UK National Screening Committee

Screening for familial hypercholesterolaemia in childhood

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: Draft 2

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

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Abbreviations List

APOB	apolipoprotein B gene
CIMT	carotid intima media thickness
DFH	definite familial hypercholesterolaemia
FH	familial hypercholesterolaemia
FFNR	fixed false negative rate
FN	false negatives
FNR	false negative rate
FP	false positives
FPR	false positive rate
HTA	health technology assessment
ICER	incremental cost effectiveness ratio
LDL-C	low density lipoprotein cholesterol
LDLR	low density lipoprotein receptor gene
LYG	life years gained
MEDPED	make early diagnosis to prevent disease
MoM	multiples of the median
MI	myocardial infarction
NHLBI	National Heart Lung and Blood Institute
NICE	National Institute of Health and Care Excellence
NPV	negative predictive value
PCSK9	proprotein convertase subtilisin/kexin type 9 gene
PFH	possible familial hypercholesterolaemia
PPV	positive predictive value
QALY	quality adjusted life year
ROC	receiver operating curve
Sn	sensitivity
Sp	specificity
TC	total cholesterol
TP	true positives

Plain English Summary

Familial hypercholesterolaemia (FH) is a condition where the body has a high amount of a fatty substance called cholesterol. The build-up and hardening of these fatty substances can block blood from being supplied to the heart and other areas of the body. This causes heart disease leading to serious illness and can cause death.

FH is passed on to those affected at birth through altered genes from either mother or father and in some cases through both. People with FH have a 1 in 2 chance of passing on the condition to their children. Around 1 in 500 people are thought to have FH in the UK and similar countries. Only an estimated 1 in 10 of those with FH in the UK are aware they have the condition.

Without the right healthcare people with FH are more likely to develop types of heart disease at an early age. Medication that helps lower the level of these fatty substances in the body is often recommended to people with FH from the age of 10 onwards.

Current NICE guidance recommends screening family members of people identified as having FH to detect more people earlier. Treatment and management of the condition can then begin earlier and help to prevent death and poor health. Screening all children for FH at a set age has been suggested as a better option. This is because it is likely to identify a higher number of people with the condition.

The most recent review of FH in 2011 recommended against screening all children. This was due to previous evidence of the balance between likely benefit and cost. This review searched for evidence between January 2004 and January 2015. The focus was on some of the areas in the 2011 review that required further evidence or were unmet.

This review found that the evidence is currently insufficient to answer the key questions around screening all children. This included:

- finding no studies that have examined how well a screening test covering all children performs in practice.
- some evidence suggesting the screening test performs best in children between 1-9 years.
- a UK study that is currently evaluating FH screening being carried out at the same time as child vaccinations at 1-2 years. The parents of any children detected with FH are themselves tested. This may help identify additional people with the condition. The study is yet to be published and the results will help us understand whether this method of screening would be of more benefit.
- no studies being identified that assessed whether child screening reduces illness and death from FH.

- It not being clear whether screening all 1-2 year old children at the same time as vaccination would be acceptable. One of the concerns with this is that medication recommended for FH is not usually given to children under 10 years old.
- there being no studies that assessed the balance between benefit and cost of screening all 1-2 year olds or in children of any age.

Executive Summary

Condition

Familial hypercholesterolaemia (FH) is a condition where high cholesterol is caused by an inherited genetic mutation. Cholesterol is elevated from birth and is associated with early development of atherosclerosis and coronary heart disease. Most cases are caused by mutations in the coding of specific genes, with coding for the low density lipoprotein receptor (*LDLR)* being the most common in identified cases.

The condition has an autosomal dominant pattern of inheritance, meaning that the child of an affected parent has a 1 in 2 chance of being affected. The estimated prevalence of heterozygous FH in western countries is 1 in 500. Homozygous FH is much rarer with an estimated prevalence of 1 in 1,000,000, and is associated with severe hypercholesterolaemia and cardiovascular disease even during childhood and adolescence. It has been estimated that only around 12% of people with FH in the UK population have been identified, and less than 1% across countries worldwide.

Treatment

The NICE clinical guidance on the identification and management of FH (CG71) recommend that treatment with lipid-modifying therapy should usually be considered by 10 years of age, and would be lifelong.

Screening

The NICE clinical guidance currently recommends cascade screening of at least first-, second- and, where possible, third-degree relatives of an index case/proband with a clinical diagnosis of FH (diagnosed according to Simon Broome criteria).It has been suggested that an alternative, universal screening of children for FH would be more beneficial by picking up a higher proportion of cases in children. The aim of screening would be to identify children earlier so that treatment and management of the condition can begin sooner and potentially prevent death and morbidity. The initial screening test involves identifying a significantly raised level of cholesterol in the blood, either through one or both total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) testing.

Previous/ Current UK NSC Review

The current UK NSC recommendation is not to carry out population screening for familial hypercholesterolaemia (FH). This follows the 2011 review of FH in adults that concluded that universal screening is not a cost-effective strategy. The current recommendation is cascade testing, where both child and adult relatives of index cases (probands) diagnosed with FH are screened. However, modelling undertaken as part of a 2000 HTA suggested that universal screening of children aged 16 years would be more cost effective than cascade testing.

This review searched the literature between January 2004 and January 2015 to answer key questions related to universal FH screening, specifically in children:

- Whether there is a reliable universal screening test for FH in children and how it performs compared with cascade testing of relatives of index cases
- Whether universal child screening reduces morbidity and mortality associated with FH

- Whether universal child screening and subsequent treatment of screen-detected cases would be ethical and acceptable to professionals and the public
- Whether universal child screening would be cost effective compared with cascade testing

The body of published evidence is currently insufficient to answer these key questions. The review has described the highest quality of evidence available to answer these key questions and found that:

- No studies were identified that have examined the performance of universal screening in practice.
- One systematic review of case-control studies aimed to determine a) the age and b) the cholesterol cut-off that would give the best discrimination between people with and without FH. This review suggested 1-9 years as the optimal age category.
- A UK prospective study due for completion this year is currently evaluating universal child (-parent) FH screening at the time of routine child immunisation at 1-2 years.
- The results of this ongoing study are needed to inform the accuracy of the proposed strategy, and its performance compared with cascade testing, which is currently suggested to identify less than a third of people with FH in the general population.
- No studies were identified that assessed whether child screening (either universal or cascade testing) reduces morbidity or mortality from FH. There would likely be feasibility issues due to the long follow-up required to examine cardiovascular outcomes, and no clearly established thresholds to indicate the presence or progression of atherosclerosis in children.
- There remain many unanswered questions related to the ethics and acceptability of universal screening at 1-2 years, including the management of screen-detected cases
- No studies were identified which assessed the cost-effectiveness of universal screening at 1-2 years. The previous HTA suggested that universal screening at 16 years would be cost effective; no further studies were identified which evaluated the cost effectiveness of child screening at any age.

Introduction

Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is a condition where high cholesterol is caused by an inherited genetic mutation.[1] Cholesterol is elevated from birth and is associated with early development of atherosclerosis and coronary heart disease. Most cases are caused by mutations of the genes coding for the low density lipoprotein receptor (*LDLR)*, apolipoprotein B (*APOB*), or an enzyme involved in the degradation of the receptor; proprotein convertase subtilisin/kexin Type 9 (*PCSK9*). A mutation in one of these three genes is reported to be found in 70% of definite and 20% of probable FH cases, and in 95% of cases where a mutation is identified it is an *LDLR* mutation.[2]

The condition has an autosomal dominant pattern of inheritance, meaning that the child of an affected parent has a 1 in 2 chance of being affected.[1] The estimated prevalence of heterozygous FH in western countries is 1 in 500.[1, 3, 4] Homozygous FH is much rarer with an estimated prevalence of 1 in 1,000,000, and is associated with severe hypercholesterolaemia and cardiovascular disease even during childhood and adolescence.[1, 3, 4]

It has been estimated that only around 12% of people with FH in the UK population have been identified, and less than 1% across countries worldwide.[4]

NICE clinical guidance on the identification and management of familial hypercholesterolaemia (CG71)[1] currently recommends cascade screening of at least first-, second- and, where possible, third-degree relatives of an index case/proband with a clinical diagnosis of FH (diagnosed according to Simon Broome criteria). In families where a genetic mutation has been identified, DNA testing is the recommended cascade testing method. In the absence of a DNA diagnosis, cascade testing by measurement of low density lipoprotein cholesterol (LDL-C) concentration is recommended.[1] This cascade testing recommendation currently applies to children as well as adults. NICE recommend that children with an affected parent should be screened (by DNA test if possible, alternatively by LDL-C concentration) by 10 years of age (by 5 years in rare cases where both parents are affected), or at the earliest opportunity thereafter.[1] Children with a diagnosis should then be referred for treatment under the care of a specialist with expertise in FH in children and young people. NICE recommend that treatment with lipid-modifying therapy should usually be considered by 10 years of age, and would be lifelong.[1]

Basis for current recommendation

The most recent UKNSC external review of familial hypercholesterolaemia in adults, conducted in 2011, concluded that:

"Universal screening for FH is not cost-effective and therefore a universal screening programme is not recommended. Best evidence currently supports cascade testing; tracing family members to identify affected relatives of known FH patients. However the NHS Health Check programme will also be testing all adults for cholesterol levels and will inevitably detect more people with FH which will complement cascade testing. It is doubtful whether existing lipid clinics could cope with the extra workload without investment."

The review therefore supported the current NICE recommendation of cascade testing of relatives of index cases (probands) with FH. The UK NSC has not published formal

recommendations on childhood FH screening, but the NSC's adult FH screening recommendation for cascade testing would apply to child relatives.

The 2011 NSC evidence review was informed by previous modelling undertaken as part of a 2000 HTA,[5] which concluded that cascade testing following identification of cases was the most cost effective strategy in adults, and universal population screening the least cost effective. However, this HTA[5] did find that universal screening may be cost effective when targeted at young people (16 year olds).

The current review therefore aimed to review the evidence for universal screening for FH in childhood or adolescence.

Current update review

The current review considers whether the evidence produced since the last review warrants a change in the current recommendation not to universally screen for FH in children. Four main criteria will be considered, and the key questions reviewed are:

Table 1. Key questions for current Universal FH screening in childhood update review

Criterion	Key Questions (KQ)	# KQ Studies Included
5 – There should be a simple, safe, precise and validated screening test.	1) What are the test characteristics of a universal screening programme for familial hypercholesterolaemia in children? a) How does the sensitivity, specificity, PPV and NPV of universal screening for familial hypercholesterolaemia in children compare to cascade testing of relatives of clinically detected cases? b) How many additional cases of FH will be found from universal screening over cascade testing? c) Has the timing of the screening test for FH in children been defined in the literature?	6
13 - There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.	2) Is there any evidence from randomised controlled trials/ trials that universal screening is more effective than cascade testing at reducing mortality and morbidity?	0

14 – There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.	3) Is there evidence that screening children for FH would be clinically, socially and ethically acceptable to health professionals and the public? a) Is there evidence that treating children with familial hypercholesterolaemia with statins would be clinically, socially and ethically acceptable?	3
16 - The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.	4) Would a universal screening programme for familial hypercholestrolaemia in children be more cost-effective than cascade testing in relatives of clinically detected cases? a) What are the modelled costs of childhood universal FH screening vs the modelled costs of cascade testing and what are their dependencies (e.g. participation rates for universal child/ cascade testing)?	1

A systematic literature search of studies published between 1 January 2004 and 16 January 2015 yielded 3043 references addressing familial hypercholesterolaemia. Of these, 241 were assessed as being potentially relevant to the key questions outlined in Table 1. These studies were further filtered at title and abstract level, and 81 were selected for appraisal at full text. Each section below provides additional information on the evidence selection process for the given criterion.

Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

5. There should be a simple, safe, precise and validated screening test.

Description of the previous UKNSC evidence review conclusion

The previous NSC review did not recommend universal screening in adults as the current system of cascade testing of the relatives of confirmed FH index cases is more cost effective. Though a formal recommendation is not in place for children, the current recommendation of cascade testing also applies to child relatives.

Current UKNSC key question

The key question addressed is:

What are the test characteristics of a universal screening programme for familial hypercholesterolaemia in children?

- *How does the sensitivity, specificity, PPV and NPV of universal screening for familial hypercholesterolaemia in children compare to cascade testing of relatives of clinically detected cases?*
- *How many additional cases of FH will be found from universal screening over cascade testing?*
- *Has the timing of the screening test for FH in children been defined in the literature?*

Description of the evidence

Fifty studies were identified as potentially relevant to this question during title and abstract sifting and were further assessed at full text. No prospective cohort studies of universal screening for FH in children were identified. Though the literature suggests that one European country may have adopted some form of universal FH screening in children ("general screening" of children at age 5 in Slovenia commenced in 1995, with data reportedly being used for research purposes[6]), no studies of universal screening in practice (e.g. before and after studies) or modelling studies were identified.

