Screening for dyslipidemias in children and adolescents

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Why to screen, who to screen, who to treat

... that is the question

Universal/cascade/nobody?
Children at risk
Family history
At age 1/5/9/adolescents?
Screening strategies

- **FH** – fulfills requirements for screening:
  - Pre-clinical diagnosis,
  - Severe diseases with known etiology, diagnose and effective therapy,
  - Cost-effectiveness

- **Cascade screening** – selective target screening of relatives of FH patients; cost-effective; Netherlands (from 1994; Defesche et al, Semin Vasc Med 2004), parts of GB and other countries

- **Universal screening** – more effective? (familial HH, multifactorial HH, polygenic HH)

- Children will benefit most from screening!!!
Lipids are important

**Energy source**

**Energy supplies**

**Cell membranes constituents**

**Steroid hormones**

**Insulation, structural support, Protection for our body**
Multiple types of lipids

- Triglycerides
- Steroids
- Lipoproteins
- Glycolipids
- Phospholipids
But elevated cholesterol is also...

- The main risk factor for atherosclerosis
- Atherosclerosis begins in early childhood
- Clinical signs develop in 2nd or 3rd decade of life
- Among risk factors:
  - Hypertension, diabetes, smoking, sedentary life style, positive family history, elevated cholesterol
  - Monogenic form of hypercholesterolemia
Different shapes?
And the evolution...

The fatty acid translocase gene CD36 and lingual lipase influence oral sensitivity to fat in obese subjects

Marta Yanina Pepino,¹ Latisha Love-Gregory, Samuel Klein, and Nada A. Abumrad
Center for Human Nutrition, Washington University School of Medicine, St. Louis, MO 63110

The Nobel Prize in Physiology or Medicine 1985 was awarded jointly to Michael S. Brown and Joseph L. Goldstein "for their discoveries concerning the regulation of cholesterol metabolism"
Lipoproteins and premature CVD

How to find children at risk?

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Screening strategies in five European countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>Screening strategy</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Cascade screening</td>
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<tr>
<td>Norway</td>
<td>Cascade screening</td>
</tr>
<tr>
<td>Slovenia</td>
<td>General screening</td>
</tr>
<tr>
<td>Italy</td>
<td>Selective screening</td>
</tr>
<tr>
<td>UK</td>
<td>Cascade screening</td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease; FH, familial hypercholesterolaemia.
<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Concentration (mmol/l)</th>
<th>Median</th>
<th>Median (SD) ($\log_{10}$)*</th>
<th>Median (SD) ($\log_{10}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Cases</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborn</td>
<td>2.59</td>
<td>0.4139 (0.0829)</td>
<td>1.81</td>
<td>0.2567 (0.0639)</td>
</tr>
<tr>
<td>1-9</td>
<td>7.80</td>
<td>0.8922 (0.0752)</td>
<td>4.16</td>
<td>0.6195 (0.0594)</td>
</tr>
<tr>
<td>10-19</td>
<td>7.27</td>
<td>0.8614 (0.0940)</td>
<td>4.31</td>
<td>0.6347 (0.0711)</td>
</tr>
<tr>
<td>20-39</td>
<td>8.79</td>
<td>0.9439 (0.0109)</td>
<td>5.12</td>
<td>0.7091 (0.0775)</td>
</tr>
<tr>
<td>40-59</td>
<td>8.68</td>
<td>0.9383 (0.1162)</td>
<td>6.14</td>
<td>0.788 (0.0810)</td>
</tr>
<tr>
<td>≥60</td>
<td>8.42</td>
<td>0.9252 (0.1183)</td>
<td>6.62</td>
<td>0.821 (0.0740)</td>
</tr>
<tr>
<td><strong>LDL cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborn</td>
<td>1.67</td>
<td>0.2230 (0.1181)</td>
<td>0.78</td>
<td>-0.1065 (0.0844)</td>
</tr>
<tr>
<td>1-9</td>
<td>5.95</td>
<td>0.7744 (0.0954)</td>
<td>2.59</td>
<td>0.4126 (0.0854)</td>
</tr>
<tr>
<td>10-19</td>
<td>5.45</td>
<td>0.7364 (0.1220)</td>
<td>2.42</td>
<td>0.3843 (0.1125)</td>
</tr>
<tr>
<td>20-39</td>
<td>7.09</td>
<td>0.8506 (0.1212)</td>
<td>3.62</td>
<td>0.5586 (0.1117)</td>
</tr>
<tr>
<td>40-59</td>
<td>6.74</td>
<td>0.8285 (0.1533)</td>
<td>4.82</td>
<td>0.6830 (0.1070)</td>
</tr>
<tr>
<td>≥60</td>
<td>6.01</td>
<td>0.7791 (0.1484)</td>
<td>5.28</td>
<td>0.7230 (0.0990)</td>
</tr>
</tbody>
</table>

