Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost effectiveness analysis
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Authors' objectives
To evaluate whether screening for familial hypercholesterolaemia (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; and to assess whether the risks outweigh the potential benefits of screening.

Searching
MEDLINE, EMBASE (via Ovid), databases on BIDS, PsycLIT, HealthSTAR, the Cochrane Library, and the Centre for Reviews and Dissemination's databases were searched; the search terms were provided. This was complemented by an Internet search and screening the references of identified papers. In addition, workers in the field of FH were contacted for unpublished studies.

Study selection
Study designs of evaluations included in the review
No inclusion criteria for the study designs were specified. The designs considered ranged from randomised controlled trials (RCTs) to secondary literature without any empirical data.

Specific interventions included in the review
Studies were eligible for the review if they looked at the mortality and morbidity associated with FH, the screening and treatment of FH since the introduction of statins, or the safety and efficacy of statin use. Studies of resin therapy in children were also eligible for inclusion. Pre-treatment publications were considered separately.

For the analysis of the psychosocial effects of genetic screening, studies that looked at screening for modifiable inherited conditions were considered.

Reference standard test against which the new test was compared
The review did not include any diagnostic accuracy studies that compared the performance of the index test with a reference standard of diagnosis.

Participants included in the review
No specific inclusion criteria for the participants were selected. The included studies were of patients with FH, patients being screened for FH, patients being treated for FH, and patients being treated with statin for other reasons than FH.

Outcomes assessed in the review
The mortality and morbidity associated with FH, and the effectiveness and cost of both treatment and screening, were addressed in the review.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection. However, the publications were apparently systematically evaluated according to a specific set of objectives.

Assessment of study quality
The reviewers developed an algorithm to evaluate qualitative and quantitative literature. This algorithm assessed the appropriateness of the method in relation to the research question, the adequacy of the design description, the justification of the conclusion with regard to the results, the transferability to other settings, and the relevance for an FH screening policy. The authors did not state how the papers were assessed for validity, or how many reviewers...
performed the validity assessment.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Details of the study design and results were presented for mortality, morbidity and treatment effect.

For the empirical data studies on the psychosocial effects of screening, details on the following were presented: key issues addressed, study design, conclusions, the number and type of patients, comments or problems, and the relevance to an FH screening policy. The setting, method and results, together with the validity assessment, were accessible in an appendix. Information from secondary papers was also extracted: main points, potential benefits, potential disadvantages, and recommendations and comments.

For the cost-effectiveness studies of statin treatment, the hypothesis, data sources and results were noted.

**Methods of synthesis**
How were the studies combined?
With the exception of the cost data, the studies were synthesised in the narrative.

How were differences between studies investigated?
The studies were presented according to their design and topic groups.

**Results of the review**
Seventeen studies of morbidity and mortality in adults since the introduction of statins and 5 pre-treatment studies were included; 8 papers on children were also included. Thirty-nine papers looked at the psychosocial effects of genetic screening. Of these, only 16 reported primary data. Four of the empirical studies of psychosocial effects were RCTs. Eight studies presenting cost-effectiveness data for treatment with statins were also reported.

Effectiveness.

The authors stated that FH is a life-threatening condition with a long presymptomatic state. Tests to diagnose FH are reasonably reliable and acceptable, while treatment with statins improves the prognosis substantially. The authors therefore believed that it is appropriate to consider systematic screening for the condition.

Psychosocial effects of screening.

Only a few papers that addressed the psychosocial effects of screening were located and their quality was poor. Problems with labelling and discrimination were hypothesised in the literature, but there were few empirical data to support these hypotheses. The review found no evidence of mental health or social functioning problems in adults following a diagnosis of FH, but there was weak evidence that children react negatively to the diagnosis. The authors stated that it is possible that diagnosis in adults may make it more difficult for them to get life insurance (statement based on opinions expressed in the included publications). The studies reported fear of discrimination as a barrier to screening. The literature supported the idea of counselling at the time of screening, but the nature of the counselling was poorly described and there were no data to support its effectiveness.

**Cost information**
A model investigating the relative cost and effectiveness of different forms of population screening (universal or opportunistic) and case-finding screening (screening relatives of FH patients) was constructed. The model assumed an identifying stage (identifying cases with cholesterol levels fitting the diagnostic criteria of FH) and further established the diagnosis on clinical signs and a family history of coronary disease, or through carrying out genetic tests. The incremental cost per year of life gained was applied as the cost-effectiveness measure.
The most cost-effective strategy was case finding amongst relatives of FH cases; the least cost-effective was universal systematic screening (except for when targeted at 16 year olds).

Screening patients admitted to hospital with premature myocardial infarction was relatively cost-effective. Screening was least cost-effective in men aged over 35 years as the gains in life expectancy are small. Following the modelling results, a combination of strategies should be applied.

Authors' conclusions
The authors concluded 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, assuming that such screening is acceptable and that at least 55% of those invited for screening do attend, seemed similarly cost-effective.

There was a lack of qualitative or quantitative evidence on the psychosocial effects of screening for FH or other treatable inherited conditions. Evidence on the effectiveness of educational and counselling interventions at the time of screening was also lacking.

The model showed that case finding in relatives, universal screening for young people, and screening hospital patients with premature myocardial infarction are probably cost-effective, but there are a lack of primary data on the effectiveness and cost implications of screening strategies; this hinders definite conclusions.

CRD commentary
This review addressed a wide range of issues in the epidemiology, screening and treatment of FH. Extensive searches were undertaken and a variety of material was screened. Active steps were taken to locate unpublished studies to reduce publication bias. The review was not restricted to studies that presented empirical data. The number of papers that definitely passed the inclusion criteria for the review could have been made clearer. The authors explained the development of an algorithm to evaluate the publications in detail. However, they did not state how it was applied, i.e. whether more than one reviewer assessed the studies independently to minimise selection bias.

In terms of transparency, it was difficult to know which results followed from the systematic review on the effectiveness of screening and treatment of FH, and which followed from the cost-effectiveness analyses.

Overall, the conclusions of the review appear to have been plausible.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research should concentrate on the systematic evaluation of potential screening strategies, i.e. case finding in relatives, universal screening in young people, and screening patients with premature myocardial infarction.

Funding
NHS R&D Health Technology Assessment (HTA) Programme, project number 95/36/02.

Bibliographic details

PubMedID
11109029
Original Paper URL
http://www.hta.ac.uk/project.asp?PjtId=998

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Algorithms; Attitude to Health; Child; Cost-Benefit Analysis; Decision Trees; Female; Great Britain /epidemiology; Humans; Hyperlipoproteinemia Type II /diagnosis /epidemiology /therapy; Male; Mass Screening /adverse effects /economics /methods /psychology; Middle Aged; Models, Econometric; Morbidity; Needs Assessment; Practice Guidelines as Topic; Research Design; Technology Assessment, Biomedical

AccessionNumber
12000008685

Date bibliographic record published
31/10/2004

Date abstract record published
31/10/2004

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.