In the absence of evidence on universal FH screening in practice, studies of highest relevance to the review question on the test performance of universal FH screening in childhood were identified. One key study was identified, a systematic review and meta-analysis of case-control studies including children with FH and non-affected controls. The purpose of this study was to identify the optimum cholesterol cut-offs for a potential universal FH screening programme seeking to discriminate between affected and non-affected children. Two further case-control studies with information of relevance were identified, both of which also looked at appropriate cholesterol cut-offs to differentiate between people with and without FH and included child age groups.

We identified three studies that estimated the performance of cascade testing at detecting FH in the general population. No studies were identified that gave specific information on the performance of cascade testing for identifying affected children in the population.

Several studies have evaluated the performance of cascade testing in terms of the accuracy of cholesterol measurement for indicating people with and without FH, compared to the arguable "gold standard" method of DNA-testing for genetic mutations.

The accuracy of cholesterol measurement as the cascade testing method is a different question from its performance in universal screening. Cascade testing screens people with an affected relative while universal would screen the general population where FH prevalence would be much lower. However, as universal screening would be carried out by blood cholesterol measure, studies that examined the accuracy of cascade testing by cholesterol measure to identify mutation carriers were included if they covered child age categories. Studies examining the accuracy of cholesterol measures to identify mutation carriers in adults, or where age was not specified, were excluded.

Other exclusions were studies only reporting the characteristics of children (and/or adults) with suspected FH who had either been referred for cascade testing or suspected clinically (e.g. mean age, BMI, proportion with a mutation, identified mutations etc.); studies assessing the accuracy of new diagnostic systems for detecting FH mutations.

One prospective study from the US was identified that had compared universal with selective cholesterol screening in young people.[7] The US National Heart Lung and Blood Institute (NHLBI) currently recommends universal lipid screening at the age of 9-11 years as part of the overall aim of reducing cardiovascular risk in youth,[8] not to specifically identify children with FH. As the universal and selective screening methods examined were not comparable to the universal screening or cascade testing methods under question here, this study was also excluded.

Results

Studies optimising parameters for universal screening for FH in children

Wald et al. (2007)[9] (Appendix 1) conducted a systematic review and meta-analysis to determine the age at which cholesterol levels give the best discrimination between those with and without FH, to propose the optimal universal screening strategy. Wald et al. (2007)[9] identified studies that had provided total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels for children with a confirmed genetic or clinical diagnosis of FH (cases) and for a comparison group of unaffected healthy controls. Controls could be unaffected siblings or unrelated population controls.

Wald et al. (2007)[9] identified 13 studies including 1,907 cases with FH (1,134 with genetic diagnosis and 773 clinical) and 16,221 controls.

Detection rates (the proportion of cases who would test positive) were calculated for TC and LDL-C cut-offs at fixed false positive rates (FFPRs) of 0.1%, 0.5% and 1%. Cholesterol cut-offs were expressed as multiples of the median (MoM) in controls (i.e. the MoM in the control would be 1.0).

Cholesterol levels gave the best discrimination between cases and unaffected controls in the 1-9 year age category. Cases in this age group had a median TC concentration of 7.80mmol/l compared to 4.16mmol/l in controls, with a MoM value of 1.87. For LDL-C the median values were 5.95mmol/l in cases vs. 2.59mmol/l with a MoM of 2.30. The MoM concentration for other child age categories was lower: 1.44 for TC and 2.14 for LDL-C in newborns; and 1.69 for TC and 2.25 for LDL-C in those aged 10-19 years.

Detection rates at all FFPRs, and using either TC or LDL-C MoM cut-offs, confirmed that the 1-9 year age category provided the best test sensitivity (detection rate; see table 2). Using the optimal FFPR of 0.1%, detection rates in the 1-9 age category were 88% for TC (using MoM 1.53) and 85% for LDL-C (using MoM 1.84). Detection rates at this FFPR were lower in all other age categories.

Table 2: Detection rates for FH based on TC and LDL-C for given age categories at set FPR and MoM cut-off[9]

Age group	0.1% FPR		0.5% FPR		1% FPR	
	Detection	MoM cut-off	Detection	MoM cut-off	Detection	MoM cut-off

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

Two studies suggested that within the 1-9 year category, peak performance was at 1-2 years. The pooled results of these studies gave detection rates of 92% for TC and 89% for LDL-C at FPR 0.1%. One was a Japanese study including 91 cases (diagnosed clinically) and 65 unrelated healthy children; the other was a Finnish study including 47 cases (diagnosed genetically) and their 40 unaffected siblings. Wald et al. (2007)[9] do not provide full references for these publications. Wald et al. (2007)[9] estimate a positive predictive value (PPV) of 64% for testing in the 1-9 age category using a FFPR of 0.1% and estimated population prevalence of 1 in 500.

Sensitivity analyses showed little effect of gender, whether controls were related or unrelated, whether cases were identified through screening or lipid clinics, or whether FH was diagnosed genetically or clinically.

The results of this systematic review and meta-analysis suggest that TC or LDL-C screening at 1-9 years would give the best discrimination between children with and without FH. Wald et al. (2007)[9] propose that children could be screened by blood spot collection when they attend for routine vaccination at 15 months. A three-year prospective study is currently in progress to examine the performance of this proposed screening strategy. It will assess screening of children when they attend for routine immunisation at 1-2 years at 80 general practices across the UK.[10] The proposal is that this would be "child-parent screening", where detection of a child with FH would lead to serum cholesterol measurement in both parents, with the parent with the higher levels assumed to be affected. Wald et al. (2007)[9] propose that a strength of this child-parent screening strategy would be that it would not need to be performed indefinitely. After a given period (estimated to be around 30 years), the "critical mass" of FH families would have been identified and the system could then switch to cascade testing of first-degree relatives thereafter.

Two further retrospective case-control studies provided information of potential relevance to the issue of optimal cholesterol cut-offs for child universal screening. Both studies consider the accuracy of cholesterol cut-offs used in current diagnostic criteria and suggest alternatives.

A small case-control study by Nicholls et al. (2008)[11] (Appendix 2) was included as it post-dates the search date of the Wald et al. (2007)[9] review (search May 2006). This study included 69 genetically-confirmed cases and their 46 unaffected siblings (without a mutation) who were seen at a single UK lipid clinic over a 25 year period. Age range of the 115 children was 3 to 16 years, and reasons for the child's referral to the clinic (e.g. cascade testing) were not given. The study reports mean cholesterol levels at the time of diagnosis, which were significantly higher ($p<0.001$) in cases (TC 7.6 and LDL-C 5.64mmol/l) than in sibling controls (TC 4.15 and LDL-C 2.13mmol/l).

Nicholls et al. (2008)[11] consider the overlap in levels between cases and controls, and report that the current Simon Broome cut-offs for children aged less than 16 years (TC 6.7mmol/l and LDL-C 4.0mmol/l) would result in several false negatives (receiver operating curve [ROC] plotted, but false negative figures for this cut-off not reported). A lower TC cut-off of 6.0 would give 86% sensitivity and 98% specificity. A lower LCL-C cut-off of 3.6 would give 95% sensitivity and 97% specificity. Further lowering the LDL-C cut-off to 3.2 gave better sensitivity (97%) at the detriment of specificity (91%).

Starr et al. (2008)[12] (Appendix 3) reviewed The Netherlands cascade testing database. It identified 825 first-degree relatives of FH probands with an *LDLR* or *APOB* mutation (cases), and 2,469 unaffected first-degree relatives without these mutations (controls). From this dataset they used a Bayesian classification model to develop age- and gender-specific LDL-C cut-offs to identify mutation carriers.

LDL-C cut-offs at which the probability of being a case/mutation carrier exceeded 50% (given that first-degree relatives have a 50:50 chance of being a carrier) were identified. The selected cut-off levels had sensitivity 84.7% (FNR 15.3%) and specificity 93.4% (FPR 6.6%) in the 0-14 age category, and sensitivity 71.1% (FNR 28.9%) and specificity 85.1% (FPR 14.9%) in the 15-24 age category. The best overall accuracy was in the 0-14 age category, with accuracy generally declining with increasing age category.

These cut-offs were validated in two similar datasets of cases and controls from Denmark and Norway. LDL-C levels were significantly lower in these cohorts, and so all cholesterol levels were reduced by the difference in LDL-C levels before the modelled cut-offs were applied. Using the modelled cut-offs, accuracy was again optimal in the 0-14 age category (data available for Norway only): sensitivity 92.5% (FNR 7.6%) and specificity 93.5% (FPR 6.5%). For the 15-24 age category sensitivity was 86.6% (FNR 13.4%) and specificity 91.3% (FPR 8.7%) for the Norwegian cohort, and sensitivity 76.2% (FNR 23.8%), specificity 91.3% (FPR 8.7%) for the Danish cohort.

Further analysis compared the modelled cut-offs with MEDPED ("make early diagnosis to prevent disease") cut-offs. Overall this suggested a differing level of accuracy depending on which cut-off was applied to the different country datasets.

NICE CG71[1] currently recommends the age- and gender-specific cut-offs developed by Starr et al. for the diagnosis of relatives of FH probands in cascade testing. Diagnosis of the probands is still recommended to be based on Simon Broome criteria.

Studies assessing the performance of cascade testing
The search identified three studies providing some information on the performance of cascade testing for identifying people of any age with FH. No studies were identified that were specific to the performance of cascade testing for identifying affected children.

The majority of identified studies were concerned with the accuracy of cholesterol measurement for indicating mutation carriers compared with the "gold standard" of genetic testing. Aside from Starr et al. (2008)[12] which provided information on age-specific categories, three studies looked at the performance of cascade testing in people of any age.

Marks et al. (2006)[13] provided some information relevant to cascade testing in the UK. This study retrospectively reviewed cascade testing of first-degree relatives of 354 probands with definite or probable FH at a single lipid clinic in Oxfordshire. They excluded probands aged <18 years, or who had no relatives in Oxfordshire. Remaining were 227 adult probands, who had 1,075 first-degree relatives. However, after exclusion of relatives who lived outside of Oxfordshire, who had been previously screened (in response to routine advice) or were considered too ill or infirm, this left them with only 338 relatives eligible for cascade testing. Of these 113 were children, and 97% of their parents gave consent for them to be tested. The positive diagnostic rate in children (using age-specific MEDPED criteria) was 32% (36/113). By comparison only 23% of eligible adult relatives received testing (52/225), and 29% of them tested positive (15/52). Based on the 2001 Oxfordshire population census, Marks et al. (2006)[13] estimated that cascade testing increased the prevalence of FH by 14.4% (from 0.58 to 0.67 per 1000), giving an overall detection rate of only 33.5% based on the estimated FH prevalence of 1 in 500.

This study suggests low cascade testing uptake among adult first-degree relatives of probands, but high uptake among child first-degree relatives. However, it is not known whether the exclusions to eligibility for cascade testing used in this study would apply in normal clinical practice; for example, the application of a county boundary when inviting for cascade testing. The small size and single centre nature of this study mean that it may not be representative of uptake rates at a national level or how well the cascade testing method performs for detecting all children with FH in the general population.

An earlier publication by Marks et al. (2004)[14] had reported that in 2004 there were 165 lipid clinics in the UK, treating an estimated 19,794 people with FH. This was estimated to represent 17% of the people with FH in the UK. This study doesn't inform on the efficacy of cascade testing, as these cases will have been variably detected – nor does it provide specific information on number of child cases – but it does suggest there may be implications for the effectiveness of cascade testing if in many affected families, a proband/index case has not been identified.

A modelling study by Morris et al. (2012)[15] evaluated the effectiveness of cascade testing and concluded that it is not a suitable method of population screening for FH. This is because a systematic method of identifying new FH index cases is needed in order to give a reasonable

level of FH detection. The study used data on family size in England and Wales to estimate the number of unrelated index cases needed to achieve an 80% detection rate of FH in the population.

Using a first strategy of only testing first degree relatives of index cases, a random sample of 47% of people with FH in the population (25% unrelated) would need to be independently identified for this to work. As a second strategy, if they tested the first degree relatives of the newly identified cases, then a random sample of 23% (11% unrelated) would be needed. As a third strategy if they tested the second and third degree relatives of index cases "when any first degree relatives [are] not available" (note not as comprehensive as current NICE recommendation) then a sample of 17% of people with FH (8% unrelated) would be needed. The three strategies would involve between 0.1% (strategy 1) and 0.6% (strategy 3) of unaffected people in the population being approached for cascade testing.

