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Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis

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ABSTRACT

Objective To develop a population screening strategy for familial hypercholesterolaemia.

Design Meta-analysis of published data on total and low density lipoprotein (LDL) cholesterol in people with and without familial hypercholesterolaemia according to age. Thirteen studies reporting on 1907 cases and 16 221 controls were used in the analysis. Included studies had at least 10 cases and controls with data on the distribution of cholesterol in affected and unaffected individuals.

Main outcome measures Detection rates (sensitivity) for specified false positive rates (0.1%, 0.5%, and 1%) in newborns and in age groups 1-9, 10-19, 20-39, 40-59, and ≥60 years.

Results Serum cholesterol concentration discriminated best between people with and without familial hypercholesterolaemia at ages 1-9, when the detection rates with total cholesterol were 88%, 94%, and 96% for false positive rates of 0.1%, 0.5%, and 1%. The results were similar with LDL cholesterol. Screening newborns was much less effective. Once an affected child is identified, measurement of cholesterol would detect about 96% of parents with the disorder, using the simple rule that the parent with the higher serum cholesterol concentration is the affected parent.

Conclusions The proposed strategy of screening children and parents for familial hypercholesterolaemia could have considerable impact in preventing the medical consequences of this disorder in two generations simultaneously.

INTRODUCTION

Familial hypercholesterolaemia is an autosomal dominant disorder affecting about two in every 1000 people.¹ It results in increased serum cholesterol concentrations and a high mortality from coronary heart disease. Affected adults aged 20-39 years have a 100-fold excess risk of dying from coronary heart disease.^{w1} Treatment to lower serum cholesterol concentration, for example with statins, is effective in prevention² so screening for familial hypercholesterolaemia may be a practical option if an effective population screening strategy were available. Cascade screening, in which the first degree relatives of affected individuals are tested,^{3,4} is currently being assessed as part of a

nationwide pilot screening programme. At present, there is no effective way of identifying index cases in the population and so there remains uncertainty over what screening strategy is likely to be effective.

We carried out a meta-analysis of published studies on total and LDL cholesterol in individuals with and without familial hypercholesterolaemia to determine the age at which cholesterol measurement discriminates best between affected and unaffected, to quantify the screening performance of such measurements, and to propose a screening strategy that could be applied to the whole population in an efficient manner.

METHODS

We sought published studies that included data on the distributions of serum total or LDL cholesterol concentrations in cases of heterozygous familial hypercholesterolaemia and unaffected controls. We searched electronic databases (Medline, Embase, and the Cochrane Library) in any language up to May 2006, using key words [hypercholesterolemia or hypercholesterolaemia] and [familial or heterozygous] and within resulting citations identified studies on humans and those of Medline subsets “diagnosis,” or “clinical prediction guides.” We examined relevant citations in the reports of studies and in review articles. In studies that reported incomplete data we contacted the individual authors for the required information.

We included studies with 10 or more cases that published the mean and SDs of total or LDL cholesterol (or data from which they could be derived) for which corresponding data in unaffected controls were either published by the authors or identified separately by us from population surveys.

The studies were included if the diagnosis of familial hypercholesterolaemia was genetically or clinically confirmed. Cases were identified from lipid clinics^{w1-w3 w5-w13} or through screening the general population.^{w4} Genetic diagnosis required the identification of a mutation in the LDL receptor gene by DNA analysis. Clinical diagnosis required a measurement of total or LDL cholesterol concentration above a given level (which varied between studies—for example, above the 90th or 95th centiles), a raised serum cholesterol concentration in a first degree relative, and a family history of tendon xanthomata. Controls were

This is version 2 of the paper. In table 1 an asterisk has been added to indicate that the outlying value was excluded in both cases and controls. In table 2 the median concentration for LDL cholesterol in the control group has been corrected to read 0.78 mmol/l (-0.1065 log10). These changes do not alter the conclusions.

from healthy populations stratified by age, geographical region, and the time period (generally within five years) when the blood samples in cases were collected. In seven out of the nine comparisons with genetically confirmed cases the controls were taken from siblings in whom DNA analysis identified no disease causing mutations, but they were not necessarily in the same age strata as their sibling “case.” We excluded case-control comparisons in which the cases of familial hypercholesterolaemia were classified as those with high cholesterol concentrations (such as ≥ 90 th centile) and controls with concentrations less than the 90th centile, as have been used in previous assessments of screening,⁵⁻⁷ as this by definition classifies people as being affected and unaffected without any independent corroboration. We excluded studies of patients taking lipid lowering treatment and in which the cases were drawn from a population where the age range exceeded 20 years.

