P(M) = 0.9517

Probabilities assigned to the stages

Probabilities employed in the modelling were derived from published data sources wherever possible. A probability was defined for each stage of each scenario. *Table 12* summarises the different probabilities used in the model. Some are taken from the literature or assumed on some other evidence, and the remainder (those denoted by a formula) are derived mathematically from the literature. The probability of leaving the programme at a specific end-point is a composite of the individual stage probabilities shown in the table. The sources and derivations, by stage of the model, are detailed below.

Stage 1 (*Table 12*, row 6)

The data sources used to estimate attendance reflect the population being considered. The sensitivity to these assumptions has been tested (see chapter 5).

Universal screening

The percentage of people who agreed to give blood to the nurses in the Health Survey for England was used for stage 1 of the universal approach.[107] Of the 16–64 year old age group, 65.5% agreed to give a blood sample, so this is the figure used for the universal strategy of all ages. For 16–24 year olds the attendance rates were lower (55.0%), so this figure was used for universal (16) screening.

Opportunistic (GP)

The decision for attendance at stage 1 of the opportunistic (GP) approach is based on the current government strategy for other forms of screening (such as cervical smear screening). GPs are set a target rate to screen 80% of eligible patients on their list. If they reach this level, there are financial incentives. We have used 80% attendance for stage 1 attendance in our model of opportunistic (GP) FH screening.

Opportunistic (MI)

Cholesterol levels go down after an MI. They only return to pre-event levels after approximately 3 months. We have to take into account that some will have died since their event, and others may be too ill or reluctant to attend for a routine test. We did not identify any reliable data to estimate what proportion of post-MI patients would attend to give blood, so we have assumed a 65.5% attendance rate, the same as for the universal strategy. This estimate is based on weak evidence, and we have therefore carried out sensitivity analysis using attendance rates of 50 and 80% to explore the robustness of the model.

Case finding

A cholesterol management screening programme of high-risk siblings reported that less than 5% of first-degree relatives refused to take part.[108] We have assumed that 95% of first-degree relatives will attend and provide a blood sample.

Stage 2 (*Table 12*, row 7)

Universal and opportunistic (GP) strategies

The 95th population percentile has been chosen as the cut-off point for the universal and opportunistic (GP) strategies.[58] We would expect the prevalence of FH (and other cholesterol risk factors) in the GP patient population to be similar to that of the general population. Therefore, in the opportunistic (GP) population we would also expect 95% of the population to be below the cut-off.

Opportunistic (MI)

We have only found one study published in 1972 that estimates the proportion of people surviving a premature MI who have elevated cholesterol levels. It was reported that 13.1% of surviving MI patients had high cholesterol levels.[2] This figure was used for the opportunistic (MI) group.

Case finding

Williams and colleagues estimate that 95% of affected first-degree relatives of FH index patients would have levels over 8 mmol/l.[57] So we assumed that 95% of **affected** relatives would have levels above the cut-off (*Table 12*, row 3).

We derived the proportion of **unaffected** relatives with high cholesterol levels using the probability multiplication rule. Assuming 5% of the whole population have high cholesterol and the 95% of those with FH (1 in 500; *Table 12*, row 1) have high cholesterol, then the implication is that only 4.82% of the rest of the population (499 in 500) have high cholesterol (*Table 12*, row 4).

The overall number of relatives who have high cholesterol levels is calculated again using the probability multiplication rule (in standard notation $P(A) = P(A|B) + P(A|'B).P('B)$, or, in the notation of Table 12, $P(HC) = P(HC|FH).P(FH) + P(HC|'FH).P('FH)$). It is therefore the number of high cholesterol counts in the affected branch multiplied by the probability that a person is affected, plus the number of high cholesterol counts among the not-affected branch multiplied by the probability that a person is not affected.

Stage 3 (*Table 12*, row 8)

Of those who had a health screening in the first year of the Oxford and Collaborators' Health Check (OXCHECK) trial of nurse-led health checks, 75% returned for a repeat screen in the fourth year.[109] We have used this figure for the universal and opportunistic (GP) strategy. It may be an underestimate since a much shorter time would elapse between the two visits in this modelled screening programme, but on the other hand, the OXCHECK study made particularly strenuous efforts to encourage re-attendance, which would not happen in routine practice.

Ninety-one per cent returned for a repeat screen in an RCT within a general practice of individuals with cholesterol levels between 6.0 and 8.5 mmol/l.[110] This is the figure that we have used for the case-finding and opportunistic (MI) strategies since the subjects are from a higher risk group (they already had CHD or a relative with FH), so may be more likely to attend.

TABLE 13 *Weightings for age–sex groups*

Age–sex group[a]	Universal (16)		Universal and case finding		Opportunistic (MI)	
	No. (× 1,000)[b]	Percentage	No. (× 1,000)[b]	Percentage	No. (absolute) of events[c]	Percentage
Men, 16 years	332.4	51.3				
Women, 16 years	315.9	48.7				
Men, 16–24 years			3,248.9	11.3	25	0.2
Men, 25–34 years			4,243.5	14.7	289	2.1
Men, 35–44 years			3,699.7	12.8	2,586	18.5
Men, 45–54 years			3,422.4	11.9	8,686	62.2
Women, 16–24 years			3,082.8	10.7	8	0.1
Women, 25–34 years			4,046.3	14.1	51	0.4
Women, 35–44 years			3,625.0	12.6	395	2.8
Women, 45–54 years			3,427.5	11.9	1,916	13.7
Total	648.3	100	28,796.1	100		100

[a] *Age in years*
[b] *England and Wales. Source:* ONS Mortality Statistics – Cause *(DH2 No. 24), Stationery Office, London*
[c] *Source:* Hospital Episodes Statistics. *Department of Health, London*

Stage 4 (*Table 12*, row 9)

The coefficient of biological and analytical variability for cholesterol measurement is estimated to be 6.5%.[111] This is the figure we have used to establish the number of 'true positives' (those who have received two results over the cut-off point).

Stages 5 and 6: clinical diagnosis (*Table 12*, row 10)

For each strategy, the probability of having FH given a high cholesterol level is calculated on the basis of

- the prevalence of FH in the target population (P(FH); *Table 12*, row 1)
- the probability of high cholesterol given FH (P(HC|FH); *Table 12*, row 3)
- the probability of high cholesterol in the target population (P(HC); *Table 12*, row 7)

using Bayes' theorem (in standard notation $P(A|B) = P(B|A).P(A)/P(B)$, or, in the notation of Table 12, $P(FH|HC) = P(HC|FH).P(FH)/P(HC)$). The derivation of the second and third bases has been discussed above. The prevalence of FH in each target population was taken from the literature as follows. The prevalence of FH in the UK population is estimated to be 1 in 500.[1] The prevalence of FH in the premature MI group (under the age of 55 years) has been estimated to be 1 in 8 (12.5%) in one paper[2] and 5% in another.[1] We have used 8.75% prevalence of FH in premature MI patients (the mid-point). The probability of a first-degree relative of a known FH index case having FH is 1 in 2 (50%).

Stages 5 and 6: genetic diagnosis (*Table 12*, row 11)

For the universal and opportunistic strategies the probability of having a diagnosis of FH through genetic confirmation is half that of a clinical confirmation because, as discussed earlier, only half of FH patients have an identifiable mutation. In the case-finding strategy, relatives are only invited if the proband has an identifiable mutation. Therefore, for this strategy, the probability of making a genetic diagnosis is the same as a clinical diagnosis.

Age–sex weightings

In order to calculate an overall cost-effectiveness ratio for each strategy, a weight had to be estimated for each age–sex group that would reflect the size of the group relative to the target population. For each strategy the total number in the general population were taken from the literature and the proportion of the total was calculated. For the universal and case-finding strategies we used the general England and Wales population, and for the opportunistic (MI) strategy the total number of non-fatal events within the International Classification of Diseases, 9th Edition (ICD-9) codes 410–411 under the age of 55 years (*Table 13*). For the opportunistic strategy, the GP-attending population was calculated as the general population in the age–sex

TABLE 14 *Age–sex weightings for opportunistic (GP) strategy*

Age–sex group[a]	General population (× 1,000)[b]	Attendance rate (%)[c]	Attending population	
			No. (× 1,000)[d]	Percentage
Men, 16–24 years	3,248.9	61.9	2,011.7	9.4
Men, 25–34 years	4,243.5	60.7	2,576.7	12.0
Men, 35–44 years	3,699.7	60.7	2,246.5	10.5
Men, 45–54 years	3,422.4	69.2	2,369.0	11.0
Women, 16–24 years	3,082.8	89.4	2,756.6	12.9
Women, 25–34 years	4,046.3	86.5	3,500.5	16.3
Women, 35–44 years	3,625.0	86.5	3,136.0	14.6
Women, 45–54 years	3,427.5	83.1	2,848.3	13.3
Total	28,796.1		21,445.1	100

[a] *Age in years*
[b] *England and Wales. Source:* ONS (1998) Mortality Statistics – Cause *(DH2 No. 24), Stationery Office: London*
[c] *Source:* Morbidity Statistics for England and Wales[108]
[d] *General population multiplied by attendance rate*

TABLE 15 *Comparison of life expectancy calculations of persons with definite FH, before and after treatment, based on Simon Broome Register (A) and 4S survival data (B)*

Age (years)	Data source	Life expectancy (years)			LYGs
		General population[a]	FH untreated[b]	FH treated[b]	
Men					
20	A	75.64	65.83	72.97	7.14
	B			70.63	4.80
45	A	76.86	76.56	76.97	0.41
	B			77.52	0.96
Women					
20	A	80.64	71.93	81.11	9.18
	B			74.87	2.94
45	A	81.37	77.03	82.38	5.33
	B			78.50	1.47

[a] *England and Wales. Source:* ONS (1998) Mortality Statistics – Cause *(DH2 No. 24), Stationary Office: London*
[b] *Scientific Steering Committee on behalf of the Simon Broome Register Group (1991, 1999)*[6,30]

group multiplied by the GP attendance rate for this group (*Table 14*).[112]

Estimating LYGs by statin therapy (effectiveness data)

LYGs attributable to statin use by FH patients were calculated using life tables for different age–sex groups. For each age–sex group, the average life expectancy is taken to be the estimated life expectancy for a person at the mid-point of the particular age range.

The life tables are derived from the spreadsheet used for the British Family Heart Study/ OXCHECK study.[113–115] This spreadsheet was based on a table in the Department of Health report entitled 'Assessing the options: CHD/ stroke' (initially through R Anderson, personal communication).[116]

TABLE 16 *Life expectancy at birth (years) as estimated by the ONS and as estimated in the model*

ONS estimate (1995)[a]	Model estimate[b]
Men	
74.1	74.17
Women	
79.4	79.52

[a] *Government Statistical Service website – UK vital statistics (http://www.statistics.gov.uk/)*
[b] *Using data from the ONS Statbase, UK mortality, 1996*

TABLE 17 *Unit costs*

Cost code	Description	Price (£)	Source
a	Invitation or results letter	0.50	Estimated cost of sending 1.5 letters
b	10 min nurse appointment	4.50	Netten *et al.*, 1998.[120] £27 is the cost per hour of patient contact time – includes salary, on costs, overheads, capital overheads, training and non-contact time
c	Cholesterol test	3.77	Total cholesterol (Diabetes Research Laboratory, Oxford)
d	30 min nurse appointment	13.50	See source for cost code b
e	Full cholesterol test	11.82	£3.77 for total cholesterol, £3.94 for HDL and £4.11 for triglycerides (Diabetes Research Laboratory, Oxford)
f	Outpatient appointment	67.00	Netten *et al.*, 1998.[120] This is the cost of a cardiology outpatient visit – total expenditure including overheads
g	Genetic test (index case)	1000	Clinical Molecular Genetics Laboratory, Institute of Child Health, London
h	Genetic test (family member)	185	Clinical Molecular Genetics Laboratory, Institute of Child Health, London
i	Proband appointments spread across all relatives	4.15	A 30 min nurse appointment (cost code d) plus a letter (cost code a) all divided by the number of invited relatives per proband (3.37)
j	Proband genetic tests spread across all relatives	593.47	The cost of two genetic tests (cost code g) divided by the number of invited relatives per proband (3.37) (the reason why there are two tests instead of one is because for every proband that is found who has a mutation there is another where no mutation is found and no family members screened)

Mortality data from the Simon Broome Register was used to estimate life expectancy. Life expectancy without statin treatment was calculated using register data from 1980 to 1989 since statins were not licensed for use until 1989. Life expectancy with statin treatment was calculated using register data from 1990 to 1998 on the assumption that this represents a cohort of patients treated with statins. In general, the life expectancy estimates of the Simon Broome Register are greater than those derived from statin treatment observed in the 4S study (42% reduction in coronary mortality).[15] For comparison, see *Table 15*.

There were few events in the 1980–89 Simon Broome Register data for the 60–79 year old age group. Consequently, mortality rates based on the combined Simon Broome Register data (1980–98) were used for this age range in both the treatment and non-treatment groups.

In the age ranges 16–19 years and 80–89 years, it is assumed that mortality rates for both treated and untreated FH patients are the same as for the general population (England and Wales, 1997). For the highest age group (90+ years) it is necessary to specify the life expectancy, as there is no age mid-point. It is assumed in the tables that the life expectancy at 'age 90 years' is 94 years for men and 96 years for women. These figures were chosen because the model then produces estimates of UK life expectancy at birth that are almost identical to the 1995 estimates provided by the Office of National Statistics (ONS) (see *Table 16*).

Life expectancy and LYGs are presented both undiscounted and discounted at 1% as recommended by the Treasury (*The Green Book*,[117] see appendix to annex G, paragraphs 14 and 17).

The mortality data used are presented in *Table 33* in appendix 2. *Table 34* in appendix 2 compares the death rates obtained from the different data sets. The life table calculations are outlined in appendix 3.

Programme costs

Table 17 provides a summary of the unit costs of searching for FH individuals, the costs of testing

TABLE 18 *Summary of costs (by strategy and stage)*

Stage	Description	Universal	Opportunistic (GP)	Opportunistic (MI)	Case finding
Stage 1 – clinical confirmation	Invitation	a = £0.50	NA	a = £0.50	a + i = £4.65
Stage 1 – genetic confirmation	Invitation (including testing proband)	a = £0.50	NA	a = £0.50	a + i + j = £598.12
Stage 2/3	First clinic appointment and first cholesterol test	a + b + c = £8.77	a + b + c = £8.77	a + b + c = £8.77	a + b + c = £8.77
Stage 4	Second clinic appointment and second cholesterol test	a + d + e = £25.82	a + d + e = £25.82	a + d + e = £25.82	a + d + e = £25.82
Stage 5/6 – clinical confirmation	Outpatient appointment and diagnosis	f = £67.00	f = £67.00	f = £67.00	f = £67.00
Stage 5/6 – genetic confirmation	Genetic test, outpatient appointment and diagnosis	f + g = £1067.00	f + g = £1067.00	f + g = £1067.00	f + h = £252.00

NA, not applicable

and the costs of confirming the diagnosis. *Table 18* shows where these costs were incurred, by stage and strategy.

The cost of searching at stage 1 is limited to the case-finding and universal approaches. The opportunistic (GP) strategy does not incur a cost of invitation as the person has already presented to the health service.

For the case-finding approach, a nurse would spend half an hour with an index patient, obtaining details of first-degree relatives that could be contacted. The cost of approaching and testing the index patient (proband) is divided by the number of relatives per proband, to give a cost of screening per relative.

The average number of first-degree relatives is not well documented. One source estimates the number of eligible first-degree relatives is 1.56 per proband (although this was restricted to relatives aged between 30 and 59 years of age).[108] This figure comes from a cholesterol management screening of siblings of index cases with elevated LDL cholesterol levels. A 1972 study that followed up the first-degree relatives of 40 post-MI, hypercholesterolaemic patients calculated how many first-degree relatives each proband could provide.[2] There were 230 first-degree relatives still alive (5.75 per proband), and 127 gave a blood sample (3.2 per proband). We used 3.2 relatives per proband, as this study did not have a lower age limit.

Drug costs

Table 19 shows the cost of a 28 day supply of atorvastatin and simvastatin.[118]

We have assumed that 70% of newly diagnosed patients would be treated with simvastatin (40 mg daily to start), and 30% would be on atorvastatin (20 mg daily) (estimate based on clinical experience of one author (AN)). Jones and colleagues have shown in the CURVES study[19] that these doses have very similar mean reductions in LDL cholesterol levels in an 8 week randomised parallel group trial in 522 hypercholesterolaemic patients. 4S[15]

TABLE 19 *Current statin costs in the UK*[114]

Atorvastatin (Lipotor®) up to 80 mg max.	10 mg per 28, £18.88 20 mg per 28, £30.30 40 mg per 28, £47.04
Simvastatin (Zocor®) up to 40 mg max.	10 mg per 28, £18.03 20 mg per 28, £29.69 40 mg per 28, £29.69

prescribed 40 mg of simvastatin to those whose cholesterol levels were out of the range of the treatment goal of 3.0–5.2 mmol/l.

A year's supply of simvastatin (40 mg daily) is £387.03,[118] and a year's supply of atorvastatin (20 mg daily) is £394.98. If 70% of patients are on simvastatin (£270.92) and 30% of patients on atorvastatin (£118.49), the average cost of a year's treatment is £389.41. The annual unit cost of statin treatment is £411.24. This includes 10 minutes of GP contact time to allow for seeing the patient and writing repeat prescriptions (£21.83, which is 0.17 of £131 per hour)[120] (this is the cost per hour of patient contact time – it includes net remuneration, practice expenses, capital overheads and non-contact time).

The expected cost of drugs over a patient's lifetime was calculated using the same life table as for life expectancy. This was done separately for each age–sex group, once each for the intervention group, and again for the comparison group. The annual cost of £389.41 for drugs plus £21.83 for an annual 10 minute GP consultation was attributed to 82% of the population for every year until death or until 60 years of age was reached (whichever comes sooner). As our model does not incorporate any health effect after the age of 60 years, we have excluded drug costs after 60 years of age as well. It was assumed that 5% of individuals were already taking statins at the time of diagnosis (estimate based on personal clinical experience of one author (AN)). Therefore, the incremental drug costs (those incurred as a result of the screening programme) are 95% of the statin costs for the treatment group.

Due to small sample size, mortality in the untreated FH cohort could not be estimated with any precision over the age of 60 years, so we have assumed for the purposes of the evaluation that

- statin treatment ceases at the age of 60 years, and therefore
- there are no mortality reductions after the age of 60 years, and
- there are no drug costs after the age of 60 years.

This does not mean that we advocate ceasing drug treatment at 60 years of age, merely that we feel that the data is not adequate at present to estimate the cost-effectiveness of treating this patient group. If we had included treatment of this group, then overall cost-effectiveness of the screening programmes might have marginally increased or decreased depending on the effectiveness of statins in this subgroup. Assuming statins are effective at older ages, then our comparison of screening programmes is biased in favour of programmes that start screening at a younger age, as these cohorts will have longer to accumulate the benefits of statin treatment.

The drug costs were discounted at a rate of 6%, in line with Treasury guidelines.[121]

CHD event costs

The mean cost (to the NHS) of a coronary event (fatal or non-fatal) has been estimated to be £1543. This figure includes inpatient stays (with tests and procedures) and a 6 month follow-up (including outpatient attendance, primary care and drug costs) – see appendix 4.

The expected cost of coronary events over a patient's lifetime was calculated using the same life table as for life expectancy and drug costs. This was done separately for each age–sex group, once each time for the intervention group and again for the comparison group. The proportion of deaths attributable to CHD at different age ranges was taken from the Simon Broome Register data set (see appendix 2). The number of non-fatal events was calculated as a ratio of non-fatal to fatal events. This ratio was provided by the Oxford Myocardial Infarction Incidence Study (OXMIS) based on residents in the Oxfordshire Health District.[123] The age-standardised ratio of non-fatal to fatal events was 1.4 in men and 1.2 in women.

The CHD costs were discounted at a rate of 6%: the same discount as used for drug costs.

Sensitivity analyses

Sensitivity analyses were performed to check the robustness of our results since we have had to make a number of assumptions. This is either because there has not been any recent reliable epidemiological data or because the input assumptions are likely to change in the future. We chose five areas where we think our estimates are most likely to alter with changing circumstances or the emergence of new data. These areas are the effectiveness of genetic screening in identifying mutations, drug costs, the average number of relatives per proband, rates of attendance for blood tests and the discount rate applied.