In order to increase population detection rates above 80%, increasing numbers of people with FH would need to be identified independently in order for cascade testing to work. For example, 90% detection would require around two-thirds of people with FH in the population to be independently identified if only first degree relatives were tested, a quarter if including second and third degree.

Morris et al. (2012)[15] report, based on a survey of lipid clinics, that only around 15% of the UK population with FH are estimated to have been identified. This identification of index cases would give population detection rates of only 40%, 65% and 77% using the three respective cascade testing strategies.

The studies by Morris et al. (2012)[15] and Marks et al. (2006 and 2004)[13, 14] suggest that cascade testing may currently be insufficient and missing a large proportion of the affected population. As Morris et al. (2012)[15] suggest, in order for cascade testing to be effective at achieving adequate detection of FH in the general population, a suitable method of systematically identifying index cases in the population is first needed. Once such a method is developed, cascade testing could then be used. Child-parent screening could be one such method, but it is not possible to say at this stage.

Evidence quality

Universal screening test performance

No prospective studies assessing a universal screening programme for FH in children were identified.

The systematic review and meta-analysis by Wald et al. (2007)[9] was the only study identified that had specific relevance to the key study question of the test characteristics of a universal screening programme for FH in children. This systematic review has various limitations related to the number of cases and controls in the included studies, their selection method, and the relatively broad age categories.

There were a variable number of studies (and sample sizes) available for each age category. For example, data on the 1-9 year age category was supplied by five studies (only four of which had data on LDL-C) with number of cases in studies ranging from 35 to 91. While 1-2 years was reported to give the best accuracy, this information was only available from two of the studies

within this category. Similarly, the newborn category, which was calculated to give poorer detection rates, was informed by two studies, with case sample sizes of only 13 and 16.

Selection of cases and controls within the 13 studies was also quite variable. Diagnosis of cases varied between genetic and clinical, and study inclusion criteria for the review did not specify need for diagnosis according to specific diagnostic criteria. For example, clinical diagnosis required TC or LDL-C above the level used in the study (not a specific cut-off), elevated cholesterol in a first-degree relative, and family history of tendon xanthomata. This doesn't match to specific diagnostic criteria, such as Simon Broome. Controls also varied between siblings without mutations and healthy unrelated population controls, and it is unclear whether cholesterol levels may differ in non-mutation carriers from "affected families" compared to the general population.

It is also unclear whether cholesterol levels were fasting or non-fasting, which could make considerable difference when it comes to universal child screening. Furthermore the exclusion of studies where cases or controls were taking cholesterol-lowering treatment may have excluded those with more severely elevated cholesterol levels, which may influence cut-off levels when applying to the whole population.

Overall these limitations make it difficult to know how applicable the cholesterol cut-offs obtained would be to the general child population who would be eligible for universal screening. For this reason prospective study to assess the effectiveness of the proposed screening strategy is needed.

The review's identified optimal age category (1-9 years) for screening using TC or LDL-C cut-off levels has informed a prospective study of universal child (-parent) screening that is currently being conducted in general practices in the UK.[10] This was reportedly a three-year study with the funded study period September 2011 to June 2015. Therefore publication of the results would not be expected until late in 2015 at the earliest. The results of this study are needed to determine how accurate the proposed age category and selected cholesterol cut-offs (expressed as MoM) would be in practice.

The two additional studies by Nicholls et al. (2008)[11] and Starr et al. (2008)[12] provide suggestions of appropriate cut-off levels that may be of relevance to the issue of universal screening. However, neither of these studies was designed for the purpose of considering a universal screening strategy. There are significant limitations to applying the evidence provided by both of these studies, including the broad age categories and selection of cases and controls in each, again making it difficult to know how applicable these results would be to the general child population in the UK.

The single centre study by Nicholls et al. (2008)[11] is notably limited by its small sample size, including only 115 children in total. There was no separate analysis of cholesterol levels by age, and all results were reported for the broad age category of 3-16 years, therefore providing limited further information on the optimal age or cut-off for universal screening. The cases in this study were mutation carriers (various, non-specified mutations) and the controls were their unaffected siblings, making it difficult to know how representative the cholesterol levels in these controls would be of children in the general population .

Starr et al.[12] used a large dataset of people referred for cascade testing in the Netherlands, Denmark and Norway. However, this study is primarily assessing the accuracy of various cholesterol testing modalities and cut-offs as a method of cascade testing rather than using these levels for universal screening.

While the cut-offs developed by Starr et al.[12] are recommended for diagnosis of FH in relatives of a proband in the NICE CG71[1] guidelines, these were originally developed for distinguishing mutation carriers from non-carriers in first-degree relatives of people with a known FH mutation. The probability of >50% was used as the differential when modelling the best cut-off because roughly 50% of first-degree relatives of a proband/index case would have FH. This would not apply to the general population where roughly 1 in 500 has FH. Therefore, it is again not known whether these cut-offs would be reliable for distinguishing between children with and without FH in the general population where the majority of unaffected children will be from unaffected families.

The applicability of the modelled cut-offs to other populations - even when all those tested are first-degree relatives of affected probands - are highlighted by the different accuracy results when applied to the Danish and Norwegian cohorts. Cholesterol levels in these two cohorts were significantly higher than in the Netherlands dataset, so LDL-C levels had to be reduced by the difference before the modelled cut-offs could be applied. Starr et al. (2008)[12] note that the reasons for the inter-country differences are not clear, but could include differences in diagnosis of FH probands, systems used to measure biochemistry, or other factors such as genetic or dietary differences. It is not known how these datasets of people referred for cascade testing from these three countries would compare with the UK.

Similar to Nicholls et al. (2008)[11] the child age categories used in this study were also broad at 0-14 years and 15-24 years – with the latter predominantly covering adult years. Therefore this would not give a reliable indication of whether different cut-offs would be apply in smaller, more defined child age groups.

Other issues regarding applicability include, similar to the Wald et al. (2007)[9] review, the exclusion of people taking cholesterol-lowering therapy (so possibly excluding cases or controls with more elevated cholesterol), and that FH mutations were restricted to either *LDLR* or *APOB*, so would not cover other less common mutations.

Overall, without prospective study in a universal screening context, it is difficult to know how applicable the LDL-C and/or TC cut-offs examined in these three studies could be for the general child population who would be eligible for universal screening.

Additional cases identified by universal over cascade testing

The above studies by Marks et al. (2006 and 2004)[13, 14] and Morris et al. (2012)[15] give an estimation of the proportion of the general population with FH (not limited to children) who may remain undetected with the current cascade testing system. It could be assumed that an accurate universal screening strategy would address this by identifying the vast majority of children in the population who have FH (and thereby also allow testing of first-degree relatives, i.e. parents). However, in the absence of modelling studies, or studies of universal screening in practice, it is not currently known how reliable universal screening of children for FH would be, or how many additional child cases of FH would be identified compared with cascade testing.

Timing of universal screening
As reported, the Wald et al. (2007)[9] review suggests that screening at the age of 1-9 years would give the best discrimination between affected and unaffected children, and it is proposed that this coincide with routine immunisation at around 1-2 years. This is currently being studied prospectively. However, no other information on the best timing for universal screening was identified.

Summary: Criterion 5 not met.
It is not possible to accurately determine the test performance of universal screening for FH in children due to the lack of published prospective studies on this question. Additionally, no studies of universal screening in practice or modelling studies were identified.

A systematic review and meta-analysis by Wald et al. (2007)[9] suggests that universal screening in the 1-9 year age category may give the best detection rate. A prospective study investigating this universal child (-parent) screening strategy is now being carried out across 80 general practices in the UK,[10] with blood spot taken at the time of routine immunisation at 1-2 years. However, there are some reservations to this, including that the selected age was informed by only two small studies which aren't referenced by the Wald et al. (2007)[9] review. It is also unknown whether cholesterol levels informing the selected cut-offs were fasting or non-fasting. The results of this prospective study are needed before it is known how accurate this universal child screening strategy may be.

In addition to the Wald et al. (2007)[9] review, case-control studies by Nicholls et al. (2008)[11] and Starr et al. (2008)[12] provided some further information on the most appropriate age-specific cholesterol cut-offs for differentiating between children with and without FH. These studies, though, have important limitations in applicability when being considered in the context of universal screening; principally, the use of non-affected siblings from FH families as controls.

Few studies were identified that evaluated the performance of cascade testing for identifying affected individuals with FH in the general population (adults or children). Studies, including evidence covered by NICE CG71[1], focussed more on the accuracy of cholesterol measurement as a cascade testing method, rather than the arguably more reliable method of DNA-based testing.

Based on population prevalence estimates, two UK-based studies suggest that cascade testing may have identified less than one third of people with FH in the general population. A further modelling study concluded that cascade testing is not an effective method at detecting people with FH in the general population, unless a systematic method for identifying a sufficient number of index cases is first developed. The proposed method of universal child screening (with subsequent testing of both parents) may be an effective strategy, but this cannot be determined without prospective study. There are furthermore many additional issues to be considered including cost effectiveness and ethics of the strategies.

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or

morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

Current UKNSC key question

The key question addressed for this criterion is whether there is any evidence from randomised controlled trials/ trials that universal screening is more effective than cascade testing at reducing mortality and morbidity.

Description of the evidence

No randomised controlled trials, or prospective or retrospective controlled studies, were identified which assessed the effect of universal FH screening in children on mortality and morbidity compared with cascade testing.

Studies looking at the effects of child screening upon morbidity and mortality may be unfeasible given the long duration of follow-up that would be required in order to look at cardiovascular disease outcomes. Future prospective studies could in theory examine the effects of screening in children upon shorter term objective measures of atherosclerosis development (e.g. blood lipids, inflammatory or thrombotic markers, carotid intima media thickness or flow mediated dilation[16]). A recent meta-analysis of eight studies demonstrated that carotid intima media thickness (CIMT), in particular, is significantly thicker in children with FH compared to those without,[16] demonstrating that atherosclerosis is already in development in children. Such outcome measures could possibly be examined in screening studies to give an indication of whether universal screening might reduce morbidity in children compared with cascade testing. However, no screening studies were identified which have looked at these outcomes. Furthermore, measurement of subclinical atherosclerosis requires specialist expertise, and there are also no accepted thresholds of CIMT for defining the presence or progression of atherosclerosis in children.[2]

Any effects of screening upon morbidity or mortality are of course going to be because identification allows the initiation of cholesterol-lowering treatment. Numerous studies have looked at whether treating children with FH has an effect on outcomes such as cholesterol levels, markers of atherosclerosis development, and adverse effects. Published studies have examined various interventions, most commonly statins, but also ezetimibe, bile acid-binding resins, LDL apheresis, and dietary approaches such as sterols.

These studies have not been considered for this criterion as they are examining the direct effects of treatment upon morbidity, rather than the effects of different screening strategies.

NICE had made recommendations regarding effective treatment for children with FH currently identified through the cascade testing programme (i.e. referral to a specialist with expertise in FH in children, with lipid-modifying therapy usually considered by 10 years of age[1]).

Therefore whether there is an effective treatment for children with FH who are identified through screening was not in question for this review, which was focused on comparing the effectiveness of universal child screening as an alternative to the current system of cascade testing.

Summary: Criterion 13 not met.
No studies were identified for the key question for this criterion.

No randomised or non-randomised controlled studies have looked at whether universal screening children for FH is associated with reduced morbidity or mortality. There are likely to be feasibility issues when examining the effects of universal compared with cascade testing in children on cardiovascular outcomes and mortality, due to the long duration of follow-up that would be required.

Future prospective studies could potentially examine the effects of universal screening upon shorter term indicators of atherosclerosis development (e.g. objective measures such as blood lipids, inflammatory or thrombotic markers, CIMT or flow mediated dilation). However, there are no clearly established threshold measures that indicate the presence or progression of atherosclerosis in children.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

Current UKNSC key question

The key question addressed for this criterion is whether there is evidence that screening children for FH, or treating diagnosed children with statins, would be clinically, socially and ethically acceptable to health professionals and the public.

Description of the evidence

Any study design that on title and abstract sifting seemed that it may provide information on public or professional views or acceptability regarding either FH screening (any method) or treatment, or information on screening uptake or treatment usage patterns, was selected for review at full text. Twenty-one such studies were identified. After exclusion of studies where issues on screening or treatment were only related to those aged over 18 years, and studies not providing any information of relevance to the question, three studies were identified for inclusion in this key question.

The studies had varied aims. One was a pilot study assessing the feasibility and acceptability of universal child FH screening; one study followed up the care of children diagnosed through cascade testing; and one nationwide study assessed child prescribing practice at UK lipid clinics.