We log transformed serum cholesterol concentrations because the distributions of LDL and total cholesterol were positively skewed. This was confirmed by results from studies in which the individual data points for serum cholesterol concentrations were published and probability plots indicated a good fit to a log Gaussian distribution. The mean and SD of the log cholesterol values that describe the Gaussian distribution for each study were derived from the reported untransformed means and SDs in each study and the published

formula for the mean and SD of the log Gaussian distribution.⁸ In one study that provided individual data on newborns, there was one outlying value (with very low total and LDL cholesterol levels),^{w3} which we excluded from the analysis. Including it had a minor effect on the results.

Data in the studies were categorised into six age groups. Within each age group we calculated an overall mean (and SD) of the \log_{10} total and LDL cholesterol concentrations for cases and controls, weighted by the number of cases and controls respectively, setting the upper limit for controls at 100 to avoid large control groups dominating the overall average (weighting by $1/SE^2$ gave similar results). As cholesterol values fit a log Gaussian distribution, the mean of the log transformed values when anti-logged is well estimated by the untransformed median value. We therefore used the median as the preferred measure of central tendency and have expressed the results as multiples of the median (MoM) in controls (the median MoM in controls is thus 1.0). This approach was originally described in screening for neural tube defects^{9,10} and is widely used in antenatal screening for Down’s syndrome.¹¹

We estimated screening performance from the overlapping Gaussian distributions of total and LDL cholesterol (expressed as \log_{10} MoM values) within each age group in cases and controls. The false positive rate (the proportion of unaffected individuals with positive

Table 1 | Source and number of cases of familial hypercholesterolaemia and controls according to age (numbers in parentheses are numbers of LDL cholesterol measurements if they differed from numbers of total cholesterol measurements)

Age group (years) and study	Number of		Country	Diagnosis of cases	Description of controls
	Cases	Controls			
Newborn					
Vuorio ^{w2}	13*	10*	Finland	DNA analysis	Siblings without mutations
Kwiterovitch ^{w3}	16 (12)	36	USA	Clinical	Unrelated healthy newborns
1-9					
Vuorio ^{w2}	18	16	Finland	DNA analysis	Siblings without mutations
Ohta ^{w4}	91	65	Japan	Clinical	Unrelated healthy children
Vuorio ^{w5}	47	40	Finland	DNA analysis	Siblings without mutations
West ^{w6}	35 (0)	13 923 (0)	USA	Clinical	Unrelated healthy children†
Assouline ^{w7}	62	41	Canada	DNA analysis	Unrelated healthy children
10-19					
Wiegman ^{w8}	742	189	Holland	DNA analysis	Siblings without mutations
Vuorio ^{w5}	44	31	Finland	DNA analysis	Siblings without mutations
Kwiterovitch ^{w9}	105 (0)	81 (0)	USA	Clinical	Unrelated healthy children
Ketomaki ^{w10}	18	29	Finland	DNA analysis	Siblings without mutations
Tonstad ^{w11}	63 (0)	30 (0)	Norway	DNA analysis	Unrelated healthy children
20-39					
Vuorio ^{w5}	127 (126)	40	Finland	DNA analysis	Siblings without mutations
Simon Broome register ^{w1}	214	804 (799)	England	Clinical	Unrelated healthy adults‡
40-59					
Simon Broome register ^{w1}	237	721 (720)	England	Clinical	Unrelated healthy adults‡
≥ 60					
Simon Broome register ^{w1}	75	165	England	Clinical	Unrelated healthy adults‡

*Not including one outlying observation.

†Lipid research clinics 1979.^{w12}

‡Diet and nutrition survey 1986.^{w13}

Table 2 | Pooled median, median log₁₀, and multiples of the median (MoM) serum total and LDL cholesterol concentrations in cases and controls according to age

