

# Paediatric screening for hypercholesterolaemia in Europe

D M Kusters,<sup>1,2</sup> C de Beaufort,<sup>3</sup> K Widhalm,<sup>4</sup> O Guardamagna,<sup>5</sup> N Bratina,<sup>6</sup> L Ose,<sup>7</sup> A Wiegman<sup>1</sup>

<sup>1</sup>Department of Pediatrics, Academic Medical Centre, Amsterdam, The Netherlands

<sup>2</sup>Department of Vascular Medicine, Academic Medical Centre, Amsterdam, The Netherlands

<sup>3</sup>DECCP, Clinique Pédiatrique/Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg

<sup>4</sup>Division of Clinical Nutrition, Department of Pediatrics, Medical University Vienna, Vienna, Austria

<sup>5</sup>Department of Pediatrics, Turin University, Turin, Italy

<sup>6</sup>Department of Pediatric Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, University Medical Centre, Ljubljana, Slovenia

<sup>7</sup>Lipid Clinic, Oslo University Hospital Rikshospitalet, Oslo, Norway

## Correspondence to

Albert Wiegman, Department of Pediatrics, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands; [a.wiegman@amc.nl](mailto:a.wiegman@amc.nl)

Accepted 24 August 2011  
Published Online First  
26 September 2011

## ABSTRACT

Different screening strategies are currently recommended to identify children with (familial) hypercholesterolaemia in order to initiate early lipid management. However, these strategies are characterised to date by low adherence by the medical community and limited compliance by parents and children. In a literature review, the authors assess which children should undergo screening and which children are in effect identified through the currently recommended strategies. Furthermore, the authors discuss the different screening tools and strategies currently used in Europe and what is known about the negative aspects of screening. The authors conclude that currently recommended selective screening strategies, which are mainly based on family history, lack precision and that a large percentage of affected children who are at increased risk of future coronary artery disease are not being identified. The authors propose universal screening of children between 1 and 9 years of age, a strategy likely to be most effective in terms of sensitivity and specificity for the identification of children with familial hypercholesterolaemia. However, this concept has yet to be proven in clinical practice.

## INTRODUCTION

Hypercholesterolaemia is one of the major modifiable risk factors for the development of atherosclerosis and cardiovascular disease (CVD).<sup>1</sup> Since the process of atherosclerosis starts in early childhood,<sup>2</sup> hypercholesterolaemia requires timely diagnosis and management. This is especially the case when marked elevated cholesterol levels are inherited and present from birth onwards. Individuals in early adulthood with untreated familial hypercholesterolaemia (FH) or familial defective ApoB (FDB) are nearly 100 times more likely to develop coronary artery disease than unaffected individuals.<sup>3</sup> As children with hypercholesterolaemia generally do not present with any complaints or symptoms, paediatric organisations have developed different screening strategies to identify such children.<sup>4–7</sup> However, the strategies that do exist are characterised by low adherence by the medical community and limited compliance from parents and children.

Screening for hypercholesterolaemia in children is worthwhile if the following three assumptions are true: children with hypercholesterolaemia are at increased risk of developing accelerated atherosclerosis and subsequent CVD; screening can accurately identify those at increased risk;

and existing therapies can effectively and safely reverse the atherosclerotic process and reduce the CVD risk in these children. We can safely assume that, based on current evidence, the first and third requirements are met, and the remaining question therefore is: which screening strategy can best identify those at increased risk? In this review we will provide an outline of the currently recommended screening strategies and will discuss which children are identified with these strategies and which children are not and might be still at risk. Subsequently, we will present some suggestions for improving these strategies across Europe. As early diagnosis and management are especially important in children with FH, the emphasis will be on these children.