*Median log_{10} cholesterol concentration is directly estimated from mean log_{10} cholesterol concentration (see www.wolfson.qmul.ac.uk/epm/webtables/), which anti-logged gives median values shown in this table.
Cascade screening

• Less stressful for the family?
• General screening as a burden?
• QOL?

– Obese children?
– High cholesterol in the family?
– Early CVD onset in the family?
– Children with diabetes, chronic kidney diseases?
– Smokers, not active children?
– Who else?
How to recognise a patient at an early phase?

Measurement of cholesterol?
• Do we measure in children?

Clinical signs?
• Xanthomas
• Xanthelasmas
• Arcus cornee
• In children? Only in HH

Family history?
• Early CVD (<55 y)
• ↑ hyperlipidemia
Is just measuring enough? Genetics?

- Final confirmation of type HH
- Genetics?
- Optimal treatment
  (if it is early enough, we ↓ risk for CVD)

- Relatives?
- Genetic counseling?
How to individualize risk-assessment? Which children must be treated (when, how)?

- Etiology of hypercholesterolemia/dyslipidemia (mono-/poligenic/multifactorial)
- Other “classic” risk factors?
- Inflammation/oxidative stress?
- “The lower/earlier the better?”
<table>
<thead>
<tr>
<th>Genetic primary disorder</th>
<th>Genetic defect</th>
<th>Incid.</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolemia (including ADH; Familial defective ApoB-100)</td>
<td>LDL-R, PCSK9, ApoB-100; Diminished LDL-C clearance</td>
<td>1/250-1/500</td>
<td>Hetero: xanthomas, arcus corneae and premature CVD; TC: 6.5-13 mmol/l (LDL-C&gt;3.5 mmol/l) Homo: xanthomas and very premature CVD; TC: 13-26 mmol/l</td>
</tr>
<tr>
<td>Autosomal recessive hypercholesterolemia</td>
<td>ARH; Diminished LDL-C clearance</td>
<td>&lt;1/mio.</td>
<td>Similar to homo FH, but generally less severe; TC&gt;13 mmol/l</td>
</tr>
<tr>
<td>Polygenic hypercholesterolemia</td>
<td>Unknown, multiple defects and mechanisms</td>
<td>???</td>
<td>Premature CVD; TC: 6.5-9 mmol/l</td>
</tr>
<tr>
<td>Familial hyperchylomicronemia / Apo-CII deficiency</td>
<td>Apo-CII (causing functional complete or partial LPL deficiency)</td>
<td>1/mio.</td>
<td>Pancreatites, metabolic syndrome; hepatosplenomegaly; TG&gt;8.5 mmol/l; chylomicrons markedly elevated, LDL-C and HDL-C low</td>
</tr>
<tr>
<td>Familial combined hyperlipidemia</td>
<td>Unknown</td>
<td>1/200</td>
<td>Premature CVD, ApoB elevated; TC: 6.5-13 mmol/l; TG: 2.8-8.5 mmol/l</td>
</tr>
<tr>
<td>Familial dysbetalipoproteinemia</td>
<td>ApoE, impaired chylomicron and VLDL-C clearance</td>
<td>1/20,000?</td>
<td>Xanthomas; premature CVD or peripheral vascular disease; abnormal glucose tolerance; TC: 6.5-13 mmol/l; TG: 2.8-8.5 mmol/l; VLDL- C markedly increased, LDL-C reduced</td>
</tr>
<tr>
<td>Familial hypoalphalipoproteinemia</td>
<td>Unknown</td>
<td>?</td>
<td>Variable, premature CVD; HDL-C: 0.4-0.85 mmol/l</td>
</tr>
</tbody>
</table>

