Abstract

Background Approximately 110,000 people in the United Kingdom are affected with familial hypercholesterolaemia (FH). At least 75 per cent are undiagnosed. Treatment with statins is effective but effective primary prevention requires early diagnosis. The best strategy to achieve this is unclear. This paper compares the costs and benefits over a 10 year period of two strategies found in our previous modelling: population screening of 16-year-olds or tracing family members of affected patients.

Methods Computer modelling of time-limited data was conducted. The number available for screening and the potential new cases in England and Wales aged 16–54 years were estimated. The costs (of screening and treatment) and benefits (deaths averted) that might be accrued over 10 years were assessed.

Results Screening 16-year-olds results in 470 new diagnoses, and over 10 subsequent years averts 11.7 deaths at a cost of £6,176,649, giving a cost per case identified and treated of £13,141 (including a 10 year drug cost of £1,584,918). By contrast, screening first-degree relatives of known FH patients results in 13,248 new diagnoses, 560 deaths averted over 10 years, at a cost of £46,430,681, giving a cost per case identified and treated of £3,505 (including 10 year drug cost of £44,645,760). The cost per death averted would be £3,187.

Conclusions Although the two approaches appear similar in cost-effectiveness over a lifetime, the shorter-term (10 year) cost-effectiveness clearly favours family tracing. This represents good value for money compared with common medical interventions, and suggests that pilot FH family tracing programmes should be conducted.

Keywords: familial hypercholesterolaemia, screening, costs, benefits

Introduction

Approximately 110,000 people in the United Kingdom are thought to be affected with familial hypercholesterolaemia (FH), which is caused mainly by mutations of the LDL receptor gene. At least 75 per cent of those affected are undiagnosed. Treatment with statins is effective in treating FH, and delays or prevents the onset of coronary heart disease. Effective primary prevention, however, requires early diagnosis.

We have compared population-wide screening strategies for FH with targeted screening strategies using computer simulation. We demonstrated that the most cost-effective screening strategy is to screen only the first-degree relatives of identified FH patients (family tracing). Screening 16-year-olds was similarly cost-effective, making the assumption that universal screening of 16-year-olds would be acceptable to society, and that such screening would achieve at least a 55 per cent attendance rate (this latter figure was based on the response rate of 16-year-olds to the Health Survey for England). However, our computer models did not provide time-limited data on costs and benefits, of the kind that are often requested by public health planners, so we report here the 10 year estimated costs (of screening and treatment) and benefits (deaths averted) for these two strategies.
ber of FH positive males and females, assuming a population frequency of 1 in 500 (0.002). The number of 16-year-olds already diagnosed with FH was derived from the Oxfordshire study. We then estimated the benefits and costs that might be accrued over 10 years if FH screening were introduced nationally.

We developed a hypothetical care pathway for each strategy. For the screening of 16-year-olds, those with a non-fasting total cholesterol concentration above the population 95th percentile were offered a fasting test. After this test, those with a total cholesterol above 7.5 mmol/l and an LDL cholesterol above 4.9 mmol/l were referred for diagnostic confirmation by either clinical examination (including a family history) by a lipid clinic consultant or by genetic testing on blood or buccal cells. Among other assumptions, this assumes a 55 per cent attendance at appointment one, and a 75 per cent attendance at the second cholesterol test.

In the family tracing strategy, we assumed that a clinic nurse would collect family histories from patients (index cases) and ask permission to contact their relatives, and that attendance would collect family histories from patients (index cases) and cholesterol test.

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The Simon Broome Register cohort data from the pre-statin era and post-statin era (post-1992) were used to estimate the death rates in people with FH not receiving and receiving treatment. Because published mortality data were given for ages 0–19 years and 20–39 years, we adjusted the death rates to smooth the transition between age groups, so that the rate of increase in the death rates was similar to that in the general population. Office for National Statistics (ONS) data allowed us to assign the respective death rates to the Simon Broome cohort mortality data using the general population ratios.

The before and after treatment death rate was calculated by working out the number of deaths in an ‘untreated’ population and the number of deaths in an identified and treated FH population. We calculated the number of deaths in each age band and then worked out the number of deaths averted as a result of screening over a 10 year period (ages 16–26 years).

Costs include the cost of invitation for screening, the cost of the cholesterol test(s), contact time with a nurse and contact time with a doctor should confirmation of FH be necessary at the final stage. All of the costs have taken into account gradual drop-out through the phases (from non-attendance for example because of any adverse psychological impact of the testing, negative results, etc.).