## EVIDENCE FOR EARLY ATHEROSCLEROSIS

It was shown that risk factors measured during the teenage years and in early adulthood predicted the presence of subclinical atherosclerosis that developed 15 years later much more accurately than the same risk factors measured at the time of lesion assessment.<sup>8,9</sup> This indicates that the prevention of risk factors in childhood or adolescence is likely to be most effective and, in fact, this 'the younger the better' strategy is rapidly gaining acceptance vis à vis 'the lower the better' concept. Evidence for this new approach comes from statin trials in children with severe hypercholesterolaemia which show that atherosclerotic lesions are reversible if drug treatment is initiated really early.<sup>10</sup>

The first indications of atherosclerosis are already present in children with FH, despite the absence of complaints or symptoms. Increased inflammatory activity is reflected by elevated levels of high-sensitivity C-reactive protein (hsCRP) in children with FH as compared with their unaffected siblings.<sup>11</sup> Additionally, functional and morphological changes in the arterial wall are observed in children with FH, which indicates that the atherosclerotic process has already begun. This is illustrated by impaired flow-mediated dilatation (FMD) of the brachial artery<sup>12</sup> and increased intima media thickness (IMT) of the carotid artery,<sup>13</sup> respectively. These findings have led to the hypothesis that treatment should be initiated early in life to reduce the incidence of CVD in later years.

Increased inflammatory activity and impaired endothelial function indicating enhanced atherogenesis is also present in obese children.<sup>14,15</sup> Furthermore, children with type 1 diabetes exhibit impaired FMD and increased carotid IMT.<sup>16</sup>

### Box 1 Screening strategies of paediatric organisations

- AAP 2008<sup>5</sup> (update from the 1992 NCEP report<sup>6</sup>)
- ▶ Screen all children with
    - a. Positive family history of dyslipidaemia OR
    - b. Positive family history of premature CVD OR
    - c. Family history not known OR
    - d. Other CVD risk factors (overweight/obesity, hypertension, cigarette smoking, diabetes)
  - ▶ Screening should take place between 2 and 10 years of age
- The recommended approach to screening is a fasting lipid profile. If values are within the reference range (according to age and gender), the patient should be retested in 3–5 years
- AHA 2003<sup>4</sup>
- ▶ Screen all children with
    - a. Positive family history of dyslipidaemia OR
    - b. Positive family history of premature CVD OR
    - c. Family history not known and other risk factors are present
  - ▶ Screening should take place above 2 years of age
  - ▶ The recommended approach to screening is a fasting lipid profile. If the averaged result of 3 fasting lipid profiles is above the cut-point, advise cardiovascular risk reduction interventions
- 2007 Update<sup>7</sup>: In addition to family history, overweight and obesity should trigger screening with a fasting lipid profile

AHA, American Heart Association; AAP, American Academy of Pediatrics; CVD, cardiovascular disease; NCEP, National Cholesterol Education Program.

### HOW TO SCREEN

#### Screening strategies

Professional paediatric organisations recommend selective instead of universal screening strategies. The strategies proposed by the American Academy of Pediatrics (AAP) and the American Heart Association (AHA)<sup>4,5,7</sup> are summarised in box 1.

These strategies are quite similar in that screening is recommended when a family history of dyslipidaemia or premature CVD ( $\leq 55$  years of age for men and  $\leq 65$  years of age for women) is present. However, several studies showed that self-reported parental history is not particularly useful when identifying children and adolescents with raised low-density lipoprotein cholesterol (LDL-C) levels (sensitivity 25–93%, specificity 21–80%).<sup>17</sup> Therefore, applying this criterion is not much more effective than general population screening. Even for children with FH, who would be expected to have a positive family history of CVD, it was shown that using family history to determine who to screen for cholesterol measurement would have failed to detect a substantial number of children with FH.<sup>18</sup> Furthermore, this approach is time-consuming, is not well defined, and is not standardised.

The use of body mass index (BMI) alone or combined with family history as a criterion, instead of family history alone, increases the sensitivity of this screening method, although it decreases specificity.<sup>19</sup> However, it is unlikely that using BMI would increase the sensitivity of screening children with FH, the group most likely to benefit from screening.

#### Screening in Europe

Several different screening strategies are currently used across Europe. In this section, we will describe the active screening strategies in five countries, summarised in table 1.