Adapted from Medscape and Orphanet
## Secondary Disorders of Lipid Metabolism

<table>
<thead>
<tr>
<th>Secondary disorder</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Increased TG, decreased HDL-C, sdLDL-C (&quot;Lipid triad&quot;)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Increased TG and TC, decreased HDL-C</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Increased TG and TC, decreased HDL-C</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Increased TG, TC and LDL-C</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Increased TC and LDL-C</td>
</tr>
<tr>
<td>Obstructive liver disease</td>
<td>Increased TC</td>
</tr>
<tr>
<td><strong>Medications</strong> (corticosteroids, b-blockers, antiretrovirals, anabolic steroids, and isoretinoin)</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Adapted from Medscape
The decision for universal screening

- Slovenia is a small country
- 2 M inhabitants
- But a well-organised health care system
- Children – pediatricians in 95%
- Organised preventional work, analyses

Unhealthy nutrition, insufficient physical activity and trends towards increasing weight are the greatest challenges facing child public health in Slovenia.
Slovenian pediatric association

- In 1995 a decision about preventive care changes was made
  - Mandatory nationwide medical examination
  - CVD are in Slovenia in 40% the cause of death
  - Leading cause of death above the age 65 years
  - In 21% at age >45 years
- A decision for a screening program for hyperlipidemias at the age of 5
  - Stable values of cholesterol after the 2\textsuperscript{nd} year
  - Early start of atherosclerosis
  - Low age allows lifestyle changes, dietary recommendation
  - Screening in children – cholesterol check in parents also
Analyses of the Ch screening in 2001

• 16 health care centres participated
• Total cholesterol screened, but in 25% also LDL cholesterol
• 2742 children from all regions of Slovenia
• Guidelines for Slovenian doctors "What to do if cholesterol is above 5 mmol/l"
  – 18% of children with cholesterol above 5 mmol/l (3600/y)
  – 2.8% of children have cholesterol above 6 mmol/l (550/y)
  – Obesity in 5 year olds:
    – 18.5% of girls and 23.2% of boys are overweight at age 5
How did it start
Conclusions. The results of the present study are in accordance with other similar published studies. General screening for hypercholesterolemia in childhood is feasible and medically indicated. Twenty-one percent of Slovenia population has total cholesterol concentration above 5 mmol/L. The follow-up work with these children must be structured and well planned. The main advantage of early detection of hypercholesterolemia is in the possibility of starting the changes of eating habits and lifestyle early in childhood. Namely, these changes are easier to perform and more successful if started early.
Bratina NU et al, Zdrav vestn 2003
Sedej K et al. EJE 2014
10 years later…

Clinical Study

K Sedej and others

Hypercholesterolaemia/obesity trends in children

170:2  295–302

Decreased prevalence of hypercholesterolaemia and stabilisation of obesity trends in 5-year-old children: possible effects of changed public health policies

Katarina Sedej¹, Primož Kotnik¹, Magdalena Avbelj Stefanija¹, Urh Grošelj¹, Andreja Širca Čampa¹, Lara Lusa², Tadej Battelino¹,³ and Nataša Bratina¹

European Journal of Endocrinology
(2014) 170, 295–302
After the first publication in 2003 a general cholesterol screening continued, and a changed national nutritional guidelines were used after 2005 – lower fat and carb intake
Results

Table 1  Anthropometric data and overweight/obesity prevalence (and change in prevalence) for 5-year-old girls and boys in the period from 2001 to 2009.