Results

Acceptability of universal screening

Wald et al. (2011)[17] (Appendix 4) was a pilot study assessing the feasibility and acceptability of the universal child screening strategy proposed in the systematic review[9] by the same authors.

The study included 200 children aged 1-2 years and their parent(s) who were attending for routine immunisation at a single London general practice. This represented 94% of those invited to participate in the study. Blood spot for measurement of TC was taken from the heel simultaneously with immunisation. In order to reduce FPR, a screen positive result was defined in this study as MoM >2.0 (higher than the 1.53 cut-off set by the review[9] as a precaution against a higher-than-expected FPR). None of the children screened positive.

Several days after the visit, 184 parents (92%) could be contacted via telephone to assess acceptability. The majority of parents contacted said that they found screening acceptable (98%) and that they would have another child screened if they had one and screening was offered (94%). All 7 practice members involved said that screening was acceptable and would adopt it into their immunisation practice if universal screening were routinely offered.

No further information on acceptability was gathered.

Uptake and acceptability of treatment

Avis et al. (2012)[18] (Appendix 5) assessed the follow-up of children (mean age 10.9 years; range 0.8 to 17.9 years) diagnosed with FH following (DNA-based) cascade testing in the Netherlands. The main outcomes of interest were whether diagnosis resulted in physician consultation and treatment over the subsequent 16 months, and the factors associated with this. The parents/guardians of 233 children agreed to participate (72% response rate), and the analysis was based on those who returned complete questionnaires (207; 64% of those asked).

Seventy-nine percent of responders (164/207) had consulted a doctor after their child was diagnosed. The first point of contact varied, with 36% first consulting a GP, half of whom were then referred to a specialist lipid clinic. In total 37% had been seen in a specialist lipid clinic. Of the 43 people (21%) who did not consult a doctor after their child's diagnosis, their main reasons were feeling they already had sufficient knowledge about the condition themselves (22%) or from family members (36%). Child's LDL-C level and a positive family history of cardiovascular disease at a young age were significantly associated with consultation.

For the 164 children who consulted a doctor, lifestyle advice was offered to 62%, and 16% were advised about plant sterol supplementation. A quarter of children were told to consult again at an older age, though it is unclear whether this was by a GP or specialist lipid clinic. Where the age for later consultation was specified, the recommendations were relatively evenly spread between 6-12 years, 12-18 years and >18 years. A quarter of children seen (43/164) were prescribed lipid-lowering medication, and in all cases this was a statin (in one case combined with ezetimibe). Factors significantly associated with prescription were LDL-C level (193mg/dL vs. 162mg/dL in those not prescribed, $p<0.01$), child age (mean age at prescription not specified, $p<0.01$), and parent educational level (at least one parent completing higher training or university; $p<0.01$).

A random sample of 27 non-responders gave variable reasons for non-participation in the study. Their children were significantly older than study participants (13.7 vs. 10.9), and they were significantly less likely to have consulted a doctor (47% vs. 79%).

Greene and Durrington (2004)[19] (Appendix 6) assessed prescription of lipid-lowering medication for children and young people across lipid clinics in the UK in 2004. The response rate was just over half of all specialist doctors eligible to participate (84/156). In 2004 each clinic was treating a median of 3.5 children aged <16, and a median of 15 young people aged 16-35.

The responses demonstrated significant age and gender differences when it came to prescription of lipid-lowering medications. Only 15% percent of clinics reported prescribing to boys under the age of 10 years, and 11% for girls under 10. By 15 years of age 65% reported prescribing to boys, and 52% to girls. These physicians were all willing to prescribe bile acid sequestrants, but significantly fewer were willing to prescribe statins (23% to boys and 12% to girls). For ages 16 to 20 years, 83% would prescribe a statin to a male and 62% to a female. Above the age of 20 years there was no significant gender difference.

Overall 30-40% of doctors reported to be unwilling to prescribe medication to any child or young person (up to 35 years) until their cholesterol exceeded 8mmol/l.

Evidence quality

The identified studies provide little evidence on whether universal child FH screening and subsequent statin treatment would currently be clinically, socially and ethically acceptable to health professionals and the public in the UK.

Wald et al. (2011)[17] is the only study of relevance to universal screening in children, assessing the feasibility of the proposal to screen children at the time of routine immunisation at 1-2 years. However, this single centre study is small, including only 200 children and their parents and 7 health professionals/GP staff. It provides very limited information on the acceptability of universal screening, as acceptability information from both parents and staff appears to be limited to the acceptability of the actual heel prick procedure. Acceptability was very high; however, this may be unsurprising given that it was a simple procedure given at the same time as immunisation, and none of the children screened positive meaning there were no repercussions.

For the minority of parents who didn't find screening acceptable, or wouldn't have future children screened, reasons for this were not explored.

No information appears to have been sought on views of universally screening young children for FH, such as the possible effects of a positive screening test or diagnosis, including treatment decisions and any psychological effects related to child health and prognosis. This is pertinent considering that all of the children in this study screened negative. Views on acceptability may have been different had screen-positives been detected, or had cholesterol testing been accompanied by DNA testing for confirmation, thereby allowing detection of false positives or negatives.

Selection bias is also a significant possibility for the sample of people studied here. The parents assessed in this study had all agreed for their child to participate in FH screening. Though participation rate was high (200/214, 94%), the views of parents not choosing to participate were not sought. Similarly, though all 7 practice members involved found the procedure acceptable, they had agreed for their practice to take part in this screening pilot suggesting that these professionals considered universal FH screening in young children to be acceptable, at least at the outset. Therefore the views of this small sample of public and professionals may not be representative of the general population.

This feasibility study also used a higher MoM cut-off than that proposed in the systematic review[9]. The 1.53 MoM cut-off point was set by the review to give a FPR of 0.1%. Wald et al. (2011)[17] report that they increased the MoM to 2.0 in case the FPR was higher than expected. It is not known what cut-offs are being used in the current prospective study of universal screening[10], but this study would need to consider the effects and outcomes for TPs, FPs and FNs. It would also be beneficial for this study to collect wider parent and professional views on the screening strategy and subsequent management of children identified.

The study by Avis et al. (2012)[18] specifically examined the effects of a positive FH diagnosis upon children and their parents following DNA-based cascade testing in the Netherlands.

Overall the study suggests that almost a quarter of parents whose children diagnosed with FH after cascade testing did not consult a doctor in the following 21 months. However, this study does not indicate the normal referral system following a positive diagnosis at cascade testing in the Netherlands. For example, whether it is the responsibility of the identified case to self-refer, and whether they would first need to contact a GP or could contact/would be contacted by a specialist lipid clinic directly. As such it is difficult to know how applicable the relatively high non-consultation rate following diagnosis would be to the UK situation – either the current system of cascade testing, or should universal child screening be introduced. The reasons given for non-consultation are also only specific to cascade testing where there is a known family history of the condition, and may not be the same for universal screening.

Risk of selection bias is another issue with this study. The results of this study are based on 64% of those eligible, with information from a sample of non-responders suggesting that non-responders were less likely to have consulted a doctor. Study participants may be more active in their care-seeking behaviour than non-participants and so may not be entirely representative of the full eligible population of children diagnosed after cascade testing.

This study also looked at treatment, finding that the majority of diagnosed children were given lifestyle advice, roughly a quarter were prescribed a statin, and a quarter told to consult at an older age. However, only quantitative information on treatment numbers is available. Though the study has examined statistical associations with treatment, it has not questioned professional reasons for treatment decisions, or gathered parent or professional views on treatment of children with FH. Age was reported to be significantly associated with whether a child was treated, though the mean age of those treated vs. untreated is not given. It would be valuable to have follow-up for the three-quarters who were untreated, to know what proportion were subsequently prescribed treatment and whether there was a mean age at which this was commenced.

The study by Greene and Durrington (2004)[19] looked at treatment of children across UK lipid clinics in 2004. The study is only representative of around half of practitioners who participated, but would give an indication of practice at that time. It found overall age and gender differences around the prescription of medications, particularly statins, up to 16 years. Reasons and views on prescription practices were not further explored.

The study may suggest that few professionals were willing follow recommended treatment practice (i.e. only 23% willing to prescribe a statin to boy with FH aged 10-15 years, and 12% to girls). However, the main limitation of this study is that it is from 2004; the NICE guidelines had not been published and prescription practice has changed since. At that time only bile acid sequestrants and fenofibrate were reported to be licensed for children, and ezetimibe was unavailable.

Though experience of lipid-lowering treatment in children is still fairly limited, statins, bile acid sequestrants, ezetimibe and fibrates are all licensed for children with FH aged 10-18 years, with dosing information on certain drugs (simvastatin, fluvastatin, pravastatin, colestyramine, fenofibrate) also given for ages <10.[20, 21] NICE CG71[1] currently recommends that lipid-lowering treatment is considered by 10 years of age, with treatment decisions taking into account LDL-C level and age of cardiovascular disease onset in the family. When the decision is made to initiate lipid-lowering treatment, NICE recommend that a statin should be the first choice.[1] These recommendations may have changed current practice in lipid clinics and mean that the results of this study from 2004 are no longer representative. The reasons for the greater reluctance to prescribe lipid-lowering treatment to girls than boys were not investigated. Whether this gender difference is still seen currently is unknown.

It would be valuable to explore professional views on currently recommended treatment practice.

Summary: Criterion 14 not met.

Only one pilot study was identified that has addressed the acceptability of the proposed strategy of universal child FH screening alongside routine immunisation at age 1-2 years. This was a small single centre study with no screen positives. Though screening was acceptable to the majority of parents and all health professionals questioned, views appear to be limited to acceptability of the actual heel prick procedure. Wider views on universal FH screening and subsequent treatment of screen-detected cases have not been explored and may have been different had any children screened positive. Additionally, all public and professionals in this study were willing to take part in a pilot of universal child screening and their views may not be fully representative of the wider population.

The two other studies reviewed were of limited applicability to the question of universal screening in the UK. One Netherlands study of children diagnosed following cascade testing found that a quarter of parents did not subsequently consult a health professional. Reasons for non-consultation were variable and may be specific to this country, and to cascade testing. Of those consulting a physician, statin treatment was only prescribed for a quarter, and a quarter were told to consult again at a later age.

A third study assessed prescribing practice for children at UK lipid clinics in 2004. It found general unwillingness to prescribe statins to under-16s, particularly girls. However, drug licensing has since changed, and NICE recommendations on the management of children with FH may mean that this study is not representative of current practice in UK lipid clinics.

Overall the studies provide limited information on public or professional views on universal child FH screening and subsequent treatment in the UK.

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost

effectiveness analyses and have regard to the effective use of available resource.

Current UKNSC key question

Would a universal screening programme for familial hypercholestrolaemia in children be more cost-effective than cascade testing of relatives of clinically detected cases?

- What are the modelled costs of childhood universal FH screening vs the modelled costs of cascade testing and what are their dependencies (e.g. participation rates for universal child/ cascade testing)?

Description of the evidence

Any study that on title and abstract sifting seemed to provide information on cost or cost-effectiveness of screening for FH, either universal or cascade, regardless of age group, was selected for further review. Ten potentially relevant studies were identified, and all were reviewed at full text.

None of the studies identified assessed the cost-utility or cost-effectiveness of universal FH screening in children. The pilot study by Wald et al. (2011)[17] was the only study identified that provided information on the direct costs of screening, from the UK perspective. The HTA by Marks et al.[5] in 2000 appears to be the only study to date that has modelled the cost-effectiveness of universal screening in children, albeit at 16 years rather than 1-2 years as is proposed by Wald et al.

No studies published since 2004 were identified that specifically examined the cost-effectiveness of cascade testing in children, though studies have examined the cost effectiveness of cascade testing in general (not specific to age). These were comparing cascade testing with no screening, or comparing cascade testing by DNA analysis with cascade testing by cholesterol testing only. They include a 2013 systematic review of economic evaluations of FH screening and/or treatment (which included publications of the Marks et al. HTA[5]), and the 2008 economic analysis as part of NICE CG71.[1] Two further economic evaluations of cascade testing have been published subsequent to the 2013 systematic review (one Australian and one UK based).

All of these studies are discussed in this section.

Results

Universal child FH screening

The pilot study by Wald et al. (2011)[17](Appendix 4) is the only study published since 2004 that provides any information on the costs of universal FH screening in children.

In this pilot study 200 children aged 1-2 attending a single general practice for their routine immunisation received heel prick for measurement of TC. The study reported the overall costs of the screening procedure (including use of the point-of-care Cholestech analyser and consumables) to be £14 per child. Based on an FH prevalence of 1 in 500 (with 1 in 250 for each child-parent pair), estimated cost per FH case detected (parent and child) was £3500 (250 x £14). The cost-effectiveness of the full screening programme has not been studied, including

further diagnostic tests, consultations and support, personnel and resources, drug costs and cardiovascular events averted, compared with cascade testing or compared with no screening.