**Table 1** Screening strategies in five European countries

Country	Screening strategy	Target population
Netherlands	Cascade screening	Children of FH families
Norway	Cascade screening	Children of FH families
Slovenia	General screening	Children at the age of 5
Italy	Selective screening	Children with a positive family history of premature CVD or dyslipidaemia
UK	Cascade screening	Children of FH families

CVD, cardiovascular disease; FH, familial hypercholesterolaemia.

In the Netherlands, there is an ongoing cascade screening programme to identify patients with FH, in which all first degree family members of an index patient are identified and offered a DNA test. Cascade screening then is offered to more distant relatives using the inheritance pattern across the pedigree. To date, >20 000 individuals with FH carrying more than 550 different mutations have been identified, which is estimated to be 50% of the total number of FH patients in the Netherlands. A literature review reported that screening of the relatives of index cases with FH is the most cost-effective screening strategy.<sup>20</sup>

In Norway, as in the Netherlands, all genetic FH tests are performed by a single centre which has been working closely with the Lipid Clinic in Oslo. The total number of FH patients has been estimated at 16 000 and approximately 5000 individuals with >140 different mutations have been identified so far. A cascade screening program has been established,<sup>21</sup> but as the national health system in Norway has not provided funding for other areas of the country, laboratory investigations will remain dependent on the Lipid Clinic and the Medical Genetic Laboratory of the University of Oslo.

The Slovenian Pediatric Society decided to initiate general cholesterol screening in preschool children at the age of 5 in 1995. Since then, more than 15 000 children have undergone screening annually. A blood sample is taken at a routine examination and total cholesterol (TC) values are measured. If TC values are elevated, a fasting lipid profile is performed. According to national guidelines, the child is referred to University Children's Hospital in Ljubljana if TC levels are  $>6$  mmol/l or  $>5$  mmol/l and there is a positive family history of premature CVD. The data of these children are used for research and from 2011 onwards selective genetic screening for FH will also be carried out.

In Italy selective screening is delegated to general practitioners or paediatricians who follow Italian guidelines.<sup>22</sup> Children considered at risk and suspected of having an inherited lipoprotein disorder (showing a positive family history of premature CVD or exhibiting dyslipidaemia with TC  $>6.2$  mmol/l, HDL-C  $<0.9$  mmol/l or triglyceride (TG)  $>3.4$  mmol/l) are invited to attend lipid units where they undergo biochemical and genetic analysis. However, only a limited number of children complete this program, accounting for less than 10% of the total number of children with possible FH. To bridge the gap between the number of children detected and the number theoretically affected, an extensive program of recruitment, diagnosis and registration is currently in progress. This program is aimed at promoting awareness of the benefits of screening, extending this practice throughout Italy, defining the genetic mutations involved in FH (LDLR, ApoB, PCSK9) and providing an Italian register of genetically detectable lipoprotein disorders.

In the UK, the National Institute of Healthcare and Clinical Excellence (NICE) has recommended a family cascade

testing approach for FH, starting with adults who have a clear (preferably genetic) diagnosis. The NICE is regarded as the main organisation that promotes evidence based clinical practice in the UK. Testing of children in families known to have a clear diagnosis of FH is recommended from the age of 10 years. Recently, this approach has been fully implemented (2010) in Wales, which is one of the devolved countries within the UK.<sup>23</sup>

Wald and colleagues recently proposed the alternative strategy of screening children in the UK when they visit their general practice for routine vaccination at about 15 months of age. In children aged 1–9 years, the use of TC levels as a cut off yields a false positive rate of 0.1% (1.53 multiples of the mean) and would identify 88% of cases with FH. Measurement of cholesterol levels in the parents of an affected child would determine which parent was affected. Applying the rule that the parent with the highest cholesterol levels has FH gives a detection rate of above 96%.<sup>24</sup>

### Screening tools

Once children are selected for screening, lipid levels are measured. A raised LDL-C level is the trigger for initiating treatment and determining therapy goals in children<sup>5–7</sup> and is generally calculated according to the Friedewald formula. However, because this is dependent on TG levels, a fasting sample is required. The advantage of a TC measurement is that it is not necessary to obtain a fasting sample. In the Bogalusa Heart Study, increased TC levels detected elevated LDL-C levels with 44–50% sensitivity and 90% specificity.<sup>25</sup>

It was shown that the apoB/apoA-1 ratio measured in adolescents (12–18 years) was superior to the LDL/HDL ratio for predicting increased IMT in adulthood.<sup>26</sup> A high apoB/apoA-1 ratio indicates the ratio between pro- and anti-atherogenic lipoprotein particles. Therefore, measuring these apolipoproteins might have additional value in risk assessment and screening in children.

