Familial hypercholesterolemia in childhood

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Chapter 2

Family History and Cardiovascular Risk in Familial Hypercholesterolemia
Data in more than 1000 children

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Abstract

**Background:** Elevated low-density lipoprotein (LDL) cholesterol levels in childhood strongly associate with premature cardiovascular disease (CVD) later in life. Familial hypercholesterolemia (FH) represents the paradigm of this relationship.

**Objectives:** To establish a specific LDL-C level that provided the most accurate diagnosis of FH in children. Secondly, to address whether lipoprotein variations in these children could be explained by environmental characteristics and whether these variations were associated with the occurrence of premature CVD in relatives. But, consequently and foremost, it was our objective to identify FH children at high risk and in need for early intervention.

**Design:** A pediatric FH cohort study and an affected parent-offspring analysis.

**Subjects:** In total 1034 consecutive children from FH kindreds were referred to us over the last 12 years.

**Results:** First, LDL-C levels above 3.50 mmol/L had 0.98 (95% CI: 0.96-0.99) post-test probability of predicting the presence of an LDL receptor mutation. Second, FH children in the highest LDL-C tertile (> 6.23 mmol/L) had 1.8 (95% CI: 1.24-2.36) times more often an FH parent with premature CVD. In addition, such a parent was found 1.7 (95% CI: 1.06-2.76) times more frequent among FH children with HDL-C below 1.00 mmol/L. Lastly, FH children whose lipoprotein (a) was > 300 mg/L had 1.5 times more often an FH parent with premature CVD than FH children below that level (RR 1.45; 95% CI: 0.99 – 2.13; p=0.053).

**Conclusions:** In FH families, LDL-C levels allow the accurate diagnosis of FH in childhood. Moreover, severely increased LDL-C, Lp(a) and decreased HDL-C levels in children identify FH kindreds with the highest CVD risk.
Introduction

The incidence of familial hypercholesterolemia (FH) among Dutch children is 1 in every 400 births and a plethora of mutations in the low-density lipoprotein (LDL) receptor gene underlie this disorder in our country. In FH children, severely increased LDL cholesterol (LDL-C) deteriorates endothelial function at very young age. Next to these functional changes, accumulation of cholesteryl esters changes the vascular morphology and the intima-media-thickness (IMT) of peripheral arteries increases more rapidly in FH children.

These findings support the notion to take preventive measures at young age instead of waiting until FH heterozygotes reach adulthood. In particular, it has been suggested that lifestyle changes can influence plasma LDL-C and, the largest and longest placebo controlled trial with statin therapy exhibited excellent safety and efficacy in FH children. These results might suggest that FH children might derive significant benefit from lifestyle modification as well as from pharmacological intervention to reduce the burden of increased LDL-C.

Analyses of mortality show a large variation of the consequences of FH and specifically, the risk of atherosclerosis varies significantly between families. Identification of children, who have severely increased familial risk of cardiovascular disease (CVD), could assist in the selection for targeted intervention. In the present study, we performed analyses in a pediatric FH cohort of unparalleled size. First, we sought to determine specific LDL-C levels for the most accurate diagnosis of FH in these children. Subsequently, we addressed whether or not the observed lipoprotein variations were associated with the occurrence of premature CVD in relatives. But, consequently and foremost, our objective was to identify FH children at high CVD risk and in need for early intervention.

Patients and methods

Study population
Between July 1989 and July 2001, 1034 children were referred to our Pediatric Lipid Clinic. A diagnosis of heterozygous FH in the parent was based on the following criteria: (1) a documented LDL receptor mutation or (2) plasma LDL-C levels persistently above the 95th percentile for age and sex in a family with a positive history of premature CVD in conjunction with (3), tendon xanthomata.
Premature CVD was defined to have occurred before the age of 60 years in women and before 55 in men. The study protocol was approved by our Review Board and analyses were performed with informed consent of the children and both parents, if alive.

