Reaching detection targets in Familial Hypercholesterolaemia; comparison of identification strategies

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Key words: Familial Hypercholesterolaemia, Screening, Detection, Targets

Word count: 2658

Abstract

Background and aims: Familial Hypercholesterolaemia (FH) is a common and preventable cause of premature heart attack but in most nations only a small proportion of FH-positive individuals have been identified. The aim of this study was to estimate the time to close this FH detection gap.

Methods: We developed a model to estimate the time to identify different proportions of FH in the population for three identification strategies (i) Cascade Testing (FH-mutation testing in relatives of someone with an FH mutation) (ii) Child-parent Screening (testing children for cholesterol and FH mutations during 1-year immunisation and parents of FH-positive children) and (iii) Child-parent Cascade Screening (integrating the first two methods). We used publicly available data to compare the strategies in terms of the time to identify 25%, 50% and 75% of all FH cases in the UK (current target is 25% in 5 years). For Child-parent Cascade Screening, we applied the model to other populations that have reported FH identification levels.

Results: In the UK, 25% of FH individuals would be identified after 47 years for Cascade Testing, 12 years for Child-parent Screening and 8 years for Child-parent Cascade Screening; 50% identification after 146, 33 and 19 years and 75% after 334, 99 and 41 years respectively. For Child-parent Cascade Screening, the times to identify 50% FH were, for Netherlands, Norway, Japan, Canada, USA, Australia/NZ, South Africa and Russia, 0, 5, 13, 15, 16, 18, 21, and 30 years respectively.

Conclusion: Child-parent Cascade Screening is the fastest strategy for identifying FH in the population. The model is applicable to any country to estimate the time to close the FH detection gap (www.screenfh.com).

Highlights

Familial Hypercholesterolaemia (FH) is a preventable cause of coronary heart disease.

Only a minority of individuals with FH have so far been identified

Cascade testing, Child-parent Screening and Child-parent Cascade Screening are feasible

Setting FH identification targets is important

Time to target for different strategies in different populations can be estimated.

Introduction

Familial hypercholesterolemia (FH) is a common and preventable cause of premature ischaemic heart disease (IHD). There are about 260,000 heterozygous affected individuals in the UK (prevalence 1 in 250) who have about a 100-fold excess risk of fatal myocardial infarction between ages 20 and 39 years. [1] A fatal or non-fatal IHD event affects about 50% of FH-positive men before age 50 and about 30% of FH-positive women by age 60. [2] Preventive treatment with statins is effective in reducing this high risk. [3]

Early identification of individuals with FH is therefore a public health priority but in most populations only a small proportion of all cases have been identified. [4] In the UK, an estimated 7% of all cases are known, leaving 93% undetected and at high risk of a premature IHD event. [5,6] This gap in identification was highlighted in a recently published National Health Service (NHS) Plan, and a target was set to increase the 7% to at least 25% in 5 years. [6] How this would be delivered was not specified. Three strategies that have been tested in practice include (i) family-based Cascade Testing, where relatives of individuals with an FH mutation are tested for the same mutation [7] (ii) universal Child-parent Screening, where children aged 1 year old are tested for cholesterol and FH mutations at the time of routine immunisation and the affected parent of positive children identified [8] and (iii) a combination of the two methods, Child-parent Cascade Screening, where Child-parent Screening systematically identifies new unrelated index cases and leads naturally to Cascade Testing of relatives. [9]

Here, we develop a model to estimate the time to identify different proportions of FH in the population for the three identification strategies. We use publicly available data to compare the time to reach 25%, 50% and 75% identification for the UK, its home nations and other countries where estimates of FH identification have been recently reported.

Materials and Methods

Cascade Testing

Supplementary Figure 1 gives the equation used to calculate the number of new FH individuals identified each year by Cascade Testing; the number of new FH relatives identified per known index FH mutation-confirmed case multiplied by the background number of new index FH cases identified each year from opportunistic/targeted testing (eg. high cholesterol level identified in an adult in primary care during a Health Check or in secondary care following a non-fatal cardiac event). We assumed that all new index cases are unrelated (or else they would identify each other) to provide a best-case estimate and that all available relatives are identified within a year of identifying an index case. In the model we reduced the number of new index cases identified per year in proportion to the population increase in FH detection each year.

