CMHC
PEDIATRIC MASTERCLASS

Addressing Cardiometabolic Risk in Children and Adolescents:

CHALLENGES AND SOLUTIONS

Educationally Partnered with FCAAP Florida Chapter of the American Academy of Pediatrics
INCORPORATED IN FLORIDA

Pediatric Dyslipidemia

Amy L. Peterson MD, MS

University of Wisconsin School of Medicine and Public Health

Madison, WI

Presented at the FCAAP FUTURE of PEDIATRIC PRACTICE 2022

Disclosures

FDA - approved lipid medications for use in pediatrics:

- Atorvastatin
- Rosuvastatin
- Pravastatin
- Simvastatin
- Fluvastatin
- Lovastatin
- Pitavastatin
- Colesevelam
- Ezetimibe
- Evolocumab
- Evinacumab-dgnb

Financial Disclosure:

Novartis (steering committee member)

Objectives

1. Define the burden of dyslipidemia and increased atherosclerotic cardiovascular disease risk in children and adolescents.
2. List treatment options and guidelines for the management of dyslipidemia in pediatric patients.
3. Discuss specifically hypercholesterolemia and hypertriglyceridemia in pediatric patients.

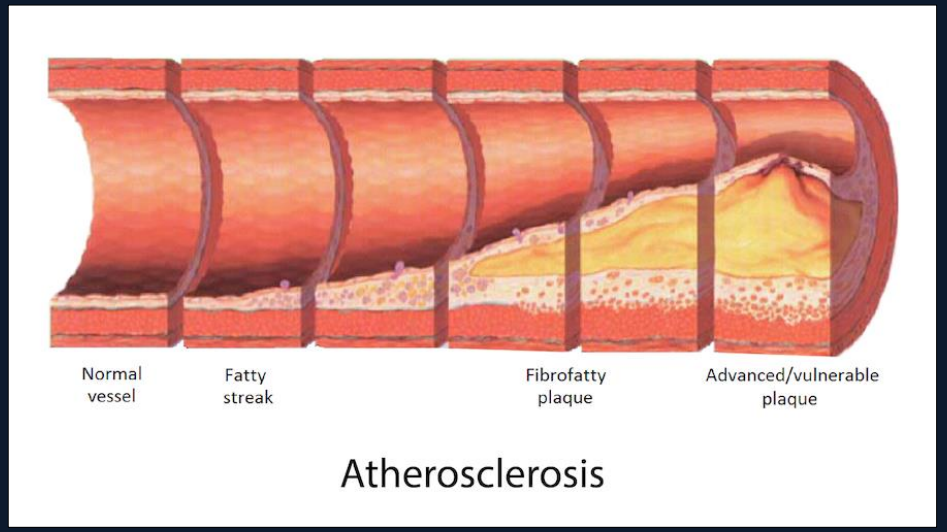
Atherogenic Dyslipidemia:

- Pattern of ↑ TG and ↓ HDL cholesterol (LDL usually normal)
- Most common pediatric dyslipidemia
- Often strong lifestyle component.
- Often comorbid with obesity, NAFLD, insulin resistance, hypertension, metabolic syndrome.

Most kids with AD have TG < 500 mg/dL
TG ≥ 500mg/dL → suspect primary genetic etiology

Familial Hypercholesterolemia:

- FH affects 1 in 250-300 people.
- High LDL levels present from birth accelerates atherosclerotic plaque development.