**Laboratory analysis**
Venous blood was collected after an overnight fast. Plasma total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were determined, using commercially available kits (Boehringer Mannheim, Mannheim, Germany). LDL-C concentrations were calculated using the Friedewald formula. Apolipoprotein A1 and apolipoprotein B100 were determined on a Behring nephelometer, BN100 (Behring, Marburg, Germany). Lipoprotein (a) \([\text{Lp(a)}]\) concentrations were determined using the Apo-Tek ELISA (Organon Teknika, Rockville MD, USA).

**Statistical analysis**
To select the LDL-C level that minimizes the proportion of false-negatives and false-positives, a receiver operating characteristic (ROC) curve was constructed according to Altman and Bland [11]. The diagnostic value of a given LDL-C level was analyzed by considering pre-test and post-test probabilities and was expressed as the post-test likelihood of having FH (odds). ANOVA and chi-squared analysis were used to compare subgroups. Statistical testing of triglycerides and \([\text{Lp(a)}]\) was performed after logarithmic transformation. To study the relationship between the lipid and lipoprotein levels and family history, FH children were divided into three groups, those with a positive family history of premature CVD in first degree relatives, in second degree relatives, and in those without such relatives with premature CVD. Trends were analyzed by multiple linear regression with concomitant inclusion of co-variables. Relative risks were analyzed with Cox's regression and cumulative event free survival was illustrated with the Kaplan-Meier method. Statistical significance was assessed at the 5% level of probability.
Results

Diagnosis of familial hypercholesterolemia
A total of 1034 children from 725 families with a certain diagnosis of FH were seen in our clinic. Until today a molecular diagnosis was obtained in 604 children: 6 homozygotes and 568 heterozygotes, while the 181 siblings did not carry that specific LDL receptor gene mutation. For these 598 heterozygotes and the 181 normal siblings, receiver operating characteristics (ROC) curves of LDL-C, age and sex-specific LDL-C percentiles and apolipoprotein B levels are shown in figure 1. All three measurements enabled accurate identification of children heterozygous for LDL receptor mutations, however, the largest area was found under the curve of plasma LDL-C. The best available LDL-C value for the diagnosis of FH in children was 3.50 mmol/L (135 mg/dl). Levels below this concentration were only found in 4.3% of children with a mutated LDL receptor (false negatives; 95% CI: 2.6-6.1%). In contrast, children with LDL-C equal to or above 3.50 mmol/L (135 mg/dl) had 0.98 (95% CI: 0.96-0.99) post-test probability of FH. It is important to note that this ROC curve and LDL-C cut-off is only valid against the background of a family investigation with a definite diagnosis of FH established. These data do not apply to the general population nor to other children with non FH dyslipidemia. Remaining children numbered 249 from families in which an LDL receptor gene mutation has not yet been identified (they are still in the cue for sequencing). However, when we apply the best available cut-off LDL level of 3.5 mmol/L (135 mg/dl), to these remaining children, 144 of them will have a 98% chance of having heterozygous FH. This brings the total of FH children to 598 (DNA diagnosis) + 144 (LDL-C level and clinical diagnosis) which equals 742 children. According to the ROC analysis the expected number of false positive diagnoses is less than 3 children (95% CI:2-7) out of the 742. In contrast, a total of 286 children (181 with DNA diagnosis and 105 according to LDL-C levels) were normolipidemic and this ratio is not expected 0.5 probability. The reason for this is that siblings with very low levels of LDL-C (measured by the general practitioner or referring specialist) were often not referred. However, in table 1 for the exact comparison between heterozygotes and children without FH we have used the 181 normal siblings since they are, by molecular means, certainly non-FH.
General characteristics

Based on the above mentioned diagnostic criteria, 742 children (397 girls and 345 boys) from 508 families were heterozygous for FH (table 1). Their mean age was 11 years (range 2-19 years). Typical physical characteristics of FH (xanthomas, xanthelasmas, or arcus cornealis) were only found in 35 children (5%; 95% CI: 3.7%). Of these children, 85% were on a fat restricted diet, compatible with the step I diet of the American Heart Association. A total of 47 (6%; 95% CI: 5.8%) children were cigarette smokers. Age, length and body mass index (BMI) were not significantly different between the children with and without FH. In table 1, lipids and lipoproteins are compared between the children with and without FH. As expected, FH children had severely increased LDL-C and decreased HDL-C levels compared to children without FH. LDL-C and apoB100 levels were highly correlated (r=0.95; p<0.001) as were HDL-C and apoA1 levels (r=0.76; p<0.001).