Age group (years)	Concentration (mmol/l)				Concentration (MoM)			
	Cases		Controls		Cases		Controls	
	Median	Median (SD) (log ₁₀)*	Median	Median (SD) (log ₁₀)*	Median	Median (SD) (log ₁₀)	Median	Median (SD) (log ₁₀)
Total cholesterol								
Newborn	2.59	0.4139 (0.0829)	1.81	0.2567 (0.0639)	1.44	0.1572 (0.0829)	1.0	0 (0.0639)
1-9	7.80	0.8922 (0.0752)	4.16	0.6195 (0.0594)	1.87	0.2727 (0.0752)	1.0	0 (0.0594)
10-19	7.27	0.8614 (0.0940)	4.31	0.6347 (0.0711)	1.69	0.2267 (0.0940)	1.0	0 (0.0711)
20-39	8.79	0.9439 (0.1019)	5.12	0.7091 (0.0775)	1.72	0.2348 (0.1019)	1.0	0 (0.0775)
40-59	8.68	0.9383 (0.1162)	6.14	0.788 (0.0810)	1.41	0.1503 (0.1162)	1.0	0 (0.0810)
≥60	8.42	0.9252 (0.1183)	6.62	0.821 (0.0740)	1.27	0.1042 (0.1183)	1.0	0 (0.0740)
LDL cholesterol								
Newborn	1.67	0.2230 (0.1181)	0.78	-0.1065 (0.0844)	2.14	0.3295 (0.1181)	1.0	0 (0.0844)
1-9	5.95	0.7744 (0.0954)	2.59	0.4126 (0.0854)	2.30	0.3618 (0.0954)	1.0	0 (0.0854)
10-19	5.45	0.7364 (0.1220)	2.42	0.3843 (0.1125)	2.25	0.3521 (0.1220)	1.0	0 (0.1125)
20-39	7.09	0.8506 (0.1212)	3.62	0.5586 (0.1117)	1.96	0.2920 (0.1212)	1.0	0 (0.1117)
40-59	6.74	0.8285 (0.1533)	4.82	0.6830 (0.1070)	1.40	0.1455 (0.1533)	1.0	0 (0.0170)
≥60	6.01	0.7791 (0.1484)	5.28	0.7230 (0.0990)	1.14	0.0561 (0.1484)	1.0	0 (0.0990)

*Median log₁₀ cholesterol concentration is directly estimated from mean log₁₀ cholesterol concentration (see www.wolfson.qmul.ac.uk/epm/webtables/), which anti-logged gives median values shown in this table.

results) was set at about 1% or less, as would be acceptable for population screening. We estimated detection rates (the proportion of affected individuals with positive results) using cholesterol cut offs (expressed as MoM values) to define false positive rates of 0.1%, 0.5%, and 1%. The 95% confidence intervals on the detection rates were based on binomial probabilities. Within each age group we assessed heterogeneity by one way analysis of variance (ANOVA) of mean log₁₀ MoM values in cases and controls.

RESULTS

Table 1 lists the 13 studies included in the analysis according to country of origin and method used to

diagnose familial hypercholesterolaemia, categorised into six age groups. The studies included a total of 1907 individuals with familial hypercholesterolaemia (1134 with a DNA confirmed diagnosis and 773 a clinical diagnosis) and 16 221 controls.^{w1-w13} The reported means and SDs for total and LDL cholesterol in the individual studies and the same data expressed as log₁₀ mmol/l and the combined weighted mean log₁₀ serum cholesterol concentrations for cases and controls in each age group can be found on our website (www.wolfson.qmul.ac.uk/epm/webtables/).

Table 2 shows the weighted average median MoM value of total and LDL cholesterol concentrations in cases and controls for each age group (with log₁₀ SD).

Table 3 | Detection rates (with 95% confidence intervals) for familial hypercholesterolaemia based on total and LDL cholesterol measurements according to specified false positive rates, age, and cholesterol cut-off levels (expressed in multiples of the median in controls (MoM))

Age group (years)	Studies	False positive rate (%)					
		0.1%		0.5%		1%	
		Detection rate (95% CI)	Cut off (MoM)	Detection rate (95% CI)	Cut off (MoM)	Detection rate (95% CI)	Cut off (MoM)
Total cholesterol							
Newborn	2	31 (15 to 51)	1.58	46 (26 to 64)	1.46	54 (36 to 74)	1.14
1-9	5	88 (84 to 92)	1.53	94 (91 to 97)	1.42	96 (93 to 98)	1.37
10-19	5	53 (50 to 56)	1.66	68 (65 to 71)	1.52	74 (71 to 77)	1.46
20-39	2	48 (43 to 54)	1.74	64 (58 to 69)	1.58	70 (65 to 75)	1.51
40-59	1	19 (15 to 25)	1.78	31 (25 to 37)	1.62	37 (31 to 44)	1.54
≥60	1	15 (8 to 25)	1.69	23 (14 to 34)	1.55	28 (18 to 40)	1.49
LDL cholesterol							
Newborn	2	72 (51 to 88)	1.82	83 (64 to 95)	1.65	87 (69 to 97)	1.57
1-9	4	85 (79 to 89)	1.84	93 (89 to 96)	1.66	96 (92 to 98)	1.58
10-19	3	51 (48 to 55)	2.23	70 (66 to 73)	1.95	77 (74 to 80)	1.83
20-39	2	33 (29 to 38)	2.21	51 (46 to 57)	1.94	60 (55 to 66)	1.82
40-59	1	11 (8 to 16)	2.14	20 (15 to 25)	1.89	25 (20 to 31)	1.77
≥60	1	5 (1 to 11)	2.02	9 (3.8 to 18)	1.80	12 (6 to 22)	1.70