The proportion of mutations that are identifiable in a genetics laboratory may not reflect a realistic

TABLE 20 *Examples of generic drug costs and their trade-named equivalents*

Cimetidine 400 mg tablets	60-tablet pack	£6.14	27% of proprietary equivalent
Tagamet® 400 mg tablets	60-tablet pack	£22.62	73% reduction in price
Ranitidine 150 mg	60-tablet pack	£17.43	63% of proprietary equivalent
Zantac® 150 mg	60-tablet pack	£27.87	17% reduction in price
Atenolol 100 mg	28-tablet pack	£1.22	18% of proprietary equivalent
Tenormin® 100 mg	28-tablet pack	£6.81	82% reduction in price

situation in non-research genetics laboratories. If genetic screening for FH were to be a national policy, it might not be feasible for laboratories outside a research setting to test for every mutation identified in this country. The possibility is that only the most common mutations would be searched for, so our model has to take this into account. As technology improves, the chances of identifying more mutations could increase. The sensitivity analysis will test the likelihood of identifying mutations in 30 and 70% of FH patients who fit the criteria for FH in our model to assess both of these options.

As the patent on simvastatin is due to expire soon, the costs of generic statins will probably decrease. Estimates of how generic statins might reduce the drug costs are based on the costs of three commonly prescribed drugs where both the generic drug and the trade-named equivalent are available. The average proportionate difference in price has been used to estimate what the generic statin price might be (*Table 20*), when the patent on these drugs expires. The end dates for the patents on three main statin drugs are 1 February 2001 for simvastatin, 9 August 2004 for pravastatin and August 2008 for atorvastatin (Drug Information Unit, Northwick Park and St Mark's NHS Trust, personal communication). We have tested a 73 and a 37% reduction in the cost of statins.

The third area where a sensitivity analysis has been performed is on the number of first-degree relatives that an index patient might provide. We have found three studies that report on the number of first-degree relatives, although they all have limitations. In one paper we are told how many relatives attended the lipid clinic to provide a blood sample, but not how many first-degree relatives there were.[66] In another, the screening was limited to relatives' ages of 30–59 years,[108] and the third paper was published in 1972, and family size and structure has changed since then, as well as there now being more population diversity.[2] The range from the papers above is 1.3–5.6 relatives per proband.

The fourth area where the robustness of the model has been tested is the attendance rates at the first and second blood test. Attendance of 50 and 80% for all strategies has been tested. The 80% rate is the current government target for cervical and breast cancer screening strategies. These rates have been applied to all screening strategies (not only opportunistic (GP) as in the baseline model).

Finally, a sensitivity analysis was performed on the discount rate used in the costs and benefits. Following the recommendations of the Washington Panel, a 5% discount rate was applied to both the costs and benefits.

Chapter 6

Modelling the cost-effectiveness of screening for FH: results

Life expectancy

Table 21 shows life expectancy (expected age at death, not the expected number of years remaining) with and without treatment for selected age and sex groups. For comparison, life expectancy for the general population is indicated for selected age and sex groups.

Expected age at death increases with age and is greater for women than for men in every age group. Expected age at death with untreated FH ranges from 65.6 years for a 16 year old male to 83.6 years for a 60 year old woman. Expected age at death with treated FH ranges from 72.8 years for a 16 year old male to 83.6 years for a 60 year old woman. Life expectancy for treated and untreated cohorts converges after age 60 years, because both cohorts share the same death rates for the ages of 60 years and above.

The data from the Simon Broome Register cohort[30] indicate that there is no excess mortality in FH patients after 60 years of age. Indeed, *Table 21* shows an expected age at death in the female treated FH group, and in the older treated FH males, which is higher than that of the general population. Moreover, untreated FH males and females had a higher life expectancy than the general population from the ages of 60 and 55 years, respectively (see appendix 2 for a comparison of death rates). This apparent contradiction might be explained by the selective nature of the cohort from which the probabilities of death were derived. The Simon Broome cohort is based on the minority of FH cases in which a person is diagnosed, and attends a specialist lipid clinic. It is possible that such people, while experiencing the expected higher rates of early coronary mortality, might experience lower rates of other fatal diseases. For example, it had been shown that the Simon Broome Register cohort has a low prevalence of current smokers (16.4% of men and 20% of women[30]), and it could therefore be expected that the cohort has relatively low death rates from lung cancer, and chronic obstructive lung disease.

LYGs are calculated as life expectancy with treatment minus life expectancy without treatment. Estimated LYGs from statin treatment in patients with FH are 0.26 year for males aged 50 years, but are 7.11 years for a 16 year old male (*Table 22*). Likewise, for females, LYGs ranged from 3.41 years at 50 years old to 9.17 years at 16 years old.

TABLE 21 *Life expectancy of persons with definite FH, before and after treatment (selected ages)*

	Life expectancy (years)		
Age (years)	**General population**	**FH untreated**	**FH treated**
Men			
16		65.64	72.76
20	75.64	65.83	72.97
35		72.96	75.05
45	76.86	76.56	76.97
55		79.11	79.23
60	78.84	80.13	80.13
Women			
16		71.87	81.04
20	80.64	71.93	81.11
35		73.96	81.69
45	81.37	77.05	82.38
55		81.63	83.26
60	82.86	83.61	83.61

TABLE 22 *Life expectancy of persons with definite FH*

Age at diagnosis (years)	Mid-point (years)	Life expectancy (years)			Life expectancy discounted (years)		
		Untreated	Treated	Increment	Untreated	Treated	Increment
Men							
16	16	65.64	72.76	7.11	53.37	58.18	4.82
16–24	20.5	66.09	73.05	6.97	55.11	60.13	5.02
25–34	30	70.72	74.42	3.70	62.08	64.87	2.79
35–44	40	75.05	75.62	0.57	68.63	69.06	0.43
45–54	50	77.92	78.18	0.26	73.63	73.85	0.21
Women							
16	16	71.87	81.04	9.17	57.42	63.03	5.60
16–24	20.5	72.01	81.14	9.13	59.19	65.12	5.92
25–34	30	73.35	81.51	8.16	63.86	69.48	5.62
35–44	40	74.51	81.84	7.33	67.91	73.42	5.51
45–54	50	79.44	82.85	3.41	74.56	77.31	2.75

TABLE 23 *Number of 20 year old FH males and females surviving to various ages based on the life tables*

Age (years)	No. of individuals surviving	
	Untreated	Treated
Men		
20	1000	1000
40	795	942
60	661	801
80	400	484
Women		
20	1000	1000
40	972	986
60	687	934
80	493	670

Discounted LYGs are by definition smaller than undiscounted gains: 0.21 year for males aged 50 years and 2.75 years for females aged 50 years (*Table 22*). The discounted life-year gains were lower for 16 year olds than for 20 year olds because the treatment effect in the model only starts at the age of 20 years.

Table 23 shows the number of people from a hypothetical cohort of 1000 males with FH who would survive to various ages. For example, if untreated, one-third of 20 year olds would die before they reach the age of 60 years. With treatment, only 1 in 5 will die before reaching the age of 60 years.

Table 15 compares the estimates of LYGs assuming the treatment effect shown in the 4S trial data[15] compared with the Simon Broome Register data[30] (the baseline results). This is illustrated for men and women aged 20 and 45 years. With the exception of men aged 45 years, the 4S treatment effect is smaller than the effect predicted using the Simon Broome Register data.

By assumption, the age- and sex-related number of LYGs per case found was the same for each screening strategy; however, overall LYGs (see *Table 26*) varies between strategies because the age and sex profiles vary between strategies. The smallest estimate of the number of LYGs (1.1 years) was for the opportunistic (MI) screening strategy, because the target population is the oldest and has the largest proportion of men. The largest estimate of the number of LYGs was for the universal (16) screening strategy, where 8.1 years would be gained. Thus, those people with FH who are still relatively young and have a high life-time risk have most to gain from statin treatment.

Number needed to screen

The number needed to screen indicates how many people would need to be invited for screening to identify one FH positive case. This figure varies by screening strategy and by the prevalence of FH in the population being screened. Other things being equal, the higher the prevalence within a particular group the lower the number needed to screen to identify one case. In addition, the higher the attendance rate the lower the number need to screen, because the likelihood of identifying the case within the population would be optimised if more people within that group present for screening.

TABLE 24 *Number needed to be invited to screening, cost per person screened in all stages and programme costs to detect one FH case*

Screening type	No. needed to screen to find one case	Cost per person screened in all stages (£)	Cost per case detected (programme cost) (£)
Clinical confirmation			
Universal (16)	1,364.6	7.15	9,754.41
Universal	1,145.9	8.42	9,645.03
Opportunistic (GP)	938.2	9.67	9,072.10
Opportunistic (MI)	21.6	13.15	283.90
Case finding	2.6	51.16	133.24
Genetic confirmation			
Universal (16)	2,729.2	26.43	72,140.39
Universal	2,291.7	31.38	71,921.64
Opportunistic (GP)	1,876.3	37.72	70,775.78
Opportunistic (MI)	43.2	86.16	3,719.68
Case finding (relatives only)	2.6	125.79	327.62 (excluding cost of testing proband)
Case finding (relatives plus cost of finding index patient mutation)		719.26	1,873.34 (including cost of testing proband)

The results of the number needed to screen range from 2.6 people screened to identify one case (case-finding strategy) to 2729 people screened for one case found with an identifiable mutation in a universal strategy (*Table 24*).

Case finding is the most effective strategy to find a case in terms of a lower number needed to screen. This is because the case-finding strategy follows up relatives of known FH cases, and the probability of a first-degree relative of an index case having FH is 1 in 2. The opportunistic (MI) strategy with a clinical confirmation is the next most effective, as the prevalence of FH within the premature MI population is higher than in the general population. Although the groups screened in the opportunistic (GP) and universal strategies have the same prevalence of FH, the Universal strategy is less effective because we have assumed it has a lower attendance at stage 1.

Genetic confirmation in a heterogeneous population not considered at high risk of FH is less effective in finding cases than clinical confirmation. Currently, the probability of identifying a genetic mutation in individuals where a mutation has not already been identified in the family is only 50%. Double the number of people will need to be screened to find one individual with a genetic mutation, if confirmation of FH is ascertained on genetic rather than clinical criteria.

Programme costs

The cost per case detected (or programme cost) is calculated by multiplying the number needed to screen to find one case by the cost per person invited for screening (described in chapter 5). The cost per person invited for screening ranged from £7.15 for universal screening up to £51.16 for case finding with clinical confirmation (*Table 24*). The more targeted the strategy the greater the cost per person screened. This is because, in the less targeted strategies, more people drop out at an early stage and therefore do not incur costs in the later stages of screening. For example, the prevalence of high cholesterol levels is highest in the case-finding strategy, so more individuals will have to have a second cholesterol test and a confirmation of diagnosis.

The cost per person invited has an inverse relationship with the number needed to screen, such that the lower the cost per person invited the higher the number needed to be invited (*Table 24*). Both are determined, inversely, by the prevalence of FH, the prevalence of high cholesterol levels and attendance

rates. Cost per person invited is also dependent on the cost at each stage (see appendix 5).

The cost per new patient detected with FH using clinical confirmation ranged from £133 (case-finding strategy) to £9754.41 (universal screening) (*Table 24*). Clearly, the effect of number needed to screen outweighs the effect of cost per person screened such that the more targeted the strategy, the lower the cost per case found. Costs only differ between the universal and the universal (16) strategies because the latter has a lower attendance rate for the first appointment.

Cost per case found was considerably higher for all strategies when genetic confirmation was used, not only because the cost per person screened increases but also because the number needed to screen increases. A substantial part of the cost of case finding was for genetically testing the probands. Using genetic confirmation, the cost per case found ranged from £1873 for case finding to £72,140 for universal (16) screening.

Drug costs

The lifetime drug cost for diagnosed individuals was higher for women than for men (*Table 25*) because of the higher mortality of men before the age of 60 years, and, similarly, drug costs were higher when the presumed age at diagnosis was younger. However, the process of discounting puts a lower weight on the cost of drugs consumed in the future relative to drugs taken in the present, so the differences in lifetime drug costs are reduced. The discounted lifetime cost of use of statins up to the age of 60 years varied from £2399 for males aged 50 years at diagnosis to £5136 for females aged 16 years at diagnosis.

Incremental drug costs are those costs incurred after screening but not incurred in the absence of screening. If we assume that 82% of cases found are prescribed and treated with statins, this is partially offset by the 5% of patients who would already be taking statins without the screening programme. Incremental drug costs were assumed to be 95% of the drug cost of diagnosed individuals.

By assumption, the age- and sex-related incremental drug cost per case found was the same for each screening strategy, so the overall drug costs varied between the strategies only because the age and sex profile varied. The smallest incremental drug cost was for patients identified in the opportunistic (MI) screening strategy, because the target population for this strategy would be predominantly in the 45–54 year age band, with a larger proportion of men than the other strategies. The largest incremental drug cost was for the universal (16) screening strategy.

CHD event costs

Based on our life tables (see appendix 3), 562 untreated 16 year old males with FH, from a cohort of 1000, will die of CHD and there will be another 787 non-fatal coronary events during their lifetimes. But if they are treated with statins, there will be 446 coronary deaths and 624 non-fatal coronary events. The number of events will be lower for cohorts at higher ages because these individuals are exposed for a shorter period of time. However,

TABLE 25 *Cost per person of drug treatment and coronary events (discounted at 6%)*

Age at diagnosis (years)	CHD event costs (£)			Drug costs (£)	
	Untreated	Treated	Increment	Treated	Increment
Men					
16	413.38	134.28	–279.10	5009.74	**4759.25**
16–24	522.22	171.49	–350.72	4820.77	**4579.73**
25–34	497.50	241.30	–256.20	4434.35	**4212.63**
35–44	397.37	370.02	–27.35	3660.25	**3477.24**
45–54	486.56	467.70	–18.86	2399.22	**2279.26**
Women					
16	176.53	59.75	–116.78	5135.81	**4879.02**
16–24	225.54	76.70	–148.83	4979.62	**4730.64**
25–34	283.36	106.02	–177.33	4578.54	**4349.61**
35–44	384.94	158.93	–226.00	3794.87	**3605.12**
45–54	403.83	246.03	–157.80	2453.62	**2330.94**

TABLE 26 *Cost-effectiveness of different FH screening strategies (clinical diagnosis)*

Strategy	Age–sex group		Weighting for age–sex group (%)	Undiscounted LYGs	Undiscounted cost per LYG (£)	Discounted at 1% LYGs	Cost per LYG (£)
	Sex	Age (years)					
Universal (age 16 years)	Men	16	51.3	7.1	2,002	4.8	2,954
	Women	16	48.7	9.2	1,582	5.6	2,591
	All		100.0	8.1	**1,798**	5.2	**2,777**
Universal (age 16–54 years)	Men	16–24	11.3	7.0	1,992	5.0	2,766
		25–34	14.7	3.7	3,671	2.8	4,883
		35–44	12.8	0.6	23,131	0.4	30,253
		45–54	11.9	0.3	46,239	0.2	56,424
	Women	16–24	10.7	9.1	1,559	5.9	2,402
		25–34	14.1	8.2	1,693	5.6	2,457
		35–44	12.6	7.3	1,777	5.5	2,363
		45–54	11.9	3.4	3,461	2.8	4,293
	All		100.0	4.9	**10,269**	3.5	**13,029**
Opportunistic (GP) (age 16–54 years)	Men	16–24	9.4	7.0	1,909	5.0	2,651
		25–34	12.0	3.7	3,517	2.8	4,677
		35–44	10.5	0.6	22,119	0.4	28,930
		45–54	11.0	0.3	44,014	0.2	53,709
	Women	16–24	12.9	9.1	1,496	5.9	2,305
		25–34	16.3	8.2	1,623	5.6	2,355
		35–44	14.6	7.3	1,699	5.5	2,259
		45–54	13.3	3.4	3,294	2.8	4,085
	All		100.0	5.2	**8,909**	3.7	**11,310**
Opportunistic (MI) (age 16–54 years)	Men	16–24	0.2	7.0	648	5.0	900
		25–34	2.1	3.7	1,145	2.8	1,522
		35–44	18.5	0.6	6,595	0.4	8,626
		45–54	62.2	0.3	9,882	0.2	12,058
	Women	16–24	0.1	9.1	533	5.9	822
		25–34	0.4	8.2	546	5.6	792
		35–44	2.8	7.3	500	5.5	665
		45–54	13.7	3.4	720	2.8	893
	All		100.0	1.1	**7,513**	0.8	**9,281**
Case finding (age 16–54 years)	Men	16–24	11.3	7.0	626	5.0	870
		25–34	14.7	3.7	1,104	2.8	1,468
		35–44	12.8	0.6	6,329	0.4	8,278
		45–54	11.9	0.3	9,297	0.2	11,344
	Women	16–24	10.7	9.1	517	5.9	796
		25–34	14.1	8.2	527	5.6	766
		35–44	12.6	7.3	479	5.5	637
		45–54	11.9	3.4	675	2.8	838
	All		100.0	4.9	**2,420**	3.5	**3,097**

the number of events will not be much lower because the highest risk is at older ages. Of a cohort of 1000 untreated 50 year old males with FH, 414 will die of CHD and there will be another 580 non-fatal coronary events during their lifetimes. These figures are slightly lower if treated (to the age of 60 years): 410 deaths and 574 non-fatal coronary events.

Undiscounted lifetime CHD event costs will be higher for younger age groups than for older ones because the former groups can expect more events during their remaining lifetime. However, the effect of discounting works in the other direction. It puts a low weighting on events in the distant future and a high weighting on those occurring nearer to the present so that the lifetime cost of

CHD events is reduced for young age groups relative to older ones. Consequently the pattern of CHD event costs is reversed for women and for treated men, so that the lower the age group the lower the discounted lifetime CHD cost (see *Table 25*). And for untreated men there is no longer a clear age trend. CHD costs were lower for women than for men because of their lower risk. The lowest discounted lifetime cost was £59.75 for treated women aged 16 years. The highest cost was £522.22 for untreated men aged 16–24 years.

Because treatment with statins was assumed to reduce the number of fatal and non-fatal coronary events there was a net saving on treatment in every scenario and for all age and sex groups (*Table 25*). The largest cost-savings were for men aged 16–24 years (£351 per case found), and the smallest savings were for men aged 45–54 years (£19 per case found). By assumption, the savings on CHD treatment per case found was the same for each age and sex group in each strategy, but the overall cost savings vary between the strategies because the age and sex profile varies between strategies. The smallest treatment cost savings were for the opportunistic (MI) screening strategy and the largest for the universal (16) screening strategy.

Cost-effectiveness

Clinical diagnosis

LYGs, drug costs, CHD costs and programme costs all contribute to the overall cost-effectiveness ratio. Results presented in this section refer to the cost per **discounted** LYG. Regardless of strategy, screening women is more cost-effective than screening men because women appear to gain more from treatment (*Tables 26* and *27*). Within each strategy, it is more cost-effective to screen younger men than older ones mainly because younger men have more to gain (the age pattern was not quite so clear for women). Consequently, inviting all 16 year olds for universal testing is more cost-effective than any of the other strategies compared despite the higher costs involved in longer-term treatment with statins.

Opportunistic (MI) screening was the least cost-effective strategy because it had the oldest population with the largest proportion of men. When the results are subdivided by age and sex group, a different pattern emerges. Universal screening is the least cost-effective strategy, followed by opportunistic (GP) screening and then opportunistic (MI) screening. The strategies that targeted higher-risk groups were the most cost-effective. For men, the most cost-effective strategy was case finding, identifying male relatives aged 16–24 years (£870 per LYG) and the least cost-effective was universal screening of males aged 45–54 years. For women, the most cost-effective strategy was case finding of the 35–44 year age group (£637 per LYG). The least cost-effective strategy for women was universal screening for those aged 45–54 years. Identifying 16 year olds in a case-finding strategy is approximately three times more cost-effective than identifying them through a universal or opportunistic (GP) approach.

The cost-effectiveness seems to be driven by the number of LYGs. Consequently, all of the least cost-effective screenings are for men aged over 35 years. Screening of women aged 35–44 years is the most cost-effective because they have large life-year gains (7.0 years per case found), and their drug costs are lower than cases identified at an earlier age (see *Table 25*).

Genetic diagnosis

Screening strategies using genetic diagnosis were less cost-effective than the same strategy with clinical diagnosis (*Table 27*). For example, a case finding cost of £3300 per LYG using genetic confirmation (where the mutation is already known in the proband) compared with £3097 per LYG for a clinically diagnosed case-finding approach. This is because we do not assume any additional benefit from genetic testing, yet it creates additional costs. These extra costs are magnified when a mutation is not found and a genetic diagnosis is not made even though the patient may have clinically defined FH.

The pattern across the genetic diagnosis strategies was similar to that of clinical diagnosis. The exception is that universal (16) screening is no longer more cost-effective than case finding. The reason for this switch is because in strategies other than case finding, twice as many individuals now have to be invited for screening to find one case because a mutation can only be detected in 50% of cases.

The case-finding approach is more cost-effective if a mutation is already known, because the cost of testing the proband is not incurred. Screening 16 year old male relatives in a case-finding strategy costs £908 per LYG where the mutation is known and £1216 per LYG where the mutation is not yet known.

A summary comparing the cost-effectiveness of overall clinical and genetic strategies is provided in *Table 28*.