Child-parent Screening

For Child-parent Screening a model was developed that avoids counting affected parents twice if more than one child in a family is identified as positive for FH. This applies from the 3rd year of screening onwards, because the average time between births in a family is 2 years. [10] We also avoided double-counting parents when a child, previously identified as positive, becomes a parent and has their own children screened. The equations for the first 2 years of screening and from the 3rd year onwards are shown in Supplementary Figure 2. The number (N) of 1-year old children (the age at screening) is the number of births per year and screening uptake (U) is the proportion attending for immunization at 1 year multiplied by the acceptance of the offer of screening among immunized children. An FH prevalence (P) was applied to all calculations and the median number of children per family (total fertility rate, FR) was used to calculate the probability that a parent might have already been identified from another child screened in previous years, since this probability increases with the number of children in a family.

Child-parent Cascade Screening

For Child-parent Cascade Screening each FH positive child also leads to the identification of their affected siblings (older siblings in the first two years of screening) and grandparent. The model was developed further to avoid double-counting grandparents and siblings when

both Child-parent Screening and Cascade Testing are happening together. This could arise, for example, if a grandparent of an FH-positive child was previously identified by Child-parent Screening through an older grandchild or if a younger sibling attended for immunisation who had already been identified by Cascade Testing. Such FH-positive individuals are counted only once in the equations in Supplementary Figure 3 (i) for the first 2 years of screening and (ii) for the 3rd year of screening onwards, which are given separately because the impact of cascade testing is greater in the first two years of screening than subsequent years, when relatives may have already been identified or not yet borne.

In the models we took account of the effect of deaths among those identified with FH over time by multiplying the number of deaths in a population in a year by the prevalence of FH and by the proportion of FH cases identified in the previous year. We assumed that the fertility and death rates remained constant over time, that the age at which children had their own children followed the same maternal age distribution as their parents and that when a child with FH had their own children, only their children would be identified (the parent and grandparent having already been identified).

Publicly available data were applied to the models to estimate the time (in years) to identify 25%, 50% and 75% of all FH individuals in the population for the three FH identification strategies for the UK and separately for its home nations, England, Scotland, Wales and Northern Ireland. An FH prevalence of 1 in 250 was applied. A published report of Cascade Testing provided the number of new per known cases [5] and national audit data gave the background number of new index cases identified each year. [11]. Office for National Statistics (2017) data were used for population size [12], fertility rate [13], maternal age distribution [10] and the number of deaths per year [14] and WHO/UNICEF data for immunization coverage. [15] A published report of a national demonstration project of Child-parent Screening in 10,095 children provided the observed percentage uptake of screening among immunized children. [8] Input data are summarised in Supplementary Table 1. Sensitivity analyses were performed to examine the effect of doubling the efficacy of Cascade Testing (number of new per known cases identified) and increasing the uptake of Child-parent Screening by 10% points.

The equations underpinning the model for Child-parent Cascade Screening are generalizable to any population, and were applied to estimate the time to identify different proportions of FH cases in 8 other countries, where estimates of the proportion of known cases have been recently published, [4] applying the FH prevalence of 1 in 250. For non-UK countries we used United Nations (UN) data on population size, the number of livebirths according to maternal age, fertility rate and number of deaths per year to obtain country-specific estimates. [16] UN data on maternal age were only available in 5-year categories, so an asymmetric sigmoid regression of the cumulative number of births according to age [17] was used to obtain the number of births at each maternal age. The input data for these 8 other countries are given in Supplementary Table 2. STATA version 15 was used for all analyses.

Results

Figure 1 shows plots of FH identification for Cascade Testing, Child-parent Screening and Child-parent Cascade Screening in the UK. The results show that the 25% NHS identification target is reached after 47 years, 12 years and after 8 years respectively. The plots are curved, because the rate of identification declines with increasing proportions of all cases found for each strategy. Comparable plots for England, Scotland, Wales and Northern Ireland are given in Supplementary Figure 4.

Table 1 gives the results of a sensitivity analysis; the time taken to identify 25%, 50% and 75% of all FH cases for each strategy based on doubling the observed number of new per known cases identified by Cascade Testing and increasing the observed uptake of Child-parent Screening by 10% points. Neither of these increases resulted in the NHS target of 25% in 5 years being reached; a 94% uptake for Child-parent Cascade Screening came closest, at 7 years.

Table 2 gives the time to identify 25%, 50% and 75% of all FH cases by Child-parent Cascade Screening for 12 countries (including the 4 home nations of the UK) where current proportions of known FH have been reported. The 25% target has already been reached in 3 countries (Norway, Netherlands and Japan), and other countries would identify 25% of all FH cases within about 12 years or half of all cases within 30 years.

Discussion

The results of this analysis show that the fastest strategy for closing the identification gap in FH is Child-parent Cascade Screening, an integration of universal screening in childhood, based on total cholesterol measurement supported by FH mutation testing during immunisation and subsequent Cascade Testing within mutation-positive families. Nation-wide implementation of this approach in the UK would reach the NHS target of 25% in about 8 years. Cascade testing alone would take 47 years.

