Cholesterol screening and family history of vascular disease

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Abstract

Hypercholesterolaemia is a major risk factor for the development of coronary heart disease (CHD). Early detection and management of hypercholesterolaemia could retard the atherosclerotic process. Given that CHD and hypercholesterolaemia cluster within families, a screening strategy based on a family history of vascular disease has been advocated.

Serum total cholesterol concentrations were measured in a random stratified sample of 1012 children aged from 12–15 years old participating in a coronary risk factor surveillance study in Northern Ireland. Information about vascular disease in close family members was obtained by means of a questionnaire. The study population was divided into two groups according to total cholesterol values: (i) normal, <5·2 mmol/l (n=822) and (ii) raised, ⩾5·2 mmol/l (n=190). A family history identified 63 out of 190 individuals with hypercholesterolaemia yielding a sensitivity of 33·2% and specificity of 71·5%.

Our data indicated that a strategy whereby only children from high risk families are screened for hypercholesterolaemia is ineffective. While primary prevention emphasising a healthy diet for all is essential, the role of universal screening deserves further appraisal.

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Raised blood cholesterol is strongly implicated in the pathogenesis of coronary heart disease (CHD). There is no population in whom CHD is common that does not have a relatively high mean concentration of total cholesterol.[1] The cholesterol associated risk is thought to be graded and continuous.[2] Clinical trials have shown that a 1% decrement in total cholesterol yields about a 2% reduction in CHD risk.[3]

Coronary heart disease begins in childhood; postmortem studies have demonstrated coronary atherosclerosis as early as the second decade of life.[4] Evidence for the CHD-cholesterol hypothesis is provided by the very existence of clinically apparent CHD in children homozygous for familial hypercholesterolaemia.[5] Furthermore, strong associations have been observed between antemortem blood lipid concentrations and the extent of coronary atherosclerosis in young adults at necropsy.[6]

Longitudinal studies indicate that total cholesterol concentrations track from adolescence into adulthood.[7] Interestingly, tracking is most consistent for those at the extremes of a distribution. Adolescence is a time when many individuals embark upon a voyage of self discovery and as a result make certain lifestyle choices. Some of the consequent behaviours, however, such as dietary indiscretion, physical inactivity, use of the contraceptive pill, and the non-avoidance of obesity can adversely affect blood lipids. It seems reasonable, therefore, to propose that the identification of hypercholesterolaemia and appropriate intervention at this stage could reap lifelong rewards.

In Britain, cholesterol screening in adults is controversial[8–10]; in children it is a non-issue. In the US, on the other hand, the screening of all adults is the stated goal of the National Cholesterol Education Program (NCEP).[11] An active debate, however, continues over the relative merits of universal and targeted screening.[12 13] The American Academy of Pediatrics (AAP) endorses a selective approach.[14] It recommends selective screening for children over 2 years of age whose risk of developing CHD can be identified by a family history of premature vascular disease and/or hyperlipidaemia. The rationale for so doing comes from research that shows that (i) children from these families tend to have higher total cholesterol concentrations[15 16] and (ii) CHD and hypercholesterolaemia cluster within families.[17 18] Accordingly, screening should include the following groups: (1) children whose parents or grandparents have a history of vascular disease before the age of 55 years and (2) children whose parents have a raised blood cholesterol concentration. Furthermore, the AAP advises that children with several coronary factors whose family history cannot be ascertained may be screened at their physician's discretion.

Recent reports, though, suggest that this selective approach is ineffective.[19–21] There are no published data on targeted cholesterol screening in British schoolchildren. The aim of this study was to evaluate the usefulness of the AAP approach to identifying hypercholesterolaemia in this population.

Subjects and methods
The study population comprised 1012 out of 1015 children participating in a national coronary risk factor surveillance study.[22] The sample size corresponds to about 2% of the entire population at each age interval. Three respondents were excluded because blood samples were not obtained. There were four age-sex groups: 250 boys and 256 girls aged 12

Table 1   *School selection policy and response rate; figures are number (%)*

	Response rate	
Policy	Boys	Girls
12 Years		
Selective	81 (92·0)	84 (80·0)
Non-selective	170 (85·0)	174 (88·3)
15 Years		
Selective	85 (84·2)	83 (79·8)
Non-selective	167 (64·7)	171 (76·0)

years and 256 boys and 254 girls aged 15 years. Subjects were selected from schools throughout Northern Ireland. Schools were stratified by education area board (representing five geographical regions) and within an area board by selection policy. Approximately two thirds of children attend non-selective schools (secondary or comprehensive) while the remainder attend selective (grammar) schools: the ratio was thus reflected in the sample. From the 10 strata so generated, a two stage cluster sample was produced. The primary units were the schools, selected with probability proportional to school size (enrolment numbers); this resulted in a total of 16 first choice schools. The secondary units were the school rolls from which pupils were randomly selected within the appropriate age band. Ethical approval was secured and written consent obtained from parent(s)/guardian(s) and participating children beforehand.