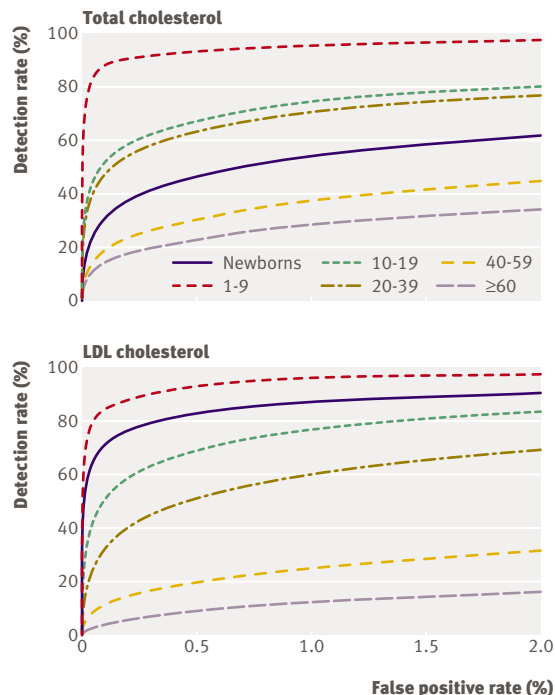


Fig 1 | Plots of detection rates against false positive rates for total and LDL cholesterol concentrations according to age in years

The median MoM in cases was greatest in the 1-9 year old age group (1.87 for total cholesterol and 2.30 for LDL cholesterol) and the SDs tended to be the lowest in this age group, indicating that the greatest discrimination between affected and unaffected individuals occurred at age 1-9 years.

Table 3 shows the detection rates (separately for total and LDL cholesterol) in the six age groups, according to specified false positive rates (0.1%, 0.5%, and 1.0%), together with the corresponding cholesterol cut-off levels (in MoM values) that determine these false positive rates. At a given false positive rate the detection rate was greatest at 1-9 years and declined with

increasing age. At a false positive rate of 0.1%, for example, the detection rate in the 1-9 year age group, based on total cholesterol measurement, was 88% (or 85% with LDL cholesterol) but only 31% (or 72% with LDL cholesterol) in newborns and as low as 5% at 60 and over. Within the 1-9 year age group, the screening performance seemed to peak at between 1 and 2 years of age, based on two studies^{w4 w5} that together yielded detection rates of 92% (with total cholesterol) or 89% (with LDL cholesterol) for a 0.1% false positive rate.

Figure 1 shows the detection rate plotted against the false positive rate for total and LDL cholesterol measured at different ages. This illustrates the maximum discrimination at 1-9 years and shows that there is little additional increase in the detection rate as the false positive rate increases above 1%.

Sensitivity analyses showed that the estimates are robust because we obtained similar results for males and females separately, genetically confirmed cases and clinically diagnosed cases separately, cases taken from lipid clinics or identified through mass screening separately, and studies that used unrelated controls or sibling controls separately. For example, for total cholesterol in the 1-9 age group, the estimate of screening performance at a 0.5% false positive was a 94% detection rate with studies that used unrelated controls compared with a 96% detection rate with studies that used sibling controls. There was no evidence of heterogeneity in the detection rates across the studies in children aged 1-9 years (fig 2), despite there being heterogeneity between mean cholesterol concentrations in cases or controls ($P \leq 0.02$) as would be expected from dietary variations between populations in different parts of the world, measured at different points in time.

DISCUSSION

Measurement of serum cholesterol concentration discriminates best between individuals with and without familial hypercholesterolaemia in children aged 1-9 years, when a high detection rate can be achieved for a false positive rate of 0.1%. Screening performance is materially reduced in newborns and young adults.

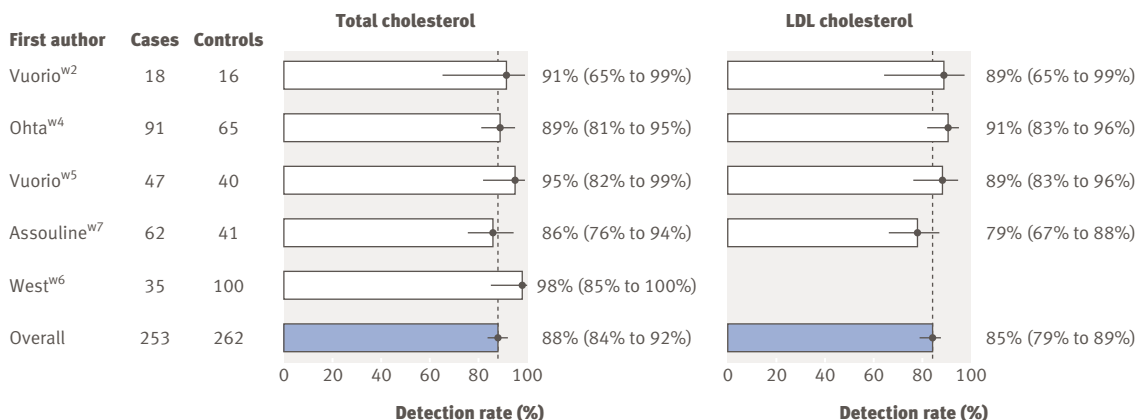


Fig 2 | Estimated detection rate for a 0.1% false positive rate for total and LDL cholesterol according to studies in children aged 1-9 years

The results indicate that population screening could be highly effective.