The model developed here is applicable to any country or region for which data on population size, fertility rate, maternal age distribution, immunisation and death rates are available [15,16] and where the proportion of FH already identified, annual number of index FH cases and new per known cases can be estimated. An interactive online tool for estimating country or region-specific times to identify different proportions of FH in the population, using the model, is available at www.screenfh.com.

Both Cascade testing and Child-parent Cascade Screening have been assessed as cost-effective in the UK healthcare setting, with estimated incremental cost effectiveness ratios of £5806/QALY [18] and £12,480/QALY respectively [19], within the £20,000/QALY threshold used by the National Institute for Health and Care Excellence. The estimate for Child-parent Cascade Screening [19] is likely to be high because it assumed a lower rate of FH identification for Child-parent Screening than was observed in practice.[8] Cascade Testing, whilst highly cost-effective, is not sufficiently medically effective, because it misses most cases in the population. The method is self-limiting and can only be sustained if supported by a separate method to provide a steady and substantial number of unrelated index cases. [7] Based on the current efficacy of Cascade Testing (number of new per known cases identified), 5098 unrelated FH index cases would need to be found each year for Cascade Testing to reach the 25% target in 5 years. [5] The current index case identification rate is 556 per year; doubling this to 1112 would still require 31 years to reach the 25% detection target. It is unlikely that even with extra efforts to find new cases through searching electronic health records in primary care databases, as recommended in practice guidelines

[20], that the 4542 per year shortfall of index cases will be met. A systematic universal screening strategy is needed.

Child-parent Cascade Screening is a strategy that has been shown to be effective and affordable, costing about £980 per new FH case identified. [9] The method has two key advantages. First it screens for FH at the time in life (early childhood) when a total cholesterol level is most discriminatory for identifying FH. [21] Any method, that relies on testing adults, such as using electronic health records from NHS health checks, results in substantial misclassification because cholesterol levels increase with age for other, principally dietary, reasons. Second, by screening children, FH is identified before the onset of clinical disease providing the opportunity for prevention in children, their siblings and their parents (median age 32 in the demonstration project). [8] Electronic health records in adults are a potential supplement to identifying new FH index cases but largely miss the preventive opportunity (median age at an NHS Health Check is about 60 years). [22]

The estimates from our model are based on data from observed reports of testing and screening combined with national statistics data and so are likely to reflect what is possible in practice. We nevertheless needed make several assumptions. First, we assumed that the number of new per known cases identified from Cascade Testing from a child was greater than the observed rate of Cascade Testing from an adult because in screening children, the parents are automatically available for testing and one will almost always be positive. Motivation to test other family members is likely to be greater when one starts with an FH-positive child than an FH-positive adult as previously described. [9] We also assumed that the effect of non-paternity (about 2% in the UK), which will reduce the efficacy of Child-parent Screening, was included in the 16% non-uptake rate of Child-parent Screening, because families where paternity is uncertain are less likely to agree to testing. Had we added the 2% to the model as a separate factor it would have had negligible impact on identification times. We may have overestimated the time taken for Child-parent Screening and Child-parent Cascade Screening to reach identification milestones, because background Cascade Testing from a low level of new index cases identified opportunistically, is likely to continue and public awareness of FH may grow, contributing to overall detection. Our model did not account for net migration, because the age distribution and proportion of

known FH among migrants is uncertain, but any error is likely to be small; in 2018 UK net migration was 274,000, among which an expected 1096 would have FH, representing about 0.4% of all FH in the population. Our projected identification times are based on the resources and readiness of health care systems to implement screening and genetic testing which will vary between countries.

Universal Screening of Children for FH has been introduced, with varying levels of uptake in Slovenia, USA and Australia. [23,24,25] We focused on screening at 1 year of age, because this is within the age range (1-9 years) when FH screening is most accurate [21] and because this has been shown to be feasible in the UK combined with immunisation. [8] Different models could be adopted in other countries if there are more suitable alternative entry points for screening in childhood. For example, in Slovenia children are screened for FH at age 4, [23] when a blood test is mandated for other reasons, and in the US, guidelines recommend screening at age 9.[24] Advantages of linking screening to immunisation include high uptake (84% in the UK demonstration project)[8] and low cost (about £5 per child screened)[9] because children are already attending their health care provider and the two activities can be combined into one. Most countries operate a national immunisation programme at about 1-2 years of age when FH screening could be considered. Whatever age is applied some missed cases are likely above the age threshold, until children themselves become parents, and can be identified through screening their own children.