A systematic review by Ademi et al. (2013)[22] identified economic evaluations published prior to June 2012 of screening and/or treatment of FH in any population. They identified nine studies, three of which examined only the cost-effectiveness of lipid-lowering treatment for prevention of coronary artery disease, rather than FH screening, and were therefore excluded. Six studies assessed FH screening and subsequent treatment. Two of the six publications are by Marks et al. (2002[23] and 2003[24]) and relate to their 2000 HTA.[5] This appears to be the only study to date to have modelled the cost-effectiveness of universal child FH screening, though at 16 years, rather than 1-2 years as is the case in the Wald et al. trial currently ongoing.

Marks et al. (2000 and 2002)[5, 23] considered five different FH screening strategies:

- Universal population screening (16 to 54 years)
- Universal screening at 16 years
- Opportunistic GP screening
- Opportunistic screening after hospitalisation for myocardial infarction (MI)
- Case finding/family tracing of first-degree relatives of an index case (proband)

Marks et al. (2000 and 2002)[5, 23] used decision analysis and life table analysis to estimate life years gained (LYG) per diagnosis as a result of screening and statin treatment. The effects of statins were determined from the Simon Broome register. Overall case finding/family tracing was the most cost-effective population strategy for identifying people with FH (i.e. had the lowest cost per life year gained). However, while universal population screening was the least cost effective strategy (i.e. had the highest cost per life year gained), universal screening at 16 years (based on cholesterol measurement) was similarly cost effective to case finding/family tracing if clinical diagnosis was used (table 3). This was due to the estimated gains in life expectancy from starting treatment at a younger age. As Marks et al. (2000 and 2002)[5, 23] suggest, adding a case finding/family tracing approach to universal screening (e.g. as in the child-parent proposal by Wald et al. 2007[9]) could further improve the cost-effectiveness of this strategy.

Table 3: Summary of overall cost-effectiveness per LYG based on clinical diagnosis, or with genetic confirmation[5, 23]

Strategy	Cost (£) per LYG (clinical diagnosis)†	Cost (£) per LYG with costs and effectiveness discounted at 3%	Cost (£) per LYG (genetic diagnosis) †	Cost (£) per LYG with costs and effectiveness discounted at 3%
Universal 16 years	**2777**	7244	**14,842**	33,882
Universal population	13,029	21,289	78,060	120,841
Opportunistic (GP)	11,310	18,578	70,009	108,578
Opportunistic (MI)	9281	15,738	21,106	32,833
Case find/family trace	**3097**	6084	**4914***	8865

*Includes cost of testing index case/proband; † baseline discount rates (1% for effectiveness and 6% for costs)

Marks et al. (2000 and 2002)[5, 23] did not consider the effects of screening children younger than 16 years, either in the universal or family tracing approaches, because of a lack of effectiveness data for this group. They consider that including screening of younger children would have made

the family tracing (cascade) approach even more cost-effective as it would have increased the number of relatives per index case (proband).

There are various limitations to this model. These include the mortality rate for older age groups being likely to decrease in future years, and the Simon Broome register containing relatively few outcome events. As the register showed no effect of treating people above the age of 60 years, the cost-effectiveness of treating older people was not considered. If statins are effective at older ages this may have biased the results in favour of programmes starting at a younger age. The focus of this cost-effectiveness analysis was also on life year gained and did not examine quality adjusted life year (QALY).

The subsequent study by Marks et al. (2003)[24] followed on from this by looking at the number of deaths prevented over 10 years with universal screening at 16 years compared with case finding/family tracing. They used previous estimates of the number of undiagnosed people with FH in Oxfordshire and applied this to the England and Wales population. Universal screening at 16 years was estimated to prevent 9.8 deaths in males and 1.9 in females over a 10 year period with a screening cost of £9,766 and £9,773 per male and female case, respectively, identified. The total cost per case identified and treated over 10 years was £13,141, with a cost of £527,919 per death averted.

Comparatively case finding/family tracing (ages 16 to 54 years) prevented 377 male deaths and 182 female deaths over 10 years with a testing cost of £135 for each case identified. The total cost per case identified and treated by family tracing over 10 years was £3,505, with a cost of £3,187 per death averted.

Therefore over the 10 year period, the results of this modelling study favoured the current strategy of family tracing. Uptake during cascade testing is likely to be higher than universal FH screening at 16 years. In this study Marks et al. (2003)[24] assumed that population uptake of the initial screen at 16 years would be 55%, with 75% subsequently attending for diagnostic confirmation. However, a lower uptake would reduce the number of cases detected and so decrease the benefit of universal screening.

Screening uptake and cost-effectiveness may be different when carrying out universal screening of children aged 1-2 years.

Cascade testing – all ages

The remaining four cost-effectiveness studies identified in the systematic review by Ademi et al. (2013)[22] examined cascade testing only (all ages). Three European studies compared with no screening, and one additional UK study compared cascade testing by DNA analysis with cascade testing by cholesterol measurement only.

The UK study was by Nherera et al. (2011).[25] It examined four cascade testing strategies for FH, which are the same as those considered in the NICE CG71[1] economic model. The cascade testing methods are:

- Cholesterol method – LDL-C testing in relatives of definite or possible (DFH or PFH) index cases (probands)
- DNA method – DNA testing of relatives of index cases with an identified mutation

- DNA + DFH method – DNA testing of relatives of index cases with an identified mutation, plus cholesterol testing of relatives of DFH index cases without an identified mutation
- DNA + DFH + PFH method – DNA testing of relatives of index cases with an identified mutation, plus cholesterol testing of relatives of DFH or PFH index cases without an identified mutation

All comparisons were made to the cholesterol method, and the DNA + DFH + PFH method as currently recommended by NICE was the most cost-effective (table 4). In all sensitivity analyses the ICER of this strategy remained below £4000 per QALY, well below the £20,000 per QALY threshold used in the UK for determining cost-effective interventions.

Table 4: ICERs of the different DNA-based cascade testing strategies compared with cholesterol method; from Nherera et al. (2011)[25]

Cascade testing method	Cost £ (diagnosis and treatment)	QALY gain	ICER (cost £ per QALY gained)
Cholesterol	44,576	10.89	
DNA	50,918	24.12	479
DNA + DFH	52,670	24.28	Extended dominance*
DNA + DFH + PFH	54,799	25.18	3666

*Ruled out by both the DNA and DNA + DFH and PFH methods being more cost-effective

NICE CG71[1] currently recommend this DNA + DFH + PFH cascade testing method as the most cost-effective. Their calculated base case analysis estimates an ICER for this strategy of £2,676 per QALY gained when compared to the cholesterol method, which was similar to the figure obtained by Nherera et al. (2011).

The three remaining economic evaluations in the Ademi et al. (2013)[22] review include two from the Netherlands (2002 and 2004) and one from Spain (2009). All three studies compared DNA-based screening with no screening and looked at a lifetime horizon. These studies differed in their methods and assumptions, including accuracy of the screening test and underlying FH prevalence. The cost-effectiveness estimates in the two Netherlands studies were €8,076 (£5,849, using a current conversion rate of €1 to £0.72)[26] per LYG (direct costs with 4% discount applied) for DNA-based screening and €23,535 to €29,554 (£17,049 to £21,409)[26] per LYG for no screening (direct and indirect costs and with no discount applied). The Spanish study estimated €3,177 (£2,301)[26] per LYG (direct costs with 3% discount applied).

Two further economic evaluations have been published since the 2013 systematic review.

Pears et al. (2014)[27] was another study from the UK NHS perspective, which adapted the NICE CG71[1] costing template to determine the cost of a 10-year FH service for the population of Southampton, Hampshire, Isle of Wight and Portsmouth. They looked at whether costs would be further reduced by use of generic statins (following atorvastatin coming off patent in 2011), and by service delivery models with less secondary care input (specialist-led, dual care, or GP-led). Generic atorvastatin was estimated to reduce the cost of a 10-year service by 42.5%, specialist-led care by 27.2%, dual care by 32.5%, and GP-led care by 35.8%. However, the three reduced service delivery models were only applied to adults. Children were still considered to receive specialist referral as recommended by NICE CG71[1].

Pears et al. (2014)[27] also only examined costs and could not review cost-effectiveness. Nherera et al. (2011)[25] had also considered the effect of atorvastatin coming off patent (reducing cost by 60%), which was estimated to reduce the ICER of the DNA + DFH + PFH method from £3,666 to £3,070 per QALY.

The final study by Ademi et al. (2013)[28] examined the cost-effectiveness of adult cascade testing and statin treatment from the Australian perspective. They constructed a Markov model with a 10 year time horizon and examined incident coronary heart disease and related death using data from 81 index cases and their 95 adult relatives. Over 10 years they estimated overall 24.9 LYG and 29.1 QALY gains, with ICERs of $4,154 per LYG and $3,565 per QALY (£2,020 per LYG and £1,733 per QALY, using current conversion rates of 1 Australian dollar to £0.52).[26]

Aside from limitations to the methods and assumptions of these individual evaluations of cascade testing (not examined in-depth here), the main limitation when applied to this criterion is that they have not examined the cost-effectiveness of cascade testing in children. The cost effectiveness of cascade testing in adults would not be expected to inform the cost effectiveness of universal screening of young children, where resource and treatment costs would need to be examined against cardiovascular events averted in the lifetime horizon.

Summary: Criterion 16 not met.
Limited information is currently available on the cost and cost-effectiveness (i.e. relative costs and outcomes) of universal FH screening in children.

The pilot study by Wald et al. (2011)[17] provides information on the direct cost of the screening procedure per child and per case detected, but this is only reported to include the cost of the analyser and consumables. The costs do not include further diagnosis and follow-up of screen positives, or subsequent treatment costs. Cost-effectiveness of the proposed strategy of universal screening at 1-2 years in comparison with other strategies has also not been modelled.

The only study to date that appears to have evaluated the cost-effectiveness of universal screening in children is the 2000 HTA by Marks et al.[5] This study suggested that universal screening of 16 year olds by cholesterol measurement was even more cost-effective than cascade testing (16-54 year olds). However, universal screening of 16 year olds has not been prospectively studied, and may differ in accuracy, uptake and cost-effectiveness compared with the currently proposed strategy of screening at 1-2 years.

Other studies have examined the cost-effectiveness of cascade testing (all ages). The UK studies show the currently implemented cascade testing method to be the most cost-effective. However, the evaluations do not specifically inform on how cost-effective cascade testing is for children, and how it could compare to universal screening.

Conclusions

Implications for policy

This report assesses universal screening for FH in childhood against select UK National Screening Committee (UK NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme.

The most recent UKNSC review was of FH screening in adults (2011), which concluded that: "Universal screening for FH is not cost-effective and therefore a universal screening programme is not recommended. Best evidence currently supports cascade testing; tracing family members to identify affected relatives of known FH patients."

The review conclusions supported the current NICE CG71[1] recommendation for cascade testing of relatives of index cases (probands) with FH. The UK NSC has not published formal recommendations on childhood FH screening since the most recent NICE guidelines, but the adult FH screening recommendation for cascade testing also currently applies to child relatives.

However, modelling undertaken as part of a 2000 HTA[5] suggested that while cascade testing was the most cost-effective strategy in adults, universal screening for FH in young people (16 year olds) could be cost-effective. This review aimed to assess whether evidence published over the last 10 years suggests that universal FH screening in childhood could be an effective strategy.

The body of evidence to date does not alter the conclusions of the 2011 evidence review or suggest that universal FH screening in children would be more effective than the currently recommended strategy of cascade testing. A summary of key findings for the four assessed criteria is provided below:

- **A simple, safe, precise and validated screening test –** No prospective studies were identified that have examined the accuracy of universal FH screening in childhood. Neither was any study of universal screening in practice identified. One systematic review of case-control studies suggested that cholesterol levels between the ages of 1-9 years age group may give the best discrimination between children with and without FH. Universal child (-parent) screening strategy at the time of routine immunisation at 1-2 years is now being prospectively studied across general practices in the UK.
- The results of this study are needed before it is known how accurate this universal child screening strategy may be, and how it compares with the current system of cascade testing. UK studies suggest that cascade testing may currently identify less than a third of people with FH in the general population. Universal screening of children with subsequent testing of their parents may, in time, provide sufficient coverage of the population to not need to be performed indefinitely and could then revert to cascade testing. Therefore if prospective study suggests that universal child FH screening is accurate, this could be a promising strategy. However, this is not known at the current time.