Figure 3 shows, for both total and LDL cholesterol, the distributions in affected and unaffected individuals aged 1-9 years. Cholesterol cut offs that yield false positive rates of 0.1%, 0.5%, and 1% are shown with the corresponding detection rates and the corresponding likelihood ratios for individuals at or above the specified cut offs. The figure shows how small differences in the selected cut off for serum cholesterol concentration have relatively large effects on the false positive rate but smaller effects on the detection rate. The likelihood ratio (the detection rate divided by the false positive rate) indicates the number of times people who are screen positive are at an increased risk of being affected compared with people in general. So, for example, with a total cholesterol cut off of 1.53 MoM, on average, individuals with a positive result on screening have 880 times the chance of being affected than people in general. With a cut off only slightly lower, at 1.37 MoM, the likelihood ratio drops to 96. In view of this, if screening were introduced it would be sensible to do so using a cholesterol cut off of about 1.53 MoM rather than 1.37 as the detection rate is only 8 percentage points lower and the likelihood ratio is about nine times greater.

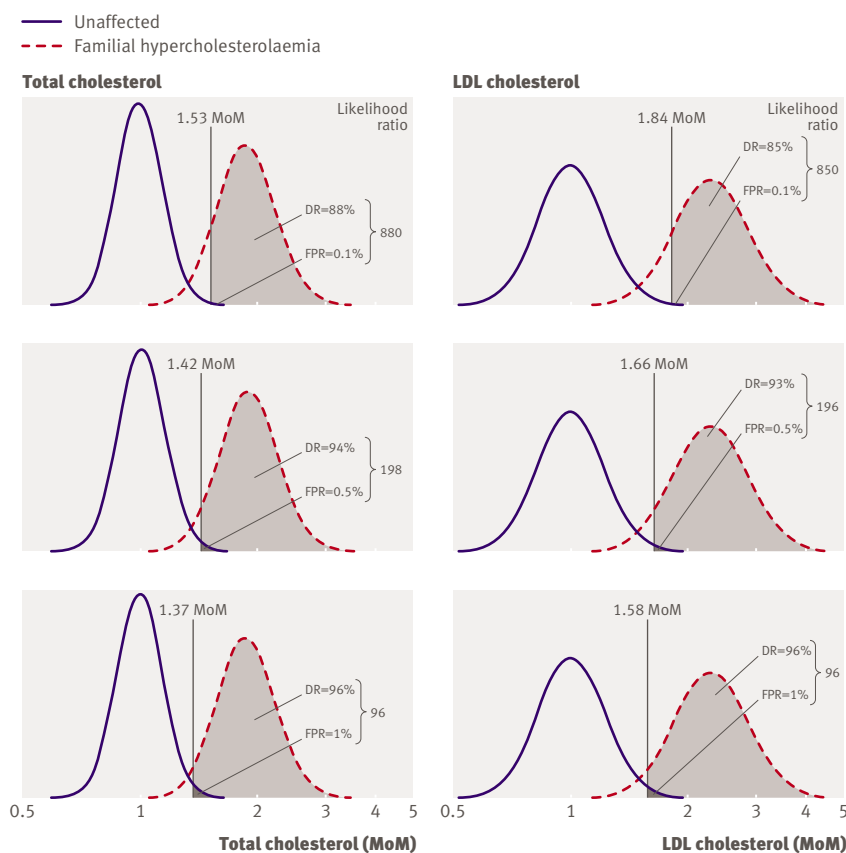


Fig 3 | Relative frequency distributions of total and LDL cholesterol in children aged 1-9 with and without familial hypercholesterolaemia, showing detection rates (DR) and likelihood ratios for cholesterol cut offs set to yield false positive rates (FPR) of 0.1%, 0.5%, and 1%

There was no advantage in measuring LDL cholesterol over total cholesterol, apart from in screening newborns (when LDL cholesterol was better), but this is too early for screening. In general, the measurement of total cholesterol was marginally (but not significantly) better than LDL cholesterol measurement as a screening test. This might reflect a coincident rise in other lipoprotein concentrations (very low density lipoprotein and intermediate density lipoprotein) in people with familial hypercholesterolaemia.¹²