Child-parent screening was effectively piloted in England in 2016 [8] but has yet to be adopted routinely in the UK. The strategy will need to be seriously considered to get close to the 25%, 5-year target. In screening children, it is important not to ignore the wider benefits in identifying the affected parent and other high-risk relatives who could be subsequently offered preventive treatment to avoid a premature heart attack. Both child, and parent benefit from such screening, from life-style interventions and the timely introduction of drug therapy (principally statins); but the child benefits twice, once by reducing his/her own risk of premature ischaemic heart disease and again by avoiding the premature death of a parent.

Our projections are presented as the proportion of all cases of FH identified in the population, rather than in specified age groups, because identification targets are likely to be set for the whole population, as they have been in the UK. A limitation of this approach is that it tends to conceal the advantage that, after say 20 years of screening beginning in childhood, most young FH-positive individuals will be identified (about 80% rather than the 50% of all FH in the population in Figure 1) and can be offered recommended treatment. [26] Recent evidence shows high adherence to statin treatment (about 80% after 20 years) among children with FH starting treatment at age 13, with a reduction in their serum LDL-cholesterol to levels similar to their unaffected siblings by age 40, with no cardiovascular events observed, compared with a 25% event rate (7% deaths) in affected parents who started treatment later. [27]

The UK's NHS 25% identification target is only a first step. The ultimate goal is to identify all or nearly all individuals with FH in the population. Child-parent Cascade Screening could identify 50% of all FH cases in about 17 years and 75% detection in about 30 years, after which most affected families would be known and Cascade Testing would continue as the main and highly cost-effective identification method. Within a single reproductive generation there is the potential to prevent most premature fatal and non-fatal heart attacks in the population due to inherited high cholesterol.

Conflicts of Interest: None
Funding: None
Acknowledgements: We are grateful to Kate Haralambos for providing audit data and to Professors Joan Morris, Nick Wald and Alan Rees for their helpful comments on the paper.

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Figure Legend

Figure 1: Proportion of all FH cases in the UK identified over time for Cascade Testing, Child-parent Screening and Child-parent Cascade Screening (integration of first two methods). NHS 25% target denoted by horizontal dotted line.

Supplementary Figure 1: Flowchart for estimating the number of FH cases identified each year by Cascade Testing

Supplementary Figure 2: Flowchart for estimating the number of FH cases identified each year by Child-parent Screening

Supplementary Figure 3:

Flowchart for estimating the number of FH cases identified by Child-parent Cascade Screening

(i): In the 1st and 2nd years of Child-parent Cascade Screening

(ii): Each year, in the 3rd year and onwards of Child-parent Cascade Screening

Supplementary Figure 4: Time to detect proportions of all FH for England, Scotland, Wales, and Northern Ireland

Fig 1: Proportion of all FH cases in the UK identified over time for Cascade Testing, Child-parent Screening and Child-parent Cascade Screening (integration of first two methods). NHS 25% target denoted by horizontal dotted line.

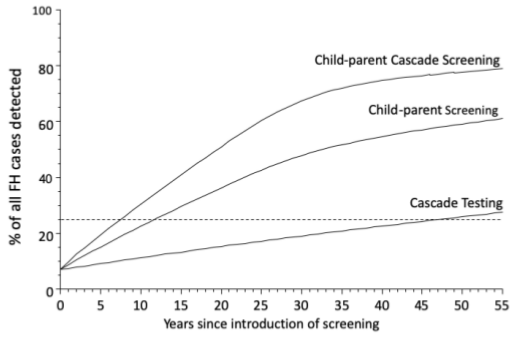

Table 1: Sensitivity analysis for time to identify different proportions of FH cases in the UK population using the three FH identification strategies.

	Years to identify % of FH in population		
	25%	50%	75%
Cascade Testing			
new per known cases identified			
1.15 (observed)	47	146	334
2.30 (observed x2)	31	99	241
Child-parent Screening			
84% uptake (observed)	12	33	99
94% uptake (observed +10%)	10	27	73
Child-parent Cascade Screening			
84% uptake (observed)	8	19	41
94% uptake (observed +10%)	7	17	30

Table 2: Time to identify different proportions of FH cases by Child-parent Cascade Screening according to population where initial identification levels are known.

	Years to identify % of FH in population		
Country	25%	50%	75%
England	9	20	43
Scotland	6	17	31
Wales	7	19	44
Northern Ireland	3	16	32
Norway	[a]	5	16
Netherlands	[a]	[a]	[a]
Russia	12	30	[b]
South Africa	9	21	51
Canada	4	15	27
USA	6	16	30
Australia/New Zealand	8	18	29
Japan	[a]	13	29

[a] Already identified

[b] Does not reach target because of low immunisation rate (see supplementary Table 1)