<table>
<thead>
<tr>
<th></th>
<th>2001</th>
<th>2004</th>
<th>2009</th>
<th>Δ From 2001 % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2004</td>
<td></td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td>1325</td>
<td>2317</td>
<td>2666</td>
<td></td>
</tr>
<tr>
<td>Subjects (n)</td>
<td>1417</td>
<td>2367</td>
<td>2830</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²; median (IQR))</td>
<td></td>
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</tr>
<tr>
<td>Girls</td>
<td>15.3 (14.4–16.5)</td>
<td>15.4 (14.4–16.5)</td>
<td>15.5 (14.5–16.5)</td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>15.4 (14.6–16.5)</td>
<td>15.4 (14.6–16.5)</td>
<td>15.5 (14.6–16.6)</td>
<td></td>
</tr>
<tr>
<td>Prevalence (n (%); 95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>387/2742 (14.1); 12.9–15.5</td>
<td>684/4684 (14.6); 13.6–15.6</td>
<td>848/5406 (15.7); 14.7–16.7</td>
<td>0.5 (−1.2 to 2.2) 1.5 (−0.1 to 3.2)</td>
</tr>
<tr>
<td>Girls</td>
<td>209/1325 (15.8); 13.9–17.8</td>
<td>387/2317 (16.7); 15.2–18.2</td>
<td>486/2666 (18.2); 16.8–19.7</td>
<td>0.9 (−1.6 to 3.5) 2.4 (0.0 to 5.0)</td>
</tr>
<tr>
<td>Boys</td>
<td>178/1417 (12.6); 10.9–14.4</td>
<td>297/2367 (12.6); 11.3–13.9</td>
<td>362/2740 (13.2); 12.0–14.5</td>
<td>0.0 (−2.2 to 2.2) 0.6 (−1.5 to 2.8)</td>
</tr>
<tr>
<td>Obese</td>
<td></td>
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</tr>
<tr>
<td>All</td>
<td>126/2742 (4.6); 3.9–5.44</td>
<td>207/4684 (4.4); 3.9–5.1</td>
<td>283/5406 (5.2); 4.7–5.9</td>
<td>−0.2 (−1.2 to 0.8) 0.6 (−0.4 to 0.7)</td>
</tr>
<tr>
<td>Girls</td>
<td>71/1325 (5.4); 4.3–6.7</td>
<td>110/2317 (4.7); 4.0–5.7</td>
<td>164/2666 (6.2); 5.3–7.1</td>
<td>−0.8 (−2.2 to 0.9) 0.8 (−0.8 to 2.4)</td>
</tr>
<tr>
<td>Boys</td>
<td>55/1417 (3.9); 3.0–5.0</td>
<td>97/2367 (4.1); 3.4–5.0</td>
<td>119/2740 (4.3); 3.6–5.2</td>
<td>0.2 (−1.1 to 1.6) 0.4 (−0.9 to 1.8)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.
# Trend in cholesterol

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>TC &gt;5 mmol/l (n (%); 95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>291/1325 (22.0); 14.6–18.5</td>
<td>256/2381 (10.8); 9.6–12.1</td>
<td>11.2% 8.6–13.8 &lt; 0.001</td>
</tr>
<tr>
<td>Boys</td>
<td>233/1417 (16.4); 19.8–24.3</td>
<td>191/2431 (7.9); 6.9–9.0</td>
<td>8.6% 6.3–10.8 &lt; 0.001</td>
</tr>
<tr>
<td>TC (mmol/l), mean (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>4.5 (4.42–4.50)</td>
<td>4.2 (4.16–4.22)</td>
<td>0.27 0.22–0.32 &lt; 0.001</td>
</tr>
<tr>
<td>Boys</td>
<td>4.3 (4.29–4.37)</td>
<td>4.1 (4.05–4.10)</td>
<td>0.25 0.20–0.30 &lt; 0.001</td>
</tr>
</tbody>
</table>
Dietary intervention works?

• But it is not enough, children – families with high risk can be identified better, not only with family history and cholesterol measurements, exclusion of other diseases

• Genetics!
Universal Screening for Familial Hypercholesterolemia in Children

Gašper Klančar, BSc,*† Urh Grošelj, MD,* Jernej Kovač, PhD,† Nevenka Bratanić, MD,* Nataša Bratina, MD,* Katarina Trebušak Podkrajšek, PhD,‡‡ Tadej Battelino, MD*§

BACKGROUND Individuals with familial hypercholesterolemia (FH) who are untreated have up to 100-fold elevated risk for cardiovascular complications compared with those who are unaffected. Data for identification of FH with a universal screening for hypercholesterolemia in children are lacking.

OBJECTIVES This study sought genetic identification of FH from a cohort of children with elevated serum total cholesterol (TC) concentration, detected in a national universal screening for hypercholesterolemia.

