Is Universal Screening and Treatment of Hypercholesterolemia in Children Justified?

No: The Evidence Does Not Support Universal Screening and Treatment.

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Children’s Hospital at Montefiore
• I have no conflicts of interest to disclose
There is a need for direct evidence of benefit with hard outcome measures for screening and treatment efforts.

Lipid values do not track into adulthood with enough sensitivity/specificity to satisfy the criteria of a good screening test.

The effectiveness of the lipid screening in practice is untested and questionable.

The safety and net benefit of statins when used long term beginning in childhood is in question.
Unanticipated Harms

Screening and treatment efforts based on surrogate measures have caused harm
Overdiagnosis

• WHI trial, RCT of 16,608 women failed to show the anticipated cardio-protective effect of postmenopausal combination therapy despite favorable changes in lipid profiles. Stopped after 5 years due to cancer, CHD and stroke.

• PSA screening in men and neuroblastoma screening in infants are also harmful.

• Atherosclerosis is similarly vulnerable to overdiagnosis. Net benefits should be established by incremental studies.

Disconnect: NHLBI and ACC/AHA Guidelines

- The ACC/AHA cites an absence of hard outcome data to withhold statins for adults <45 with LDL-C <190 based on risk scoring.

- Pediatric NHLBI guidelines advocate statins for LDL-C of ≥130-160 with additional risk factors starting at 10.

- Gooding et al. applied NHLBI guidelines to NHANES data set: 2.5% of 17-21 year olds would get statins vs. 0.4% of 17-21 year olds using AHA/ACG adult guidelines.

- Pediatricians would treat 400,000 individuals nationally that internists would not because of lack of evidence.

Performance Characteristics of Lipid Screening

Can’t predict adult outcomes with childhood risk assessment
We can’t predict which children will become adults for whom the use of statin is recommended.
However, numerous studies have examined tracking of lipids, the stability of lipid percentiles over time.
### Princeton Lipid Research Clinics Prevalence Program Follow-up Study

<table>
<thead>
<tr>
<th>LDL-C of ≥130 as a child</th>
<th>LDL-C of ≥160 as an adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Screening</td>
<td>Sensitivity %</td>
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<tr>
<td>9-11</td>
<td>26-69</td>
</tr>
<tr>
<td>17-19</td>
<td>67</td>
</tr>
</tbody>
</table>

Obesity Related CV disease
A False Negative in the Cholesterol Testing Paradigm

- As obese/overweight children age into adulthood over the next 20 years, there is a projected marked increase in CV disease over current rates.

- CHD increase driven by DM, HTN, milder forms of dyslipidemia.

- The vast majority -79% have LDL-C < 130 in childhood.


Effectiveness
NHLBI: “The Childhood Medical office as the Setting for Cardiovascular Health Management”

Testing
Diet Counseling
Effectiveness
Testing paradigm

- Universal screening at 9-11, and 17-21. Non fasting
  - If Non HDL-C is $\geq 145$ or HDL-C $< 40$
  - Then obtain 2 fasting lipid profiles within 3 months

- CATCH trial result: Only 20% followed-up on a recommended single fasting LP.
- 2 other studies, <50% and 62% followed up for 1 fasting lipid profile.


Effectiveness
DISC - Effect of Diet on LDL-C

- Multi-center RCT of low fat diets in 663, 8-10 yr. old children with LDL-C of ≥80th ile.
- YR 1 11 Group meetings +3 individual meetings
- YR 2+3 4-6 Group meetings
- YR 3 LDL-C 3.23 mg/dl lower than control!

Effectiveness
CATCH-Effect of Diet on LDL-C

- 96 Schools-5016 kids.
- RCT of diet activity in 3rd graders decreased fat in lunches, increased physical activity.
- Lunch fat decreased 38-32%. Daily self report activity increased (59 vs. 47 minutes).
- No change in BP, BMI, or Lipids.

Effect of Diet Vs. Measurement Variation

- Includes analytical variability, biological variability.
- Coefficient of Variation of LDL-C ≈ 7.3 %, 7.5% , 8%
- Month to month variability 12%.
- Measurement variation ≥ dietary effects
- Strong disincentive to both families and clinicians. An unstudied harm.