An important issue is the accuracy of paediatric lipid levels to identify children at increased risk. Approximately 40–55% of children with elevated lipid levels will continue to have elevated lipid levels in adulthood.<sup>27</sup> On the other hand, subjects with multifactorial/polygenic causes of hypercholesterolaemia often exhibit normal lipid levels during childhood. Therefore, those with a strong family history of premature CVD in particular should be retested after puberty. At least two measurements are necessary to ensure that the mean measurement reflects the true value to within 10%. Children with very high LDL-C levels (>4.1 mmol/l (>160 mg/dl)) are likely to have substantially lower levels (mean decrease 0.5–0.75 mmol/l) at re-examination, which is attributable to regression to the mean.<sup>28</sup> Furthermore, as childhood is a time of rapid growth and development, especially during puberty, and cholesterol is involved in the structure of cellular membranes and hormones, lipids vary with age among children.<sup>29</sup> This must also be taken into account when interpreting cholesterol levels.

The criteria for a clinical diagnosis of FH are LDL-C levels above the 95th percentile for age and gender, a family history positive for CVD, and physical symptoms of cholesterol deposits in the skin, eyes or tendons known as xanthelasma, arcus corneae and tendon xanthomas, respectively, which are typical for FH although rare in children.<sup>30</sup> Once there is a clinical diagnosis, a definite diagnosis may be made using DNA based mutation screening methods. Once the causative mutation in the index patient has been identified, reasonably cheap molecular testing in relatives is possible. Molecular testing is

### Box 2 AAP recommendations for the treatment of hypercholesterolaemia in children, 2008<sup>5</sup>

1. Diet/lifestyle
  - a. All children >2 years of age: healthy diet according to Dietary Guidelines for Americans
  - b. Children between 12 months and 2 years of age with family history of obesity, dyslipidaemia or CVD, or for whom overweight is a concern: use low-fat milk
  - c. Children and adolescents at high risk of CVD: diet with <7% saturated fat, cholesterol <200 mg/day and <1% trans fats
  - d. For overweight or obese children with high triglyceride or low HDL-C levels: weight management, including dietary counselling and increased physical activity
2. Pharmacology
  - a. For patients ≥8 years of age, pharmacological intervention should be considered if:
    - ▶ LDL ≥4.9 mmol/l (190 mg/dl) OR
    - ▶ LDL ≥4.1 mmol/l (160 mg/dl) AND family history of premature heart disease OR ≥2 additional risk factors (obesity, hypertension, cigarette smoking) OR
    - ▶ LDL ≥3.4 mmol/l (130 mg/dl) AND diabetes mellitus
  - b. When there is a strong family history of CVD, especially with other risk factors, target levels for LDL-C as low as 3.4 mmol/l (130 mg/dl) or even 2.8 mmol/l (110 mg/dl) should be considered

AAP, American Academy of Pediatrics; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

simple in countries with only a few different mutations causing FH. On the other hand, in the majority of countries with full-blown genetic heterogeneity, DNA sequencing could fail to identify a mutation, with detection rates ranging from only 20% to 90%.<sup>31–35</sup> However, as mentioned previously, extreme hypercholesterolaemia in children is less likely than in adults to be polygenic, which allows a higher mutation detection rate. In fact, in a recently published study it was found that in 95% of children with an FH phenotype, a functional gene mutation could be found in the LDL receptor or ApoB genes.<sup>36</sup>

Identification of the FH-causing mutation in a family permits a definite diagnosis, and the diagnostic problem caused by the overlap in cholesterol levels between the general population and the FH patient is thereby eliminated. A single test, performed once only, will ascertain FH status, and early diagnosis in these children, at least, becomes a reality.