Girls with FH had mean LDL-C of 5.80 mmol/L (95% CI: 5.64-5.96 mmol/L) versus 5.42 mmol/L (95% CI: 5.27-5.57 mmol/L; p=0.001) for FH boys. Mean TG levels in FH girls were 0.90 mmol/L (95% CI: 0.84-0.96 mmol/L) versus 0.77 mmol/L (95% CI: 0.73-0.81 mmol/L) in boys (p<0.001).
Mean BMI, 18.8 kg/m², was significantly higher in FH girls (95% CI: 18.4-19.2 kg/m²) than the 18.1 kg/m² in FH boys (95% CI: 17.8-18.4 kg/m²; p=0.005). No significant differences were found with regards to HDL-C and apoA1 between girls and boys. Adjustment for age or triglyceride levels did not change these results (data not shown).

**Table 1.** Characteristics of heterozygous FH children and non-affected siblings.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FH (n=742)</th>
<th>Siblings (n=181)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range)</td>
<td>11.0 (2.0-18.7)</td>
<td>11.0 (3.1-19.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Gender, m/f</td>
<td>345/397</td>
<td>93/88</td>
<td>0.2</td>
</tr>
<tr>
<td>Menses, n (%)</td>
<td>144 (36.3)</td>
<td>29 (33.0)</td>
<td>0.6</td>
</tr>
<tr>
<td>Diet, n (%)</td>
<td>625 (84.9)</td>
<td>120 (66.3)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>47 (6.3)</td>
<td>6 (3.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Stigmata, n (%)</td>
<td>35 (4.8)</td>
<td>–</td>
<td>n.a.</td>
</tr>
<tr>
<td>BMI, kg/m² (range)</td>
<td>18.49 (12.2-41.1)</td>
<td>18.05 (12.9-29.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>7.26 ± 0.06</td>
<td>4.28 ± 0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>5.62 ± 0.06</td>
<td>2.55 ± 0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.25 ± 0.01</td>
<td>1.40 ± 0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC / HDL-C</td>
<td>6.09 ± 0.07</td>
<td>3.18 ± 0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>0.84 ± 0.02</td>
<td>0.73 ± 0.03</td>
<td>0.001⁴</td>
</tr>
<tr>
<td>Apo A-I (g/L)</td>
<td>1.27 ± 0.01</td>
<td>1.37 ± 0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apo B100 (g/L)</td>
<td>1.59 ± 0.02</td>
<td>0.83 ± 0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/L)</td>
<td>212 ± 10</td>
<td>196 ± 19</td>
<td>0.04⁴</td>
</tr>
</tbody>
</table>

BMI=body mass index, TC=total cholesterol, LDL=low-density lipoprotein, HDL=high-density lipoprotein, Apo A-I=apolipoprotein A-I, Apo B100=apolipoprotein B100, of the mean, values are given as means ± standard error of the mean (SEM). ⁴statistical testing after logarithmic transformation

**Lifestyle and plasma lipoprotein levels**

FH children (742) grouped by LDL-C tertiles had similar distributions of age, diet, smoking and body mass index (data not shown). Also, LDL-C levels of FH children not on a diet versus FH children on a fat restricted diet did not differ.

