

WHAT IS ALREADY KNOWN ON THIS TOPIC

Various forms of education on breast feeding are effective but only by increasing rates of initiation of breast feeding

While there is evidence for the effectiveness of professional lactation support in prolonging duration of breast feeding, the strength of its effect on the rate of exclusive breast feeding is unclear

WHAT THIS STUDY ADDS

Hospital based antenatal education on breast feeding and postnatal lactation support both significantly improve rates of exclusive breast feeding for up to six months after birth

Postnatal lactation support is marginally more effective than antenatal education

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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. 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 individuals, 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 information on the distributions of serum total or LDL cholesterol concentrations in cases of heterozygous familial hypercholesterolaemia and unaffected controls in which 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} Data in the studies were categorised into six age groups. Within each age group we calculated an overall mean (and SD) of the log₁₀ 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/SE² gave similar results). We estimated screening performance from the overlapping Gaussian distributions of total and LDL cholesterol (expressed as log₁₀ multiples of the median (MoM) values in controls) within each age group in cases and controls (the median MoM in controls is thus 1.0). We estimated detection rates (the proportion of affected individuals with positive results) using cholesterol cut offs (expressed as MoM values) to yield false positive rates (proportion of unaffected individuals with positive results) of 0.1%, 0.5%, and 1%. 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.

RESULTS

We identified 13 studies with 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 table 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%,

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

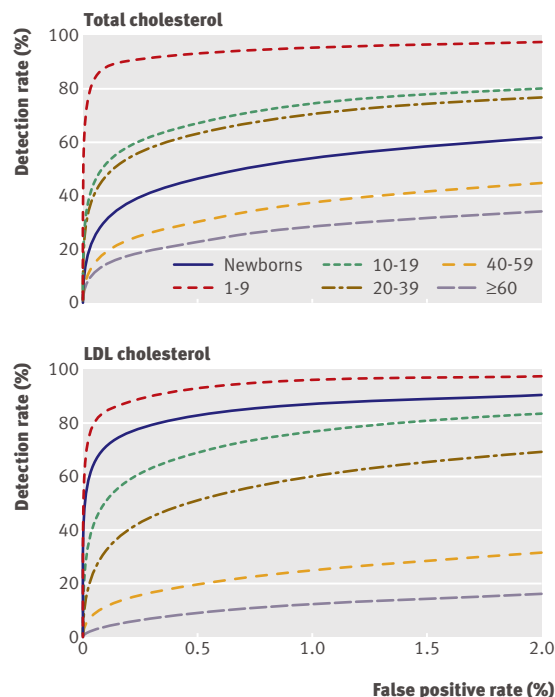


Fig 1 | Plots of detection rates against false positive rates for total and LDL cholesterol concentrations according to age in years

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%.

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. The results indicate that population screening could be highly effective.

Figure 2 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. 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.

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.

Proposed population screening strategy

Serum cholesterol measurement in children

Children could be screened when they visit their general practice for routine immunisation at about 15 months of age (for example, when attending for the measles, mumps, and rubella (MMR) immunisation). 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, 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. About one affected child in 500 will have both parents affected, but this has only a minor effect on the detection rate. 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 through their children. 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% (and a false positive rate of 4%) (see fig 4 on bmj.com).

Impact of the proposed screening strategy

We estimated the predicted impact of screening a population of 10 000 children attending for vaccination at 15 months of age.(see bmj.com for full details). Given a prevalence of familial hypercholesterolaemia of two per 1000, there would 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 with a total cholesterol cut off of 1.53 MoM (from the table, 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. 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.⁵

Cholesterol measurement in parents of screen positive children and adoption of the rule that the parent with the higher cholesterol concentration is positive would correctly identify 17 affected parents (96% of 18) and falsely classify 11 unaffected parents as positive (the 10 arising from the 10 false positive children and one from the parental testing (4% of 18); see figs 5 and 6 on bmj.com).

The alternative strategy using DNA testing in screen positive children and their parents would correctly identify all the affected parents among these children but, of course, would miss the 20% of parents of affected children in whom no mutation was found. It would be necessary to test the parents of each affected child only for the mutation found in their child. Screening followed by DNA testing to make a diagnosis is therefore more specific but less sensitive and more complicated and costly than screening without including such a DNA diagnosis.

One 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 summarised^{3,4} and judged potentially useful for autosomal dominant disorders like familial hypercholesterolaemia but not for autosomal recessive disorders such as cystic fibrosis.

Our proposed 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 programme⁶; 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 immunisation 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 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.