The advantage of using MoM values rather than absolute mass units (such as mmol/l) is that they tend to overcome systematic variation between laboratories in serum cholesterol measurement, provide a simple measure of how high or low a person's cholesterol is compared with a typical "average" population level, and a given MoM cut off will tend to yield the same screening performance (detection rates and false positive rates) in different populations. Within a given population any MoM value can easily be converted into a local cholesterol concentration cut off in mmol/l. For example, our results indicate that a MoM cut off of 1.53 (table 3) will have a detection rate of 88% and a false positive rate of 0.1% at ages 1-9. If the median total cholesterol in a given population of 1-9 year olds was 4 mmol/l the cut off would be 1.53×4 mmol/l or 6.1 mmol/l. In practice it may be better to convert all serum cholesterol values in to MoM values by using local normal cholesterol medians, as is routinely done in antenatal screening for neural tube defects and Down's syndrome.¹¹

The confidence intervals on our results are narrow. They reflect sample size but do not take in to account possible imprecision arising from variation in estimates between studies and deviation of fit of the data from a Gaussian distribution. The sensitivity analyses, however, indicate that we can be reasonably confident in the results, particularly in relation to the relative differences between the age groups. Some cases of familial hypercholesterolaemia may have been missed because not all mutations are known, but this would not lead to bias if the cholesterol distributions in people with known and unknown mutations were similar. If cholesterol concentrations in people with "unknown" mutations were, on average, lower than those in people with "known" ones, screening performance would be overestimated, or underestimated if they were higher. Such "missed" cases are, however, unlikely to represent an important source of bias because it is estimated that over 80% of mutations have been identified.¹³

Proposed population screening strategy

Serum cholesterol measurement in children

Children could be screened when they visit their general practice for routine vaccination at about 15 months of age (for example, when attending for the measles, mumps, and rubella (MMR) vaccination). A blood spot could be collected at the same time as the vaccination is given. Use of an appropriate total (or LDL) cholesterol cut off that yields a false positive rate of 0.1% (for example, 1.53 MoM and 1.84 MoM,

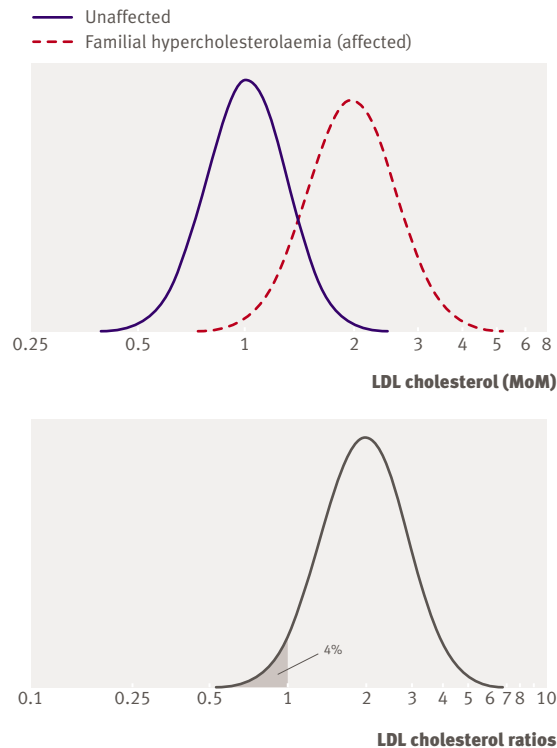


Fig 4 | Top: distributions of LDL cholesterol (MoMs) in individuals aged 20-39 with and without familial hypercholesterolaemia; **bottom:** distribution of ratio of all possible pairs of affected and unaffected individuals with familial hypercholesterolaemia (shaded area (4%) indicates proportion of differences <1 (affected less than unaffected) and represents proportion of parents who would be misclassified if parent with higher cholesterol concentration was assumed to have disorder)

respectively, based on the results from this analysis) would identify about 90% of cases.

Serum cholesterol measurement in parents

As familial hypercholesterolaemia is an autosomal dominant disorder, a child with the disorder will have

an affected parent. The identification of affected children aged 1-9 provides an opportunity to identify affected parents. Screening children in this way therefore accomplishes two aims simultaneously: screening children and screening their parents. Treatment to lower cholesterol could be initiated immediately in the parent and delayed in the child until adulthood.