- **RCT evidence that screening reduced morbidity and mortality –** No randomised or non-randomised controlled studies (prospective or retrospective) were identified that looked at whether universally screening children for FH is associated with reduced morbidity or

mortality. There are likely to be feasibility issues when examining the effects of screening children due to the long duration of follow-up that would be required to look at cardiovascular outcomes and mortality. Future prospective studies could potentially examine the effects of universal screening upon shorter term biomarkers. However, there are no clearly established threshold measures that indicate the presence or progression of atherosclerosis in children.

- **Acceptability of the screening programme –** One single centre UK study has assessed the feasibility and acceptability of the proposed strategy of universal child FH screening alongside routine immunisation at age 1-2 years. This study included 200 children, all who screened negative. Though over 90% of parents and all health professionals said screening was acceptable, views appear limited to acceptability of the actual heel prick procedure. Wider views on universal FH screening and subsequent treatment of screen-detected cases have not been explored and may have been different had any children screened positive. There may also be issues of selection bias considering that all parents and professionals agreed to take part in a pilot of universal screening. One Netherlands study assessed whether parents consulted a doctor after their child screened positive on cascade testing, but this study may have limited applicability to the UK and to universal screening. Another UK study reviewed prescribing practice for children in lipid clinics in 2004. This study is outdated and practice may have changed following NICE recommendations and changes in drug licensing. However, given the reluctance in this study to prescribe children under 16 lipid-lowering medication, particularly statins, further understanding of current specialist compliancy with NICE recommendations to start statin treatment by 10 years of age in a child with FH would be valuable.

  Overall the studies provide limited current information on public or professional views on universal child FH screening or subsequent management and treatment in the UK.

- **Cost-effective programme –** Limited information is currently available on the cost and cost-effectiveness of universal FH screening in children. The HTA from 2000 remains the only study to date to have modelled the cost-effectiveness of universal screening in children, though this was of one-off screening at 16 years, rather than screening at 1-2 years as is being prospectively studied. This modelling study suggested that universal screening at 16 years would be cost-effective compared with family tracing (both cholesterol method, £2,777 vs. £3,097 per LYG). However, universal screening of 16 year olds has not been prospectively studied, and may differ in accuracy, uptake and cost-effectiveness compared with the proposed strategy of screening at 1-2 years. The UK feasibility study was the only study identified to have provided information on the direct costs of universal screening at 1-2 years, which estimated a cost of £14 per child, and £3,500 per case identified.

It is well established that children with FH are at high risk of developing atherosclerosis from a young age and subsequent cardiovascular disease. It is also known that there is effective lipid-lowering treatment available that will reduce the risk of atherosclerosis. However, there is currently limited evidence addressing the above key questions related to universal FH screening of children. High quality studies in the following areas are needed in order to resolve uncertainties:

- Prospective study of the accuracy of universal child FH screening at age 1-2 years. This is currently being carried out across general practices in the UK. The performance of universal screening at identifying affected children in the population will need to be determined, including the accuracy of the TC or LDL-C MoM cut-offs used and number of false positives and negatives.
- Further information on public and professional views and the ethics of universal FH screening in 1-2 year old children. In particular looking at the implications of a screen positive result, such as psychological effects related to the child's health and prognosis and consensus on management and treatment. Information would be valuable on aspects such as:
    - What information or advice is needed on lifestyle behaviours and the effects this may have on the child
    - Decisions around statin treatment, including what age/ cholesterol threshold to start
    - What/ whether any alternative medication should be provided prior to commencement of statins
    - Ethical implications of providing a child-parent universal screening programme that would arguably give more short-term benefit to parents (who would be providing consent for their child to be screened) than to the child being screened
- Study of cost effectiveness of universal child FH screening at 1-2 years compared with cascade testing, and its various dependencies (e.g. uptake patterns, resources).
- Resource and reputational implications of universal child FH screening at 1-2, particularly when aligned to the vaccinations programme.

Methodology

The draft update report was prepared by Bazian Ltd., and then adapted in line with comments from the National Screening Committee.

Search strategy

BACKGROUND: A literature search was performed to find citations on screening for familial hypercholesterolaemia published since 2004.

SOURCES SEARCHED: Medline, EMBASE and the Cochrane Library. A simple search of NICE Evidence, National Guidelines Clearinghouse and the Guidelines Information Network for relevant guidance, was also performed.

DATES OF SEARCH: January 2004 to 16 January 2015

SEARCH STRATEGY: Medline (Ovid)

The strategy was designed to be as broad as possible to ensure nothing related to screening for familial hypercholesterolaemia in children was missed. As a result many hits that were not relevant were also retrieved.

1 Hyperlipoproteinemia Type II/

2 ((hypercholesterol* or hyperlipoprotein*) adj2 (familial or essential)).ti,ab.

3 ((lipoprotein* adj2 hyper) and Type II).ti,ab.

4 ((cholesterol* or lipoprotein*) adj3 hyper).ti,ab.

5 ((cholesterol* or lipoprotein*) adj3 (familial or essential)).ti,ab.

6 Apolipoprotein B-100/

7 apolipoprotein B-100.ti,ab.

8 1 or 2 or 3 or 4 or 5 or 6 or 7

This was then limited by year (2004 to January 2015) and to articles in English.

RESULTS: The above strategy retrieved 2507 citations from Medline. A similar search was conducted in EMBASE and the Cochrane Library.

Database	Number of references
Medline	2507
EMBASE	460
Cochrane Library	268
Total	3235

There was some duplication of references between different database searches.

The titles and abstracts of these citations were scanned for relevance to familial hypercholesterolaemia in children. Where references covered participants with a range of ages,

including participants under 18 years old, these were also included for more detailed assessment of relevance. 241 citations were deemed to be relevant.

Quality

Several factors were assessed to determine the quality of the identified evidence, including study design and methodology, risk of bias, directness and generalisability of the evidence. Factors that were determined to be pertinent to the body of evidence identified for each criterion are outlined in the results section as well as the comment section of the Appendix tables. The overall level of evidence was assessed by considering the quantity, quality and consistency of evidence across the body of studies for each criterion reviewed.

Appendices

Appendix number	1
Relevant criteria	5
Publication details	Wald et al. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. BMJ. 2007; 335:599.[9]
Study details	Systematic review and meta-analysis of case-control studies
Study objectives	To develop a population screening strategy for familial hypercholesterolaemia (FH). The study aimed to conduct a meta-analysis of studies that provided total and low density lipoprotein (LDL) cholesterol levels for cases and controls, and so determine the age at which cholesterol levels give the best discrimination between those with and without FH.
Inclusions	Published studies including ≥10 cases with a confirmed genetic or clinical diagnosis of FH and data on their mean and standard deviation total and LDL cholesterol levels (or data from which they could be derived), and corresponding data available for unaffected healthy controls (either published by the study authors or identified through population studies). Genetic diagnosis required the identification of a mutation in the *LDLR* gene; clinical diagnosis required total or LDL cholesterol above the level used in the study, elevated cholesterol in a first degree relative, and family history of tendon xanthomata. Controls were matched to cases by age (though could also be unaffected siblings of different age), geographic region and time period of blood collection (generally within five years). Search: May 2006 in Medline, Embase and the Cochrane Library for studies published in any language using key words [hypercholesterol(a)emia] and [familial or heterozygous], supplemented by hand search of reference lists and contact with authors where required.
Exclusions	Studies where cases and controls were defined only by high and low cholesterol levels (e.g. ≥ and <90th centile) without confirmation of diagnosis; where people were taking cholesterol-lowering treatment; and where cases were drawn from a population where the age range exceeded 20 years.
Population/included studies	13 studies including 1907 cases with FH (1134 with genetic diagnosis and 773 clinical) and 16,221 controls. Origins: England, Finland, Holland, Norway, Japan, USA and Canada. Two studies included measures from newborns, five studies 1-9 years, five studies 10-19 years, two studies 20-39 years, and one study 40-59 and ≥60 years. One English study used data on 526 cases from the Simon-Broome register, and separate comparison data on 1690 unrelated healthy adults from a 1986 diet and nutrition survey. One US study compared 35 cases with data on 13,923 unrelated healthy children from lipid research clinics in 1979. Other studies are not reported to have used separate population data on controls.

Intervention/test	Total (TC) and LDL cholesterol (LDL-C) concentration (mmol/l). As cholesterol levels fit a Gaussian distribution, concentrations were log transformed and mean and standard deviation (SD) obtained from each study for cases and controls in the six age group categories. Mean $\log_{10}$ gives a good estimation of median $\log_{10}$ which when anti-logged gives a good estimation of the untransformed median cholesterol value. This was used as the preferred measure of central tendency and expressed as multiples of the median (MoM) in controls (MoM in controls being 1.0). Detection rates (proportion of cases with a positive result) using cholesterol cut-offs (expressed as MoM values) were estimated at false positive rates (FPR) of 0.1%, 0.5% and 1%.
Comparator	NA
Results/outcomes	Median cholesterol concentration for cases and controls (mmol/l): • Newborn: TC 2.59 cases vs. 1.81 controls; LDL-C 1.67 cases vs. 0.78 controls • 1-9 years: TC 7.80 cases vs. 4.16 controls; LDL-C 5.95 cases vs. 2.59 controls • 10-19 years: TC 7.27 cases vs. 4.31 controls; LDL-C 5.45 cases vs. 2.42 controls • 20-39 years: TC 8.79 cases vs. 5.12 controls; LDL-C 7.09 cases vs. 3.62 controls • 40-59 years: TC 8.68 cases vs. 6.14 controls; LDL-C 6.74 cases vs. 4.82 controls • ≥60 years: TC 8.42 cases vs. 6.62 controls; LDL-C 6.01 cases vs. 5.28 controls Median MoM cholesterol values for cases: • Newborn: TC 1.44; LDL-C 2.14 • 1-9 years: TC 1.87; LDL-C 2.30 • 10-19 years: TC 1.69; LDL-C 2.25 • 20-39 years: TC 1.72; LDL-C 1.96 • 40-59 years: TC 1.41; LDL-C 1.40 • ≥60 years: TC 1.27; LDL-C 1.14 This suggested the 1-9 year age category had the greatest discriminatory ability. Table 2 of the main report shows the detection rates for FH based on TC and LDL-C for given age categories at set FPR and MoM cut-off. Detection rates at any given FPR were highest for the 1-9 year age category and decline with increasing age.

	Two studies suggested that within the 1-9 year category, peak performance was at 1-2 years, the pooled results of which gave a 92% detection rate for TC and 89% for LDL-C at a FPR 0.1%. Plots of detection rate against FPR showed little increase in detection rate when FPR increases above 1%. Sensitivity analyses were reported to give similar results when separately analysed by gender; genetic or clinical FH diagnosis; case selection from lipid clinics or screening; and related or unrelated controls. Given a population prevalence of 1 in 500, per 10,000 children there would be 20 affected. At a detection rate of 88% for TC and a FPR of 0.1%, 18/20 would be accurately identified and 10 children would be false positives. Given a 18:10 (2:1) odds of being affected given a positive result gives a positive predictive value (PPV) of 64% (18/28). If cholesterol measurement was followed by DNA analysis, this would exclude all false positives so give a PPV of 100%, but miss the 20% of those with FH who would have been false negatives.
Comments	This is a systematic review and meta-analysis of case-control studies with the purpose of developing a proposed universal screening strategy for FH. The pooled results suggest that measuring TC and LDL-C at 1-9 years gives the best discrimination between children with and without FH. The proposal is that children would be screened by blood spot collection when they attend for routine vaccination at 15 months. It is proposed that this would be child-parent screening, where detection of a child with FH would lead to serum cholesterol measurement (TC or LDL-C) in both parents, with the parent with the higher level assumed to be affected. This form of parental screening is estimated to have a detection rate of 96% and FPR of 4%. It is estimated that in 1 in 500 screen-positive children both parents will be affected, but this is reported to have a minor effect on detection rate in parents reducing it only by 0.2%. It is further estimated that the father would not be the biological father in 4% of families, so 2% of men would be misclassified as having the disorder. A proposed strength of this child-parent screening strategy is that screening would not need to be performed indefinitely. It is estimated that within about 30 years (given that most children are born to women aged 15-45), the system could then switch to cascade testing of first degree relatives thereafter, as the “critical mass” of FH families would have been identified. Prospective studies are now needed to examine the performance of such child-parent or universal child screening for FH. <u>Limitations</u> The review has performed meta-analysis of case-control studies to identify the optimal cholesterol cut-off for screening. Age categories were broad, and the number of studies (and sample size) that had data by age category was variable.