Effectiveness
An Overburdened Well Child Visit

• The Core Set Children’s Quality- Measures 2015.
  • Immunizations, Weight and Activity counseling, Formalized developmental screening, Chlamydia Screening, Asthma, ADD, Depression. Access, Experience of care. Not Lipids.

• Bright Futures Agenda - Only 42% health supervision topics are covered

• AAP Policy Recommendations-162 General Health Advice Directives.

Statins in Children

- Rhabdomyolysis
- Statins are pleiotropic
- In 2012 the FDA revised the packing insert for statins to include warnings about diabetes and about memory loss cognitive impairment.
Effect of statin treatment on new-onset type 2 diabetes
Random-effects meta-analysis.

<table>
<thead>
<tr>
<th>Statin treatment</th>
<th>Case</th>
<th>Non-case</th>
<th>Control</th>
<th>Case</th>
<th>Non-case</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
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<tr>
<td>Placebo-controlled or standard care-controlled</td>
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<td>SSSS</td>
<td>198</td>
<td>1918</td>
<td>193</td>
<td>1933</td>
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<td>1.03 (0.84-1.27)</td>
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<td>WOSCOPS</td>
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<td>105</td>
<td>1612</td>
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<td>0.89 (0.67-1.19)</td>
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<td>UPS</td>
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<td>707</td>
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<td>MEGA</td>
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<td>2841</td>
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<td>1.11 (1.03-1.20)</td>
<td>66.98</td>
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Intensive vs moderate dose

<table>
<thead>
<tr>
<th>Intensive vs moderate dose</th>
<th>Case</th>
<th>Non-case</th>
<th>Control</th>
<th>Case</th>
<th>Non-case</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
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<tbody>
<tr>
<td>PROVE-IT TIMI22</td>
<td>101</td>
<td>1606</td>
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<td>1589</td>
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<td>A to Z</td>
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<td>1703</td>
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<td>1.37 (0.94-2.01)</td>
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<td>TNT</td>
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<tr>
<td>Subtotal</td>
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<td>14959</td>
<td>1300</td>
<td>15044</td>
<td></td>
<td>1.12 (1.04-1.22)</td>
<td>33.02</td>
</tr>
</tbody>
</table>

Overall

<table>
<thead>
<tr>
<th>Overall</th>
<th>Case</th>
<th>Non-case</th>
<th>Control</th>
<th>Case</th>
<th>Non-case</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
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<tr>
<td></td>
<td>3858</td>
<td>60700</td>
<td>3481</td>
<td>61131</td>
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<td>1.12 (1.06-1.18)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Daniel I Swerdlow, David Preiss, Karoline B Kuchenbaecker, Michael V Holmes, Jorgen E L Engmann, Tina Shah, ...

HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials
The Lancet, Volume 385, Issue 9965, 2015, 351 - 361
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Statins and Diabetes

Existing data on statin safety in children is both too short term and underpowered to detect significant important side effects. Statin related diabetes risk is an object lesson.
Implementation: An Issue

- Cholesterol testing at only 3% of 10,159 health maintenance visits from 1995-2010 vs. 35% eligible.

- Survey Results for 548 Pediatric Providers in Minnesota
  - 34% perform no screening
  - 50% selective screening
  - 16% Screen universally
  - 83% Uncomfortable with managing lipids
  - 57% opposed to the use of lipid lowering medications.


Summary

• The chain of indirect evidence that links childhood risk to adult outcomes and that justifies treating risk factors in childhood is vulnerable to causing overdiagnosis.

• Obesity tracks well into adulthood. LDL-C tracking is debatable, and in the eye of the beholder.

• The effectiveness of the NHLBI lipid testing recommendations and of diet counseling children done in the context of well child visits is not established.

• Statins cause diabetes. The benefit/risk ratio of statins is unclear. This evidence became clear only after 100 times more adults than children were studied in RCTs.

• Pediatric statin studies are markedly underpowered to detect important and potentially lifelong adverse effects.
There is an Alternative

- Cascade screening and the FH registry
- Broad public health efforts in lieu of universal lipid screening
- Incremental studies starting with older, higher risk adolescents, from engaged families.