METHODS Slovenian children born between 1989 and 2009 (n = 272) with TC >6 mmol/l (231.7 mg/dl) or >5 mmol/l (193.1 mg/dl) plus a family history positive for premature cardiovascular complications, identified in a national universal screening for hypercholesterolemia at 5 years of age were genotyped for variants in LDLR, PCSK9, APOB, and APOE.
FH causative genes

Familial hypercholesterolemia
- **LDLR** - LDL-C receptor (binding to the APOB, removal of LDL)
- 85 - 90% patients

Familial defective apolipoprotein B-100
- **APOB** - apolipoprotein B100 (main ligand for LDL receptor)
- ≈ 10% patients (common mutation p.Arg3527Gln)

ADH type 3
- **PCSK9** - proprotein convertase subtilisin/kexin 9 (regulation of LDLR number)
- < 1% patients

Heterozygous ADH → ↑ incidence
Homozygous ADH → ↑ severe clinical presentation
• 5-times faster increase of IMT in children with FH as compared to their unaffected siblings (significantly at 12 y) (Wiegman et.al., Lancet 2002)

Difference in mean carotid intima-media thickness (IMT) and 95% CI between children with familial hypercholesterolaemia and unaffected siblings (n=281) plotted against age, taking account of family relations

Mean=thick line. 95% CI=dashed lines.
FH – underdiagnosed

- Frequent (~ DM1), but very underdiagnosed, especially in children
- Canada and GB dg “FH” only in 15% affected

Timeline of Universal Screening introduction

Klančar G et al, unpublished.
• **Screening from 1995** – approx. 90% patients referred after screening at 5 years; approx. 30% of patients with identified mutations without positive family history

### RESULTS
Of the referred children, 57.0% carried disease-causing variants for FH: 38.6% in LDLR, 18.4% in APOB, and none in PCSK9. Nine novel disease-causing variants were identified, 8 in LDLR, and 1 in APOB. Of the remaining participants, 43.6% carried the APOE E4 isoform. Estimated detection rate of FH in the universal screening program from 2009 to 2013 was 53.6% (95% confidence interval [CI]: 34.5% to 72.8%), peaking in 2013 with an upper estimated detection rate of 96.3%. Variants in LDLR, APOB, or the APOE E4 isoform occurred in 48.6%, 60.0%, and 76.5%, respectively, of patients with a family history negative for cardiovascular complications.

### CONCLUSIONS
Most participants who were referred from a national database of universal screening results for hypercholesterolemia had genetically confirmed FH. Data for family history may not suffice for reliable identification of patients through selective and cascade screening. (J Am Coll Cardiol 2015;66:1250-7) © 2015 by the American College of Cardiology Foundation.

• **Treatment**
  
  **6-8 y**: 75% diet, 25% cholestyramine  
  **>8 y**: 31% diet, 13% cholestyramine, **56% statins** (atorva, prava, rosuva), 9% ezetimibe
### Table 1: Clinical and Genetic Characteristics of the Study Cohort

<table>
<thead>
<tr>
<th></th>
<th>Familial Hypercholesterolemia (n = 155) (57.0%)</th>
<th>Multifactorial Hypercholesterolemia (n = 117) (43.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>LDLR</strong></td>
<td><strong>APOB</strong></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>149 (54.8)</td>
<td>45 (42.9)</td>
</tr>
<tr>
<td><strong>At universal screening for hypercholesterolemia at 5 years of age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC, mmol/l</td>
<td>7.0 ± 3.4</td>
<td>7.9 ± 1.2</td>
</tr>
<tr>
<td>TC, mg/dl</td>
<td>258.7 ± 131.3</td>
<td>305.0 ± 46.3</td>
</tr>
<tr>
<td><strong>Family history‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>90 (33.1)</td>
<td>46 (43.8)</td>
</tr>
<tr>
<td>Negative</td>
<td>168 (61.8)</td>
<td>51 (48.6)</td>
</tr>
<tr>
<td>Data NA</td>
<td>14 (5.1)</td>
<td>8 (7.6)</td>
</tr>
<tr>
<td><strong>At first evaluation at the tertiary outpatient clinic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>7.3 ± 3.1</td>
<td>7.0 ± 3.2</td>
</tr>
<tr>
<td>BMI</td>
<td>0.6 ± 1.2</td>
<td>0.5 ± 1.2</td>
</tr>
<tr>
<td>TC, mmol/l</td>
<td>6.5 ± 1.2</td>
<td>7.3 ± 1.2</td>
</tr>
<tr>
<td>TC, mg/dl</td>
<td>251.0 ± 46.3</td>
<td>281.9 ± 46.3</td>
</tr>
<tr>
<td>LDL, mmol/l</td>
<td>4.6 ± 1.2</td>
<td>5.4 ± 1.3</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>177.6 ± 46.3</td>
<td>208.5 ± 50.2</td>
</tr>
<tr>
<td>HDL, mmol/l</td>
<td>1.5 ± 0.4</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>57.9 ± 15.4</td>
<td>54.1 ± 15.4</td>
</tr>
<tr>
<td>Non-HDL, mmol/l</td>
<td>51.2 ± 1.2</td>
<td>58.2 ± 12</td>
</tr>
<tr>
<td>Non-HDL, mg/dl</td>
<td>196.9 ± 46.3</td>
<td>223.9 ± 46.3</td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>1.2 ± 0.8</td>
<td>1.1 ± 1.1</td>
</tr>
<tr>
<td>TG, mg/dl</td>
<td>106.2 ± 70.8</td>
<td>97.4 ± 53.1</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD. Non-HDL was calculated as [total cholesterol – HDL]. SI conversion factors: to convert TC, LDL, HDL, and non-HDL to mg/dl, multiply by 38.61. To convert TG to mg/dl, multiply by 88.50. *No participants had disease-causing variants in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene. †No presence of disease-causing or disease-associated variants in the LDLR, APOB, PCSK9, or APOE gene was found. ‡Simon Broome Register criteria (1) were used for assessment of family history. Positive family history was defined as myocardial infarction before 50 years of age in any second-degree relative or before 60 years of age in any first-degree relative or as serum TC concentration of >7.5 mmol/l (289.6 mg/dl) in any first- or second-degree relative (first-degree relatives included parent(s), offspring, or sibling; second-degree relatives includes grandparent, grandchild, nephew, niece, or half-sibling).