TABLE 27 *Cost-effectiveness of different FH screening strategies (genetic diagnosis)*

Strategy	Age–sex group		Weighting for age–sex group (%)	Undiscounted LYGs	Undiscounted cost per LYG (£)	Discounted at 1% LYGs	Cost per LYG (£)
	Sex	Age (years)					
Universal (age 16 years)	Men	16	51.3	7.1	10,775	4.8	15,901
	Women	16	48.7	9.2	8,383	5.6	13,726
	All		100.0	8.1	**9,610**	5.2	**14,842**
Universal (age 16–54 years)	Men	16–24	11.3	7.0	10,932	5.0	15,179
		25–34	14.7	3.7	20,481	2.8	27,238
		35–44	12.8	0.6	133,138	0.4	174,132
		45–54	11.9	0.3	288,113	0.2	351,576
	Women	16–24	10.7	9.1	8,381	5.9	12,917
		25–34	14.1	8.2	9,322	5.6	13,530
		35–44	12.6	7.3	10,274	5.5	13,661
		45–54	11.9	3.4	21,701	2.8	26,915
	All		100.0	4.9	**61,661**	3.5	**78,060**
Opportunistic (GP) (age 16–54 years)	Men	16–24	9.4	7.0	10,768	5.0	14,951
		25–34	12.0	3.7	20,171	2.8	26,827
		35–44	10.5	0.6	131,114	0.4	171,485
		45–54	11.0	0.3	283,663	0.2	346,146
	Women	16–24	12.9	9.1	8,255	5.9	12,724
		25–34	16.3	8.2	9,182	5.6	13,326
		35–44	14.6	7.3	10,118	5.5	13,453
		45–54	13.3	3.4	21,366	2.8	26,499
	All		100.0	5.2	**55,283**	3.7	**70,009**
Opportunistic (MI) (age 16–54 years)	Men	16–24	0.2	7.0	1,141	5.0	1,584
		25–34	2.1	3.7	2,072	2.8	2,756
		35–44	18.5	0.6	12,665	0.4	16,564
		45–54	62.2	0.3	23,226	0.2	28,342
	Women	16–24	0.1	9.1	909	5.9	1,402
		25–34	0.4	8.2	967	5.6	1,403
		35–44	2.8	7.3	969	5.5	1,288
		45–54	13.7	3.4	1,726	2.8	2,141
	All		100.0	1.1	**17,116**	0.8	**21,106**
Case finding (age 16–54 years) (excluding cost of testing proband)	Men	16–24	11.3	7.0	654	5.0	908
		25–34	14.7	3.7	1,156	2.8	1,538
		35–44	12.8	0.6	6,673	0.4	8,727
		45–54	11.9	0.3	10,052	0.2	12,266
	Women	16–24	10.7	9.1	538	5.9	829
		25–34	14.1	8.2	551	5.6	800
		35–44	12.6	7.3	506	5.5	672
		45–54	11.9	3.4	732	2.8	908
	All		100.0	4.9	**2,580**	3.5	**3,300**
Case finding (age 16–54 years) (including cost of testing proband)	Men	16–24	11.3	7.0	876	5.0	1,216
		25–34	14.7	3.7	1,574	2.8	2,093
		35–44	12.8	0.6	9,403	0.4	12,298
		45–54	11.9	0.3	16,055	0.2	19,591
	Women	16–24	10.7	9.1	707	5.9	1,090
		25–34	14.1	8.2	741	5.6	1,075
		35–44	12.6	7.3	717	5.5	953
		45–54	11.9	3.4	1,185	2.8	1,470
	All		100.0	4.9	**3,856**	3.5	**4,914**

Sensitivity analysis

Sensitivity analyses have been performed in five areas (*Tables 29* and *30*). The number of relatives per proband was reduced to 1.31 and increased to 5.75. This only affects the case-finding approach, as the yield of relatives per index patient could have an impact only on the effectiveness of this strategy. For the clinical and genetic case-finding approach where the cost of testing the proband is not included (relatives only), there is very little change in the cost per LYG. Where the cost of the genetic test of the proband is included, the cost-effectiveness does change. With fewer relatives per probands, there is a 38% increase in the cost per LYG and where there are more relatives per proband the cost per LYG reduces by 11%. No changes were identified in the relative cost-effectiveness ratios between or within the strategies as a result of changing these assumptions.

The number of identifiable mutations affects all the genetic confirmation strategies apart from case finding of relatives only. This is because once a mutation has been identified in a family member, an unequivocal genetic diagnosis can be made in the relative. If the number of identifiable mutations falls to 30%, there is an increase of approximately 60% in the cost per LYG for the universal and opportunistic (GP) strategies and a 17% increase for the case-finding strategy (including the cost of proband testing). Where the number of identifiable mutations increased, there was a 7% decrease in cost per LYG for the case-finding approach, 15% decrease for the opportunistic (MI) strategy and a 27% decrease for the other two strategies. The order of the cost-effectiveness does not change between the strategies.

The third area that we have adjusted is the cost of genetic testing. A fall of 50% does not alter the order of cost-effectiveness within or between the strategies but there is a reduction of approximately 35% in the universal and opportunistic strategies and a 15% reduction in the case-finding approach that includes the cost of proband testing.

The next area of uncertainty tested was a reduction in the cost of statins. A reduction in the statin price should follow the end of the patent period (from 2001), and we have estimated a 37 and 73% drop in price. This reduction has resulted in a big effect on the strategies with the lowest programme costs (the case-finding and opportunistic (MI) strategies). If the statin price were to fall, then the

TABLE 28 *Comparison of the overall cost-effectiveness of clinical and genetic strategies*

Strategy	Cost per LYG (clinical) (£)	Cost per LYG (genetic) (£)
Universal (16)	2,777	14,842
Universal	13,029	78,060
Opportunistic (GP)	11,310	70,009
Opportunistic (MI)	9,281	21,106
Case finding	3,097	3,300 (relatives **only**: proband with known mutation) 4,914 (cost of testing proband included)

TABLE 29 *Sensitivity analysis – clinical confirmation*

Changed assumptions	Universal (16)	Universal	Opportunistic (GP)	Opportunistic (MI)	Case finding
Baseline cost per LYG for each strategy (£)	2,777	13,029	11,310	9,281	3,097
1.31 relatives per proband	No change	No change	No change	No change	3,113
5.75 relatives per proband	No change	No change	No change	No change	3,092
30% identified mutations	No change	No change	No change	No change	No change
70% identified mutations	No change	No change	No change	No change	No change
37% reduction in drug cost	2,451	11,972	10,352	6,344	2,040
73% reduction in drug cost	2,134	10,944	9,419	3,787	1,011
80% attendance	2,651	12,461	10,919	9,338	3,102
50% attendance	3,499	17,043	14,441	9,683	3,128
Discount rate 5% for costs and benefits	13,131	30,377	26,553	19,978	7,887

TABLE 30 *Sensitivity analysis – genetic confirmation*

Changed assumptions	Universal (16)	Universal	Opportunistic (GP)	Opportunistic (MI)	Case finding (not costing proband)	Case finding (costing proband)
Baseline cost per LYG for each strategy (£)	14,842	78,060	70,009	21,106	3,300	4,914
1.31 relatives per proband	No change	No change	No change	No change	3,316	7,258
5.75 relatives per proband	No change	No change	No change	No change	3,295	4,192
30% identified mutations	24,142	128,128	114,894	29,670	No change	5,990
70% identified mutations	10,856	56,602	50,772	17,448	No change	4,453
50% reduction in cost of genetic testing	9,753	50,580	44,975	15,682	3,198	4,065
37% reduction in drug cost	14,516	77,003	69,050	18,168	2,273	3,857
73% reduction in drug cost	14,198	75,974	68,117	15,311	1,214	2,828
80% attendance	14,589	76,923	69,226	21,218	3,305	5,142
50% attendance	16,286	86,088	76,270	21,908	3,331	6,270
Discount rate 5% for costs and benefits	67,533	177,685	160,037	43,865	8,346	12,001

overall clinical case-finding approach becomes more cost-effective than the universal (16) strategy. Women of all ages in this strategy become the most cost-effective group to screen. A 37% reduction in drug costs produces a cost per LYG of £408 for 35–44 year olds and £541 per LYG for 45–54 year olds. Screening men up to the age of 34 years in a universal or opportunistic (GP) approach (with clinical confirmation) become as cost-effective as case finding for all ages at baseline. A 73% reduction in drug costs gives a cost per LYG of £185 for women aged 35–44 years in a clinical case-finding strategy. Men aged 25–34 years cost £477 per LYG (opportunistic (MI) strategy) and £423 per LYG (clinical case-finding strategy). Costs of some statins have already started to fall and Appendix 7 shows how the earlier, higher costs of these statins resulted in higher costs and lower cost-effectiveness of strategies.

If attendance rates were set at 80% for all strategies at all stages (in compliance with current government target rates), there is very little change in the cost-effectiveness of the strategies, and the order between and within them remains the same as the baseline.

Discussion and summary

The cost-effectiveness of the strategies

Generally, case finding was the most cost-effective strategy, and universal screening the least cost-effective (see *Tables 31* and *32* for a summary). However, when targeted on the young (16 year old school leavers in our example), universal screening also appears relatively cost-effective. Screening is least cost-effective in men aged over 35 years. This is because the gains in life expectancy for these individuals are small.

A combination of strategies might be the most acceptable option. For example, universal screening at 16 years of age could be carried out alongside both opportunistic screening of patients with an early MI (males 16–34 years, females 16–54 years) **and** case finding for family members of index cases (males aged 16–34 years, females aged 16–54 years). Once a new case (not related to an 'index' patient) has been found through a universal or opportunistic approach, his or her relatives could be followed up using a systematic case-finding approach. Our results have shown case finding to be the most cost-effective strategy if all ages and both sexes are considered. Therefore, adding a case-finding approach to population strategies improves the cost-effectiveness of the other strategies.

Where a genetic mutation is known for a proband, there is little difference in cost-effectiveness of case finding, regardless of whether the diagnosis is clinically or genetically based. Even if the genetic status has not been ascertained within a family, genetic case finding for women of all ages and men up to the age of 34 years is similarly cost-effective as clinical case finding. With genetic confirmation, an unequivocal diagnosis can be made, and younger

TABLE 31 *Comparing overall cost-effectiveness of clinical strategies by age and sex*

	Cost per LYG (clinical) for each strategy (£)			
Age (years)	**Universal**	**Opportunistic (GP)**	**Opportunistic (MI)**	**Case finding**
Men				
16–24	2,766	2,651	900	870
25–34	4,883	4,677	1,522	1,468
35–44	30,253	28,930	8,626	8,278
45–54	56,424	53,709	12,058	11,344
Women				
16–24	2,402	2,305	822	796
25–34	2,457	2,355	1,792	766
35–44	2,363	2,259	665	637
45–54	4,293	4,085	893	838
All	13,029	11,310	9,281	3,097

TABLE 32 *Comparing overall cost-effectiveness of genetic strategies by age and sex*

Age bands	**Cost per LYG (genetic) for each strategy (£)**				
	Universal	**Opportunistic (GP)**	**Opportunistic (MI)**	**Case finding (excluding cost of proband test)**	**Case finding (including cost of proband test)**
Men					
16–24	15,179	14,951	1,584	908	1,216
25–34	27,238	26,827	2,756	1,538	2,093
35–44	174,132	171,485	16,564	8,727	12,298
45–54	351,576	346,146	28,342	12,266	19,591
Women					
16–24	12,917	12,724	1,402	829	1,090
25–34	13,530	13,326	1,403	800	1,075
35–44	13,661	13,453	1,288	672	953
45–54	26,915	26,499	2,141	908	1,470
All	78,060	70,009	21,106	3,300	4,914

members of the family can be informed of their predisposition without the problems of fluctuating and overlapping cholesterol levels, which are most problematic in the young.

All strategies will probably become cheaper and more effective in the long term as drug costs fall (when patents for statins expire) and as the technology improves (especially DNA diagnostic techniques). Also, in the future, with advances in genetics, we could be better able to determine which particular mutations have a higher risk of CHD due to higher penetrance of certain LDL receptor mutations. Sensitivity analysis on the cost of statins shows that a reduction in costs could lead to a large improvement in the overall cost-effectiveness of particular strategies.

Much of the benefits of screening (especially opportunistic screening) depend on the ability of practitioners to identify FH. It is also important that once FH has been diagnosed in a non-specialist clinic, the relatives of the newly identified index patient be followed up. Awareness by GPs, hospital accident and emergency staff, cardiology teams and the general public is important in ensuring the long-term effectiveness of an FH screening policy. The most effective method of achieving this goal should be further investigated, but educating the necessary sectors seems essential.

None of our FH screening strategies appear as cost-effective as breast cancer screening, according to a recent evaluation. Boer and colleagues[124] estimated the cost-effectiveness of breast screening to be £467 per LYG for women aged 50–64 years, and £573 for women aged 65–69 years (**undiscounted** life-years). This compares with £2420 for case finding (age range 16–54 years) and £1798 for universal (16) screening (both with clinical confirmation).

However, these strategies are **more** cost-effective than screening asymptomatic adults for coronary risk factors (assuming a 3 year treatment effect) as evaluated by the OXCHECK study (£3900 per LYG) and the British Family Heart Study (£5100 per LYG).[114] A computer simulation of FH mortality data published in 1993 found that primary prevention in FH patients had similar cost-effectiveness ratios to secondary prevention of non-FH patients.[50]

However, the data in our model is best interpreted in its comparative rather than absolute form. This is to say that the relative effectiveness of one strategy or one age group is more appropriately compared with the relative effectiveness of a different age group or strategy rather than a different intervention. This is because other studies may be making different methodological assumptions, and the quality of data varies between studies.

Limitations of the model

The effectiveness data used in our model is imprecise for several reasons. First, the life tables used probably underestimate the life expectancy of people alive today because, by the time they reach higher age ranges, mortality will have dropped below current estimates. This, however, may not have any effect on the estimates of changes in life expectancy. Second, the use of before and after mortality data for the treatment and non-treatment groups is likely to overestimate the number of LYGs because it does not take account of the underlying trend of decreasing mortality. Third, there were relatively few events in the Simon Broome Register data set. Consequently, the age bands in the life tables are very broad, so death rates are held constant over several years, instead of increasing gradually. Fourth, anyone dying within a particular age range is given a life expectancy of the mid-point of the age range, whereas they could have died at the beginning or end of the age range.

There are three consequences of FH screening that have been omitted for logistical reasons. First, we have not considered the health and cost implications of treating patients over the age of 60 years. This is because the effectiveness data from the Simon Broome Register cohort show no effect in FH patients over 60 years old. In fact, treated FH patients appear to have a longer life expectancy than the general population. This might be due to a 'healthy medical services user effect', where people seek medical advice when needed and adopt a healthy lifestyle.

We do not advocate ceasing drug treatment at the age of 60 years, but the data are not adequate at present to estimate the cost-effectiveness of treating this patient group. If treatment of this group had been included, then overall cost-effectiveness of the screening programmes might have marginally increased or decreased depending on the effectiveness of statins in this subgroup. Assuming statins are effective at older ages, then our comparison of screening programmes is biased in favour of programmes that start screening at a younger age, as these cohorts will have longer to accumulate the benefits of statin treatment.

Second, due to a lack of effectiveness data, the consequences of screening and treating children have been omitted. If children were included in the case-finding approach, this strategy might become even more cost-effective (as the number of relatives per proband increases).

Third, we have not considered the effect of identifying people without FH but with a raised cholesterol level, including those with familial combined hypercholesterolaemia. There will be a health gain, since they too could benefit from lipid-lowering treatment and consequent reductions in CHD and total mortality. Where genetic screening is considered, the inclusion of these individuals does not change the estimates of cost-effectiveness.

Chapter 7
Conclusions

The Wilson and Jungner[5] criteria (see chapter 1) for screening should be considered before population-wide screening is instituted. FH affects 1 in 500 of the UK population, and carries a high risk of premature CHD. The natural history of FH is well understood and the condition can be detected by a simple test long before clinical symptoms are apparent. The diagnosis of FH, whether by clinical or genetic testing, requires nothing more intrusive than venepuncture, and, once the diagnosis is made, there will be no need for further diagnostic tests.

There is strong evidence that early treatment is beneficial. Although there are no RCTs of clinical end-points of statin treatment in FH patients, the clear message that can be drawn from the trials of patients at moderately high risk of CHD is that statins are effective in reducing cholesterol levels and CHD mortality, and appear to be most cost-effective in the highest CHD risk groups, which is the case for FH patients.

Adverse psychological effects of screening have been reported in some small studies. However, most studies conclude that screening should not be delayed due to these effects, which appear to be relatively minor. The methodological shortcomings of these studies need to be addressed. Identification of a group of people who are more vulnerable to adverse psychological effects would facilitate targeting education and, possibly, counselling to ameliorate adverse effects, but this strategy has not been evaluated. Further education of the public and the regulation of the insurance sector may be useful to avoid stigmatisation and discrimination of those testing positive, but there is little evidence for the existence of stigmatisation and discrimination.

A provisional conclusion based on the limited information is that a diagnosis of FH does not adversely affect the health of adults, although it may affect them financially if insurance companies discriminate against them. There is a small amount of data to support the hypothesis that a diagnosis of FH in childhood arouses adverse anxieties and tensions within families. Until current treatments in children are proven to be safe, there is, at present, little justification for screening before they are old enough to be treated with statins in the general population. However, within families affected with FH, it is usually recommended that children are tested before the age of 10 years.[43] Further research into the psychological and social effects of screening in adults and children is urgently needed.

In summary, the findings of our modelling suggest the following:

- When comparing strategies across the whole age range, case finding amongst relatives of FH cases was the most cost-effective strategy, and universal systematic screening the least cost-effective.
- Systematic screening of 16 year olds using clinical methods of diagnosis appears to be similarly cost-effective to case finding, but this assumes that such screening would be acceptable to society and that at least 55% of those 16 year olds invited for screening would attend.
- Screening women for FH is consistently more cost-effective than screening men in all the scenarios.
- Screening patients admitted to hospital with premature MI may also be worth considering.
- The modelling results would support a combination of strategies. For example, systematic screening at 16 years of age could be carried out alongside both opportunistic screening of patients with an early MI (men aged 16–34 years, women aged 16–54 years) **and** case finding for family members of index cases (men aged 16–34 years, women aged 16–54 years).

Changing knowledge base

Genetics

Over the next 2–3 years, several changes in our ability to identify mutations in patients with FH can be confidently predicted. Technical advances will increase the speed and sensitivity of mutation detection. For example, the use of high-performance liquid chromatography for heteroduplex analysis,[125,126] or 'chip' technology,[127] will both allow rapid screening of all base pairs within the low-density lipoprotein receptor (LDLR) gene. Although currently the cost of these

techniques is high (roughly £500 per screen), they will become considerably cheaper in the future.

The second advance will be in the identification of other genes, apart from the LDLR and apoB genes, that cause FH. Recently, two reports have demonstrated that one gene is located on chromosome 1[128,129] and that another gene may be located on chromosome 10.[129] With the availability of the sequencing of the entire human genome, it is inevitable that these genes, and possibly others, will be identified. It is unclear to what extent mutations in these genes contribute to FH in the UK, but they may represent the major part of the genetic cause of FH in patients where no mutation can currently be detected in the LDLR or apoB genes. The application of current or newly developed mutation-screening techniques to these genes might therefore increase the mutation detection rate to 90% or higher.

Both of these advances will therefore have beneficial implications for the specificity and sensitivity of mutation detection, and therefore the cost–benefit analysis of the genetic component of FH screening.

Effectiveness of lipid-lowering drugs

More effective lipid-lowering drugs are being introduced on to the market, and when the patent for some of the older statins expires, the costs of these drugs should decrease. The effect of this will be to improve the overall cost-effectiveness of all the strategies. Costs of some statins have already started to fall, and appendix 7 shows how the earlier, higher costs of these statins resulted in higher costs and lower cost-effectiveness of strategies.

Social and psychosocial issues

Several reports of the social and psychological impact of an FH diagnosis will become available in the next couple of years. A London-based group is conducting an RCT comparing the reactions of patients who receive their FH diagnosis by genetic or by clinical means. The group has recently published an analysis of interviews with the parents of 24 children who received a positive result informing them that their child was at risk for having FH.[130] When the test was seen as detecting a raised cholesterol level, it was perceived as controllable and familiar, whereas when the test was seen as genetic in origin, it was considered uncontrollable and more threatening.

As a result of enquiries carried out during the literature retrieval, data should be available from Sweden where a nurse is examining (initially with a questionnaire) how screening for FH may affect a range of potential psychological consequences (G Hollman, personal communication) and a medically qualified anthropology researcher is setting up a qualitative study of FH patients at a lipid clinic in Norway (J Frich, personal communication).

Effectiveness of screening

A pilot family-tracing programme of relatives of identified FH patients is being conducted in Oxfordshire. This systematic case-finding approach within a defined boundary will allow more accurate assessment of the yield of new patients obtainable through this method of detection. A cost-effectiveness analysis will be performed as part of this study (A Neil, personal communication).