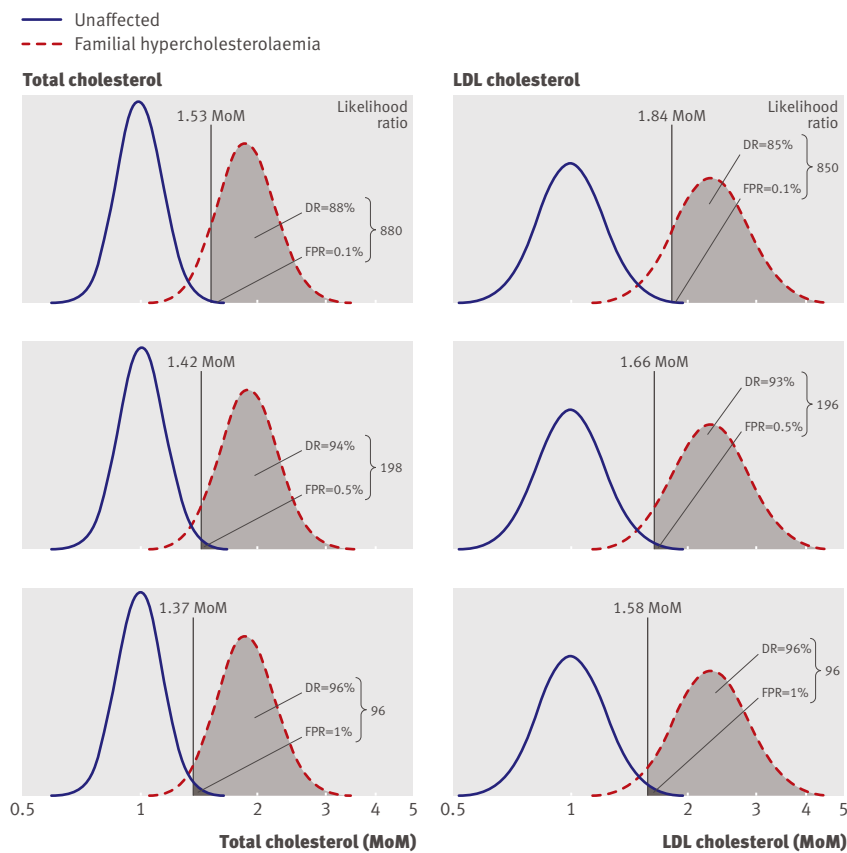


Fig 2 | Relative frequency distributions of total and LDL cholesterol in children aged 1-9 with and without familial hypercholesterolaemia, showing detection rates (DR) and likelihood ratios for cholesterol cut offs set to yield false positive rates (FPR) of 0.1%, 0.5%, and 1%

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

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Mental health consequences of overstretch in the UK armed forces: first phase of a cohort study

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ABSTRACT

Objective To assess the relation between frequency and duration of deployment of UK armed forces personnel on mental health.

Design First phase of a cohort study.

Setting UK armed forces personnel.

Participants Operational history in past three years of a randomly chosen stratified sample of 5547 regulars with experience of deployment.

Main outcome measures Psychological distress (general health questionnaire-12), caseness for post-traumatic stress disorder, physical symptoms, and alcohol use (alcohol use disorders identification test).

Results Personnel who were deployed for 13 months or more in the past three years were more likely to fulfil the criteria for post-traumatic stress disorder (odds ratio 1.55, 95% confidence interval 1.07 to 2.32), show caseness on the general health questionnaire (1.35, 1.10 to 1.63), and have multiple physical symptoms (1.49, 1.19 to 1.87). A significant association was found between duration of deployment and severe alcohol problems. Exposure to combat partly accounted for these associations. The associations between number of deployments in the past three years and mental disorders were less consistent than those related to duration of deployment. Post-traumatic stress disorder was also associated with a mismatch between expectations about the duration of deployment and the reality.

Conclusions A clear and explicit policy on the duration of each deployment of armed forces personnel may reduce

the risk of post-traumatic stress disorder. An association was found between deployment for more than a year in the past three years and mental health that might be explained by exposure to combat.

INTRODUCTION

British commanders have raised concerns about the ability of the armed forces to cope with simultaneous major operations in Iraq and Afghanistan, and the UK armed forces have been asked to do more than was envisaged in the most recent defence review.¹⁻³ The UK armed forces acknowledge that excessive deployments may affect job satisfaction and have recommended maximum deployment levels, called harmony guidelines.

The pace of military operations, "operational tempo," may have an effect on health, place strain on families, lower morale, and influence intentions to remain in the armed forces.⁴⁻⁶ Overstretch is conceived as over-committing the armed forces at a time of simultaneous major deployments. Thus it should be associated with operational tempo. Although deployment is considered a valuable feature of a military career it can also be a source of conflict and tension within families and may have consequences on mental health.^{4,5}

We assessed the relations between operational tempo and psychological health in the context of the harmony guidelines.⁷ We also studied the associations between operational tempo and problems at home.