Non-fasting venous blood samples were taken one hour after the application of local anaesthetic cream (EMLA, Astra) and transported at room temperature to the regional laboratory at the Department of Medicine, the Queen's University of Belfast. Samples were centrifuged and separated within four hours of being drawn. Total cholesterol was estimated using a fully enzymatic technique (CHOD-PAP, Boehringer Mannheim). The assay was performed in a laboratory conforming to World Health Organisation standards and which regularly participates in their external quality control scheme.

Information on vascular disease in close family members was among the data gathered from parents in a self administered questionnaire. A positive family history was defined as an event (heart attack, angina, stroke) occurring in (i) either parent at any age and/or (ii) first degree grandparents, uncles, or aunts under the age of 55 years. Questionnaires were distributed to children by a liaison teacher upon receipt of a signed consent form, and brought home for completion by parents. They were returned in preaddressed sealable envelopes identifiable by code number only

Table 3   *Mean age (years) of parents and proportion reporting a history of vascular disease; figures are number (%)*

	Age	Angina	Heart attack	Stroke
Boys				
12 Years				
Mother	39·9	0	0	0
Father	42·0	2 (0·8)	2 (0·8)	0
15 Years				
Mother	42·6	1 (0·4)	0	0
Father	45·3	2 (0·8)	6 (2·4)	1 (0·4)
Girls				
12 Years				
Mother	39·2	2 (0·8)	3 (1·2)	0
Father	41·7	3 (1·2)	4 (1·6)	0
15 Years				
Mother	42·2	4 (1·6)	1 (0·4)	0
Father	44·3	9 (3·5)	9 (3·5)	0

and collected at the start of testing in the school. A second questionnaire was despatched in the event of non-response.

Results
(1) RESPONSE
All 16 first choice schools agreed to take part. The overall response rate for the coronary risk factor surveillance study was 79·3%. Table 1 gives the response rate for each age-sex group by school selection policy. Parental questionnaires were returned by 966 out of the 1012 children (95·5%). For the purposes of analysis missing data have been coded as a negative family history of vascular disease.

(2) TOTAL CHOLESTEROL
Table 2 gives the distribution of serum total cholesterol by age-sex group. A total of 190 children (18·8%) had a total cholesterol >5·2 mmol/l. The cut off point chosen to define hypercholesterolaemia corresponds to the 95th centile of the Lipid Research Clinic's reference values.[23]

(3) FAMILY HISTORY
A personal history of vascular disease was elicited only in a small number of parents (table 3). Most of the children were designated positive for a family history of vascular disease because one parent reported a premature event in a first degree relative (table 4). Overall a total of 297 out of 1012 (29·3%) children met the criteria for a positive family history.

(4) SENSITIVITY AND SPECIFICITY (TABLE 5)
The sensitivity of a family history of vascular disease for identifying children with raised total cholesterol concentrations was 33·2%. It was calculated by dividing the number of children who had both a positive family history of vascular disease and a total cholesterol >5·2 mmol/l by the total number with a total cholesterol ≥5·2 mmol/l, expressed as a percentage. The specificity, that is, the chance of correctly labelling a normocholesterolaemic child, was 71·5%. It was calculated by dividing the number of children who had both a negative family history of vascular disease and a total cholesterol <5·2 mmol/l by the total number

Table 2   *Distribution of serum total cholesterol (mmol/l)*

			Centile			
	No	Mean (SD)	10	50	90	Range
Boys						
12 Years	250	4·58 (0·82)	3·61	4·51	5·55	2·73–7·43
15 Years	252	4·23 (0·73)	3·37	4·12	5·24	2·03–6·74
Girls						
12 Years	256	4·72 (0·77)	3·89	4·64	5·69	2·42–7·72
15 Years	254	4·60 (0·77)	3·70	4·56	5·55	2·82–7·61

Missing values, n=4.

Table 4 Family history of vascular disease by group

	Boys		Girls	
	12 Years	15 Years	12 Years	15 Years
One parent positive for premature vascular disease	4	10	11	21
Both parents positive for premature vascular disease	–	–	1	2
One parent positive for family history only	73	55	67	39
Both parents positive for family history only	4	4	1	5
	81	69	80	67

with a total cholesterol <5·2 mmol/l, expressed as a percentage.

Discussion

The results of the study show that selective screening based on a family history of vascular disease fails to identify effectively adolescents with hypercholesterolaemia. Two thirds of subjects with abnormal total cholesterol concentrations would have gone undetected if such a screening policy had been implemented. Indeed, estimates from the US suggest that one third to one half of children with raised cholesterol concentrations would be missed by a targeted testing practice.