Measurement of serum cholesterol (total or LDL) in each parent of an affected child would determine which one is affected. Applying a simple rule—namely, that the parent with the higher cholesterol concentration has the disorder—is an effective way of determining which parent is affected, with a detection rate of about 96%. The accuracy of this rule can be estimated from the distributions of serum cholesterol concentration in affected and unaffected individuals aged 20-29 (shown for LDL cholesterol in fig 4). The distribution of the differences between affected and unaffected individuals is estimated by subtracting the means and summing the variances (expressed in logs as LDL cholesterol has a log Gaussian distribution) and this can be expressed as the ratio of LDL cholesterol in pairs of affected and unaffected people (shown in fig 4). The shaded area indicates the proportion of differences below one (affected less than unaffected) and represents the proportion of parents who would be misclassified according to the rule—4% for LDL cholesterol (3% for total cholesterol), leaving 96% (100% - 4%) correctly identified. In this situation a 4% false negative rate equals the false positive rate because for every missed affected parent the other unaffected parents will be classified as positive. The cholesterol distributions in figure 4 are shown in MoMs so the results are generalisable; in practice, all that need be done is to identify the parent with the higher serum cholesterol concentration. In about one in 500 screen positive children, both parents will be affected, but this has a minor effect on the detection rate in parents (reducing it by only about 0.2%). It has been estimated that the father is not the biological parent in about 4% of families,¹⁴ so about 2% of men tested in this way would be misclassified as having the disorder when they did not. But this

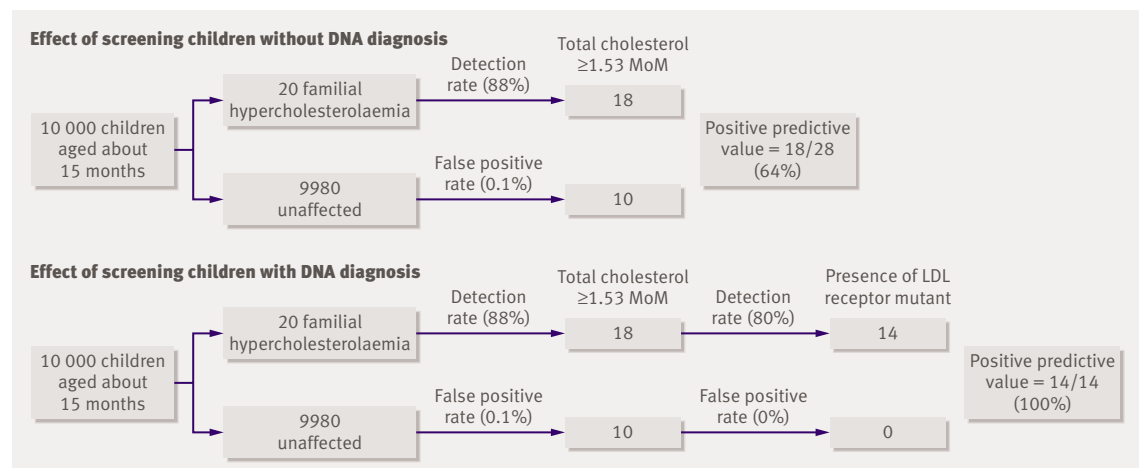


Fig 5 | Effect of screening children without and with DNA diagnosis

would apply to only about 1 in 25 000 men (2% of 2 per 1000).

Expected impact of proposed screening strategy

Figure 5 shows two flow diagrams to illustrate the effect of screening a population of 10 000 children attending for vaccination at 15 months of age, one without and one with the use of DNA diagnosis. Given a prevalence of familial hypercholesterolaemia of two per 1000, there should be 20 affected and 9980 unaffected children. Eighteen out of the 20 affected children would be detected and 10 unaffected children would be falsely classified as positive (from table 3, detection rate 88% for a 0.1% false positive rate). The odds of being affected given a positive result is therefore about 2:1 (18:10); the positive predictive value being 64% (18/28). There is no diagnostic test available that can identify all affected individuals so intervention would have to be based on the screening results alone. Alternatively, DNA analysis to identify LDL receptor mutations could be used in children with positive results on screening (lower flow diagram in fig 5). This has the advantage of excluding all false positives (positive predictive value 100%) but at the expense of missing 20% of affected children because not all mutations have been identified.¹³

Figure 6 shows the effect of parental testing without and with DNA diagnosis. Without DNA diagnosis, parents of a child with positive results on screening would be offered measurement of serum cholesterol. Adoption of the rule that the parent with the higher cholesterol concentration has the disorder would correctly identify 17 affected parents (96% of 18) and falsely classify 11 unaffected parents as positive (10 false positives from the screening of the children and one from parental screening; see fig 6). Treatment to lower serum cholesterol would be offered to each parent with positive results on screening (and later to the

child), recognising that out of about every three individuals identified one would not have the inherited abnormality.

The alternative strategy using DNA diagnosis would correctly identify all the affected parents of affected children but would miss the 20% of affected parents of children who had an undetectable mutation. It would be necessary to test the parent only for the mutation found in the child. Screening without DNA diagnosis has the advantage of being simpler and less expensive.