In contrast, HDL-C below 1.00 mmol/L (the lowest quintile) was found in 132 children. This group had similar age, percentage of boys and girls, and smokers compared to the 610 FH children with HDL-C levels in the other quintiles (data not shown). However, in the low HDL-C group, 79% was on a fat restricted diet compared to 86% in the high HDL-C group (χ²=4.93, df=1; p=0.03). In addition,
the mean BMI of FH children with low HDL-C was 19.3 kg/m² (95% CI: 18.5-20.0 kg/m²) versus 18.3 kg/m² (95% CI: 18.1-18.6 kg/m²; p=0.007) in the high HDL-C group. Mean TG levels of the low HDL-C group were 1.16 mmol/L (95% CI: 1.02-1.29 mmol/L) versus 0.77 mmol/L (95% CI: 0.74-0.80 mmol/L) in the high HDL-C group; after logarithmic transformation (p<0.001).

Adjustment for age and gender did not improve the diagnostic value of LDL-C levels as shown in the ROC curve and no influence of age on lipoproteins became evident in our cohort of FH children.

Parameters, such as diet, BMI, plasma TG and HDL-C were correlated. Therefore, we analyzed these relationships with different logistic regression models with subsequent inclusion of diet and BMI and of diet, BMI and plasma TG (table 2). Diet and BMI were weakly correlated (R=-0.11, p=0.005). In the regression model, diet did not change the influence of BMI on HDL-C levels (data not shown). However, TG levels included in the model showed a strong inverse relationship with HDL levels (OR 0.25, 95% CI: 0.16-0.39; p<0.001) and fully explained the effect of BMI on HDL-C (OR 1.01, 95% CI: 0.96-1.07; p=0.7) and partly of diet (OR 1.49, 95% CI: 0.90-2.48; p=0.1).

In brief, FH children with lower HDL-C levels were heavier and had higher TG levels. In contrast, LDL-C levels were mostly independent of lifestyle characteristics or anthropomorphic measures.

### Table 2. Relationships between HDL cholesterol above 1.00 mmol/l, diet, BMI and plasma TG.

<table>
<thead>
<tr>
<th>Determinants</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>1.71</td>
<td>1.06-2.76</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI</td>
<td>0.93</td>
<td>0.89-0.98</td>
<td>0.006</td>
</tr>
<tr>
<td>Plasma TG</td>
<td>0.25</td>
<td>0.16-0.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 1:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>1.62</td>
<td>1.00-2.65</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI</td>
<td>0.94</td>
<td>0.89-0.98</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 2:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>1.49</td>
<td>0.90-2.48</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI</td>
<td>1.01</td>
<td>0.96-1.07</td>
<td>0.7</td>
</tr>
<tr>
<td>Plasma TG</td>
<td>0.25</td>
<td>0.16-0.39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Logistic regression analyses were performed with single, two, and three co-variables, respectively. CI=confidence interval, BMI=body mass index.
A slight difference was evident in mean Lp(a) levels between FH children (212 ± 10 mg/l) and unaffected siblings (196 ± 19 mg/l; after logarithmic transformation p=0.04). However, adjusted for parental gender and calendar period, the 110 FH children whose Lp(a) was ≥ 300 mg/l had 1.5 times more often a FH parent with premature coronary artery disease than the 327 FH children with low Lp(a) levels (RR 1.45; 95% CI: 0.99 – 2.13; p=0.053). In similar analyses comparing the children with and without detectable Lp(a), no differences were observed between the groups (RR 1.04; 95% CI: 0.59 – 1.85; p=0.9).

Family history of premature CVD

The analyses of the relation between premature CVD and lipoprotein levels in children were restricted to one child per family (508 index children with FH). Their general characteristics, including lipids and lipoproteins, are shown in table 3. A positive family history for premature CVD in first degree relatives was found in 155 (31%) children. A total of 290 (57%) children had a positive family history of premature CVD in a second and/or third degree relative.