Neonatal screening has been examined in some studies, but none followed abnormal results with mutation analysis, which makes it difficult to determine the value of such screening.<sup>27</sup> The usefulness of IMT measurement as a screening tool in children must be further explored.

### WHO TO SCREEN?

Lipid screening could identify three groups of children: those with monogenic hypercholesterolaemia (mainly heterozygous FH and FDB), secondary causes of hypercholesterolaemia and multifactorial (polygenic) hypercholesterolaemia. The last group is less common in children. Once children with hypercholesterolaemia are identified, lipid management can be started. The recently updated treatment recommendations of the AAP<sup>5</sup> are summarised in box 2.



Because FH is characterised by markedly elevated levels of LDL-C from birth onwards, leading to premature atherosclerosis and CVD, the importance of early diagnosis and management is well established. Underdiagnosis of (heterozygous) FH is a worldwide problem<sup>37</sup> and therefore screening for FH is strongly advocated. The problem is that both TC and LDL-C levels show considerable overlap between FH and normal individuals plays a lesser role in children as compared with adults. It was recently shown in a meta-analysis that cholesterol levels discriminate best between people with and without FH at the ages of 1–9 years.<sup>24</sup> Therefore, a diagnosis of FH should always be considered in children with elevated lipid levels.

Children with diseases known to possibly cause secondary dyslipidaemia, such as nephrotic syndrome, HIV treated with protease inhibitors, systemic lupus erythematosus or conditions after solid organ transplantation, should also be screened.

Screening for hypercholesterolaemia (and/or hypertriglyceridaemia) is of special importance in children with disorders that are characterised by the presence of other cardiovascular risk factors, such as diabetes and obesity. According to the 2006 AHA statement, children with type 1 diabetes are classified in tier 1, the highest cardiovascular risk category.<sup>38</sup> Screening guidelines within the European Union for children and adolescents with type 1 or type 2 diabetes have been recently published in the SWEET report.<sup>39</sup>

### POTENTIALLY HARMFUL ASPECTS OF SCREENING

Children with FH or other causes of severe hypercholesterolaemia do not have clinical disease, but the knowledge of future risks and the awareness of having the disorder and taking medication every day, raises the question of whether this influences their quality of life. There is limited evidence on this subject, but it was shown that children diagnosed with FH did not have elevated anxiety levels, that taking medication made the children feel safer and that they did not 'mind' taking this medication for the rest of their lives.<sup>40</sup> Another study showed that children generally coped well with their carrier status and its implications.<sup>41</sup> Studies in adults suggested that relatives usually believe that genetic information is beneficial<sup>42</sup> and reports on the impact of receiving a diagnosis of FH showed that the proportion of individuals experiencing anxiety was no higher than in the general population.<sup>43</sup> A study involving participants of the Dutch cascade screening program reported that 87% of parents from FH families wanted their children to undergo a genetic test.<sup>44</sup>

As with all medical conditions, a diagnosis of FH may lead to difficulties in obtaining life insurance because of the increased risk of CVD. In the Netherlands, special guidelines for insurance companies have been developed on how to deal with risk assessment and genetic screening for FH. This guideline states that (treated) individuals with FH who apply for life or disability insurance should be accepted at standard rates if their LDL-C level is below 4 mmol/l and no additional cardiovascular risk factors are present.<sup>45</sup>

### THE IMPORTANCE OF ADEQUATE FOLLOW-UP

Screening is only valuable if adequate follow-up is guaranteed. The full implementation of cascade screening requires an infrastructure that allows for both family tracing and the increasing clinical workload as new cases are identified. For example, in the Netherlands, cascade testing is coordinated through national centres supported by the government, and patient care is delivered by existing lipid clinics. However, such

arrangements are still limited for children. In the ideal situation, all identified children should be linked to a recognised specialist network managed by a paediatrician. This should ensure that all children are referred to a specialised paediatric lipid clinic and are adequately informed and treated. More specialised paediatric lipid clinics should be established to provide sufficient capacity to admit identified paediatric patients with FH and other types of dyslipidaemia.