A strength of the proposed child-parent strategy is that the “population sweep” to identify index cases through screening children would not need to be repeated indefinitely. Once a “critical mass” of “seed” families had been identified (which may take about 30 years as most children are born to women aged 15–45), measurement of serum cholesterol concentration in all first degree relatives could thereafter be used to identify the remaining people with familial hypercholesterolaemia in the population—so called “cascade screening.” This concept has been summarised³⁴ and judged potentially useful for autosomal dominant disorders like familial hypercholesterolaemia but not for autosomal recessive disorders such as cystic fibrosis.

Our strategy is a screening approach that offers a simple means of screening children, their parents, and then their family members for familial hypercholesterolaemia. The strategy fulfils eight out of the 10 requirements for a worthwhile screening programme¹⁵; two criteria (availability of facilities for implementation and cost effectiveness) have yet to be determined. There are practical challenges in implementation. A pilot study and a simple means of blood sampling at the time of vaccination would be needed. A potential strength of screening at the time of childhood immunisation is that it would take place at a time when parents are receptive to the possibility of

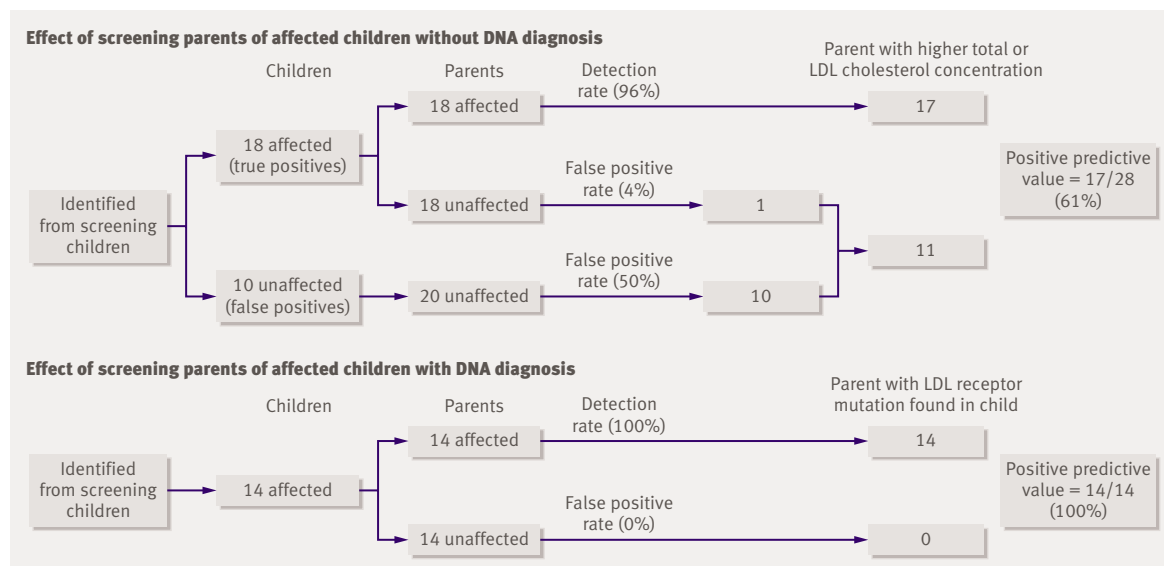


Fig 6 | Flow diagrams to illustrate the effect of screening parents of affected children without and with DNA diagnosis

WHAT IS ALREADY KNOWN ON THIS TOPIC

Familial hypercholesterolaemia is an autosomal dominant disorder affecting about two per 1000 people

The disorder results in a high mortality from coronary heart disease

Lowering serum cholesterol reduces risk substantially, but there is no accepted strategy for population screening

WHAT THIS STUDY ADDS

Screening by measurement of serum cholesterol is most effective if done in early childhood after the first year of life; between ages 1 and 9 years, an estimated 88% of affected children would be identified with a false positive rate of 0.1%

For every affected child there would be one affected parent, identifiable as the one with the higher serum cholesterol concentration

Such a proposed child-parent screening strategy has the potential to prevent the medical consequences of this disorder in two generations simultaneously

preventing disease in their child and therefore may be receptive to a family based strategy to prevent the consequences of the same disease within the family as a whole. Systems would need to be developed to track affected children over time to ensure that appropriate treatment is started when they are older. If, after a few decades, the uptake of screening were high enough, the need to test children at 15 months of age would disappear because all or nearly all affected individuals would be known and it would be necessary to test only the children of families known to have the disorder. The strategy has the potential to prevent a major cause of coronary heart disease in young adults.

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Competing interests: DW has filed a patent application (GB 2414186A) for a medical device that combines medicinal injection and blood sampling.

Ethical approval: Not required.

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