Recommendations for further research

Health policy decisions

Social and psychological effects of screening

There are insufficient data available to assess whether longer-term negative social or psychological negative consequences result from screening or from diagnosis. There is a lack of qualitative or quantitative evidence on the psychosocial effects of screening for FH or other treatable inherited conditions, or on the effectiveness of educational and counselling interventions to reduce negative effects at the time of screening. Well-designed qualitative research with clearly specified aims, and a good understanding of what is methodologically possible, is required in all these areas. In addition, qualitative or quantitative studies are specifically required with respect to our recommendation to screen all 16 year olds, since little is known about the acceptability of this strategy, but experience in health education and service provision generally suggests that young people are particularly resistant to lifestyle interventions, and this would substantially reduce its projected cost-effectiveness.

Determining cost-effectiveness of screening strategies

The results of our model show that case finding in the relatives of known FH patients is cost-effective, as is a screening strategy in young people, and screening of patients admitted to hospital with premature MI. However, data on the effectiveness and cost implications of screening strategies is lacking, so it is difficult to conclude with certainty that one strategy is more effective or less costly than another. Further research should concentrate

on systematic evaluation of each of these potential screening strategies.

Epidemiological data on FH

The modelling was limited by a lack of data from longitudinal studies of people with FH and by a lack of data on the effect of treatment with statins on risk of CHD in people with FH. With the data available from trials of statins in people at only moderate risk of CHD, trials in people with FH would be unethical. However, consideration should be given to undertaking observational studies, particularly longitudinal cohort studies of people with FH.

Clinical decision-making

Treatment of children

Uncertainty remains about the treatment of children under 16 years of age with FH. The long-term safety of statin treatment in children has not been adequately studied. Moreover, little is known about the longer-term effects on drug adherence and development of atherosclerosis of starting diet or resin treatment in childhood. More experimental data on the safety of statin treatment in children (especially adolescents) are needed before population-screening policies for children can be recommended. Within affected families, children should be tested before the age of 10 years.

Treatment of women of child-bearing age

Evidence on the safety of treating women of child-bearing age (during pregnancy and breast feeding) is lacking. More evidence is needed before treatment protocols for such women can be developed.

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References

1. Goldstein JL, Brown MS. Familial hypercholesterolaemia. In: Scriver CR, Beudet AL, Sly WS, Valle D, editors. The metabolic basis of inherited disease. New York: McGraw Hill; 1995. p. 1215–45.
2. Patterson D, Slack J. Lipid abnormalities in male and female survivors of myocardial infarction and their first degree relatives. *Lancet* 1972;**i**:1393–9.
3. Humphries SE, Galton D, Nicholls P. Genetic testing for familial hypercholesterolaemia: practical and ethical issues. *Q J Med.* 1997;**90**:169–81.
4. Slack J. Risks of ischaemic heart disease in familial hyperlipoproteinaemic states. *Lancet* 1969;**ii**: 1380–2.
5. Wilson J, Jungner YG. Principles and practice of mass screening for disease. Geneva: WHO; 1968 Oct. Public Health Papers No. 34. Report No.: 65 (iv).
6. Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. *BMJ* 1991;**303**:893–6.
7. Cotton RGH. Current methods of mutation detection. *Mutation Res* 1993;**285**:125–44.
8. Mashal R, Mashal RD, Koontz J, Sklar JK. Detection of mutations by cleavage of DNA heteroduplexes with bacterio- phage resolvases. *Nature Genet* 1995;**9**:177–83.
9. Humphries S, Gudnason V, Whittal RE, Day INM. SSCP analysis and DNA sequencing for genetic characterization of a multi-allelic disease, familial hypercholesterolaemia. In: Elles R, editor. Molecular diagnosis of genetic disease. Totowa, NJ: Humana Press; 1996. p. 121–40.
10. Nissen H, Hansen AB, Guldberg P, Petersen NE, Larsen ML, Haghfelt T, *et al.* Genetic diagnosis with the denaturing gradient gel electrophoresis technique improves diagnostic precision in familial hypercholesterolemia. *Circulation* 1995;**91**(Pt 6): 1641–6.
11. Gudnason V, Day IN, Humphries SE. Effect on plasma lipid levels of different classes of mutations in the low-density lipoprotein receptor gene in patients with familial hypercholesterolemia. *Arterioscler Thromb* 1994;**14**(Pt 11):1717–22.
12. Whittall R, Gudnason V, Weavind GP, Day LB, Humphries SE, Day IN. Utilities for high throughput use of the single strand conformational polymorphism method: screening of 791 patients with familial hypercholesterolaemia for mutations in exon 3 of the low density lipoprotein receptor gene. *J Med Genet* 1995;**32**(Pt 7):509–15.
13. Day IN, Haddad L, O'Dell SD, Day LB, Whittall RA, Humphries SE. Identification of a common low density lipoprotein receptor mutation (R329X) in the south of England: complete linkage disequilibrium with an allele of microsatellite D19S394. *J Med Genet* 1997;**34**(Pt 2):111–16.
14. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, *et al.* The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *New Engl J Med* 1996;**335**(Pt 14):1001–9.
15. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.
16. The Long Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with prevastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *Lancet* 1998;**339**:1349–57.
17. Shepherd J, Cobbe M, Ford I, Isles CG, Lorimer AR, MacFarlane PW. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New Engl J Med* 1995;**333**(Pt 20):1301–7.
18. Keech A, Collins R, MacMahon S, Armitage J, Lawson A, Wallendszus K, *et al.* Three-year follow-up of the Oxford Cholesterol Study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality study. *Eur Heart J* 1994; **15**(Pt 2):255–69.
19. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol* 1998;**81**(Pt 5): 582–7.
20. Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. *BMJ* 1997;**314**:112–17.
21. Tang JL, Armitage JM, Lancaster T, Silagy CA, Fowler GH, Neil HAW. Systematic review of dietary intervention trials to lower blood total cholesterol in free-living subjects. *BMJ* 1998;**316**:1213–20.

22. Jones PJ, Raeini-Sarjaz M, Ntanios F, Vanstone C, Feng JY, Parsons W. Modulation of plasma lipids levels and cholesterol kinetics by phytosterol versus phytostanol-esters. *J Lipid Res* 2000;**41**:697–705.

23. Miettinen TA, Puska P, Gylling H, Vanhanen H, Vartianen E. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolaemic population. *New Engl J Med* 1995;**333**: 1308–12.

24. Weststrate JA, Meijer GW. Plant sterol-enriched margarines and reduction of plasma total- and LDL-cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects. *Eur J Clin Nutr* 1998;334–43.

25. Greenhalgh T. How to read a paper: the basics of evidence based medicine. *BMJ* 1997;**52**(5).

26. Stone NJ, Levy RI, Fredrickson DS, Verter J. Coronary artery disease in 116 kindred with familial type II hyperproteinemia. *Circulation* 1974;**49**: 476–88.

27. Gagne C, Moorjani S, Brun D, Toussaint M, Lupien PJ. Heterozygous familial hypercholesterolaemia. *Atherosclerosis* 1979;**34**:13–24.

28. Beaumont VB, Jacotot B, Beaumont J-L. Ischaemic disease in men and women with familial hypercholesterolaemia and xanthomatosis. *Atherosclerosis* 1976;**24**:441–50.

29. Jensen J, Blankenhorn DH, Kornerup V. Coronary disease in familial hypercholesterolemia. *Circulation* 1967;**36**:77–82.

30. Scientific Steering Committee on behalf of the Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. *Atherosclerosis* 1999;**142**:105–12.

31. Vuorio AF, Turtola H, Kontula K. Neonatal diagnosis of familial hypercholesterolaemia in newborns born to a parent with a molecularly defined heterozygous familial hypercholesterolaemia. *Arterioscler Thromb Vasc Biol* 1997;**17**: 3332–7.

32. Kwiterovich PO, Levy RI, Fredrickson DS. Neonatal diagnosis of familial hyperlipoproteinemia. *Lancet* 1973;**i**:118–22.

33. Leonard JV, Whitelaw AGL, Wolff OH, LLoyd JK, Slack J. Diagnosing familial hypercholesterolaemia in childhood by measuring serum cholesterol. *BMJ* 1977;**1**:1566–1568.

34. West RJ, Lloyd JK, Leonard JV. Long-term follow-up of children with familial hypercholesterolaemia treated with cholestyramine. *Lancet* 1980;**ii**:873–5.

35. Tonstad S, Knudtzon J, Sivertsen M, Refsum H, Ose L. Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr* 1996;**129**(Pt 1):42–9.

36. Tonstad S, Sivertsen M, Aksnes L, Ose L. Low dose colestipol in adolescents with familial hypercholesterolaemia. *Arch Dis Child* 1996;**74**(Pt 2):157–60.

37. Hennermann JB, Herwig J, Marz W, Asskali F, Bohles HJ. Lipid and lipoprotein profiles in children with familial hypercholesterolaemia: effects of therapy. *Eur J Pediatr* 1998;**157**(Pt 11): 912–18.

38. Stein EA, Illingworth DR, Kwiterovich PO Jr, Liacouras CA, Siimes MA, Jacobson MS, *et al.* Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA* 1999;**281**(Pt 2): 137–44.

39. Wray R, Neil HAW, Rees J. Screening for hyperlipidaemia in childhood: recommendations of the British Hyperlipidaemia Association. *J R Coll Phys London* 1996;**30**(Pt 2):115–18.

40. Durrington PN. Familial hypercholesterolaemia. In: Durrington PN, editor. Hyperlipidaemia: diagnosis and management, 2nd ed. Oxford: Butterworth-Heinemann; 1995. p. 108–40.

41. Kwiterovich PO Jr. Pediatric implications of heterozygous familial hypercholesterolemia: screening and dietary treatment. *Arteriosclerosis* 1989;**9**(1 Suppl 1):111–20.

42. Kwiterovich POJ. Identification and treatment of heterozygous familial hypercholesterolemia in children and adolescents. *Am J Cardiol* 1993;**72**: 30D–7D.

43. Neil A, Rees A, Taylor C, editors. Hyperlipidaemia in childhood. London: Royal College of Physicians of London on behalf of The British Hyperlipidaemia Association; 1996.

44. National Cholesterol Education Program. Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics* 1992;**89**:525–84.

45. Ose L, Tonstad S. The detection and management of dyslipidaemia in children and adolescents. *Acta Paediatr* 1995;**84**(Pt 11):1213–15.

46. Jonsson B, Johannesson M, Kjekshus J, Olsson AG, Pedersen TR, Wedel H. Cost-effectiveness of cholesterol lowering: results from the Scandinavian Simvastatin Survival Study (4S). *Eur Heart J* 1996;**17**: 1001–7.

47. Johannesson M, Jonsson B, Kjekshus J, Olsson AG, Pedersen TR, Wedel H. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. *New Engl J Med* 1997;**336**(Pt 5):332–6.

48. Caro J, Klittich W, McGuire A, Ford I, Norrie J, Pettitt D, *et al.* The West of Scotland coronary prevention study: economic benefit analysis of primary prevention with pravastatin. *BMJ* 1997; **315**:1577–82.

49. Morris S, McGuire A, Caro J, Pettitt D. Strategies for the management of hypercholesterolaemia: a systematic review of the cost-effectiveness literature. *J Health Serv Res Policy* 1997;**2**(Pt 4):231–50.

50. Goldman L, Goldman PA, Williams LW, Weinstein MC. Cost-effectiveness considerations in the treatment of heterozygous familial hypercholesterolemia with medications. *Am J Cardiol* 1993;**72**:75D–9D.

51. Human Genetics Programme. Familial hypercholesterolaemia – report of a WHO consultation. Paris: WHO; 1997.

52. Sheldon T. Problems of using modelling in the economic evaluation of health care. *Health Econ* 1996;**5**:1–11.

53. Smith GD, Song F, Sheldon TA. Cholesterol lowering and mortality: the importance of considering initial level of risk. *BMJ* 1993; **306**:1367–73.

54. NHS Centre for Reviews and Dissemination. Cholesterol and coronary heart disease: screening and treatment. *Effect Health Care* 1998;**4**(Pt 1):1–16.

55. Ward AJ, O'Kane M, Nicholls DP, Young IS, Nevin NC, Graham CA. A novel single base deletion in the LDLR gene (211delG): effect on serum lipid profiles and the influence of other genetic polymorphisms in the ACE, APOE and APOB genes. *Atherosclerosis* 1996;**120**(Pt 1–2):83–91.

56. Koivisto UM, Hamalainen L, Taskinen MR, Kettunen K, Kontula K. Prevalence of familial hypercholesterolemia among young north Karelian patients with coronary heart disease: a study based on diagnosis by polymerase chain reaction. *J Lipid Res* 1993;**34**(Pt 2):269–77.

57. Williams RR, Hunt SC, Schumacher C, Hegele RA, Leppert MF, Ludwig EH, *et al.* Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardiol* 1993;**72**:171–6.

58. Colhoun H, Prescott-Clarke P, editors. Health survey for England, 1994. London: HMSO; 1996.

59. Association of British Insurers. Genetic testing: ABI code of practice. London: Association of British Insurers; 1997.

60. Low L, King S, Wilkie T. Genetic discrimination in life insurance: empirical evidence from a cross sectional survey of genetic support groups in the United Kingdom. *BMJ* 1998;**317**:1632–5.

61. Fost N. Ethical implications of screening asymptomatic individuals. *FASEB J* 1992;**6**:2813–17.

62. Hudson KL, Rothenberg KH, Andrews LB, Kahn MJE, Collins FS. Genetic discrimination and health insurance: an urgent need for reform. *Science* 1995;**270**:391–3.

63. Lerman C, Croyle RT. Genetic testing for cancer predisposition: behavioural science issues. *J Natl Cancer Inst Monograph* 1995;**17**:63–5.

64. Skovby F, Micic S, Jepsen B, Larsen SO, Hansen B, Tegllund L, *et al.* Screening for familial hypercholesterolaemia by measurement of apoliproteins in capillary blood. *Arch Dis Child* 1991;**66**:844–7.

65. Williams RR, Schumacher C, Barlow GK, Hunt SC, Ware JL, Pratt M, *et al.* Documented need for more effective diagnosis and treatment of familial hypercholesterolemia according to data from 502 heterozygotes in Utah. *Am J Cardiol* 1993;**72**:18D–24D.

66. Bhatnagar D, Morgan J, Siddiq S, Mackness MI, Miller JP, Durrington PN. Outcome of case-finding amongst relatives of patients with known heterozygous familial hypercholesterolaemia. *BMJ* 2000 (in press).

67. Leadbeatter S, Williams DW, Stansbie D. Incidence of familial hypercholesterolaemia in premature deaths due to coronary heart disease. *Am J Forens Med Pathol* 1987;**8**(Pt 4):280–2.

68. Taylor CJ, Olpin S, Rattenbury J, Whippey A, Lunt C, Beckles-Wilson N, *et al.* Familial hypercholesterolaemia: pilot study to identify children at risk. *J Clin Pathol* 1993;**47**:730–3.

69. Irvine MJ, Logan AG. Is knowing your cholesterol number harmful? *J Clin Epidemiol* 1994;**47**(Pt 2): 131–45.

70. Meland E, Laerum E, Maeland JG. Life style intervention in general practice: effects on psychological well-being and patient satisfaction. *Qual Life Res* 1996;**5**:348–54.

71. Andersen LK, Jensen HK, Juul S, Faergeman O. Patients' attitudes towards detection of heterozygous familial hypercholesterolemia. *Arch Int Med* 1997;**157**:553–60.

72. Sachs L. Causality, responsibility and blame – core issues in the cultural construction and subtext of prevention. *Sociol Health Illness* 1996;**18**(Pt 5):632–52.

73. Tonstad S. Familial hypercholesterolaemia: a pilot study of parents' and children's concerns. *Acta Paediatr* 1996;**85**(Pt 11):1307–13.

74. Rosenberg E, Lamping DL, Joseph L, Pless IB, Franco ED. Cholesterol screening of children at high risk: behavioural and psychological effects. *Can Med Assoc J* 1997;**156**(Pt 4):489–96.

75. Rosenthal SL, Knauer-Black S, Stahl MP, Catalanotto TJ, Sprecher DL. The psychological functioning of children with hypercholesterolaemia and their families: a preliminary investigation. *Clin Pediatr* 1993;**32**:135–41.

76. Croyle RT, Smith KR, Botkin JR, Baty B, Nash J. Psychological responses to BRCA1 mutation testing: preliminary findings. *Health Psychol* 1997;**16**(Pt 1): 63–72.

77. Lerman C, Schwartz MD, Lin T-H, Hughes C, Narod S, Lynch HT. The influence of psychological distress on use of genetic testing for cancer risk. *J Consult Clin Psychol* 1997;**65**(Pt 3):414–20.

78. Tessaro I, Borstelmann N, Regan K, Rimer BK, Winer E. Genetic testing for susceptibility to breast cancer: findings from women's focus groups. *J Women's Health* 1997;**6**(Pt 3):317–27.

79. Kash KM, Holland JC, Osborne MP, Miller DG. Psychological counseling strategies for women at risk of breast cancer. *J Natl Cancer Inst Monograph* 1995;**17**:73–9.

80. Lerman C, Biesecker B, Benkendorf JL, Kerner J, Gomez-Caminero A, Hughes C, *et al.* Controlled trial of pre-test education approaches to enhance informed decision-making for BRCA1 gene testing. *J Natl Cancer Inst* 1997;**89**(Pt 2):148–57.

81. Marteau TM, Kinmonth AL, Thompson S, Pyke S. The psychological impact of cardiovascular screening and intervention in primary care: a problem of false reassurance? *Br J Gene Pract* 1996;**46**(October):577–81.

82. Glanz K, Gilboy MB. Psychosocial impact of cholesterol screening and management. In: Croyle RT, editor. Psychological effects of screening for disease prevention and detection. New York: Oxford University Press; 1995. p. 39–64.

83. Neil HAW, Mant D. Cholesterol screening and life assurance. *BMJ* 1991;**302**:891–3.

84. Human Genetics Advisory Commission. The implications of genetic testing for insurance. London: Human Genetics Advisory Commission; 1997.

85. Billings PR, Kohn MA, de Cuevas M, Beckwith J, Alper JS, Natowicz MR. Discrimination as a consequence of genetic testing. *Am J Human Genet* 1992;**50**:476–82.

86. Tonstad S, Novik TS, Vandvik IH. Psychosocial function during treatment for familial hypercholesterolemia. *Pediatrics* 1996;**98**(Pt 2):249–55.

87. Lerman C. Psychological aspects of genetic testing: introduction to the special issue. *Health Psychol* 1997;**16**(Pt 1):3–7.

88. Tijmstra T. The psychological and social implications of serum cholesterol screening. *Intl J Risk Safety Med* 1990;**1**:29–44.

89. Marshall KG. Prevention. How much harm? How much benefit? 3. Physical, psychological and social harm. *Can Med Assoc J* 1996;**155**(Pt 2):169–76.

90. Biesecker BB, Garber JE. Testing and counseling adults for heritable cancer risk. *J Natl Cancer Inst Monograph* 1995;**17**:115–18.

91. Wardle J, Pope R. The psychological costs of screening for cancer. *J Psychosom Res* 1992;**36**(Pt 7):609–24.

92. Marteau TM, Croyle RT. Psychological responses to genetic testing. *BMJ* 1998;**316**:693–6.

93. Davison C, Macintyre S, Davey Smith G. The potential social impact of predictive genetic testing for susceptibility to common chronic diseases: a review and proposed research agenda. *Sociol Health Illness* 1994;**16**(Pt 3):340–65.

94. Richards MPM. The new genetics: some issues for social scientists. *Sociol Health Illness* 1993;**15**(Pt 5):567–86.

95. Lerman C, Croyle RT. Emotional and behavioural responses to genetic testing for susceptibility to cancer. *Oncology* 1996;**10**(Pt 2):191–5.

96. Marteau TM. Screening in practice: reducing the psychological costs. *BMJ* 1990;**301**:26–8.

97. Lefebvre RC, Hursey KG, Carleton RA. Labeling of participants in high blood pressure screening programs: implications for blood cholesterol screenings. *Arch Int Med* 1988;**148**:1993–7.

98. Brett AS. Psychologic effects of the diagnosis and treatment of hypercholesterolemia: lessons from case studies. *Am J Med* 1991;**91**:642–7.

99. Wagner EH, Strogatz DS. Hypertension labelling and well-being: alternative explanations in cross-sectional data. *J Chron Dis* 1984;**37**(Pt 12):943–7.

100. Macdonald LA, Sackett DL, Haynes RB, Taylor DW. Labelling in hypertension: a review of the behavioural and psychological consequences. *J Chron Dis* 1984;**37**(Pt 12):933–42.

101. Alderman MH, Lamport B. Labelling of hypertensives: a review of the data. *J Clin Epidemiol* 1990;**43**(Pt 2):195–200.

102. Holtzman NA, Shapiro D. Genetic testing and public policy. *BMJ* 1998;**316**:852–6.

103. Alper JS, Natowicz MR. Genetic testing and insurance: emphasises the irreconcilable dilemma in underwriting. *BMJ* 1993;**307**:1506–7.