### CONCLUSIONS AND RECOMMENDATIONS

Screening for dyslipidaemia in children is only rational if screening tests and strategies can accurately identify those at increased risk. In 2007, the US Preventive Service Task Force concluded that the evidence is insufficient to recommend for or against routine screening for lipid disorders in infants, children, adolescents or young adults.<sup>46</sup> Based on the mainly observational studies discussed above, we conclude that there is good evidence that currently recommended selective screening strategies mainly based on family history are not accurate and that an important proportion of children at risk are not being identified. Furthermore, the need for fasting samples and repeated measurements is likely to affect feasibility and compliance with cholesterol screening, even in a targeted approach. There is also evidence that enhanced atherogenesis is present in some children, and that this process is reversible when early treatment is initiated. We will make some recommendations based on the current evidence, although clinical trials are needed to determine the best screening approach.

Paediatricians should screen children with disorders known to possibly cause secondary dyslipidaemia, such as obesity and diabetes. The most difficult but important challenge, however, is to identify children with FH, as they experience no symptoms while the importance of early disease management is well established. The imprecision of clinical screening strategies for FH emphasises the importance of genetic testing for a definite diagnosis of FH. Although cascade screening has been very successful in the Netherlands, this strategy may not be cost-effective in larger countries where families are small and geographically dispersed, and genetic heterogeneity is prevalent.

The proposed strategy of universal screening of children when they visit their general practitioner for routine vaccination at about 15 months of age, or at 5 years in Slovenia,<sup>24</sup> is promising. However, this strategy is based on theoretical considerations and has not been proven in practice. Furthermore, as drug treatment is currently not initiated before the age of 8, the correct age for screening needs to be discussed. If this approach is as effective as claimed, it should be followed by mutation analysis to establish the diagnosis of FH. Once a child has been identified as having FH, cascade screening of more distant relatives should be performed using the inheritance pattern across the pedigree.

Once children with FH or other causes of hypercholesterolaemia are identified, lipid management can be started. Clinicians should strongly consider statin therapy in children with FH and elevated LDL-C, when LDL-C cannot be adequately reduced by lifestyle modification alone. However, there are no data on the safety of life-long lipid-lowering therapy and the exact age at which therapy should be initiated is also uncertain. Future research should address these questions. Nevertheless, an adequate screening program with sufficient follow-up is very likely to improve the management of children with hypercholesterolaemia, leading to better control of cardiovascular risk.

**Acknowledgements** The authors would like to thank Jan Taminiu from the European Medicine Agency, for initiating this European collaboration, and Ian McDowell and Graham Shortland for their critical appraisal and suggestions for improving the manuscript.