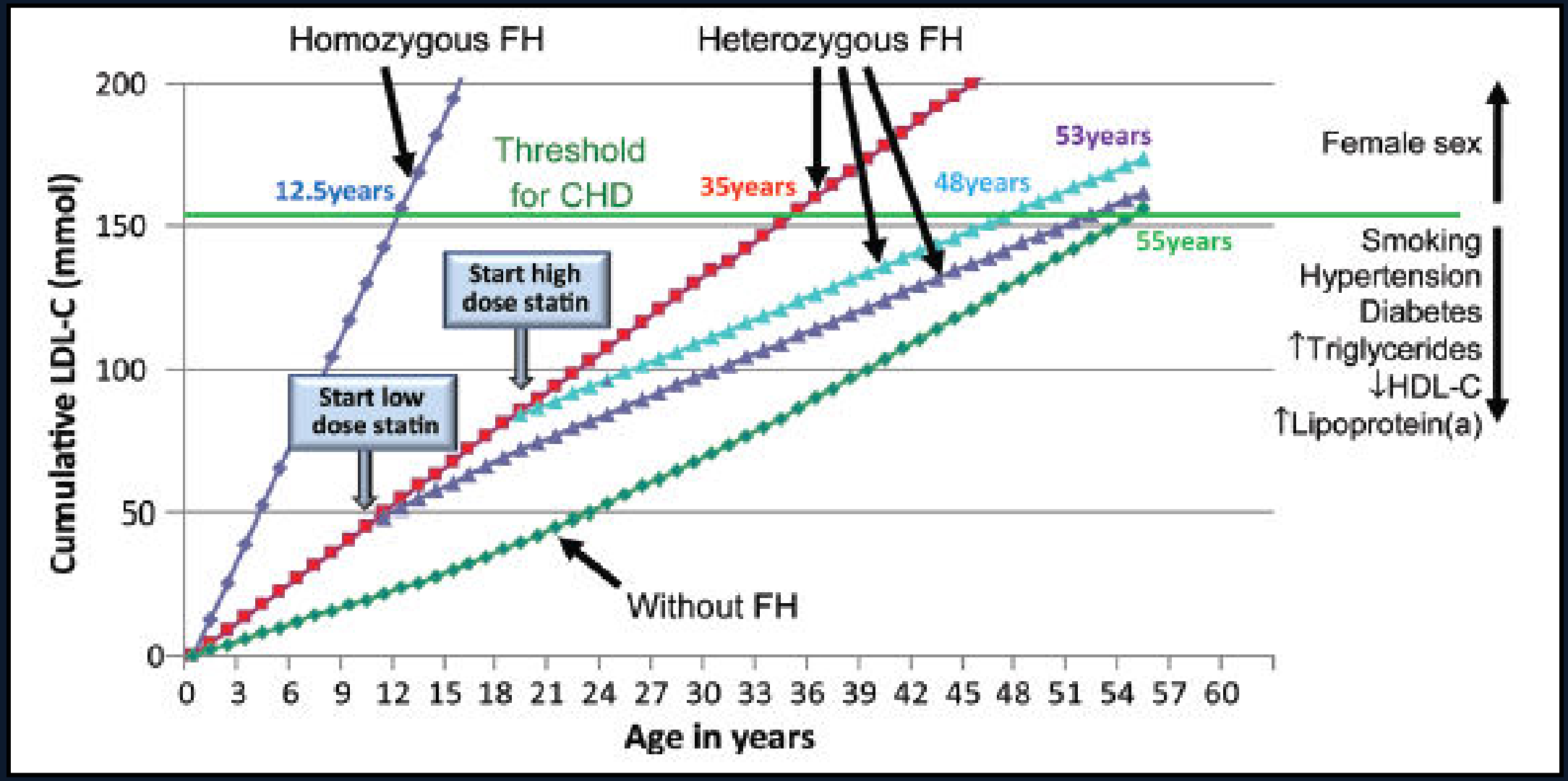


- About 10% of people with FH know their diagnosis.
- Autosomal dominant inheritance – cascade screening of family members is critical.