104. Rothstein MA. Genetic testing: employability, insurability and health reform. *J Natl Cancer Inst Monograph* 1995;**17**:87–90.

105. Murray TH. Ethics, genetic prediction and heart disease. *Am J Cardiol* 1993;**72**:80D–4D.

106. Quaid KA. Psychological and ethical considerations in screening for disease. *Am J Cardiol* 1993;**72**:64D–7D.

107. Department of Health. Health survey for England, 1996. London: HMSO; 1998.

108. Becker DM, Raqueno JV, Yook RM, Kral BG, Blumenthal RS, Moy TF, *et al.* Nurse-mediated

cholesterol management compared with enhanced primary care in siblings of individuals with premature coronary disease. *Arch Int Med* 1998;**158**:1533–9.

109. Langham S, Thorogood M, Normand C, Muir J, Jones L, Fowler G. Costs and cost effectiveness of health checks conducted by nurses in primary care: the OXCHECK study. *BMJ* 1996;**312**:1265–8.

110. Neil HA, Roe L, Godlee RJ, Moore JW, Clark GM, Brown J, *et al.* Randomised trial of lipid lowering dietary advice in general practice: the effects on serum lipids, lipoproteins, and antioxidants. *BMJ* 1995;**310**:569–73.

111. Neil HAW. Problems in measurement: cholesterol. In: Lawrence M, Neil A, Mant D, Fowler GH, editors. Prevention of cardiovascular disease – an evidence-based approach. Oxford: Oxford University Press; 1996. p. 253–7.

112. OPCS. Morbidity statistics from general practice: fourth national study, 1991–1992. London: HMSO; 1995.

113. Wonderling D, McDermott C, Buxton M, Kinmonth A-L, Pyke S, Thompson S, *et al.* Costs and cost effectiveness of cardiovascular screening and intervention: the British family heart study. *BMJ* 1996;**312**:1269–73.

114. Wonderling D, Langham S, Buxton M, Normand C, McDermott C. What can be concluded from the OXCHECK study and British family heart studies: commentary on cost-effectiveness analyses. *BMJ* 1996;**312**:1274–8.

115. Wonderling D, McDermott C, Buxton M. Costs and cost-effectiveness of cardiovascular screening and intervention: economic evaluation of the British family heart study and comparison with other studies**.** HERG Research Report No. 23. Uxbridge: Brunel University; 1996.

116. Department of Health. Assessing the options: CHD/stroke. London: NHS Executive; 1995.

117. HM Treasury. Appraisal and evaluation in central government 'The green book'. London: Stationery Office; 1997.

118. BMA and Royal Pharmaceutical Society of Great Britain. British national formulary. London: BMA/ Pharmaceutical Press; 2000.

119. Doctors' and Dentists' Review Body. General medical practitioners' workload survey 1989–90. Main findings. London: DOH, Statistics and Management Information Division; 1991.

120. Netten A, Dennett J, Knight J. Unit costs of health and social care. Canterbury: PSSRU, University of Kent at Canterbury; 1998.

121. HM Treasury. Appraisal and evaluation in central government. London: Stationery Office; 1997.

122. Stevens W, Langham S, Normand C. The cost of CHD in North Thames Region. London: School of Hygiene and Tropical Medicine; 1999.

123. Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, Neil HAW. Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. *Heart* 1998;**80**(Pt 1):40–4.

124. Boer R, deKoning H, Threlfall A, Warmderdam P, Street A, Friedman E, *et al.* Cost effectiveness of shortening screening interval or extending range of NHS breast screening programme: computer simulation study. *BMJ* 1998;**317**:376–9.

125. Gross E, Arnold N, Goette J, Schwarz-Boeger U, Kiechle M. A comparison of BRCA1 mutation analysis by direct sequencing, SSCP and DHPLC. *Human Genet* 1999;**105**(Pts 1–2):72–8.

126. Jones AC, Austin J, Hansen N, Hoogendoorn B, Oefner PJ, Cheadle JP, *et al.* Optimal temperature selection for mutation detection by denaturing HPLC and comparison to single-stranded conformation polymorphism and heteroduplex analysis. *Clin Chem* 1999;**45**(8 Pt 1):1133–40.

127. Tang K, Fu DJ, Julien D, Braun A, Cantor CR, Koster H. Chip-based genotyping by mass spectrometry. *Proc Natl Acad Sci USA* 1999;**96**(Pt 18): 10,016–20.

128. Hunt SC, Hopkins PN, Bulka K, McDermott MT, Thorne TL, Wardell BB *et al.* Genetic localization to chromosome 1p32 of the third locus for familial hypercholesterolemia in a Utah kindred. *Arterioscler Thromb Vasc Biol* 2000;**20**:1089–93.

129. Varret M, Rabes JP, Saint JB, Cenarro A, Marinoni JC, Civeira F, *et al.* A third major locus for autosomal dominant hypercholesterolaemia maps to 1p34.1-p32. *Am J Med Genet* 1999;**64**:1378–87.

130. Senior V, Marteau TM, Peters TJ. Will genetic testing for predisposition for disease result in fatalism? A qualitative study of parents' responses to neonatal screening for familial hypercholesterolaemia. *Soc Sci Med* 1999;**48**(Pt 12):1857–60.

131. ONS. Mortality statistics, cause 1997 (DH2 No. 24). London: The Stationery Office; 1998.

132. Stevens W *et al.* Cost of CHD in North Thames Region. London: London School of Hygiene and Tropical Medicine.

133. Betteridge DJ, Dodson PM, Durrington PN, Hughes EA, Laker MF, Nicholls DP, *et al.* Management of hyperlipidaemia: guidelines of the British Hyperlipidaemia Association. *Postgrad Med J* 1993;**69**: 359–69.

134. Office for National Statistics. Key health statistics from general practice. London: Stationery Office; 1996.

Appendix 1

Algorithms from the studies on the social and psychosocial aspects of screening for FH: summaries and assessment of study quality

A	Study ID number	1 – Andersen, 1997[71]		
B	Questions addressed	1. To examine attitudes toward detection of disease 2. To examine present well-being in persons at risk of disease with a modifiable outcome		
C	Type of population	Lipid clinic attendees plus their relatives		
D	Number of subjects	150 (88% response rate)		
E	Setting	Outpatient clinic		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	Only one open-ended question	Yes but not followed through	No
	Quantitative	Postal questionnaire using series of established scales looking at psychological distress	Mixed approach would be appropriate but priority to quantitative only	Yes
G	Results	1. Majority in favour of screening for relatives (84%) 2. Anxiety and fear of FH and related CHD (more frequent in the 40–59 year age range) 3. Diminished well-being reported by 13% – most pronounced in those who experienced reaction at the time of diagnosis or who had symptoms of heart disease		
H	Brief description of conclusions	Those with increased knowledge of disease and with higher education are more likely to approve of screening. Majority in favour of FH screening		
I	Were they justified by the results?	Yes		
J	Transferability of study/limitations/ comments	The study may be under-reporting the scope of psychological problems because it only included clinic attendees, and lack of attendance may reflect psychological problems. The individuals in the sample here are attending a clinic so are not representative of a population sample but may be appropriate for a targeted approach. Methodological shortcoming arise from 80% of relatives already being aware of the hypercholesterolaemic state. Reactions are reported retrospectively, which may be affected by recall bias		
K	Relevance to policy	In this study, psychological reactions were not severe enough to warrant not initiating a screening programme – these data could be more severe in the general population sample as individuals have less knowledge of the disease and its consequences		

A	Study ID number	7 – Rosenberg *et al*., 1997[74]		
B	Questions addressed	To assess the behavioural and psychological effects of screening asymptomatic children at high risk of hyperlipidaemia		
C	Type of population	Children aged 4–17 years. Lipid clinic attendees		
D	Number of subjects	52 from longitudinal approach (67% completed all three stages of the 93% who agreed; 34 = case, 18 = control), 48 from cross-sectional approach (83% response). 100 in total		
E	Setting	Paediatric lipid clinic. Longitudinal group interviewed in the waiting room; cross-sectional group was sent questionnaire to home address		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	None	Might have benefited	–
	Quantitative	Observational study with longitudinal (new diagnosis and controls) and cross-sectional portions (previous diagnosis). Series of standard psychological questionnaires measuring anxiety, depression, behaviour, etc., using scales	Mixed approach might have helped understand a child's depth of feeling/range of problems	Yes
G	Results	Much higher percentage of diagnosed children had behavioural problems after diagnosis than controls		
H	Brief description of conclusions	Results do not justify screening children at moderately high risk of hyperlipidaemia because of adverse psychological effects on families (mainly the mother's perception of children's behaviour, not child's self-report). Risks of deleterious effects do not outweigh possible benefits of treatment of hyperlipidaemia in children		
I	Were they justified by the results?	Yes, but there was a low response rate – selection bias?		
J	Transferability of study/limitations/ comments	Could be used in an assessment of a population screening but probably not relevant for a targeted approach of the high-risk group. Unable to separate effects of screening to that of diagnosis to that of family history. No comparison with children not undergoing screening. 'Controls' were children at high risk		
K	Relevance to policy	Study of population sample not the high-risk group		

A	Study ID number	74 – Croyle *et al*., 1997[76]		
B	Questions addressed	To compare levels of psychological distress in women who tested positive for the *BRCA1* mutation with those who tested negative		
C	Type of population	Women aged 19–83 years at high risk of carrying the *BRCA1* mutation enrolled in an ongoing prospective study		
D	Number of subjects	60 (58 Mormon women)		
E	Setting	Unspecified clinic setting and telephone contact.		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	–	No	–
	Quantitative	Various scales measuring general psychological distress and test-related distress	Yes	Measures with proven validity were used, so not described in detail
G	Results	Greatest distress in carriers but a decline in distress by approximately 20% between the baseline and follow-up. Women who had never experienced cancer or cancer-related surgery but were found to be carriers showed the greatest distress		
H	Brief description of conclusions	Test results cause distress in the short term. A decline in anxiety at follow-up suggests that knowledge of carrier status can alleviate distress. Prior experience of cancer-related personal events alleviates the effects of a positive result. Results would be more interesting if a longer than 2 week follow-up were investigated		
I	Were they justified by the results?	Yes		
J	Transferability of study/limitations/ comments	1. Part of single kindred 2. Participants already part of research projects – given blood samples before. Increased health knowledge and cancer awareness 3. Given genetic and psychological counselling, so without this the levels of distress may have been higher 4. Small sample size 5. Preliminary results 6. Follow-up only 1–2 weeks		
K	Relevance to policy	Majority in population-based screening would not have same awareness of disease implications – results show that those without cancer/cancer-related surgery have the highest distress, so there are implications for blanket screening programmes		

A	Study ID number	76 – Lerman *et al.*, 1997[77]		
B	Questions addressed	To explore the relationship between psychological distress and requests for *BRCA1* test results in high-risk individuals – psychological predictors of test use		
C	Type of population	Members of a register known to have hereditary breast and ovarian cancers in the family – 37% male		
D	Number of subjects	149 (76% response rate)		
E	Setting	Patients already part of a cancer registry		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	–	Yes, because comparison	–
	Quantitative	Baseline structured telephone interview using computer-assisted telephone interviewing techniques and then given 1–2 hour education and genetic counselling session	Yes	Yes
G	Results	58% requested *BRCA1* results. Cancer-specific distress was significantly and positively associated with requests for test results (not global distress)		
H	Brief description of conclusions	Absence of elevated psychological distress may be due to previous education and counselling (all belong to cancer registry) or that non-participants had higher levels and were not included in this study		
I	Were they justified by the results?	Women, younger ages, elevated risk and cancer-specific risk were all positively correlated with a request for test results		
J	Transferability of study/limitations/ comments	Everyone received education and genetic counselling, so it was not possible to evaluate the effect of these sessions on distress levels Participants were members of a cancer registry Some participants were part of a previous study, but this did not look at psychological predictors of test use. Psychological impact of diagnosis was not measured. 24% refused to participate in the baseline interview – if these individuals are more distressed and were included in the study, high distress could provoke avoidance of receiving test results		
K	Relevance to policy	If the extent that the role psychological stress plays in test utilisation can be ascertained, psychological counselling can be targeted more effectively and the benefits of screening improved		

A	Study ID number	105 – Marteau, 1996[81]		
B	Questions addressed	To examine the extent that participation in a population-based cardiovascular screening programme aimed at reducing risk of CHD raises concerns of health or undermines belief in ability to reduce that risk. Three factors were investigated: (1) perception of current health, (2) perceived risk of suffering heart attack and (3) perceived ability to reduce that risk		
C	Type of population	Randomly selected men and women aged 40–59 from 13 GP practices in England, Wales and Scotland		
D	Number of subjects	2984 offered cardiovascular risk-screening and intervention 3576 undergoing screening without intervention		
E	Setting	GP practice in the UK		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	–	No way to assess what the range of psychological effects may be	–
	Quantitative	RCT comparing intervention screening programme with non-intervention: (1) self-assessed health (two questions), (2) perceived ability to reduce risk of CHD and (3) epidemiol-ogically assessed risk	Yes	Yes
G	Results	No sign of adverse reaction overall in men or women or at different levels of intervention intensity. The intervention group was slightly more positive		
H	Brief description of conclusions	No evidence to suggest that participation in intervention screening raises concerns about current health or the risk of suffering a heart attack. Participation seen as reassuring rather than threatening. Most noticeable effect was the reduction in the perceived ability to reduce the risk of future heart attack		
I	Were they justified by the results?	Yes – as far as no evidence of harmful effects is concerned No – with regard to complacency – since without more research one cannot tell whether people were complacent (not interested in further improvement) or not		
J	Transferability of study/limitations/ comments	Patient-centred approach with nurses who were aware of potential negative consequences. Difficult to transfer results if protocol differs. Also, subjects were within the population range of risk		
K	Relevance to policy	No signs of negative effects of cholesterol screening – **but** the sample was not a high-risk group! Focus is population screening, so for a target approach may not be transferable		

A	Study ID number	47 (66) – Tonstad, 1996[73 (86)]		
B	Questions addressed	To assess the psychological concerns of parents and children with FH. Parental concerns over diet, family and social relationships, and emotional difficulties		
C	Type of population	Children aged 6–16 years attending a national lipid clinic that accepts children with any psychosocial problems. Had to have attended the clinic at least twice		
D	Number of subjects	154 parents, 154 children (only one from each family; the one with the worse psychosocial function score)		
E	Setting	Norwegian specialist lipid clinic		
F	Study design	*Methods* Self-completed questionnaire based cross sectional study	*Appropriateness*	*Adequately described?*
	Qualitative	Parental questionnaire. Semi-structured interview with one child Blank space on questionnaire for comments!	A mixed approach would be appropriate, but no account of how/when qualitative assessed or reported given	No
	Quantitative	Reply to series of statements relating to diagnosis, follow-up, dietary treatment and psychosocial adverse effects. Scale: 'strongly agree' to 'totally disagree'. Child behaviour checklist for children	A mixed approach would be appropriate	Yes
G	Results	11% of parents thought their quality of life would have been better had they not known about FH. None wished diagnosis had not been made. Majority felt the advantages of treatment outweighed the disadvantages (in accordance with anecdotal evidence that diagnosis and subsequent dietary changes are better than uncertainty of postponement of treatment). 20% reported familial conflict		
H	Brief description of conclusions	Do not postpone treatment owing to fears of psychological effects but be aware of individual vulnerabilities and provide counselling for these. Also, due to effectiveness of statins, treatment may be postponed to adulthood (states problem of non-compliance in middle adolescence). Parents' preference, risk assessment and severity of hypercholesterolaemia should guide treatment. Only included those who have attended the clinic at least twice before. Non-attendance may reflect psychosocial problems, which may be more frequent than study suggests. There was a failure to use appropriate methods to elicit qualitative data. A blank space was provided for general comments, but few responded. The author acknowledges that more open-ended questions could have provided greater nuances		
I	Were they justified by the results?	No evidence given about the value of counselling. The author stated that the Child Behaviour Checklist is reliable in eliciting psychosocial function in children.		
J	Transferability of study/limitations/ comments	The participants were clinic attendees, so the results are less severe than may be the case for a less adherent group, whose members would have less awareness of the consequences of diagnosis of a particular disease or predisposition to a disease		
K	Relevance to policy	Psychological problems should not be a barrier to implementing an FH-screening programme		

A	Study ID number	100 – Irvine and Logan, 1994[69]		
B	Questions addressed	To determine whether there are negative psychosocial consequences of being labelled as hypercholesterolaemic and whether potential negative consequences can be mitigated by management of hypercholesterolaemia in the workplace (three levels of intervention; only one at the workplace).		
C	Type of population	Men at a car and a steel factory in Canada		
D	Number of subjects	229 (normal cholesterol group – controls). Complete data on 184 272 (high cholesterol group – cases). Complete data on 196		
E	Setting	Workplace (factory)		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	None	Yes – because of original questions asked	–
	Quantitative	RCT of advice-giving. Cohort study of men with normal and raised cholesterol levels. Psychological scales	Yes	Yes
G	Results	Hypercholesterolaemia detection and treatment were not associated with adverse changes in perceptions of psychological or physical health, participation in social/leisure activities or a global measure of life satisfaction. Role of denial: only half accepted the hypercholesterolaemic label, and had a more negative attitude to dietary changes and less change in total cholesterol levels; these men had the best 'mental health' scores		
H	Brief description of conclusions	Denial may be a risk factor for CHD as men in this group adapted their lifestyle least of all. The relationship between cholesterol level, mental health and denial should be further investigated		
I	Were they justified by the results?	No, as the 'denial' label was assigned with little thought for the implications of this or an attempt to understand it. Does not take into account the role of mental health in the overall index of 'well-being'. There was an inverse relationship between mental and physical health		
J	Transferability of study/limitations/ comments	The problem with this and other similar studies is that they test the labelling phenomenon rather than eliciting from the participants what the effect of the diagnosis may be. The perceived control over risk factors is likely to influence labelling effects		
K	Relevance to policy	As far as a population approach would be appropriate, these findings could support a screening for hypercholesterolaemia, as there appear to be no labelling effects. Diagnosis and labelling as 'hypercholesterolaemic' does not lead to adverse psychological consequences whereas hypertension labelling has been shown to. The study looked at moderately high cholesterol levels so not exactly relevant to FH, but it did investigate the effects of dietary advice		

A	Study ID number	141 – Rosenthal *et al.*, 1993[75]		
B	Questions addressed	To examine the relationship between family functioning, impact of the diagnosis of hypercholesterolaemia and the family's dietary habits. Three specific questions are addressed: 1. Do children with hypercholesterolaemia experience psychological distress (behaviour problems, self-esteem or depressive symptomatology)? 2. Is the degree of impact on the parents related to the length of time since the diagnosis? 3. Is either the family's functioning or locus of control related to implementation of good dietary choices?		
C	Type of population	Predominantly white, suburban families (90% Caucasian in the hypercholesterolaemic group and 100% in the comparison group)		
D	Number of subjects	36 children between 8 and 11 years (19 were hypercholesterolaemic and 17 had normal levels)		
E	Setting	One large suburban private paediatric office in the USA		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	–	Could have benefited from range of open-ended questions to elicit attitudes	–
	Quantitative	Cross-sectional study. Children filled in their own questionnaires (questions read out to them) and parents filled out questionnaires in a separate room. A number of standardised assessment measures were used (self-perception, depression, locus of control, family functioning, impact of the diagnosis)	Closed questions do not provide range of reactions if screening affects 'satisfaction with life' or gauge whether the child understands the impact of the diagnosis	Yes
G	Results	Children with hypercholesterolaemia and their families did not differ in measures of psychological functioning from their peers. Only 7 of the 18 affected and 3 of the 14 unaffected families 'made good dietary choices'. Cohesive and organised families with less conflict were more likely to implement the recommended diets.		
H	Brief description of conclusions	Concern over negative psychological consequences of cholesterol screening is unfounded. Family support and organisation in the treatment of chronically ill children may be a key component of dietary advice		
I	Were they justified by the results?	The results were overinterpreted. Very selected and small sample. No attempt was made to explore what the children or parents understood about the condition or the required diet		
J	Transferability of study/limitations/ comments	There are a number of problems: 1. lack of prospective design limits the ability to evaluate whether families were able to make changes in their diet or had good dietary practices anyway 2. sample bias (white, suburban families) 3. small sample size which resulted in large variation in psychological measures 4. no assessment of the child's understanding of the condition		
K	Relevance to policy	Important issue in terms of diet being the form of intervention most appropriate for the treatment of hypercholesterolaemia. Family conflict and cohesion could be important factors. Also, study of children with 'milder' diagnosis		