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

## REFERENCES

1. Yusuf S, Hawken S, Ounpuu S, *et al*. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**:937–52.
2. Mabuchi H, Koizumi J, Shimizu M, *et al*. Development of coronary heart disease in familial hypercholesterolemia. *Circulation* 1989;**79**:225–32.
3. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ* 1991;**303**:893–6.
4. Kavey RE, Daniels SR, Lauer RM, *et al*. American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. *Circulation* 2003;**107**:1562–6.
5. Daniels SR, Greer FR. Lipid screening and cardiovascular health in childhood. *Pediatrics* 2008;**122**:198–208.
6. American Academy of Pediatrics. National Cholesterol Education Program; report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics* 1992;**89**:525–84.
7. McCrindle BW, Urbina EM, Dennison BA, *et al*. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation* 2007;**115**:1948–67.
8. Li S, Chen W, Srinivasan SR, *et al*. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA* 2003;**290**:2271–6.
9. Raitakari OT, Juonala M, Kahonen M, *et al*. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA* 2003;**290**:2277–83.
10. Rodenburg J, Vissers MN, Wiegman A, *et al*. Statin treatment in children with familial hypercholesterolemia: the younger, the better. *Circulation* 2007;**116**:664–8.
11. Ueland T, Vissers MN, Wiegman A, *et al*. Increased inflammatory markers in children with familial hypercholesterolaemia. *Eur J Clin Invest* 2006;**36**:147–52.
12. de Jongh S, Lilien MR, op't Roodt J, *et al*. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol* 2002;**40**:2117–21.
13. Wiegman A, de Groot E, Hutten BA, *et al*. Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia. *Lancet* 2004;**363**:369–70.
14. Meyer AA, Kundt G, Steiner M, *et al*. Impaired flow-mediated vasodilation, carotid artery intima-media thickening, and elevated endothelial plasma markers in obese children: the impact of cardiovascular risk factors. *Pediatrics* 2006;**117**:1560–7.
15. Tounian P, Aggoun Y, Dubern B, *et al*. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet* 2001;**358**:1400–4.
16. Jarvisalo MJ, Raitakari M, Toikka JO, *et al*. Endothelial dysfunction and increased arterial intima-media thickness in children with type 1 diabetes. *Circulation* 2004;**109**:1750–5.
17. O'Loughlin J, Lauzon B, Paradis G, *et al*. Usefulness of the American Academy of Pediatrics recommendations for identifying youths with hypercholesterolemia. *Pediatrics* 2004;**113**:1723–7.
18. Ritchie SK, Murphy EC, Ice C, *et al*. Universal versus targeted blood cholesterol screening among youth: The CARDIAC project. *Pediatrics* 2010;**126**:260–5.
19. Eissa MA, Wen E, Mihalopoulos NL, *et al*. Evaluation of AAP guidelines for cholesterol screening in youth: Project HeartBeat! *Am J Prev Med* 2009;**37**:S71–S77.
20. Marks D, Wonderling D, Thorogood M, *et al*. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. *BMJ* 2002;**324**:1303.
21. Leren TP, Finborud TH, Manshaus TE, *et al*. Diagnosis of familial hypercholesterolemia in general practice using clinical diagnostic criteria or genetic testing as part of cascade genetic screening. *Community Genet* 2008;**11**:26–35.
22. Società italiana di nutrizione pediatrica. Raccomandazioni per la prevenzione in età pediatrica dell'aterosclerosi. *Riv Ital Pediatr* 2000;**26**:13–28.
23. Shortland G. Familial Hypercholesterolemia (FH) - preventive treatment in paediatric populations. *Welsh Paed J* 2010;**33**:46. Ref Type: Abstract
24. Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. *BMJ* 2007;**335**:599.
25. Dennison BA, Kikuchi DA, Srinivasan SR, *et al*. Serum total cholesterol screening for the detection of elevated low-density lipoprotein in children and adolescents: the Bogalusa Heart Study. *Pediatrics* 1990;**85**:472–9.
26. Juonala M, Viikari JS, Kahonen M, *et al*. Childhood levels of serum apolipoproteins B and A-I predict carotid intima-media thickness and brachial endothelial function in adulthood: the cardiovascular risk in young Finns study. *J Am Coll Cardiol* 2008;**52**:293–9.
27. Haney EM, Huffman LH, Bougatsos C, *et al*. Screening and treatment for lipid disorders in children and adolescents: systematic evidence review for the US Preventive Services Task Force. *Pediatrics* 2007;**120**:e189–e214.