The family tracing strategy costs include an additional half an hour nurse time with the known index case to obtain a family history of relatives eligible to be approached (see full details in Ref. 5). Drug costs were calculated after allowing for an 18 per cent rate of non-adherence to therapy. The annual cost was attributed to 82 per cent of the population, which is the rate of adherence used in the report and is based on the average of reported statin trial data and the Dutch StOEH programme, which identified FH patients based on genetically diagnosed cascade screening.

### Results

**Estimated 10 year deaths averted by screening all 16-year-olds**

We estimated that in England and Wales there are 1284 people aged 16 years with FH, of whom 100 have already been diagnosed, giving a potential yield from screening of 1184 (from 642 000 eligible cases). Using the same assumptions as in our earlier work, we estimated that 470 newly diagnosed cases would be identified by this screening programme (see Table 2). The model suggests that in these 470 subjects, no deaths would be averted.

<table>
<thead>
<tr>
<th>Description</th>
<th>Universal 16-year-olds</th>
<th>Case finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Prevalence of FH</td>
<td>0.002</td>
<td>0.5</td>
</tr>
<tr>
<td>2 Probability an individual does not have FH</td>
<td>0.998</td>
<td>0.5</td>
</tr>
<tr>
<td>3 Probability of attending first appointment (Stage 1)</td>
<td>0.55</td>
<td>0.95</td>
</tr>
<tr>
<td>4 Probability of a high cholesterol result (Stage 2)</td>
<td>0.05</td>
<td>0.4991</td>
</tr>
<tr>
<td>5 Probability of attending second appointment (Stage 3)</td>
<td>0.75</td>
<td>0.9</td>
</tr>
<tr>
<td>6 Probability of a low cholesterol result after a high result first time (Stage 4)</td>
<td>0.065</td>
<td>0.065</td>
</tr>
<tr>
<td>7 Probability of FH given a high cholesterol (Stage 5)</td>
<td>0.038</td>
<td>0.9517</td>
</tr>
</tbody>
</table>
in men or women aged 16–19 years as a result of screening. This is because it is derived from data showing no significant difference in death rates pre- and post-statin therapy in this age group in the Simon Broome cohort, although this is based on a small number of individuals. Between ages 20–24 years this model suggests 1.6 deaths per year would be averted in males and 0.3 deaths per year in females. At age 25 years, 1.8 deaths per year would be averted in males and 0.4 deaths per year in females. Ten years after screening a total of 9.8 deaths would have been averted in young men and 1.9 deaths in young women if identified at age 16 years.

Table 2 shows the expected death rates for a cohort of 16-year-olds with FH, and for 16-year-olds in the general population. Between 9 and 10 deaths per thousand per year can be expected in unidentified and untreated FH males aged 20–26 years and about 2 deaths per thousand per year in untreated FH females. This reduces to just over 2 deaths per thousand per year for males if identified and treated with statins, and 0.5 deaths per thousand per year in females aged 20–26 years and about 2 deaths per thousand per year in untreated FH males aged 20–26 years and 0.3 deaths per year in females. At age 25 years, 1.8 deaths per year would be averted in males and 0.4 deaths per year in females. Ten years after screening a total of 9.8 deaths would have been averted in young men and 1.9 deaths in young women if identified at age 16 years.

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**Estimated 10 year deaths averted by family tracing**

We used the data from the Oxfordshire study to estimate the number of diagnosed index cases for family tracing. There were 313 known cases of FH within the Oxfordshire health authority boundaries (from a population of 616,707). Based on population figures for England and Wales, we estimated that there would be 26,742 ‘index’ cases. We assumed that each index case would have 3.37 first-degree relatives (the derivation of this estimate has been described in Ref. 5). Thus, there would be 90,120 first-degree relatives available for screening. However, in the previous modelling we limited screening eligibility to people aged between 16–54 years, because the Simon Broome cohort data showed a treatment effect only within these ages. As 53.9 per cent of the population are aged 16–54 years, we estimated that 48,454 relatives would be of an age where diagnosis and treatment would affect mortality and would be available for screening. We assigned these relatives to 5 year age bands using ONS population statistics.

**Estimated costs**

The yield of new cases and costs of screening for both strategies are shown in Table 4. Cost per person invited for screening in the 16-year-old strategy is £7.15 and the cost per person invited for the family tracing strategy is £51.16. The number of people needed to be invited for screening to find one case of FH for 16-year-olds is 1366 but only 2.6 for family tracing. Fewer people will drop out at earlier stages in the family tracing strategy than in population screening of 16-year-olds because we have assumed higher compliance at each stage of the screening, which is not unlikely, and because of the prediction based on Mendelian inheritance of a 50 per cent prevalence of a positive diagnosis.