A	Study ID number	139 – Meland *et al.*, 1996[70]		
B	Questions addressed	1. To see if an opportunistic screening of CHD risk factors influenced satisfaction with life of those labelled 'high risk' compared with other screened persons. Two groups: (A) patient-centred self-directed intervention (PCSD) and (B) conventional care (CC) 2. To evaluate patient satisfaction and psychological well-being in high CHD risk subjects during a 1 year intervention study		
C	Type of population	Male GP patients aged 30–50 years offered an opportunistic screening for CHD risk factors		
D	Number of subjects	127 total (69 PCSD and 58 CC) (out of 468 initially screened)		
E	Setting	22 GP practices in Norway		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	–	–	–
	Quantitative	Cross-sectional screening and RCT of two intervention strategies. 16-item questionnaire completed at the initial screening to gauge risk status. High-risk group then filled in a questionnaire at home with the General Health Questionnaire and a quality of life satisfaction scale	A mixed approach would be appropriate, but not enough emphasis on qualitative analysis of labelling or other possible effects	Yes
G	Results	No significant differences between the reference and intervention groups. No adverse effects on satisfaction with life could be detected from labelling high CHD risk individuals, but 50% expressed distaste at being reminded of the risk of CHD		
H	Brief description of conclusions	Labelling as a high risk does not adversely affect emotional well-being. An attempt was made to increase patient responsibility, and self-determination for a lifestyle change may increase self-satisfaction but also dissatisfaction with care Patients may dislike reminders of disease risk and be dissatisfied with their own efforts		
I	Were they justified by the results?	It does not seem obvious looking at the results to say that there was no adverse effect on satisfaction with life due to labelling – in the results section, over 50% reported distaste at being reminded of risk of CHD. Also, authors note that results vary according to the scale questionnaire being used		
J	Transferability of study/limitations/ comments	Questionable because of possible unreliability of results. There was only one question measuring labelling, 'I found it unpleasant to be reminded of the risk of heart disease'. Not too relevant for FH; not told of degree of risk of subjects or their cholesterol levels		
K	Relevance to policy	Not really relevant, apart from the finding that no adverse effects of labelling were found, but questions arise on the way this was measured and the conclusion that no labelling effects were present		

A	Study ID number	145 – Tessaro *et al.*, 1997[78]		
B	Questions addressed	To gain a better understanding of women's knowledge, perceived benefits, risks, and concerns about testing and potential influences and support needs in making a decision whether or not to have a genetic test for breast cancer		
C	Type of population	Women recruited through breast programme at a major medical centre and two community hospitals in the USA		
D	Number of subjects	66 women in 8 focus groups. Five groups of affected women, and three groups of relatives of affected women		
E	Setting	Semi-structured group session in an informal setting moderated by a group facilitator		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	Focus groups	Yes. Data are open-ended. No attempt was made to put experiences and events into predetermined, standardised categories. Rather, an attempt was made to capture ideas in women's own words	Yes – eliciting attitudes on (1) knowledge of disease, (2) altruism, (3) support and normative influences, (4) concern for family members, (5) stress and uncertainty, (6) lack of proven options and (7) confidentiality of information
	Quantitative	–	–	–
G	Results	Lack of knowledge about genetics or implications of positive or negative test. Concern over stress on families, confidentiality and insurance implications. Altruism in decision to undergo screening		
H	Brief description of conclusions	There is a need to provide women with balanced information about the pros and cons of screening, ascertain how best to involve doctors in women's decision to be screened, and consider the effects on family relationships. Also, public education is needed on the implications of genetic testing		
I	Were they justified by the results?	Yes		
J	Transferability of study/limitations/ comments	Yes – because the study has managed to elicit some of the important concerns that people face when undergoing genetic screening Sample had better than average educational level		
K	Relevance to policy	Main advantages: provides information to reduce uncertainty and assist with future decision-making over treatment, surveillance and lifestyle changes Main disadvantages: concerns over confidentiality and loss of insurance, lack of proven options postscreening and stress of knowing you are a mutation carrier		

A	Study ID number	103 – Kash *et al.*, 1995[79]		
B	Questions addressed	To assess whether counselling strategies reduce emotional distress and whether they decrease perceived vulnerability		
C	Type of population	High-risk women who were part of a cancer surveillance programme		
D	Number of subjects	40		
E	Setting	Psycho-educational intervention (pilot) to develop appropriate counselling initiatives		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	Group interventions a particular strategy. To help women assess risk accurately, increase knowledge of disease and improve adherence to screening behaviours. Not clear if authors conducted a review or simply reported from a literature review	Yes	No
	Quantitative	Measured psychological distress by an established 'scale' index. It is unclear if a questionnaire was used or if the trial was randomised	Yes	No. Very little information on numbers, setting, response rate or data collection methods and measures
G	Results	80% of women overestimated their risk of developing breast cancer, which can be a major barrier to screening. High levels of distress were shown to diminish quality of life and contribute to lower rates of screening adherence. Cancer anxiety and psychological distress were significant predictors of poor adherence. Denial and avoidance mentioned as ways of coping with fears (not clear if this came out of intervention sessions or is a comment from the existing literature)		
H	Brief description of conclusions	The way risk information (positive communication) is conveyed can affect psychological distress and, consequently, adherence. 6 week intervention was shown to reduce the perception of risk, and increase adherence to screening behaviour, but this is based on inadequately described results		
I	Were they justified by the results?	Difficult to comment upon because there is no account of the study methodology. Results were not reported, and unsubstantiated statements were given		
J	Transferability of study/limitations/ comments	No indication how the study was conducted, how the participants were chosen, or what questions were asked or in what manner. Although the intervention appears to address key problems in screening adherence, there is no detailed account of how the programme was designed, which limits the validity of the positive conclusions		
K	Relevance to policy	The intervention programme could be very useful in providing accurate information about the nature of the disease being screened for. If overestimation of risk and disease misbeliefs contribute to poor screening adherence, then educational intervention would be beneficial. Need evidence		

A	Study ID number	156 – Lerman *et al*., 1997(b)[80]		
B	Questions addressed	To evaluate the impact of alternate strategies for pretest education and counselling on decision-making regarding *BRCA1* testing (1 = education/information approach; other = counselling/interpretative approach versus control group)		
C	Type of population	Women at low to moderate risk of breast and/or ovarian cancer. Aged 18–75 years with at least one first-degree relative with breast cancer. Women with a personal history of cancer were excluded		
D	Number of subjects	440/578. 400 completed the baseline, intervention and follow-up. 76% response rate, but 578/740 eligible women (78%) was the initial response, so should not the response rate be 400/740 (54%)?		
E	Setting	Recruited from one of two cancer centres in Washington, DC, USA		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	–	Yes	–
	Quantitative	RCT	Yes	Yes
G	Results	Increases in knowledge of about 20% in both the education (E) and education and counselling (E plus C) groups at the 1 month follow-up compared with the control group, whose knowledge decreased. Group E alone also showed a small, but statistically significant, decreases in personal risk of having mutation. The E plus C approach, but not E alone, is superior to the control group in producing increases in perceived limitations and risks of *BRCA* testing		
H	Brief description of conclusions	Educational approach alone may be as effective as education and counselling in increasing knowledge. The E plus C approach may succeed in providing a balanced evaluation of the consequences of alternate decisions, but this does not mean that it will increase the intention of having a test		
I	Were they justified by the results?	Yes		
J	Transferability of study/limitations/ comments	The majority of the subjects were white, well-educated and above-average-income women. There is thus still a need to measure the effects of these strategies on different ethnic and socioeconomic backgrounds		
K	Relevance to policy	There was no significant difference between the E and E plus C groups in enhancement of knowledge, which is a key aspect of medical decision-making. Intention to have a test was not altered by the different interventions. There is still debate whether counselling and the opportunity to evaluate the positive and negative consequences provide optimal decision-making and whether this is more effective		

A	Study ID number	116 – Billings *et al.*, 1992[85]		
B	Questions addressed	To discover whether incidents which may reflect genetic discrimination are occurring in the workplace, in access to social services, in insurance underwriting and in the delivery of health care		
C	Type of population	Mailings to professionals working in the field of clinical genetics, genetic counselling, disability medicine, paediatrics and social services in New England, USA A request for information was published in the *American Journal of Human Genetics*		
D	Number of subjects	1119 letters mailed, 42 responses received; 29 eligible		
E	Setting	Not stated		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	Case history study	Yes	Yes
	Quantitative	–	–	–
G	Results	29/42 responses received met the inclusion criteria. 41 incidents recorded. All but two involved insurance (32) or employment issues (7). Three themes emerged: (1) the asymptomatic ill – only 'abnormality' lies in one's genotype; (2) problem of variability – see the 'label' but not differences in severity of a condition or concept of incomplete penetrance; (3) the at risk – to test or not to test. Problems of both promise and burden of genetic testing. Individuals detected early and successfully treated but still stigmatised and denied insurance		
H	Brief description of conclusions	Decisions, e.g. about insurance cover, often made by an associated diagnostic label rather than the actual health status of the individual. Consequences for people getting a job, health and life insurance. The ability to change jobs may be limited, and this is largely a result of poor interpretation of the genetic diagnosis. Genetic conditions misperceived as universally serious, disabling and potentially life-threatening. Produces stigmatisation, discrimination and infringement of rights following diagnostic labelling		
I	Were they justified by the results?	Yes		
J	Transferability of study/limitations/ comments	A very small proportion of replies were received. This is not surprising as people would be reluctant to formally acknowledge discrimination. Will be difficult for any study to elicit data on discrimination as it tends to be anecdotal. The UK may be slightly different to USA regarding health insurance policies (but still relevant)		
K	Relevance to policy	It is relevant in that the study aims to find out whether genetic discrimination appears to exist and it also covers issue of the 'asymptomatic ill'. If the range and extent of discrimination revealed by this study exists in the UK, policy will have to take this into account. The study strongly suggests the need for more systematic investigation and review of screening programmes before implementation to check for possible discriminatory effects of diagnosis		

A	Study ID number	41 – Neil and Mant, 1991[83]		
B	Questions addressed	To examine how insurance companies assess proposals for life assurance from raised cholesterol applicants and to determine the excess rating applied		
C	Type of population	49 UK companies underwriting term life assurance using four fictional men, aged 30 years		
D	Number of subjects	Four fictional men 30 years seeking 20 year policies payable only on death. Two had cholesterol levels of 6.4 and 8.1 mmol/l but no other risk factors, one was overweight, hypertensive, smoked 20 cigarettes per day and had a cholesterol level of 8.1 mmol/l . The final man had possible FH and a total cholesterol level of 10.7 mmol/l after treatment		
E	Setting	UK		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	Four fictional case studies. Preliminary survey for exclusion purposes	Yes	Yes
	Quantitative	Cross-sectional survey	Yes	Yes
G	Results	All companies used explicit criteria to assess the mortality risk of hyperlipidaemic individuals. There was no excess for the 6.4 mmol/l man, and a small/variable increase for the 8.1 mmol/l man (median excess 50%, range 0–75%). Man 3, with multiple risk factors, had a median excess of 135% and a range of 50–200%. The man with possible FH had a smaller but more variable excess (75% median; range 0–200%). There was considerable variation in excess applied		
H	Brief description of conclusions	Mild hypercholesterolaemia (without other risk factors) is unlikely to result in higher premiums. Excess ratings for a 30 year old, uncomplicated, well-controlled insulin-dependent diabetic individual has 100% excess, and a 30 year old with possible FH has a 75% excess. This suggests hypercholesterolaemia is considered relatively less important than diabetes or hypertension (55–285% depending on severity)		
I	Were they justified by the results?	Yes		
J	Transferability of study/ limitations/comments	The excess rating applied depends on the type and term of the policy and whether other cardiovascular risk factors are present		
K	Relevance to policy	Some companies applied little or no excess mortality to a possible FH patient (but others were very high). Identified FH patients will most likely have to pay higher premiums. This may deter asymptomatic individuals from being screened		

A	Study ID number	177 – Low *et al.*, 1998[60]		
B	Questions addressed	To gather empirical evidence on how families with genetic conditions feel they have been treated by the insurance industry, the medical profession, employers and social services in the UK (the omnibus group was asked if problems were experienced in obtaining life insurance)		
C	Type of population	7000 members from seven support groups for families with genetic disorders in the UK (study group) and 1033 members of the general public (omnibus survey)		
D	Number of subjects	8033		
E	Setting	Postal survey		
F	Study design	*Methods*	*Appropriateness*	*Adequately described?*
	Qualitative	–		
	Quantitative	Cross-sectional structured, postal survey	Yes, as far as preliminary enquiries are concerned, but open questions may have added to it	Yes, but only for two questions
G	Results	The response rate was 53% after excluding replies from people not affected, or who had no family member affected by a genetic disorder. 33.4% had problems when applying for life insurance compared with 5% in the omnibus survey. Furthermore, 13% of people believed they were discriminated against due to their family's genetic risk and they presented no adverse actuarial risk on genetic grounds		
H	Brief description of conclusions	Inconsistent results suggest error on behalf of insurers rather than a coherent industry-wide policy of genetic discrimination. The 13% (17/533) who believed they were discriminated against suggests treatment by insurers is unjustified and discriminatory		
I	Were they justified by the results?	Yes		
J	Transferability of study/limitations/ comments	The study covers perceptions of discrimination rather than providing any objective measure of it. Also, because some people's health is affected by their disorder while others are not, interpreting the results is more difficult (whether it is genetic reasons for the discrimination or actual health problems)		
K	Relevance to policy	Inconsistency on behalf of insurers could be a problem for FH patients too, especially if actuarial risk is not based on the epidemiological evidence		

Appendix 2

Mortality and death rate data

The raw mortality data used in the life tables is shown in *Table 33* . *Table 34* compares death rates. For all age–sex groups, the 1980–89 cohort has higher death rates than the 1990–98 cohort. At ages 20–39 and 40–59 years, death rates are lower for the general population than for the Simon Broome Register cohorts with the exception of females aged 40–59 years in the 1990–98 cohort. At 60–79 years of age, death rates are lower in the combined Simon Broome Register cohort than they are in the general population despite ischaemic heart disease death rates being higher.

With the exception of the Simon Broome Register 1980–89 cohort for the 40–59 years age group, death rates are lower in women than in men.

TABLE 33 *Mortality data*

Age range (years)		Breadth of age range (years)	Population (× 1,000)	All deaths	IHD deaths	Age range (years)		Breadth of age range (years)	Population (× 1,000)	All deaths	IHD deaths
(*y*)	(*z*)	(*x*)	(*b*)	(*c*)	(*d*)	(*y*)	(*z*)	(*x*)	(*b*)	(*c*)	(*d*)
Male FH mortality (1980–89)[a]						***Female FH mortality (1980–89)***[a]					
20 –	39	20	0.439	5	5	20 –	39	20	0.335	1	1
40 –	59	20	0.653	6	4	40 –	59	20	0.447	7	4
Male FH mortality (1980–98)[b]						***Female FH mortality (1980–98)***[b]					
60 –	79	20	1.007	25	16	60 –	79	20	1.698	28	16
Male FH mortality (1990–98)[b]						***Female FH mortality (1990–98)***[b]					
20 –	39	20	1.340	4	2	20 –	39	20	1.413	1	1
40 –	59	20	2.475	20	13	40 –	59	20	1.851	5	2
Male mortality, England and Wales (1997)[c]						***Female mortality, England and Wales (1997)***[c]					
15 –	19	5	1,621.0	947	3	15 –	19	5	1,533.8	426	0
20 –	24	5	1,627.9	1,442	3	20 –	24	5	1,549	490	4
25 –	29	5	2,036.8	1,789	22	25 –	29	5	1,935.1	679	4
30 –	34	5	2,206.7	2,151	87	30 –	34	5	2,111.2	1,039	23
35 –	39	5	1,983.8	2,374	221	35 –	39	5	1,925.2	1,593	57
40 –	44	5	1,715.9	3,333	618	40 –	44	5	1,699.8	2,144	113
45 –	49	5	1,749.4	5,267	1,245	45 –	49	5	1,749	3,571	240
50 –	54	5	1,673.0	8,217	2,296	50 –	54	5	1,678.5	5,445	443
55 –	59	5	1,317.6	11,429	3,369	55 –	59	5	1,335.8	7,042	868
60 –	64	5	1,206.3	17,478	5,351	60 –	64	5	1,249.7	10,907	1,844
65 –	69	5	1,104.1	27,802	8,244	65 –	69	5	1,227.3	18,307	3,548
70 –	74	5	943.6	40,222	11,395	70 –	74	5	1,164.7	29,986	6,421
75 –	79	5	691.8	46,371	12,854	75 –	79	5	1,010.3	41,934	9,613
80 –	84	5	401.7	43,836	10,974	80 –	84	5	739.8	53,574	12,058
85 –	89	5	191.9	32,343	7,186	85 –	89	5	469.5	57,139	11,673
90+			65.9	16,723	3,051	90+			261.5	53,794	8,598

IHD, ischaemic heart disease
[a] *Scientific Steering Committee (1991)*[6]
[b] *Unpublished data from the Simon Broome Register*
[c] *Office of National Statistics (1998)*[131]

TABLE 34 *Death rates – by age, sex and data set*

	Men		Women	
	All deaths	**IHD deaths**	**All deaths**	**IHD deaths**
Age 20–39 years				
England and Wales (1997)	0.0010	0.00004	0.0005	0.00001
Simon Broome Register (1980–89)	0.0114	0.0114	0.0030	0.0030
Simon Broome Register (1990–98)	0.0030	0.0015	0.0007	0.0007
Age 40–59 years				
England and Wales Register (1997)	0.0044	0.0012	0.0028	0.0003
Simon Broome Register (1980–89)	0.0092	0.0061	0.0157	0.0089
Simon Broome Register (1990–98)	0.0081	0.0053	0.0027	0.0011
Age 60–79 years				
England and Wales (1997)	0.0334	0.0096	0.0217	0.0046
Simon Broome Register (1980–98)	0.0248	0.0159	0.0165	0.0094

Appendix 3

Explanation of the life table calculations

An outline of how life expectancy, drug costs and CHD event costs were calculated using life tables is provided here. The examples given are for a cohort of males aged 16 years, but the same methods are applied for all cohorts.

General calculations (*Tables 35 and 36*)

Columns (y) and (z) indicate the age-ranges, and column (x) is the breadth of the age-range:

$$x_i = z_i - y_i + 1$$

Columns (b) and (c) are mortality data from appendix 2.

Column (f) gives the all-cause age-range-specific death rate, calculated as (c_i) divided by (b_i) for age group i:

$$f_i = c_i/(b_i \times 1000)$$

Column (g) shows how many men from an initial cohort of 1000 men aged 20 years would survive a particular age range. This is the survival rate (1 minus the death rate (f)) to the power of (x) multiplied by the number surviving from the previous age-range (g_{-1}):

$$g_i = g_{i-1}(1 - f_i)^{x_i}$$

Column (j) shows the mid-point of each age range:

$$j_i = y_i + (x_i/2) \qquad Y_i < 90$$
$$j_i = 94 \qquad \text{males } Y_i \geq 90$$
$$j_i = 96 \qquad \text{females } Y_i \geq 90$$

Column (l) shows the proportion of the original cohort that will die in each age range:

$$l_i = (g_i - g_{i-1})/1000$$

Column (m) is the product of columns (j) and (l):

$$m_i = j_i l_i$$

The life expectancy (expected age at death, not the expected number of years remaining) is the sum of column (m):

$$\text{LE} = \sum_i m_i$$

Column (t) gives the mid-point of the age range (j_i) minus the age at diagnosis (y_1 in example 16) for age group i:

$$t_i = j_i - y_i$$

Column (u) gives (t_i) discounted at 1%:

$$U_i = \sum_{A=1}^{t_i} [1/(1.01)^A]$$

Column (r) gives the discounted mid-point of the age range for age group i:

$$r_i = u_i + y_1$$

Column (s) is the product of columns (r) and (l):

$$s_i = r_i l_i$$

The discounted life expectancy is the sum of column (s):

$$\text{LE} = \sum_i s_i$$

Column (a) is the number of deaths in age range (i) from an original cohort of 1000 individuals:

$$a_i = g_{i-1} - g_i$$

Column (e) is the number of coronary deaths in age range (i) from an original cohort of 1000 individuals. It is the total number of deaths (e) multiplied by the ratio of coronary deaths (d) to all deaths (c):

$$e_i = e_i(d_i/c_i)$$

Column (h) is the ratio of non-fatal to fatal coronary events:

$$h_i = 1.4 \qquad \text{men}$$
$$h_i = 1.2 \qquad \text{women}$$

Column (o) is the number of non-fatal coronary

events in age range (i) from an original cohort of 1000 individuals. It is the number of fatal events (e) multiplied by the ratio of non-fatal to fatal events (h):

$$o_i = h_i e_i$$

Column (v) is the cost of all events occurring in the age range for a cohort of 1000 individuals. It is the number of events ((e) + (o)) multiplied by the average cost of a coronary event (£1543.62):

$$v_i = 1543.62(o_i + e_i)$$

Column (w) gives the total cost (v_i) discounted at 6%:

$$w_i = v_i/(1.06)^{t_i}$$

The cost of CHD events per person is the sum of column (w) divided by 1000:

$$\text{CHD cost} = (1/1000)\sum_i w_i$$

Column (B) is the annual cost of treatment (£569.53) multiplied by the compliance rate (82%):

$$B_i = 467.01$$

Column (C) shows the number of years of drug treatment for individuals dying in age range (i):

$$C_i = t_i \qquad Z_i < 60$$
$$C_i = 60 - y_1 \qquad Z_i \geq 60$$

Column (D) is the product of columns (B), (C) and (l). It is the undiscounted treatment cost associated with those individuals dying in age range (i) weighted by the probability of dying in that age range:

$$D_i = B_i C_i l_i$$

Column (E) gives (t) discounted at 6%:

$$E_i = \sum_{A=1}^{C_i} [1/(1.06)^A]$$

Column (F) is the product of columns (B), (E) and (l). It is the discounted treatment cost associated with those individuals dying in age range (i) weighted by the probability of dying in that age range:

$$F_i = B_i E_i l_i$$

The cost of statin treatment per person is the sum of column (F):

$$\text{DRUG cost} = \sum_i F_i$$

Calculations based on 4S results (*Table 37*)

Column (d) is coronary mortality data from appendix 2.