	For example, 5 studies had data on the 1-9 year age category (only 4 studies for LDL-C) with number of cases in studies ranging from 35 to 91. Similarly for the 10-19 category there were 5 studies (only 3 for LDL-C) with number of cases ranging from 18 to 742. Only two studies were available on newborns with case sample sizes of just 13 and 16. Diagnosis of cases varied between genetic and clinical, and the review's inclusion criteria did not specify need for diagnosis according to specific diagnostic criteria. For example, genetic diagnosis required the identification of a mutation in the *LDLR* gene; and though this is the most common mutation, this would exclude cases with other gene mutations. Similarly clinical diagnosis required total or LDL cholesterol above the level used in the study (not a given specified level), elevated cholesterol in a first degree relative, and family history of tendon xanthomata, which doesn't match to a specific standard set of diagnostic criteria such as Simon Broome. Controls also varied between siblings without mutations and healthy unrelated population controls, and it is unclear whether levels may differ in non-mutation carriers from "affected families" or the general population. It is unclear whether cholesterol levels were fasting or non-fasting. Studies where cases or controls were taking cholesterol-lowering treatment were excluded, this may have excluded individuals with more severely elevated cholesterol levels, which may mean the cut-off levels will perform differently when applied to the whole population.

Appendix number	2
Relevant criteria	5
Publication details	Nicholls et al. Diagnosis of heterozygous familial hypercholesterolaemia in children. Int J Clin Pract. 2008; 62(7):990-4.[11]
Study details	Case-control Setting: UK, single centre. Retrospective review of case notes of children aged 3 to 16 years seen at a Regional Lipid Clinic over a 25 year period (not specified).
Study objectives	To study TC and LDL-C levels in children with genetically-determined FH compared with their unaffected siblings, so as to define appropriate diagnostic cut-off levels.
Inclusions	NA
Exclusions	NA
Population	115 children (65 male, 50 females) from 31 different families: 69 cases with FH genetic mutations and 46 unaffected sibling controls without mutations. There were 21 different mutations across the families (not specified). In all families, the mutation had previously been identified through mutation

	screening. Reasons for the child's referral to the clinic (e.g. cascade testing) are not given.
Intervention/test	TC and LDL-C concentration (mmol/l). Levels were recorded at the time of diagnosis. TC was measured using the cholesterol oxidase method, LDL-C was estimated from TC, high density lipoprotein cholesterol (HDL-C) and fasting triglyceride (TG).
Comparator	NA
Results/outcomes	Mean TC and LDL-C levels (mmol/l) were significantly higher in cases than unaffected sibling controls: • TC: 7.6 +/-0.18 (range 4.7 to 10.9) in cases vs. 4.15 +/- 0.11 (range 2.37 to 6.05) in controls ($p<0.001$) • LDL-C: 5.64 +/-0.18 (range 3.0 to 8.94) in cases vs. 2.13 +/- 0.12 (range 0.42 to 3.7) in controls ($p<0.001$) (LDL-C measurements only available for 63/69 cases and 35/46 controls) TC levels were significantly higher in the 31 female cases (8.0 +/- 0.28) than the 38 male cases (7.26 +/- 0.23) ($p<0.05$). There were no significant differences in TC levels by gender among controls, or any significant differences in LDL-C by gender in either cases or controls. There was no significant age trend in either TC or LDL-C levels. Overlap range: • Lowest TC level in a case was 4.7mmol/l and the highest TC level in a control was 6.05mmol/l giving a 4.7 to 6.05 overlap range containing 21 (18%) values. • Lowest LDL-C level in a case was 3.0mmol/l and the highest LDL-C level in a control was 3.7mmol/l giving a 3.0 to 3.7 overlap range containing 8 (8%) values. When plotted against current cut-offs for children aged <16 years used in Simon Broome criteria (TC 6.7mmol/l and LDL-C 4.0mmol/l), several cases would be false negatives (receiver operating curve [ROC] plotted but specific figures not reported). • Selecting a TC cut-off of 6.0mmol/l would give 86% sensitivity and 98% specificity. • Selecting a LDL-C cut-off of 3.2mmol/l would give 97% sensitivity and 91% specificity • Selecting a LDL-C cut-off of 3.6mmol/l would give 95% sensitivity and 97% specificity. • An LCL-C cut-off >5.06mmol/l would give 66% sensitivity and 100% specificity.

Comments	This was a retrospective case review of a small number of children with FH and their unaffected sibling controls seen at a single centre over a 25 year period. The study was not designed for the purpose of establishing a suitable cut-off for universal screening of children for FH, and the TC and LDL-C ranges in the small number of cases and controls studied may not be the same as that from study of larger or different samples. The age range is broad at 3 to 16 years, which doesn't indicate whether different cut-offs may apply in smaller, more defined age groups. Controls were also all non-mutation carriers from affected families who may have differing cholesterol levels from the general population from non-affected families. It is further unclear why the children were referred to the centre (e.g. whether selected for cascade testing or identified for other reasons). It is unclear whether cholesterol levels were fasting or non-fasting.

Appendix number	3
Relevant criteria	5
Publication details	Starr B et al. Development of sensitive and specific age- and gender-specific low-density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. Clin Chem Lab Med. 2008;46(6):791-803.[12]
Study details	Case-control. This involved a retrospective review of people with known mutation status who were referred for cascade testing in The Netherlands, being first-degree relatives of an FH proband (index case) in whom a *LDLR* or *APOB* mutation had been found. A Bayesian classification model was then used to identify age- and gender-specific cut-offs which were tested in two further cohorts of people with known mutation status from Denmark and Norway.
Study objectives	To use a molecularly defined dataset and a Bayesian classification model to develop age and gender-specific LDL cut-offs to identify "affected" first-degree relatives with a FH mutation.
Inclusions	Data on first-degree relatives with known mutation status was obtained from the StOEH in The Netherlands, Department of Medicine and Cardiology, Aarhus Sygehus in Denmark, and Medical Genetics Laboratory, Rikshospitalet in Norway.
Exclusions	People on lipid-lowering therapy; with non-fasting samples (eaten within 2 hours of the sample being taken); and with triglyceride level >2mmol/l.
Population	Per dataset: overall number of mutation positive (cases) and mutation negative (controls) in the cohort (mean age, mean TC, mean LDL-C and age-and-gender-adjusted LCL-C concentration [all mmol/l]), followed by the specific number of cases and controls in the child/adolescent age categories (specific data for them

	not available): • The Netherlands: 825 cases (age 30.7, TC 6.23 +/-1.43, LDL-C 4.36 +/-1.39, adjusted 4.41) and 2469 controls (age 42.8, TC 4.99 +/-1.05, LDL-C 3.02 +/-0.94, adjusted 2.96) o 0-14 years: 183 cases, 243 controls o 15-24 years: 187 cases, 276 controls • Denmark: 160 cases (age 35.5, TC 7.74 +/-1.88, LDL-C 5.72 +/-1.86, adjusted 5.77) and 161 controls (age 41.2, TC 5.64 +/-1.28, LDL-C 3.56 +/-1.14, adjusted 3.51) o 0-14 years: no data available o 15-24 years: 42 cases, 23 controls • Norway: 374 cases (age 27.3, TC 7.55 +/-1.77, LDL-C 5.71 +/-1.69, adjusted 5.76) and 742 controls (age 37.0, TC 5.32 +/-1.18, LDL-C 3.4 +/-1.03, adjusted 3.45) o 0-14 years: 106 cases, 107 controls o 15-24 years: 82 cases, 103 controls (Numbers in other age categories are not reported here).
Intervention/test	LDL-C concentration (mmol/l). Histograms of age- and gender-adjusted LDL-C levels for mutation positive (cases) and negative (controls) from The Netherlands cohort were plotted, which indicated broadly normal distributions. The Bayesian model $P(E|C_{FH})$ was used - the probability that a mutation positive or negative relative in a particular age- and gender- cohort would have the measured LDL-C level. Age and gender-specific LDL-C cut-offs above which the probability that a person had an FH mutation exceeded 50% were calculated. To compensate for the significantly higher ($p<0.05$) mean LDL-C levels in both cases and controls in the Danish and Norwegian datasets, LDL-C levels were decreased by the difference in LDL-C levels in controls (0.55mmol/l in Denmark 0.49mmol/l in Norway) before the cut-offs from The Netherlands data were applied. The modelled LDL-C cut-offs were compared with published MEDPED ("Make early diagnosis to prevent disease") cut-offs (3.97mmol/l for <20 years; 4.36 for 20-29 years; 4.87 for 30-39 years; and 5.26mmol/l for ≥40 years).
Comparator	NA
Results/outcomes	<u>Netherlands dataset</u> Mean LDL-C levels in cases of both genders decreased during adolescence (difference between 0-14 and 15-24 years) and also decreased in male controls but to a lesser extent. After adolescence LDL-C levels in controls increased with

	age in both genders. In cases, LDL-C levels generally declined after 35-44 years, more markedly in males than females. Calculated LDL-C cut-offs (mmol/l) (the point when the probability of being a case/mutation-carrier exceeds 50%) for categories including children/adolescents: • 0-14 age category: males 3.11 and females 3.37 • 15-24 age category: males 3.01 and females 3.32 (Older age categories not reported here) The accuracy of these LDL-C cut-offs for the three cohorts are given as below with definitions as follows: • Sensitivity (Sn): true positive result in a FH mutation carrier (case) • Specificity (Sp): true negative result in a person without a FH mutation (control) • False positive rate (FPR): rate of a positive result in a control • False negative rate (FNR): rate of a negative result in a case • Youden's index : summary of test accuracy (sensitivity + specificity -1) which ranges from -1 (all diagnoses incorrect) to +1 (all correct) Netherlands: • 0-14 years: Sn 84.7% (95% CI 78.7 to 89.6), Sp 93.4% (95% CI 89.5 to 96.2), FPR 6.6% (95% CI 3.8 to 10.5), FNR 15.3% (95% CI 10.4 to 21.3), Youden's Index 0.781 • 15-24 years: Sn 71.1% (95% CI 64.1 to 77.5), Sp 85.1% (95% CI 80.4 to 89.1), FPR 14.9% (95% CI 10.9 to 19.6), FNR 28.9% (95% CI 22.5 to 35.9), Youden's Index 0.572 Denmark: • 0-14 years: no data available • 15-24 years: Sn 76.2% (95% CI 60.5 to 87.9), Sp 91.3% (95% CI 72.0 to 98.9), FPR 8.7% (95% CI 1.1 to 28.0), FNR 23.8% (95% CI 12.1 to 39.5), Youden's Index 0.675 Norway: • 0-14 years: Sn 92.5% (95% CI 85.7 to 96.7), Sp 93.5% (95% CI 87.0 to 97.3), FPR 6.5% (95% CI 2.7 to 13.0), FNR 7.6% (95% CI 3.3 to 14.3), Youden's Index 0.859 • 15-24 years: Sn 86.6% (95% CI 77.3 to 93.1), Sp 91.3% (95% CI 84.1 to 95.9), FPR 8.7% (95% CI 4.1 to 15.9), FNR 13.4% (95% CI 6.9 to 22.7), Youden's Index 0.779

	Greatest accuracy was for the 0-14 age cohort compared with all older age cohorts.
	
	Accuracy of MEDPED LDL-C cut-offs for identifying cases (vs. accuracy using the modelled cut-offs) when applied to the three cohorts (Denmark and Norway unadjusted LDL-C). Accuracy data was only given overall for the combined cohort, not specific to age category:
	
	• Netherlands cohort (825 cases, 2469 controls): Sn 42.3% (vs. 68.0), Sp 97.8% (vs. 85.2), FPR 2.2% (vs. 14.8), FNR 57.7% (vs. 32.0), Youden's Index 0.4 (vs. 0.53)
	  o All measures significantly different between the modelled and MEDPED cut-offs ($p<0.05$). Overall the modelled cut-offs were more accurate, but MEDPED gave better specificity and fewer false positives.
	• Denmark cohort (160 cases, 161 controls): Sn 68.8% (vs. 79.4), Sp 89.4% (vs. 85.1), FPR 10.6% (vs. 14.9), FNR 31.3% (vs. 20.6), Youden's Index 0.58 (vs. 0.64)
	  o Similar performance between MEDPED and modelled cut-offs (no significant differences)
	• Norway cohort (374 cases, 742 controls): Sn 74.9% (vs. 83.7), Sp 92.7% (vs. 83.8), FPR 7.3% (vs. 16.2), FNR 25.1% (vs. 16.3), Youden's Index 0.68 (vs. 0.68)
	  o Overall similar accuracy to modelled cut-offs, but MEDPED significantly poorer Sn and more FNs, but better Sp and fewer FPs ($p<0.05$).