APOB = presence of disease-causing variant in the apolipoprotein B gene; APOE E4 isoform = presence of disease-associated variant in the apolipoprotein E gene; BMI = body mass index; HDL = high-density cholesterol; LDLR = presence of disease-causing variant in the LDL receptor gene; LDL = low-density cholesterol; NA = not available; non-HDL = non-high-density cholesterol; TC = total cholesterol; TG = triglyceride.
Mutations in **LDLR**
- 37.2% patients
- 7 novel causative mutations
- 22 known causative mutations
- 1 deletion of the whole coding region
- 4 variants of unknown clinical significance
- 7 patients with multiple mutations

Mutations in **APOB**
- 17.2% patients common p.Arg3527Gln
- 1 novel causative mutation
- 1 known causative mutation
- 4 variants of unknown clinical significance
- 1 patient with multiple mutations

Mutations in **PCSK9**
- 0/274 analyzed patients

Klančar G et al, JACC
A national universal screening for hypercholesterolemia in children 5 years of age (referral criteria: serum total cholesterol (TC) level > 6 mmol/L [231.7 mg/dL] without a family history of premature cardiovascular (CV) complications, or serum TC level > 5 mmol/L [193.1 mg/dL] together with a family history of premature cardiovascular complications) identified a disease-causing genetic variant for familial hypercholesterolemia (FH) in 57.0% of children, with an additional one-fifth identified with the most common multifactorial form of hypercholesterolemia, amounting to >75.0% of referred participants carrying a disease-causing or disease-associated genetic variant. Assuming the commonly reported FH incidence numbers, the predicted detection rate from the data for the previous 5 years (2009 to 2013) was 53.6% (95% confidence interval [CI]: 34.5% to 72.8%), reaching its peak in 2013 (children born in 2008), with an upper estimated detection rate of 96.3% for an incidence of 1 in 500; nevertheless, when a greater incidence of 1 in 200 was assumed, the upper estimated detection rate was only 38.5%. Relative risk (RR) of having the disease-causing genetic variant when a participant had a CV-positive familial history was 1.53 (RR: 1.529; 95% CI: 1.25 to 1.88; p = 0.0001). APOB — presence of disease-causing variant in the apolipoprotein B gene; APOE E4 isoform — presence of disease-associated variant in the apolipoprotein E gene; LDLR — presence of disease-causing variant in the LDL receptor gene; Other — no presence of disease-causing or associated variant in LDLR, APOB, PCSK9, or APOE.
The story must continue...

**PERSPECTIVES**

**COMPETENCY IN SYSTEMS-BASED PRACTICE:**
Screening for hypercholesterolemia in children at 5 years of ages for familial hypercholesterolemia (FH) identified disease-causing variants in genes for LDLR and APOB in almost two-thirds of participants, and one-fifth were carriers of disease-associated variant encoding APOE E4 isoform. These data support proposals by the National Heart, Lung, and Blood Institute, National Lipid Association Expert Panel in the United States, and the European Expert Panel for universal screening as a preferred method of identifying FH as part of comprehensive primary prevention efforts.