Column (n) gives the number of expected coronary deaths after intervention, based on the 4S results:

$$n_i = 0.58 d_i \qquad \text{age} < 60 \text{ years}$$

Column (p) gives the number of expected deaths after the intervention, based on the 4S results:

$$p_i = c_i - d_i + n_i \qquad \text{age} < 60 \text{ years}$$

Column (q) gives the all-cause age-range-specific death rate after intervention, based on the 4S results, calculated as (p_i) divided by (b_i) for age groups below the age of 60 years:

$$q_i = p_i/(b_i \times 1000) \qquad \text{age} < 60 \text{ years}$$
$$q_i = c_i/(b_i \times 1000) \qquad \text{age} \geq 60 \text{ years}$$

All other calculations are the same as *Table 35*.

TABLE 35 *Life table for a 16 year old male with definite FH (left-hand portion)*

Untreated

	Age range			Population (× 1,000)	All deaths	Coronary deaths	Death rate	Survivors	Mid-point of age range	% of cohort dying in age range		Mid-point minus start age
(*i*)	(*y*)	(*z*)	(*x*)	(*b*)	(*c*)	(*d*)	(*f*)	(*g*) 1,000	(*j*)	(*l*)	(*m*)	(*t*)
1	16	19	4	1,621	947	3	0.0005842	997.6652	18	0.2%	0.042026078	2.0
2	20	39	20	0.439	5	5	0.0113895	793.3942	30	20.4%	6.12813078	14.0
3	40	59	20	0.653	6	4	0.0091884	659.6461	50	13.4%	6.687404168	34.0
4	60	79	20	1.007	25	16	0.0248262	398.9802	70	26.1%	18.24661323	54.0
5	80	84	5	389.8	44,966	12,517	0.1153566	216.1686	82.5	18.3%	15.08195886	66.5
6	85	89	5	159.6	27,596	6,847	0.1729073	83.6688	87.5	13.2%	11.59373002	71.5
7	90			249.3	12,316	2,631		0	94	8.4%	7.86486823	78.0
										100.0%		
										Life expectancy =	**65.64473137**	

Treated

	Age range			Population (× 1,000)	All deaths	Coronary deaths	Death rate	Survivors	Mid-point of age range	% of cohort dying in age range		Mid-point minus start age
(*i*)	(*y*)	(*z*)	(*x*)	(*b*)	(*c*)	(*d*)	(*f*)	(*g*) 1,000	(*j*)	(*l*)	(*m*)	(*t*)
1	16	19	4	1,621	947	3	0.0005842	997.6652	18	0.2%	0.042026078	2.0
2	20	39	20	1.34	4	2	0.0029851	939.7623	30	5.8%	1.737086998	14.0
3	40	59	20	2.475	20	13	0.0080808	798.9947	50	14.1%	7.038381612	34.0
4	60	79	20	1.007	25	16	0.0248262	483.2638	70	31.6%	22.10116427	54.0
5	80	84	5	389.8	44,966	12,517	0.1153566	261.8337	82.5	22.1%	18.26798465	66.5
6	85	89	5	159.6	27,596	6,847	0.1729073	101.3436	87.5	16.0%	14.04287626	71.5
7	90			249.3	12,316	2,631		0	94	10.1%	9.526301813	78.0
										100.0%		
										Life expectancy =	**72.75582167**	

TABLE 36 *Life table for a 16 year old male with definite FH (right-hand portion)*

Untreated

	All deaths	Coronary deaths	Ratio of non-fatal to fatal	Non-fatal events	Total cost (undiscounted)	Mid-point minus start age	Total cost (discounted)
(*i*)	(*a*)	(e)	(*h*)	(*o*)	(*v*)	(*t*)	(*w*)
1	2.3	0.0	1.4	0.0	£27.40	2.0	£24.39
2	204.3	204.3	1.4	286.0	£756,760.42	14.0	£334,715.86
3	133.7	89.2	1.4	124.8	£330,329.95	34.0	£45,556.31
4	260.7	166.8	1.4	233.6	£618,038.94	54.0	£26,576.58
5	182.8	50.9	1.4	71.2	£188,526.08	66.5	£3,913.19
6	132.5	32.9	1.4	46.0	£121,792.62	71.5	£1,889.09
7	83.7	17.9	1.4	25.0	£66,216.53	78.0	£703.25
		561.9	786.7	Undiscounted cost per 1,000 =	£2,081,691.93	Discounted cost per 1,000 =	£413,378.67
				Mean cost =	£2,081.69	Mean cost =	**£413.38**

Treated

	All deaths	Coronary deaths	Ratio of non-fatal to fatal	Non-fatal events	Total cost (undiscounted)	*mid*-point minus start age	Total cost (discounted)	Annual cost per patient	Years (undiscounted)	Cost (undiscounted)	Years (discounted)	Cost (discounted)
(*i*)	(*a*)	(e)	(*h*)	(*o*)	(*v*)	(*t*)	(*w*)	(*B*)	(*C*)	(*D*)	(*E*)	(*F*)
1	2.3	0.0	1.4	0.0	£27.40	2.0	£24.39	£467.01	2.0	£2.18	1.83	£2.00
2	57.9	29.0	1.4	40.5	£107,256.09	14.0	£47,439.47	£467.01	14.0	£378.58	9.29	£251.35
3	140.8	91.5	1.4	128.1	£338,975.10	34.0	£46,748.58	£467.01	34.0	£2,235.18	14.37	£944.57
4	315.7	202.1	1.4	282.9	£748,598.11	54.0	£32,190.82	£467.01	44.0	£6,487.84	15.38	£2,268.26
5	221.4	61.6	1.4	86.3	£228,351.74	66.5	£47,39.85	£467.01	44.0	£4,550.09	15.38	£1,590.79
6	160.5	39.8	1.4	55.7	£147,521.00	71.5	£2,288.15	£467.01	44.0	£3,297.85	15.38	£1,152.99
7	101.3	21.6	1.4	30.3	£80,204.60	78.0	£851.81	£467.01	44.0	£2,082.47	15.38	£728.07
		445.6	623.9	Undiscounted cost per 1,000 =	£1,650,934.04	Discounted ost per 1,000 =	£134,283.06		Undiscounted		Discounted	
				Mean cost =	£1,650.93	Mean cost =	**£134.28**		cost =	£19,034.20	cost =	**£6,938.03**

TABLE 37 *Life expectancy for males with definite FH aged 20 years (4S treatment effect)*

Male untreated FH mortality							After treatment						
	Age range			Population (× 1000)	All deaths	IHD deaths	All deaths	IHD deaths	Death rate	Survivors	Mid-point of age range	% of cohort dying in age range	
(*i*)	(*y*)	(*z*)	(*x*)	(*b*)	(*c*)	(*d*)	(*p*)	(*n*)	(*q*)	(*g*)			(*m*)
										1,000			
1	20	– 39	20	0.439	5	5	2.9	2.9	0.0066059	875.8532	30	12.4%	3.724403541
2	40	– 59	20	0.653	6	4	4.32	2.32	0.0066156	766.9691	50	10.9%	5.444206063
6	60	– 79	20	1.007	25	16			0.0248262	463.8934	70	30.3%	21.21529747
7	80	– 84	5	401.7	43,836	10,974			0.1091262	260.3149	82.5	20.4%	16.79522349
8	85	– 89	5	191.9	32,343	7,186			0.1685409	103.4436	87.5	15.7%	13.72624474
9	90+			65.9	16,723	3,051				0	94	10.3%	9.723696608
												100.0%	
												Life expectancy =	**70.62907191**

Appendix 4

CHD cost components*

TABLE 38 *Summary of cost per patient (£)*

	Computed tomography/ surgery	Angiography	No computed tomography/ angriography	
Event				
Hospital stay[a]	270.14	506.45	521.41	
Angiography	55.88	42.47	9.31	
Percutaneous transluminal coronary angioplasty (stent)	199.12	41.07	9.96	
Coronary artery bypass graft	119.57	68.03	–	
Stress test	2.67	4.21	5.34	
Total cost	**647.38**	662.22	**546.02**	
Cost over 6 month follow-up				
Angiography	33.34	37.63	37.07	
Percutaneous transluminal coronary angioplasty (stent)	87.11	77.16	51.02	
Coronary artery bypass graft	144.31	111.32	146.37	
Hospital episodes	888.23	639.88	466.48	
Outpatient attendances	33.09	40.37	22.28	
Primary care services[b]	18.06	18.06	18.06	
Prescription drugs[b]	23.74	23.74	23.74	
Total cost	**1,227.89**	**948.16**	**765.02**	
Mean cost per patient	1,875.27	1,610.38	1,311.04	
Proportion of patients	20%	40%	40%	
Cost for 1000 patients	375,053	644,153	524,416	1,543,622
Overall mean cost per patient				**1,543.62**

[a] *Includes drugs*

Assumptions in the CHD cost modelling:

- Excludes people over the age of 69 years.
- When rehospitalised, it is to the same (or an equivalent) institution, with an equivalent mean length of stay.
- Outpatient attendances are based on means from the cost of CHD study.*
- Primary care costs from the cost of CHD study.*
- Gross primary care drug costs include all drugs.
- Net primary care costs exclude drugs that were already prescribed prior to the event.
- All 'bed days' unit costs include the cost of drugs (ranges between £7 and £60 per bed day).
- Cost per event is the mean of all hospital types and is not specific to age bands.
- Prevalence of FH by age group is unaffected by mortality.
- Each mean cost per patient is a mean across the total sample, not for specific individuals who follow specific pathways .
- Each event, irrelevant of age or sex, is equally likely to be fatal.

* Data prepared by Stevens and co-workers.[122]

Appendix 5

Results of the programme costs in all the scenarios

Universal 16 (clinical confirmation)

	Stage at which subject leaves programme	Probability (reaching stage)	Probability (leaving at stage)	Probability (overall)	Cost (of stage)	Cost (overall)	**Screen cost per person invited**
A	Stage 1	1.00000	0.45000	0.45000	£0.50	£0.50	£0.23
B	Stage 2	0.55000	0.95000	0.52250	£8.77	£9.27	£4.84
C	Stage 3	0.02750	0.25000	0.00688	£0.00	£9.27	£0.06
D	Stage 4	0.02063	0.06500	0.00134	£25.82	£35.09	£0.05
E	Stage 5	0.01928	0.96200	0.01855	£67.00	£102.09	£1.89
F	Stage 6	0.00073	1.00000	0.00073	£0.00	£102.09	£0.07
				1.00000	£102.09		***£7.15***

Number needed to screen to find 1 case = 1364.6
Cost per case detected = £9754.41

2
Universal 16 (genetic confirmation)

	Stage at which subject leaves programme	Probability (reaching stage)	Probability (leaving at stage)	Probability (overall)	Cost (of stage)	Cost (overall)	**Screen cost per person invited**
A	Stage 1	1.00000	0.45000	0.45000	£0.50	£0.50	£0.23
B	Stage 2	0.55000	0.95000	0.52250	£8.77	£9.27	£4.84
C	Stage 3	0.02750	0.25000	0.00688	£0.00	£9.27	£0.06
D	Stage 4	0.02063	0.06500	0.00134	£25.82	£35.09	£0.05
E	Stage 5	0.01928	0.98100	0.01892	£1067.00	£1102.09	£20.85
F	Stage 6	0.00037	1.00000	0.00037	£0.00	£1102.09	£0.40
				1.00000	£1102.09		***£26.43***

Number needed to screen to find 1 case = 2729.2
Cost per case detected = £72,140.39

3
Universal (clinical confirmation)

	Stage at which subject leaves programme	Probability (reaching stage)	Probability (leaving at stage)	Probability (overall)	Cost (of stage)	Cost (overall)	**Screen cost per person invited**
A	Stage 1	1.00000	0.34500	0.34500	£0.50	£0.50	£0.17
B	Stage 2	0.65500	0.95000	0.62225	£8.77	£9.27	£5.77
C	Stage 3	0.03275	0.25000	0.00819	£0.00	£9.27	£0.08
D	Stage 4	0.02456	0.06500	0.00160	£25.82	£35.09	£0.06
E	Stage 5	0.02297	0.96200	0.02209	£67.00	£102.09	£2.26
F	Stage 6	0.00087	1.00000	0.00087	£0.00	£102.09	£0.09
				1.00000	£102.09		***£8.42***

Number needed to screen to find 1 case = 1145.9
Cost per case detected = £9645.03

4
Universal (genetic confirmation)

	Stage at which subject leaves programme	Probability (reaching stage)	Probability (leaving at stage)	Probability (overall)	Cost (of stage)	Cost (overall)	**Screen cost per person invited**
A	Stage 1	1.00000	0.34500	0.34500	£0.50	£0.50	£0.17
B	Stage 2	0.65500	0.95000	0.62225	£8.77	£9.27	£5.77
C	Stage 3	0.03275	0.25000	0.00819	£0.00	£9.27	£0.08
D	Stage 4	0.02456	0.06500	0.00160	£25.82	£35.09	£0.06
E	Stage 5	0.02297	0.98100	0.02253	£1067.00	£1102.09	£24.83
F	Stage 6	0.00044	1.00000	0.00044	£0.00	£1102.09	£0.48
				1.00000	£1102.09		***£31.38***

Number needed to screen to find 1 case = 2291.7
Cost per case detected = £71,921.64

5
Opportunistic GP – clinical confirmation

	Stage at which subject leaves programme	Probability (reaching stage)	Probability (leaving at stage)	Probability (overall)	Cost (of stage)	Cost (overall)	**Screen cost per person invited**
A	Stage 1	1.00000	0.20000	0.20000	£0.00	£0.00	£0.00
B	Stage 2	0.80000	0.95000	0.76000	£8.77	£8.77	£6.67
C	Stage 3	0.04000	0.25000	0.01000	£0.00	£8.77	£0.09
D	Stage 4	0.03000	0.06500	0.00195	£25.82	£34.59	£0.07
E	Stage 5	0.02805	0.96200	0.02698	£67.00	£101.59	£2.74
F	Stage 6	0.00107	1.00000	0.00107	£0.00	£101.59	£0.11
				1.00000	£101.59		***£9.67***

Number needed to screen to find 1 case = 938.2
Cost per case detected = £9072.10

6
Opportunistic GP – genetic confirmation

	Stage at which subject leaves programme	Probability (reaching stage)	Probability (leaving at stage)	Probability (overall)	Cost (of stage)	Cost (overall)	**Screen cost per person invited**
A	Stage 1	1.00000	0.20000	0.20000	£0.00	£0.00	£0.00
B	Stage 2	0.80000	0.95000	0.76000	£8.77	£8.77	£6.67
C	Stage 3	0.04000	0.25000	0.01000	£0.00	£8.77	£0.09
D	Stage 4	0.03000	0.06500	0.00195	£25.82	£34.59	£0.07
E	Stage 5	0.02805	0.98100	0.02752	£1067.00	£1101.59	£30.31
F	Stage 6	0.00053	1.00000	0.00053	£0.00	£1101.59	£0.59
				1.00000	£1101.59		***£37.72***

Number needed to screen to find 1 case = 1876.3
Cost per case detected = £70,775.78

7
Opportunistic early MI – clinical confirmation

	Stage at which subject leaves programme	Probability (reaching stage)	Probability (leaving at stage)	Probability (overall)	Cost (of stage)	Cost (overall)	**Screen cost per person invited**
A	Stage 1	1.00000	0.34500	0.34500	£0.50	£0.50	£0.17
B	Stage 2	0.65500	0.86900	0.56920	£8.77	£9.27	£5.28
C	Stage 3	0.08581	0.09000	0.00772	£0.00	£9.27	£0.07
D	Stage 4	0.07808	0.06500	0.00508	£25.82	£35.09	£0.18
E	Stage 5	0.07301	0.36546	0.02668	£67.00	£102.09	£2.72
F	Stage 6	0.04633	1.00000	0.04633	£0.00	£102.09	£4.73
				1.00000	£102.09		***£13.15***

Number needed to screen to find 1 case = 21.6
Cost per case detected = £283.90

8
Opportunistic early MI – genetic confirmation

	Stage at which subject leaves programme	Probability (reaching stage)	Probability (leaving at stage)	Probability (overall)	Cost (of stage)	Cost (overall)	**Screen cost per person invited**
A	Stage 1	1.00000	0.34500	0.34500	£0.50	£0.50	£0.17
B	Stage 2	0.65500	0.86900	0.56920	£8.77	£9.27	£5.28
C	Stage 3	0.08581	0.09000	0.00772	£0.00	£9.27	£0.07
D	Stage 4	0.07808	0.06500	0.00508	£25.82	£35.09	£0.18
E	Stage 5	0.07301	0.68273	0.04984	£1067.00	£1102.09	£54.93
F	Stage 6	0.02316	1.00000	0.02316	£0.00	£1102.09	£25.53
				1.00000	£1102.09		***£86.16***

Number needed to screen to find 1 case = 43.2
Cost per case detected = £3719.68

9
Case finding – clinical confirmation

	Stage at which subject leaves programme	Probability (reaching stage)	Probability (leaving at stage)	Probability (overall)	Cost (of stage)	Cost (overall)	**Screen cost per person invited**
A	Stage 1	1.00000	0.05000	0.05000	£4.65	£4.65	£0.23
B	Stage 2	0.95000	0.50090	0.47586	£8.77	£13.42	£6.39
C	Stage 3	0.47414	0.09000	0.04267	£0.00	£13.42	£0.57
D	Stage 4	0.43147	0.06500	0.02805	£25.82	£39.24	£1.10
E	Stage 5	0.40342	0.04828	0.01948	£67.00	£106.24	£2.07
F	Stage 6	0.38395	1.00000	0.38395	£0.00	£106.24	£40.79
				1.00000	£106.24		***£51.16***

Number needed to screen to find 1 case = 2.6
Cost per case detected = £133.24

10
Case finding – genetic confirmation (excluding cost of testing probands)

	Stage at which subject leaves programme	Probability (reaching stage)	Probability (leaving at stage)	Probability (overall)	Cost (of stage)	Cost (overall)	**Screen cost per person invited**
A	Stage 1	1.00000	0.05000	0.05000	£4.65	£4.65	£0.23
B	Stage 2	0.95000	0.50090	0.47586	£8.77	£13.42	£6.39
C	Stage 3	0.47414	0.09000	0.04267	£0.00	£13.42	£0.57
D	Stage 4	0.43147	0.06500	0.02805	£25.82	£39.24	£1.10
E	Stage 5	0.40342	0.04828	0.01948	£252.00	£291.24	£5.67
F	Stage 6	0.38395	1.00000	0.38395	£0.00	£291.24	£111.82
				1.00000	£291.24		***£125.79***

Number needed to screen to find 1 case = 2.6
Cost per case detected = £327.62

11
Case finding – genetic confirmation (including cost of testing probands)

	Stage at which subject leaves programme	Probability (reaching stage)	Probability (leaving at stage)	Probability (overall)	Cost (of stage)	Cost (overall)	**Screen cost per person invited**
A	Stage 1	1.00000	0.05000	0.05000	£598.13	£598.13	£29.91
B	Stage 2	0.95000	0.50090	0.47586	£8.77	£606.90	£288.80
C	Stage 3	0.47414	0.09000	0.04267	£0.00	£606.90	£25.90
D	Stage 4	0.43147	0.06500	0.02805	£25.82	£632.72	£17.74
E	Stage 5	0.40342	0.04828	0.01948	£252.00	£884.72	£17.23
F	Stage 6	0.38395	1.00000	0.38395	£0.00	£884.72	£339.68
				1.00000	£884.72		***£719.26***

Number needed to screen to find 1 case = 2.6
Cost per case detected = £1873.34

Appendix 6

Keywords used in the electronic searches

The following keywords have been used for searching the electronic databases:

BREAST CANCER
CARDIOVASCULAR-DISEASES
COST-BENEFIT-ANALYSES
COSTS-AND-COST ANALYSIS
COUNSELLING
DEATH
GENETIC-COUNSELLING
GENETIC-SCREENING
GENETIC-SCREENING
HYPERCHOLESTEROLEMIA, -FAMILIAL
HYPERCHOLESTEROLEMIA
MASS-SCREENING
MORTALITY
MYOCARDIAL-ISCHEMIA
RANDOMIZED-CONTROLLED-TRIALS
SCREEN*
SOCIAL-PROBLEMS
STRESS,-PSYCHOLOGICAL

The explode command was used, and searches with all subheadings and without subheadings were tried to maximise the effectiveness of the search strategy. In addition, specific authors who had published numerous papers in relevant areas of our search were included in the electronic search strategy by name.