Comments	The study was not designed with the purpose of establishing LDL-C cut-offs for the purpose of universal screening for FH. The study had the purpose of using modelling to try and identify age- and gender-specific LDL-C cut-offs that would give the best accuracy in the context of cascade testing for identifying whether a first-degree relative of a proband/index case was a mutation carrier or not. This would effectively be for the purpose when, as the authors report, the "gold standard" cascade testing method of DNA testing is not available. The people in this study were all first degree relatives of people with a known FH mutation – either affected themselves or unaffected. The LDL-C overlap between these cases and controls may differ compared with controls from non-FH families. Also the probability of >50% was used as the differential when modelling the best cut-off because roughly 50% of first-degree relatives of an index case would have FH. This would not apply to the general population. As the authors also state, exclusion of people who were already on lipid-lowering therapy may mean that the most serious cases were excluded which could mean less of a difference in

	LDL-C levels between cases and controls. Known mutations were also restricted to either *LDLR* or *APOB*, so would not cover other less common mutations. The Netherlands cohort is reportedly the largest available of cascade testing worldwide, though the dataset from the Danish cohort in particular was notably smaller. LDL-C levels for both cases and controls were also significantly lower in the Netherlands than both Denmark and Norway. The different possible explanations for the inter-country difference are not clear, but could include differences in selection criteria for identification of index cases; in systems used to measure biochemistry; or other factors such as genetic or dietary. It is not known how these datasets of people referred for cascade testing from these three countries would compare with the UK. The two categories covering child age groups were also very broad at 0-14 years and 15-24 years – the latter of course predominantly covering adult years. Therefore this would not give a reliable indication of whether different cut-offs would apply in smaller, more defined age groups. Overall this population of first-degree relatives referred for cascade testing may not give a reliable indication of the most appropriate LDL-C cut-offs to use in the general population who could be eligible for universal screening. The authors advise, for the purpose of cascade testing, that these cut-offs should only be used in the absence of genetic testing and then with caution, particularly as FPRs could lead to subjects becoming index cases for further cascade testing.

Appendix number	4
Relevant criteria	14, 16
Publication details	Wald et al. Child-parent screening for familial hypercholesterolaemia. Journal of Pediatrics. 2011; 159:865-7.[17]
Study details	Pilot survey study assessing the feasibility and acceptability of child-parent screening. Setting: immunisation clinic of a single London general practice, UK.
Study objectives	Routine child immunisation clinics at 1-2 years of age could provide an appropriate time and setting for universal FH screening. This study aimed to assess the feasibility and acceptability of this method.
Inclusions	Children aged 1-2 years requiring immunisation and identified from the register of a London general practice. 214 parents were asked for their consent to FH screening, and 200 (94%) agreed to participate. Parents were telephoned several days after the visit with the screening result and

	to assess acceptability of screening.
Exclusions	None reported.
Intervention/test	Blood spot from left heel for measurement of TC using MoM. A cut-off of >2.0 defined a screen-positive result. Heel prick was performed simultaneously with immunisation and added approximately 2 minutes to the immunisation procedure. TC was measured using the point-of-care Cholestech analyser (Hayward, California). Accuracy of the analyser was assessed in 100 consecutive children by taking paired samples and also testing by standard laboratory method.
Comparator	Not applicable.
Results/outcomes	Of 200 parents accepting screening, 198 children were tested as 2 blood spots failed. Median TC level was 3.8mmol/l and no child had TC above the cut-off 2.0 MoM <u>Criterion 14</u> 184 of 200 parents (92%) could be subsequently contacted via telephone. 181 of 184 (98%) said they found screening acceptable. 173 of 184 (94%) said they would have another child screened if they had one and screening was offered. All 7 practice members said screening was acceptable and would adopt it into their immunisation practice if screening were routinely offered. Average staff time required was 14 minutes per child. <u>Criterion 16</u> Cost of screening was £14 per child, including cost of the analyser and consumables. Based on an FH prevalence of 1 in 500 (with 1 in 250 per child-parent pair), estimated cost per FH case detected (parent and child) was £3500 (250 x £14).
Comments	This is a small single centre study including only 200 parents and children, and 7 health professionals/GP staff. Only brief yes/no information on acceptability is provided. The reasons for non-acceptability or not choosing to have a child screened in future are not assessed. Acceptability information in both parents and staff appears limited to acceptability of the heel prick procedure. No information is given on views or acceptability of universal screening for the condition, or effects of receiving a positive diagnosis and subsequent care and management, including emotional effects of prognosis or views on use of statins in children. The study is also too small to provide information on the accuracy of the 2.0 cut-off used, which was higher than the TC cut-off of 1.53 MoM proposed in the

	earlier review[9] in order to reduce false positives. No cases were identified using this cut-off. Views on acceptability may have been different had screen-positives been detected, or had testing been accompanied by DNA testing for confirmation, thereby allowing detection of false positives or negatives. Larger prospective study is needed to assess the accuracy, which would also benefit from assessing parent and professional views on universal screening and subsequent treatment. This study can only provide information on direct costs. Cost effectiveness analysis cannot be performed.

Appendix number	5
Relevant criteria	14
Publication details	Avis et al. Follow-up of children diagnosed with familial hypercholesterolemia in a national genetic screening program. J Pediatr. 2012;161(1):99-103.[18]
Study details	Qualitative questionnaire-based study. Setting: nationwide (DNA-based) cascade testing programme in the Netherlands, January 2007 to May 2008.
Study objectives	To explore whether child diagnosis of FH following cascade testing resulted in consultation of a physician for advice and treatment. To further examine what factors were associated with consultation and initiation of treatment.
Inclusions	Children (age 0 to 18 years) who were given a positive diagnosis following cascade testing. Parents/guardians were invited to participate in the study 18 months after child diagnosis.
Exclusions	None specific.
Population	322 eligible children/their parents were invited to participate, of whom 233 (72%) gave consent. 64 gave no response; 16 declined participation; 9 invitation letters were returned undelivered. Of 233 questionnaires sent, 207 (89%) were returned complete. Mean age of the 207 children was 10.9 years (range 0.8 to 17.9 years; 51 children [25%] aged <8 years) and 48% were male. Mean time since diagnosis was 21 (+/- 3) months.
Intervention/test	Cascade testing by DNA test.
Comparator	Not applicable.
Results/outcomes	<u>Information about testing and diagnosis</u> Reasons for testing: • 56% of responders reported that potential benefits of testing were first discussed by the visiting nurse of the screening programme

	• 33% were encouraged by family members • 13% requested testing themselves • 8% said the physician treating another family member had suggested testing their child Receipt of further information at the time of screening: • 39% didn't search for further information about a possible diagnosis of FH in their child • 26% received further information from family members • 25% from a physician • 25% from the nurse of the screening programme • 5% from Internet searching Receipt of further information after positive diagnosis • 21% said they already had enough information • 16% said they acquired no further information • 51% acquired more information from a physician • 12% from the nurse of the screening programme • 28% from the Internet • 2% from the FH Patient Association • 4% from the doctor or nurse that led the clinical research they were participating in <u>Consulting a physician</u> 164 of 207 responders (79%) had consulted a physician since diagnosis, 148 (90%) of those where the child was ≥8 years. • 47/164 (29%) who consulted a physician then consulted a second or third • 59/164 (36%) first consulted a GP, 51% of whom were then referred to a specialist • 61/164 (37%) consulted a specialist lipid clinic • 109/164 (66%) were still in the care of the physician they had consulted a mean 21 months later 43 of 207 (21%) who didn't consult a physician gave reasons of: • 36% having enough knowledge of FH from affected family members • 22% feeling they had sufficient knowledge themselves • 13% were afraid of labelling

	• 4% said the child didn't want to consult a physician
	• 4% said it was because of no time
	
	Factors significantly associated with consultation (164/207 cases) were family history of first or second-degree relative with cardiovascular disease before age 60 in men/65 in women; p=0.03), and LDL-C level at diagnosis (not specified; p=0.04).
	
	<u>Treatment</u>
	
	After consultation with a physician (164 children):
	
	• 62% received lifestyle advice about smoking, diet and activity
	• 26% were advised to consult at an older age
	  o For 35 cases where age was specified, 37% were told to come back at 6-12 years, 37% at 12-18 years, 26% at >18 years
	• 26% were prescribed cholesterol-lowering medication
	  o Statin in all cases; in one case combined with ezetimibe
	• 16% were advised plant sterols or stanols
	• 20% were referred to a specialist lipid clinic
	
	Factors significantly associated with medication prescription (43/164 cases) were LDL-C level (193mg/dL vs. 162mg/dL in those not prescribed, p<0.01), child age (not specified, p<0.01), and parent educational level (at least one parent completing higher vocational training or university; p<0.01). Family history and child gender were not significantly associated.
	
	43% of parents reported their child changing to a healthier lifestyle after diagnosis, the remainder did not. 45% reported starting dietary plant sterols. 27% reported their child increasing physical activity, though 56% of children who did not were reported to have had active lifestyles before.
	
	<u>Non-participants in the study</u>
	
	Attempt was made to contact a random sample of 27 non-responders to the study invitation. 30% could not be contacted by phone, 30% said they had forgotten to respond, 19% said they had not received the invitation letter; 14% declined participation for unclear reasons; 7% feared invasion of privacy. There were no significant difference in child characteristics in non-participants other than that they were older age (13.7 vs. 10.9). However, only 47% of non-responders had contacted a physician, compared with 79% of responders.

Comments	This is a small study including only 207 children/their parents, and is an assessment limited to positive FH diagnosis following DNA-based cascade testing. There is a risk of selection bias where parents who are more active in care seeking for their child may be more likely to participate in the study, so may not reflect all children diagnosed following cascade testing.

	The study does not inform on any issues related to universal screening, or address views on true/false positive or negative diagnosis following cholesterol-based testing. Information on treatment is limited to data on numbers prescribed medication, offered lifestyle advice or offered later consultation. Though associations with prescription have been examined, the study has not assessed professional reasons for prescription, or looked at parent or professional views on treatment of children. The initial point of professional contact and the referral system following a positive diagnosis (e.g. GP or specialist) are not completely clear, and may differ from the UK situation.

Appendix number	6
Relevant criteria	14
Publication details	Greene O and Durrington P. Clinical management of children and young adults with heterozygous familial hypercholesterolaemia in the UK. J R Soc Med. 2004;97(5):226-9.[19]
Study details	Cross sectional survey study. Setting: UK lipid clinics.
Study objectives	To determine current UK practice with regard to prescribing statins to children and young people (with view to the feasibility and acceptability of a trial randomising children to statin or placebo).
Inclusions	All 169 physicians listed as having responsibility for lipid clinics in the UK. Questionnaires asked about indications for lipid-lowering in males and females up to 35 years with heterozygous FH. 156 were eligible after exclusion of 3 physicians with no care for anyone aged <35 years, and 10 who had retired or ran joint clinics with others contacted.
Exclusions	None.
Intervention/test	Not applicable.
Comparator	Not applicable.
Results/outcomes	84/156 complete questionnaires were returned with a response rate of 54%. Reported findings: • Median number of children aged <16 years at each clinic was 3.5 (range 0-10). • Median number in the age range 16-35 was 15 (range 5-26). • Clinics reporting prescribing lipid lowering medication to those aged <10

	years: 15% for boys and 11% for girls
	• Clinics reporting prescribing lipid lowering medication by 15 years: 65% for boys and 52% for girls
	• The gender difference in prescribing was only reported before 20 years but not after
	• Bile acid sequestrants were preferred over statins up to 16 years:
	  ○ 65% (95% CI 55 to 75) willing to prescribe bile acid sequestrants to boys aged 10-15 years vs. 23% (95% CI 14 to 30) willing to prescribe statins
	  ○ 52% (95% CI 41 to 63) willing to prescribe bile acid sequestrants to girls aged 10-15 years vs. 12% (95% CI 5 to 19) willing to prescribe statins (significant gender difference, p not reported)
	• Age 16 to 20 years: 83% (95% CI 75 to 91) would prescribe statins to a male, 62% (95% CI 71 to 72 [sic]) to a female (significant gender difference, p not reported)
	• 30-40% of physicians were not willing to prescribe medication until cholesterol exceeded 8mmol/l (full age range 0-35).

Comments	The study does not contain information related to parental or health professional views of child FH screening, cascade or universal. Data on reported prescribing practice does not explore reasons for difference in prescribing practice by age or by gender. Though the coverage was of all lipid clinics, questionnaire response rate was only 54% so may not be representative. The study is from 2004 and management of children with FH may have changed since. The study reports that only bile acid sequestrants and fenofibrate are licensed for children. However, though experience of lipid lowering medication in children is still limited, statins, bile acid sequestrants, ezetimibe and fibrates all appear to be licensed for children with FH aged 10-18 years, with dosing information on certain drugs (simvastatin, fluvastatin, pravastatin, colestyramine, fenofibrate) also given for ages <10. Ezetimibe was also unavailable at the time of this study.

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