From this age structure we applied the previously described assumptions to estimate how many people would be detected as a result of the screening. This is shown in Table 3. We then subtracted the estimated number of people that are already diagnosed with FH. We estimated that 6916 men and 6332 women aged 16–54 years would be identified as a result of screening. The greatest yield should come from the younger ages, as the data indicate a much lower proportion of them are already identified (range from 2.5 per cent of males aged under 9 years to 91 per cent of males aged 50–59 years currently diagnosed with FH).

The number of deaths averted was estimated over 10 years as for the 16-year-old cohort (Table 3). The 10 year figure estimates number of deaths averted for that 5 year band plus the number of deaths averted in the next 5 year age band. If a male is identified at age 16–19 years, almost 31 deaths will be averted (all which would occur in the 20–24 year period). A total of 108 deaths would be averted for males identified between 30 and 34 years, and 54 deaths will be averted over 10 years for females identified between ages 40 and 44 years.

The number of deaths averted for 16-year-olds is higher in the family tracing strategy than in population screening of 16-year-olds because we have assumed higher compliance at each stage of the screening, which is not unlikely, and because of the prediction based on Mendelian inheritance of a 50 per cent prevalence of a positive diagnosis.

**Table 2 Death rates with and without treatment and number of deaths averted from screening for FH (16-year-old strategy)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Pre-treatment death rate/1000</th>
<th>Death rate*</th>
<th>Post-treatment death rate/1000</th>
<th>Post-treatment death rate</th>
<th>Deaths per year pre-treatment†</th>
<th>Deaths per year post-treatment per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16–19</td>
<td>0.58</td>
<td>0.58</td>
<td>0.58</td>
<td>0.58</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>20–24</td>
<td>11.39</td>
<td>8.96</td>
<td>2.99</td>
<td>2.35</td>
<td>2.2</td>
<td>0.6</td>
</tr>
<tr>
<td>25–26</td>
<td>11.39</td>
<td>10.09</td>
<td>2.99</td>
<td>2.64</td>
<td>2.4</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>9.8 deaths averted over 10 year period if identified at age 16 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16–19</td>
<td>0.28</td>
<td>0.28</td>
<td>0.28</td>
<td>0.28</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>20–24</td>
<td>2.99</td>
<td>1.73</td>
<td>0.71</td>
<td>0.41</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>25–26</td>
<td>2.99</td>
<td>2.31</td>
<td>0.71</td>
<td>0.55</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>1.9 deaths averted over 10 year period if identified at age 16 years</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*Death rate adjusted to population age structure/1000.
†From 242 newly diagnosed males and 228 newly diagnosed females.
The annual cost of therapy was estimated to be £411 with a treatment regimen of statin therapy (70% Simvastatin, 40 mg daily, and 30% Atorvastatin, 20 mg daily, based on data from a specialist lipid clinic), and an annual general practitioner appointment until the age of 60 years. This results in an annual statin cost of £337 per year (or £3370 per newly identified case over the 10 year period) based on 82% adherence.

Screening all 16-year-olds would result in 470 new diagnoses, and would avert 11.7 deaths over 10 subsequent years, at a cost of £6 176 649, giving a cost per case identified and treated of £13 141. This includes a 10 year drug cost of £1 584 918. The cost per death averted is £527 919. By contrast, screening the first-degree relatives of known cases would result in 13 248 new diagnoses, 560 deaths averted over 10 years, at a cost of £46 430 681, giving a cost per case identified and treated of £3505 (this includes a 10 year drug cost of £44 645 760). The cost per death averted is £3187.

### Discussion

Screening all 16-year-olds for FH is associated with a larger number needed to screen to find one case than family tracing.
(here estimated as approximately 1370 versus 2.6). The important finding of this paper is the effect of this difference on the costs per death averted over a limited period of 10 years. We have previously shown that, over a lifetime, these two strategies show similar costs per life year gained (£2777 versus £3097, respectively), and that both these approaches have better cost-effectiveness than other strategies such as universal screening for men over 35 years (£30 253). However, as mortality from FH is fairly low until the fourth to fifth decade of life, there are few deaths averted in 10 years from screening 16-year-olds. First-degree relatives of FH probands will, on average, be 20 years older and the number of deaths averted over 5 years is greater.