**TRANSLATIONAL OUTLOOK:** Larger confirmatory studies are needed to determine the optimum timing and strategy for universal screening for FH using an expanded panel of FH-associated genes, and to define long-term efficacy and cost-effectiveness of this population-based approach.
Conclusions

- Dyslipidemias common in childhood; mostly hypercholesterolemia

- Hypercholesterolemia as a major risk factor for ATS and CVD

- Need to individualized risk assessment – e.g. with genetic diagnostics, other risk factors, family history

- FH underdiagnosed in developed world, (not in Slovenia?)

- Importance of timely dg in th (primary prevention) - screening (universal + cascade) with genetic dg
Comparing costs and benefits over a 10 year period of strategies for familial hypercholesterolaemia screening

Dalya Marks, Margaret Thorogood, H. Andrew W. Neil, David Wonderling and Steve E. Humphries

Conclusions Although the two approaches appear similar in cost-effectiveness over a lifetime, the shorter-term (10 year) cost-effectiveness clearly favours family tracing. This represents good value for money compared with common medical interventions, and suggests that pilot FH family tracing programmes should be conducted.
Familial Hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients

Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

3. Management issues in pediatrics

3.1 Screening

3.1.1 Universal screening at age 9 to 11 years with a fasting lipid profile or nonfasting non-HDL cholesterol measurement is recommended to identify all children with FH. This age identifies individuals at the potential onset of advanced atherosclerosis, and provides the best discrimination between those with and without inherited dyslipidemias by avoiding confounding due to changes in lipid levels associated with puberty.
### Table 2: Suspicion and Screenings of FH

#### Who to Screen
- Anyone with elevated cholesterol by age 20.
- All children aged 9 to 11.
- Children as young as 2 with family history of premature cardiovascular disease or very high cholesterol levels.

#### Who to Suspect
- Adults aged 20 or older with LDL cholesterol >190 mg/dL or non-HDL cholesterol >220 mg/dL.
- Children aged 9 to 11 with LDL cholesterol 160 mg/dL or non-HDL >190 mg/dL cholesterol.

Lipid Screening in Children*

Stephen R. Daniels, MD, PhD

Unfortunately, such epidemiological data in children, which could be used to calculate a lifetime risk of the development of cardiovascular disease for individual patients, are lacking. This means that lipid screening in children is fundamentally different from that in the adult population. The primary focus of lipid screening in children should be on how to identify young individuals with genetic causes of dyslipidemia, such as familial hypercholesterolemia (FH). FH results in LDL-C, which is elevated substantially above the 95th percentile for age and is a clearly elevated lifetime risk of cardiovascular disease (5). However, even if one accepts genetic dyslipidemia as the target for screening, a number of questions remain regarding the best approach to accomplishing this in practice.

In this issue of the Journal, the study by Klančare et al. (6) provides some useful information. They took advantage of a universal lipid screening process in children that was adopted in Slovenia, which has a population of ~2 million citizens. The country adopted a universal lipid screening program in children 5 years of age in 1995. By 2013, this screening program was reaching 20,000 children at 5 years of age. Evaluation of this experience is important as there are few studies of universal pediatric lipid screening in practice.
These screening results from Slovenia are most consistent, with a prevalence of heterozygous FH of 1 in 500 individuals, which suggests that the prevalence of genetic abnormalities in this population is higher than in the United States. Although the work of Klančar et al. (6) is helpful in elucidating some aspects of universal screening, there are many practical aspects of this approach to screening in childhood for FH that remain unclear. Some of the important unanswered issues include the detection of asymptomatic individuals and the definition of an acceptable screening level.

More evidence is required to determine the optimal approach to screening for children with FH. Experience with screening programs such as the one in Slovenia is useful, but well-designed prospective studies to evaluate the screening process will be even more important to provide the needed answers.

This was designed to avoid the decrease in LDL-C, which occurs during puberty. However, it is not clear how quickly individuals who are screened in the United States and have a positive result are then seen for further evaluation and treatment. The result would also tend to support the universal approach to screening for individuals with FH as opposed to cascade screening.