28. Freedman DS, Wang YC, Dietz WH, *et al*. Changes and variability in high levels of low-density lipoprotein cholesterol among children. *Pediatrics* 2010;**126**:266–73.
29. Tamir I, Heiss G, Glueck CJ, *et al*. Lipid and lipoprotein distributions in white children ages 6–19 yr. The Lipid Research Clinics Program Prevalence Study. *J Chronic Dis* 1981;**34**:27–39.
30. Defesche JC. Familial hypercholesterolaemia. In: Betteridge DJ, ed. *Lipids and Vascular Disease*. 2000:65–76.
31. Punzalan FE, Sy RG, Santos RS *et al*. Low density lipoprotein–receptor (LDL-R) gene mutations among Filipinos with familial hypercholesterolemia. *J Atheroscler Thromb* 2005;**12**:276–83.
32. Damgaard D, Larsen ML, Nissen PH, *et al*. The relationship of molecular genetic to clinical diagnosis of familial hypercholesterolemia in a Danish population. *Atherosclerosis* 2005;**180**:155–60.
33. Graham CA, McIlhatton BP, Kirk CW, *et al*. Genetic screening protocol for familial hypercholesterolemia which includes splicing defects gives an improved mutation detection rate. *Atherosclerosis* 2005;**182**:331–40.
34. Assouline L, Levy E, Feoli-Fonseca JC, *et al*. Familial hypercholesterolemia: molecular, biochemical, and clinical characterization of a French-Canadian pediatric population. *Pediatrics* 1995;**96**:239–46.
35. Campagna F, Martino F, Bifulco M, *et al*. Detection of familial hypercholesterolemia in a cohort of children with hypercholesterolemia: results of a family and DNA-based screening. *Atherosclerosis* 2008;**196**:356–64.
36. van der Graaf A, Avis HJ, Kusters DM, *et al*. Molecular Basis of Autosomal Dominant Hypercholesterolemia: Assessment in a Large Cohort of Hypercholesterolemic Children. *Circulation* 2011;**123**:1167–73.
37. Marks D, Thorogood M, Neil HA, *et al*. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis* 2003;**168**:1–14.
38. Kavey RE, Allada V, Daniels SR, *et al*. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2006;**114**:2710–38.
39. Recommendations for Diabetes Care and Treatment in Pediatric Centres of Reference in the EU 2009. Report No.: SWEET 2007104, 2010.
40. de Jongh S, Kerckhoffs MC, Grootenhuys MA, *et al*. Quality of life, anxiety and concerns among statin-treated children with familial hypercholesterolaemia and their parents. *Acta Paediatr* 2003;**92**:1096–101.
41. Meulenkamp TM, Tibben A, Mollema ED, *et al*. Predictive genetic testing for cardiovascular diseases: impact on carrier children. *Am J Med Genet A* 2008;**146A**:3136–46.
42. Newson AJ, Humphries SE. Cascade testing in familial hypercholesterolaemia: how should family members be contacted? *Eur J Hum Genet* 2005;**13**:401–8.
43. Andersen LK, Jensen HK, Juul S, *et al*. Patients' attitudes toward detection of heterozygous familial hypercholesterolemia. *Arch Intern Med* 1997;**157**:553–60.
44. Umans-Eckenhausen MA, Oort FJ, Ferenschild KC, *et al*. Parental attitude towards genetic testing for familial hypercholesterolaemia in children. *J Med Genet* 2002;**39**:e49.
45. Homsma SJ, Huijgen R, Middeldorp S, *et al*. Molecular screening for familial hypercholesterolaemia: consequences for life and disability insurance. *Eur J Hum Genet* 2008;**16**:14–7.
46. Screening for lipid disorders in children: US Preventive Services Task Force recommendation statement. *Pediatrics* 2007;**120**:e215–19.



## Paediatric screening for hypercholesterolaemia in Europe

D M Kusters, C de Beaufort, K Widhalm, O Guardamagna, N Bratina, L Ose and A Wiegman

*Arch Dis Child* 2012 97: 272-276 originally published online September 26, 2011

doi: 10.1136/archdischild-2011-300081

---

Updated information and services can be found at:

<http://adc.bmj.com/content/97/3/272>

---

### References

*These include:*

This article cites 44 articles, 21 of which you can access for free at:

<http://adc.bmj.com/content/97/3/272#BIBL>

### Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

### Topic Collections

Articles on similar topics can be found in the following collections

[Screening \(epidemiology\)](#) (543)

[Screening \(public health\)](#) (543)

[Lipid disorders](#) (17)

[Metabolic disorders](#) (751)

[Drugs: cardiovascular system](#) (508)

---

### Notes

---

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>