Appendix 7

Cost-effectiveness of strategies prior to the reduction in statin costs

The following versions of *Tables 19* and *25–32* indicate how the cost-effectiveness of all the strategies has improved as a result of falling statin costs. The calculations for the tables in this appendix were made before the reduction in statin costs in September 1999.

TABLE 19 *Current statin costs in the UK*[114]

Atorvastatin (Lipotor®) up to 80 mg max.	10 mg per 28, £18.88 20 mg per 28, £30.30 40 mg per 28, £47.04
Simvastatin (Zocor®) up to 40 mg max.	10 mg per 28, £18.29 20 mg per 28, £31.09 40 mg per 28, £47.04

TABLE 25 *Cost per person of drug treatment and coronary events (discounted at 6%)*

Age at diagnosis (years)	CHD event costs (£)			Drug costs (£)	
	Untreated	Treated	Increment	Treated	Increment
Men					
16	413.38	134.28	–279.10	6938.03	**6591.13**
16–24	522.22	171.49	–350.72	6676.32	**6342.51**
25–34	497.50	241.30	–256.20	6141.17	**5834.11**
35–44	397.37	370.02	–27.35	5069.12	**4815.66**
45–54	486.56	467.70	–18.86	3322.71	**3156.57**
Women					
16	176.53	59.75	–116.78	7112.63	**6757.00**
16–24	225.54	76.70	–148.83	6896.32	**6551.50**
25–34	283.36	106.02	–177.33	6340.86	**6023.82**
35–44	384.94	158.93	–226.00	5255.55	**4992.77**
45–54	403.83	246.03	–157.80	3398.04	**3228.14**

TABLE 26 *Cost-effectiveness of different FH screening strategies (clinical diagnosis)*

Strategy	Age–sex group		Weighting for age–sex group (%)	Undiscounted LYGs	Undiscounted cost per LYG (£)	Discounted at 1% LYGs	Cost per LYG (£)
	Sex	Age (years)					
Universal (age 16 years)	Men	16	51.3	7.1	2,259	4.8	3,334
	Women	16	48.7	9.2	1,787	5.6	2,926
	All		100.0	8.1	**2,029**	5.2	**3,136**
Universal (age 16–54 years)	Men	16–24	11.3	7.0	2,261	5.0	3,139
		25–34	14.7	3.7	4,138	2.8	5,504
		35–44	12.8	0.6	25,689	0.4	33,598
		45–54	11.9	0.3	50,071	0.2	61,101
	Women	16–24	10.7	9.1	1,770	5.9	2,728
		25–34	14.1	8.2	1,911	5.6	2,774
		35–44	12.6	7.3	1,981	5.5	2,634
		45–54	11.9	3.4	3,756	2.8	4,659
	All		100.0	4.9	**11,266**	3.5	**14,305**
Opportunistic (GP) (age 16–54 years)	Men	16–24	9.4	7.0	2,163	5.0	3,003
		25–34	12.0	3.7	3,954	2.8	5,259
		35–44	10.5	0.6	24,483	0.4	32,022
		45–54	11.0	0.3	47,421	0.2	57,867
	Women	16–24	12.9	9.1	1,695	5.9	2,613
		25–34	16.3	8.2	1,828	5.6	2,653
		35–44	14.6	7.3	1,888	5.5	2,511
		45–54	13.3	3.4	3,556	2.8	4,411
	All		100.0	5.2	**9,730**	3.7	**12,364**
Opportunistic (MI) (age 16–54 years)	Men	16–24	0.2	7.0	901	5.0	1,251
		25–34	2.1	3.7	1,582	2.8	2,104
		35–44	18.5	0.6	8,960	0.4	11,718
		45–54	62.2	0.3	13,289	0.2	16,216
	Women	16–24	0.1	9.1	732	5.9	1,129
		25–34	0.4	8.2	751	5.6	1,090
		35–44	2.8	7.3	689	5.5	916
		45–54	13.7	3.4	982	2.8	1,218
	All		100.0	1.1	**10,123**	0.8	**12,508**
Case finding (age 16–54 years)	Men	16–24	11.3	7.0	879	5.0	1,221
		25–34	14.7	3.7	1,542	2.8	2,050
		35–44	12.8	0.6	8,694	0.4	11,370
		45–54	11.9	0.3	12,704	0.2	15,502
	Women	16–24	10.7	9.1	716	5.9	1,104
		25–34	14.1	8.2	733	5.6	1,063
		35–44	12.6	7.3	669	5.5	889
		45–54	11.9	3.4	938	2.8	1,164
	All		100.0	4.9	**3,326**	3.5	**4,258**

TABLE 27 *Cost-effectiveness of different FH screening strategies (genetic diagnosis)*

Strategy	Age–sex group		Weighting for age–sex group (%)	Undiscounted LYGs	Undiscounted cost per LYG (£)	Discounted at 1% LYGs	Cost per LYG (£)
	Sex	Age (years)					
Universal (age 16 years)	Men	16	51.3	7.1	11,032	4.8	16,281
	Women	16	48.7	9.2	8,588	5.6	14,061
	All		100.0	8.1	**9,842**	5.2	**14,842**
Universal (age 16–54 years)	Men	16–24	11.3	7.0	11,217	5.0	15,574
		25–34	14.7	3.7	20,977	2.8	27,899
		35–44	12.8	0.6	135,889	0.4	177,729
		45–54	11.9	0.3	292,370	0.2	356,771
	Women	16–24	10.7	9.1	8,604	5.9	13,262
		25–34	14.1	8.2	9,554	5.6	13,867
		35–44	12.6	7.3	10,493	5.5	13,953
		45–54	11.9	3.4	22,028	2.8	27,321
	All		100.0	4.9	**62,748**	3.5	**79,450**
Opportunistic (GP) (age 16–54 years)	Men	16–24	9.4	7.0	11,021	5.0	15,302
		25–34	12.0	3.7	20,609	2.8	27,409
		35–44	10.5	0.6	133,479	0.4	174,557
		45–54	11.0	0.3	287,070	0.2	350,304
	Women	16–24	12.9	9.1	8,455	5.9	13,031
		25–34	16.3	8.2	9,387	5.6	13,624
		35–44	14.6	7.3	10,307	5.5	13,705
		45–54	13.3	3.4	21,628	2.8	26,825
	All		100.0	5.2	**56,104**	3.7	**71,062**
Opportunistic (MI) (age 16–54 years)	Men	16–24	0.2	7.0	1,394	5.0	1,936
		25–34	2.1	3.7	2,510	2.8	3,338
		35–44	18.5	0.6	15,029	0.4	19,656
		45–54	62.2	0.3	26,633	0.2	32,500
	Women	16–24	0.1	9.1	1,109	5.9	1,709
		25–34	0.4	8.2	1,172	5.6	1,701
		35–44	2.8	7.3	1,158	5.5	1,540
		45–54	13.7	3.4	1,989	2.8	2,466
	All		100.0	1.1	**19,727**	0.8	**24,332**
Case finding (age 16–54 years) (excluding cost of testing proband)	Men	16–24	11.3	7.0	907	5.0	908
		25–34	14.7	3.7	1,594	2.8	1,538
		35–44	12.8	0.6	9,037	0.4	8,727
		45–54	11.9	0.3	13,459	0.2	12,266
	Women	16–24	10.7	9.1	737	5.9	829
		25–34	14.1	8.2	756	5.6	800
		35–44	12.6	7.3	695	5.5	672
		45–54	11.9	3.4	995	2.8	908
	All		100.0	4.9	**3,487**	3.5	**3,300**
Case finding (age 16–54 years) (including cost of testing proband)	Men	16–24	11.3	7.0	1,129	5.0	1,568
		25–34	14.7	3.7	2,011	2.8	2,675
		35–44	12.8	0.6	11,767	0.4	15,391
		45–54	11.9	0.3	19,462	0.2	23,749
	Women	16–24	10.7	9.1	907	5.9	1,397
		25–34	14.1	8.2	946	5.6	1,373
		35–44	12.6	7.3	906	5.5	1,205
		45–54	11.9	3.4	1,488	2.8	1,796
	All		100.0	4.9	**4,762**	3.5	**6,075**

TABLE 28 *Comparison of the overall cost-effectiveness of clinical and genetic strategies*

Strategy	Cost per LYG (clinical) (£)	Cost per LYG (genetic) (£)
Universal (16)	3,136	15,200
Universal	14,190	79,221
Opportunistic (GP)	12,364	71,062
Opportunistic (MI)	12,508	24,332
Case finding	4,258	4,461 (relatives **only**: proband with known mutation) 6,075 (cost of testing proband included)

TABLE 29 *Sensitivity analysis – clinical confirmation*

Changed assumptions	Universal (16)	Universal	Opportunistic (GP)	Opportunistic (MI)	Case finding
Baseline cost per LYG for each strategy (£)	3,136	14,190	12,364	12,508	4,258
1.31 relatives per proband	No change	No change	No change	No change	4,274
5.75 relatives per proband	No change	No change	No change	No change	4,0253
30% identified mutations	No change	No change	No change	No change	No change
70% identified mutations	No change	No change	No change	No change	No change
37% reduction in drug cost	2,659	12,645	10,962	8,213	2,712
73% reduction in drug cost	2,195	11,140	9,597	4,033	1,208
80% attendance	3,009	13,662	11,972	12,564	4,263
50% attendance	3,858	18,204	15,494	12,910	4,289
Discount rate 5% for costs and benefits	14,985	33,355	29,280	26,972	10,865

TABLE 30 *Sensitivity analysis – genetic confirmation*

Changed assumptions	Universal (16)	Universal	Opportunistic (GP)	Opportunistic (MI)	Case finding (not costing proband)	Case finding (costing proband)
Baseline cost per LYG for each strategy (£)	15,200	79,221	71,062	24,332	4,461	6,075
1.31 relatives per proband	No change	No change	No change	No change	4,477	8,419
5.75 relatives per proband	No change	No change	No change	No change	4,456	5,354
30% identified mutations	24,501	129,289	115,947	32,866	No change	7,151
70% identified mutations	11,214	57,763	51,825	20,675	No change	5,614
50% reduction in cost of genetic testing	10,111	51,742	46,028	18,909	4,359	5,167
37% reduction in drug cost	14,723	77,675	69,660	20,037	2,915	4,529
73% reduction in drug cost	14,259	76,171	68,296	15,857	1,411	3,025
80% attendance	14,947	78,084	70,279	24,444	4,446	6,303
50% attendance	16,644	87,249	77,323	25,135	4,492	7,431
Discount rate 5% for costs and benefits	69,387	180,603	162,764	50,858	11,324	14,979

TABLE 31 *Comparing overall cost-effectiveness of clinical strategies by age and sex*

	Cost per LYG (clinical) for each strategy (£)			
Age (years)	**Universal**	**Opportunistic (GP)**	**Opportunistic (MI)**	**Case finding**
Men				
16–24	3,117	3,003	1,251	1,221
25–34	5,465	5,259	2,104	2,050
35–44	33,346	32,022	11,718	11,370
45–54	60,582	57,867	16,216	15,502
Women				
16–24	2,710	2,613	1,129	1,104
25–34	2,755	2653	1,090	1,063
35–44	2,615	2,511	916	889
45–54	4,616	4,411	1,218	1,164
All	14,190	12,364	12,508	4,258

TABLE 32 *Comparing overall cost-effectiveness of genetic strategies by age and sex*

Age bands	**Cost per LYG (genetic) for each strategy (£)**				
	Universal	**Opportunistic (GP)**	**Opportunistic (MI)**	**Case finding (excluding cost of proband test)**	**Case finding (including cost of proband test)**
Men					
16–24	15,531	15,302	1,936	1,260	1,216
25–34	27,820	27,409	3,338	2,120	2,093
35–44	177,224	174,577	19,656	11,819	12,298
45–54	355,734	350,304	32,500	16,423	19,591
Women					
16–24	13,255	13,031	1,709	1,136	1,397
25–34	13,624	13,624	1,701	1,098	1,373
35–44	13,828	13,913	1,540	924	1,205
45–54	27,241	27,241	2,466	1,234	1,796
All	79,221	71,062	24,332	4,461	6,075

Appendix 8

National Screening Committee's criteria for appraising the viability, effectiveness and appropriateness of a screening programme

The text from the National Screening Committee's criteria for appraising the viability, effectiveness and appropriateness of a screening programme is reproduced in italics. Our comments, in roman type, are interleaved.

The criteria, which are set out below, are based on the classic criteria first promulgated in a WHO report in 1966 but take into account both the more rigorous standards of evidence required to improve effectiveness and the greater concern about the adverse effects of healthcare; regrettably some people who undergo screening will suffer adverse effects without receiving benefit from the programme.

These criteria have been prepared taking into account international work on the appraisal of screening programmes, particularly that in Canada and the United States. It is recognised that not all of the Criteria and questions raised in the Format will be applicable to every proposed programme, but the more that are answered will obviously assist the NSC to make better evidence based decisions.

All of the following criteria should be met before screening for a condition is initiated:

The condition

1. *The condition should be an important health problem.*

   FH affects approximately 1 in 500 people in this country (around 110,000). Those affected are at a much increased risk of ischaemic heart disease, as much as 90-fold in subjects aged under 40 years, and fivefold in subjects aged 40–59 years.[6,30]

2. *The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, or disease marker and a latent period or early symptomatic stage.*

   The natural history of this disorder has been well defined by a number of longitudinal studies undertaken before effective lipid-lowering therapy was available. The cumulative risk of a fatal or non-fatal myocardial infarction in untreated FH patients by the age of 50 years is about 50% in men and 10% in women. By the age of 60 years, men had an 85.4% risk, and women a 56.5% risk of a fatal or non-fatal event.[4,26]

   FH can be diagnosed at any time from childhood by measurement of plasma lipids together with an examination of the family history. It can also be diagnosed at any time by genetic screening.

3. *All the cost-effective primary prevention interventions should have been implemented as far as practicable.*

   FH is a genetic condition for which no primary prevention is possible.

The test

4. *There should be a simple, safe, precise and validated screening test.*

   FH can be detected by a simple blood test to measure cholesterol levels, together with a family history of premature CHD.

5. *The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.*

   A diagnostic definition of FH, originally proposed by the Simon Broome Research Group based on clinical signs and family history[6] has become widely used. A definite diagnosis requires:

   a. a total cholesterol level above 7.5 mmol/l (290 mg/dl) in adults or a total cholesterol level above 6.7 mmol/l (260 mg/dl) in children under 16 years of age **or** LDL levels above 4.9 mmol/l (190 mg/dl) in adults (4.0 mmol/l in children)

   plus

b. tendon xanthomas in patient or in first- or second-degree relatives.

A possible diagnosis of FH requires (a) above plus one of the following:

c. a family history of MI before the age of 50 years in second-degree relatives or before the age of 60 years in first-degree relatives
d. a family history of raised cholesterol above 7.5 mmol/l (290 mg/dl) in first- or second-degree relatives.

6. *The test should be acceptable to the population.*

Both the forms of testing which are proposed in this review (measuring plasma lipid levels and carrying out genetic screening) involve nothing more than venepuncture to take a few millilitres of blood. It is also possible to obtain adequate amounts of DNA from a mouthwash sample. Samples so obtained are stable at room temperature for several days, and can easily be sent through the post.

7. *There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.*

If an individual receives a total cholesterol test result above the cut-off value, a fasting lipid profile will be undertaken. Treatment options for FH are, in order of effectiveness, HMG CoA reductase inhibitors (statins), resins and dietary advice.

The treatment

8. *There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.*

HMG CoA reductase inhibitors (statins) inhibit the hepatic biosynthesis of cholesterol. Large randomised placebo-controlled trials have conclusively demonstrated that statins are effective in the primary and secondary prevention of CHD.[14–17] Although none of these trials specifically studied patients with FH, it is appropriate to extrapolate from these results. Statins are now the first-line treatment for most patients with FH, and are well tolerated. Only about 1% of patients experience side-effects, and serious adverse reactions are very rare.[18] There are differences in efficacy between drugs in this class. A maximum reduction in LDL cholesterol levels of nearly 60% can be achieved with atorvastatin 80 mg daily and about 40% with simvastatin 40 mg daily.[19] Other statins at currently licensed dosages achieve smaller reductions in LDL cholesterol levels. Statins result in a modest elevation in HDL cholesterol levels of 6–10%, and a reduction in triglyceride levels of 10–15%, although larger reductions may be achieved in patients with hypertriglyceridaemia.[19]

FH patients not treated with effective cholesterol-lowering medication are much more likely to develop atherosclerosis and premature CHD than those in the population without FH.[4,26] Data from the Simon Broome Register cohort also indicate that mortality can be reduced in FH patients with statin treatment.[6,30]

9. *There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.*

Guidelines on the appropriate treatment of FH patients have been published by the British Hyperlipidaemia Association.[143]

10. *Clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme.*

This is outside the remit of this review.

The screening programme

11. *There must be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.*

Since the introduction of effective cholesterol-lowering medication, it is not ethical to conduct placebo-controlled trials on such a high-risk group. See point 8 above for a discussion of the lipid-lowering randomised controlled trials.

Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

This is not applicable to FH patients.

12. *There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.*

    There is insufficient evidence to comment on this at this point.

13. *The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).*

    Adverse psychological effects have been reported, but most studies conclude that screening should not be delayed due to these effects since these appear to be relatively minor. Identification of the vulnerable group could facilitate targeting effective and appropriate education and possible counselling to ameliorate deleterious effects, but the utility of this strategy has not been evaluated. Educating the public and insurance sector may also be necessary to avoid unnecessary stigmatisation and discrimination of those testing positive, but, again, the evidence for the existence of stigmatisation and discrimination is weak.

14. *The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie value for money).*

    This report has shown that the most cost-effective method of screening for, and treating, FH is to identify family members of known FH cases. For men and women of all ages, this approach is more cost-effective than a population-wide screening programme of all 16–55 year olds. However, it may be cost-effective to screen 16 year olds if the programme were clinically, socially and ethically acceptable to health professionals and the public.

15. *There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.*

    We are unable to comment on this at this time.

16. *Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be made available prior to the commencement of the screening programme.*

    There are 1250 definite FH patients registered by 20 lipid clinics on the Simon Broome Register. Assuming that only half of any one clinic's patients are registered, there would be around 2500 FH patients attending these 20 clinics. We know of a further 90 clinics in the UK, and we therefore estimate that at most 13,750 patients with FH are currently being cared for in lipid clinics. Allowing for a few being cared for in primary care, we estimate that, at most, 15,000 patients with FH have been diagnosed. That is, only 10–15% of existing carriers have been diagnosed, leaving some 95,000 additional patients. Using published data from the General Practice Research Database we estimate that at least 1,050,000 people in England and Wales were treated with a lipid-lowering drug in 1994,[144] and since the more recent trial publications[14–16] this number has probably increased. In the event of a screening programme being 80% effective in identifying and treating those at risk from FH, the number of people treated with statins would increase by no more than 8%. The current cost of 1 year treatment with 40 mg daily of simvastatin is £387 (see the BNF). There would also be additional requirements for lipid clinics to care for the extra patients identified.

17. *All other options for managing the condition should have been considered (eg improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.*

    This is not applicable to FH patients.

18. *Evidence based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.*

    Education may facilitate decision-making, allowing individuals to understand potential risks and benefits, but the precise content of counselling and education sessions needs evaluating. The Family Heart Association has information leaflets about the potential benefits and disadvantages of testing for FH.

19. *Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.*

    FH is a genetic condition, and once a positive or negative result is obtained, no further testing would be required.

References

Department of Health. Screening of pregnant women for hepatitis B and immunisation of babies at risk. Department of Health, 1998. (Health Service Circular: HSC 1998/127).

Wilson JMG, Jungner G. Principles and practice of screening for disease. Public Health Paper Number 34. Geneva: WHO, 1968.

Cochrane AL. Holland WW. Validation of screening procedures. Br Med Bull. 1971, 27, 3.

Sackett DL, Holland WW. Controversy in the detection of disease. Lancet 1975; 2:357–9.

Wald NJ (Editor). Antenatal and Neonatal screening. Oxford University Press, 1984.

Holland WW, Stewart S. Screening in Healthcare. The Nuffield Provincial Hospitals Trust, 1990.

Gray JAM. Dimensions and definitions of screening. Milton Keynes: NHS Executive Anglia and Oxford, Research and Development Directorate, 1996.

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The HTA programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

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