Steiner *et al* specifically examined the AAP screening criteria in a teenage population.[19] Using a combination of the 1985 and 1988 criteria they reported a sensitivity of 69%. In a study of 6500 children aged from 3–18 years, Garcia and Moodie found that 48% of children judged to be significantly hypercholesterolaemic had no family history of premature myocardial infarction or known hypercholesterolaemia.[20] Similarly, Dennison *et al* showed that only 40% of white children and 21% of black children with a raised low density lipoprotein cholesterol fraction had a parental history of vascular disease.[21] For black children a parental history of vascular disease was not associated with an increased risk for raised serum total cholesterol concentrations.

We did not attempt to identify children whose parents have a raised blood cholesterol concentration as few adults in Britain actually know their total cholesterol value. By contrast, in the US the NCEP[11] recommendations mean that an increasing number of parents can be expected to have that information. A recent study, though, has cast doubts on the usefulness of this criterion.[24] In a school based study only 7–10% of children with raised total cholesterol concentrations would have been identified on the basis of parental self reported hypercholesterolaemia alone.

We further modified the AAP proposals by employing a broader definition of family history in that we included first degree aunts and uncles. In this way we hoped to maximise

the number of children identifiable by family history and so increase the sensitivity. Although few vascular events were reported by parents due to their relatively young age, the expanded definition meant that a substantial proportion of children (29·3%) were actually deemed to have a positive family history. This is, of course, a reflection of the high prevalence of CHD in the UK in general, and in Northern Ireland in particular.

The poor yield of targeted screening has led some authorities in the US,[13 25 26] including the American Heart Foundation,[27] to support universal screening. They highlight the scale of the problem in that large numbers of children in industrialised nations already have total cholesterol concentrations that increase their chance of future CHD. We found that on a single estimation almost one in five children exceeded a concentration of 5·2 mmol/l, the arbitrary cut off point chosen to define hypercholesterolaemia. Values in early life that predict CHD are not yet known. In adults, however, there is broad agreement among a number of bodies on an upper limit of 5·2 mmol/l,[28 29] extrapolated from data on the cholesterol associated risk. While those with the highest total cholesterol concentrations are at very great risk of CHD, they account for only a small fraction of the overall mortality. Most of the morbidity and mortality from CHD occurs at moderately raised concentrations. A similar phenomenon probably exists for children in developing silent coronary atherosclerosis. Bearing in mind, however, that considerable age related increases occur in cholesterol concentrations from birth through to adult life, the cut off point used in the present study is a conservative one.[30]

Advocates of universal childhood screening would further contend that behaviour in adults is notoriously difficult to alter and that interventions aimed at changing dietary habits might be more effective if begun at the time they are being formed. Furthermore, Resnicow *et al* have emphasised the positive effects of screening, such as increased awareness and motivation on the part of the child and family. In their study of 2000 schoolchildren, a cholesterol screening programme produced significant changes in the knowledge, attitude, and diet of participating children, thus supporting the notion that those who 'know their number' are more likely to respond to messages from health professionals.

Proponents of targeted screening, on the other hand, point to the difficulties of population screening.[12 14] The AAP has cited problems such as poor standardisation of equipment, diurnal and seasonal variations in total cholesterol concentrations, and the potential for inappropriate treatment after a single sporadically raised concentration.[14] Instead, Liftshitz and Moses reported growth failure in 20% of patients referred for dietary management of hypercholesterolaemia after routine total cholesterol screening due to the unsupervised application of low fat, low cholesterol diets,[31] Newman *et al* have lent support to the AAP stance against universal

Table 5 Family history of vascular disease and high total cholesterol

Total cholesterol (mmol/l)	Boys				Girls			
	12 Years		15 Years		12 Years		15 Years	
	Yes	No	Yes	No	Yes	No	Yes	No
<5·2	66	133	57	168	60	135	51	152
≥5·2	15	36	12	15	21	41	16	35
Total	81	169	69	183	80	176	67	187

screening.[12] They argue that evidence is lacking as to how predictive childhood measurements are of subsequent CHD as long term coherent studies have not been undertaken. They raise, too, the issue of psychological morbidity in relation to labelling healthy children 'at risk' of dying decades later.

Besides universal and targeted screening, an alternative option is not to screen at all, which is essentially the practice in Britain. Lloyd recommends that screening should be carried out only in children of families known to have the genetic disorder of familial hypercholesterolaemia, and that a population approach to dietary change should be adopted.[32] The major drawback of this type of low impact intervention is that many children with very raised total cholesterol concentrations will inevitably go undetected and, if dietary advice is ignored, untreated.

Any decision to implement a screening programme should take into account a number of well established epidemiological criteria.[33] Issues such as the efficiency of interventions aimed at lowering total cholesterol concentrations and the economics of screening have not been addressed in this paper. We have shown, though, that a policy in which only children from high risk families are screened is unsatisfactory and ineffective in this population.

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