This modelling has been based on published data from various sources, and a number of derived assumptions have had to be made because of a lack of available data. It is not clear to what extent the screening of 16-year-olds for a disorder of middle age will be acceptable or will be taken up, even though there is a relatively safe and successful therapy available. The modelling assumes a 55 per cent attendance at appointment one, and a 75 per cent attendance at the second cholesterol test, based on data from the Health Survey for England and a general practice based cardiovascular health check. Clearly, a higher dropout rate at either stage would reduce the number of FH subjects detected and thus the potential benefit that would accrue. By contrast, the observed take-up rate for cholesterol testing of relatives of FH patients is high, probably in part because of the knowledge of the disorder in affected relatives. Even with a second cholesterol measure there will be an overlap between FH and non-FH subjects, and this ambiguity in the diagnosis could lead to a negative psychological impact, but this has not been demonstrated for FH screening. Further data of take-up rates, and the psychological impact of the FH diagnosis particularly in 16-year-olds, would be helpful to predict with greater accuracy these aspects of the model.

Sensitivity analyses have been performed previously. The altered parameters applicable here were: (1) the number of first-degree relatives of the proband, which affects the cost-effectiveness of a family tracing strategy (cascade screening); (2) drug costs (which are likely to decrease after the expiry of patents for some statins); (3) attendance rates; (4) discount rates for cost and effectiveness data; (5) cost of a coronary event; (6) life years gained. The ranking between the strategies did not alter, but cost-effectiveness was improved when the cost of drug treatment fell, and when the cost of genetic testing was reduced. For the family tracing strategy, the number of relatives per proband could affect the number of available relatives for screening and therefore the yield of newly identified cases. These data are being collected in a pilot study in Oxfordshire.

Many of the data used in this modelling (numbers of index cases available, proportion undiagnosed) have come from one lipid clinic in Oxfordshire in which the screening of relatives of index cases has been actively encouraged over many years. Thus, the degree of under-diagnosis may be much greater elsewhere. The estimate of 26 742 people with diagnosed FH in England and Wales may be an overestimate by 2–3-fold. To date only 2000 subjects are known from the Simon Broome FH Register. The important implication of this possible overestimate is that the yield of new cases will be higher if the number of those already diagnosed is lower. More new cases would result from screening and the number of deaths averted would be higher than reported here. Conversely, if there are fewer index cases for family tracing, the yield of new cases would be smaller. Undeclared non-biological parent relationship may also lower the yield by a small amount. If family tracing were extended to second- or third-degree relatives of affected subjects, this would increase the yield again. This approach has been adapted successfully in the Netherlands, where cascade tracing of first-, second- and third-degree relatives has resulted in the identification of 2039 FH subjects out of the predicted 32 000 in the country (based on a 1/500 frequency). The death rate in untreated FH subjects was taken from the Simon Broome Register cohort data from the pre-statin era. These were the best estimates available, although these subjects were all on some form of lipid-lowering therapy. There are no reliable data on completely untreated people with FH. The most recently published Simon Broome Register cohort data were used to estimate the reduction in death rate with effective cholesterol lowering medication (statins). Data presented in this paper are restricted to fatal coronary deaths averted, but for each fatal event, there are likely to be two non-fatal coronary events.

These patients were all prescribed statins from 1992 onwards, and their beneficial effect in FH patients as well as in non-FH hypercholesterolaemic subjects is well documented. Currently, treatment of statins usually begins at age 18 years in men, and in women of child-bearing age it would be restricted to those on adequate contraception. As subjects pre-1992 were not completely untreated, their observed death rate may underestimate the mortality in untreated FH. Also, patients since 1992 have experienced lipid-lowering benefits only in the short term, so the benefits of statin treatment, especially treatment with the newer, more powerful statins, may have been underestimated. Other additive effects of statins have recently been demonstrated. It is also possible that clinics contributing to the Simon Broome Register provided closer medical supervision and more aggressive statin therapy than elsewhere. Thus, the assumptions used in this model may underestimate the benefit achievable by the early identification of FH patients.

In the family tracing strategy, the number of lives saved per year (over a 10 year period) is greatest in men below the age of 40 years and women below the age of 50 years. This suggests that a strategy would be even more cost effective if limited to the screening of younger age groups.

This modelling clearly demonstrates the favourable cost-benefit of cascade family tracing for FH, although if acceptable in 16-year-olds, early identification has added benefits and if funding were available, both strategies could be run in parallel. However, it would not overcome the problem of finding cur-
rently unidentified FH families. These programmes represent good value for money compared with common medical interventions,\textsuperscript{27} and our findings suggest that pilot evaluation programmes for FH family tracing should be conducted.

Acknowledgements

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References


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