Table 3. General characteristics, lipids, and lipoproteins of FH index children according to premature CVD in relatives.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1st degree relatives with premature CVD (n=155)</th>
<th>2nd degree relatives with premature CVD (n=290)</th>
<th>No such relatives (n=63)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range)</td>
<td>11.0 (3.2-18.0)</td>
<td>10.8 (2.0-18.7)</td>
<td>11.6 (3.3-18.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Gender, m/f</td>
<td>66/89</td>
<td>126/164</td>
<td>29/34</td>
<td>0.9</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>7.55 ± 0.13</td>
<td>7.32 ± 0.09</td>
<td>6.79 ± 0.17</td>
<td>0.02</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>5.90 ± 0.13</td>
<td>5.67 ± 0.09</td>
<td>5.09 ± 0.18</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.25 ± 0.02</td>
<td>1.26 ± 0.02</td>
<td>1.33 ± 0.04</td>
<td>0.1</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>0.91 ± 0.04</td>
<td>0.86 ± 0.03</td>
<td>0.81 ± 0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Apo A-I (g/l)</td>
<td>1.28 ± 0.02</td>
<td>1.27 ± 0.01</td>
<td>1.36 ± 0.03</td>
<td>0.1</td>
</tr>
<tr>
<td>ApoB100 (g/l)</td>
<td>1.65 ± 0.04</td>
<td>1.62 ± 0.03</td>
<td>1.45 ± 0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/l)</td>
<td>259 ± 27</td>
<td>179 ± 13</td>
<td>242 ± 35</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Statistical testing was performed with multiple linear regression. All analyses with and without adjustment for gender and age yielded similar results. Additional adjustment for triglyceride concentration, diet, or cigarette smoking did not change the results on HDL-C and apolipoprotein A-1. Value’s are given as means ± standard error of the mean (SEM).

*statistical testing after logarithmic transformation.
No family history of premature CVD in first, second or third degree relatives was found in 63 (12%) children. Sex and age of the index children was equally distributed among these three groups. Strikingly, children with premature CVD among first degree relatives, second degree relatives, and those without such relatives showed, respectively, higher, intermediate, and lower LDL levels ($p_{\text{for trend}}=0.001$). ApoB100 levels showed a similar trend ($p_{\text{for trend}}=0.01$). Triglyceride levels also exhibited a similar trend, but testing with and without logarithmic transformation did not reach statistical significance ($p_{\text{for trend}}=0.06$).

**LDL and HDL cholesterol of the index child in relation with CVD in the FH parent**

In support of these findings, FH children with LDL-C levels ≥ 6.23 mmol/L (the highest tertile) had 1.7 times (95% CI: 1.24-2.36; $p=0.001$) more often an FH parent with premature onset of CVD than those with LDL-C below 6.23 mmol/L. This analysis is shown in figure 2; parents of children with these high LDL-C levels had shorter event free survival than parents of children with low LDL-C levels (logrank = 10.35; df = 1; $p=0.001$). Strikingly, adjusted for parental gender and calendar period with Cox' regression analysis, FH children with HDL-C levels below 1.00 mmol/L had 1.8 times (95% CI: 1.20-2.59; $p=0.004$) more often an FH parent with premature onset of CVD (figure 3). In agreement with the Cox' regression analysis, parents of children with low HDL-C levels had shorter event free survival compared to parents of children with high HDL-C levels (logrank = 3.93; df = 1; $p=0.048$).

In conclusion, these data indicate that both severely elevated LDL-C and Lp(a) levels and decreased HDL-C levels point to a subgroup of FH families exposed to severe CVD risk.
**Figure 2.** Event free survival among FH parents. The data represent Kaplan-Meier estimates according to LDL-C levels of their children. The event free survival was significantly better in the parents of children who had LDL-C levels below 6.23 mmol/L (logrank test p=0.001).

**Figure 3.** Event free survival among FH parents. The data represent Kaplan-Meier estimates according to HDL-C level in their children. The event free survival was significantly better in the parents of children who had HDL-C levels or above or equal to 1.00 mmol/L (logrank test p=0.048).
Discussion

We could show in this large cohort of FH families that LDL-C levels below 3.50 mmol/L (135 mg/dl) are only found in 4.3% of children with a mutation in the LDL-receptor gene. Elevated LDL-C levels in childhood suggest a diagnosis of classical FH and in early and seminal study by the NIH group it was shown that this diagnosis could be made on the basis of cord blood LDL-C levels. However, the same authors also showed that cholesterol levels overlap to a certain extent between affected and normal children. The demonstration of a defect in the LDL receptor gene is more accurate for the diagnosis of FH than an LDL-C measurement, but DNA sequencing is only available to a limited number of physicians and our data support the use of an LDL-C cut-off level at minimal loss of specificity and sensitivity. However, it should be stated explicitly that the ROC curves and LDL-C cut off levels in our study only apply to families, in which the diagnosis of FH is certain. They cannot be extrapolated to other dyslipidemias nor to the general population.

We could also show, as is known since three decades, that these children have severely elevated TC, LDL-C and apolipoprotein B levels, in conjunction with decreased HDL-C and apolipoprotein A1 levels. Already in the early seventies Kwiterovich and colleagues established, by investigating cord blood, that HDL-C levels were significantly lower in FH children than in non-affected siblings. This finding was subsequently confirmed in older FH children by the same authors. The reason(s) for low HDL-C in heterozygous FH have not been fully elucidated. They could be related to increased very low density lipoprotein (VLDL) synthesis as seen in FH, or due to the fact that intermediate density lipoproteins (IDL), also cleared by the LDL-receptor, accumulate in this disorder. These metabolic alterations of TG rich lipoproteins could cause increased cholesteryl ester transfer protein (CETP) activity, with subsequent depletion of cholesterol in the HDL-particle, as has indeed been suggested by Inazu and colleagues. Kinetic studies have suggested both increased fractional catabolic rate and decreased synthesis of HDL-apoAI. Schaefer and colleagues suggested that deficiency of the LDL-receptor leads to an increased pool size of apoE, which in turn could lead to apoE enriched HDL and subsequent increased clearance of these particles in FH. Taken together, increased CETP activity in conjunction with increased HDL-C clearance could be hypothesized to underlie the lower HDL-C levels in FH children.
LDL-C levels exhibited a wide range in our cohort. In healthy twin children, the variation of cholesterol levels was attributed for 24% to genetic influences and for a stunning 76% to environmental influences. This is in sharp contrast to our findings; age, diet, body mass index and smoking frequency were essentially similar across all LDL tertiles in FH children. The loss of half of LDL receptor function might be an overriding force and overwhets any subtle environmental or other genetic influence on LDL-C levels, as was shown previously for apo E genotype and diet in relation to FH.

At the present time, the recommended therapeutic regimen for children with FH is restricted to bile acid binding resins in conjunction with a lipid-lowering diet total cholesterol reductions of 12% are modest, only slightly more effective than diet alone. In contrast Stein and colleagues reported on the long-term efficacy and safety of lovastatin in children and adolescents with FH, showing excellent tolerability and lack of serious side-effects in this age cohort.

However, not all FH children suffer the dire consequences of accelerated atherosclerosis, but, in fact, may have a normal life expectancy. In our opinion, targeted intervention of FH children should take family history and notably the severity of parental coronary disease into account. Event-free survival of the affected FH parent exhibited in our study a strong relationship with both LDL-C and HDL-C levels in children. Indeed, a positive family history is a strong and independent risk factor for both sexes and its effect is synergistic with other CVD risk factors as well, also for individuals without FH. In addition, FH children whose Lp(a) level was above 300 mg/L, had 1.5 times more often an FH parent with premature CAD than the FH children with lower Lp(a) levels.

Our observations therefore suggest that a high familial risk of CVD may be identified in a FH child before it becomes family history by analyzing its lipid profile.

In conclusion, when the diagnosis of FH is certain in the family, simple measurement of the most important lipoproteins, LDL-C, HDL-C and Lp(a) allows an accurate diagnosis of FH in childhood and also leads to identification of FH families with the highest risk of CVD. It would therefore follow to study efficacy and safety of long term statin use in exactly that risk category of childhood FH.
References