If **LDL ≥ 160** mg/dL → suspect FH
If **LDL ≥ 190** mg/dL → 80% chance of FH

Circulation 2015;132:2167-2192

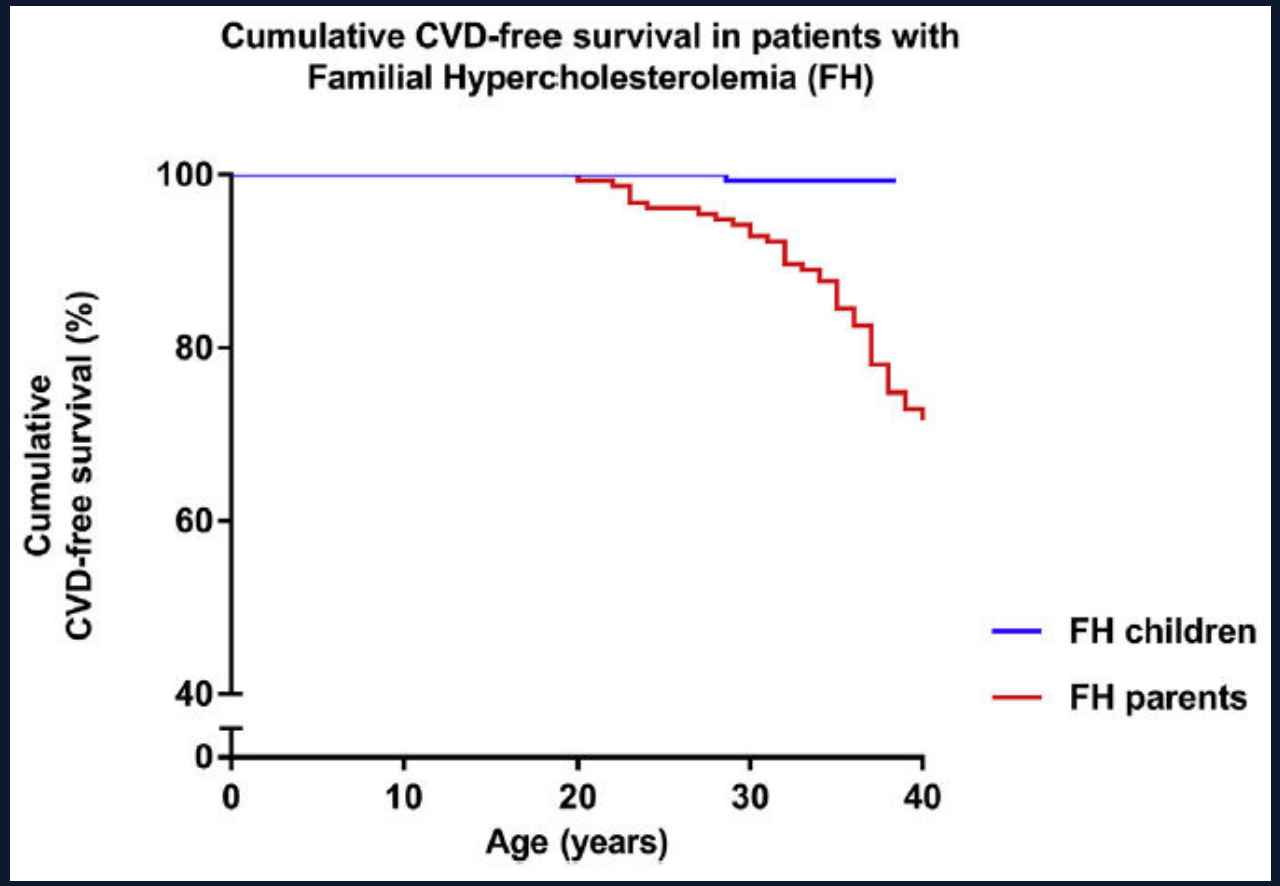
An ounce of prevention…



***Cumulative* LDL exposure *over the lifetime* determines onset of CV events.**

Circ Cardiovasc Genet 2012;5:354-359 *Clin Chem Lab Med* 2008;46:791-803.

20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia



"Children" = started statins in childhood, taking for 20+ years
"Parents" = started statins in adulthood

<u>At age 39:</u>
99.3% of children are event-free, no AEs
73.7% of parents were event-free
7.3% of parents had died from CVD

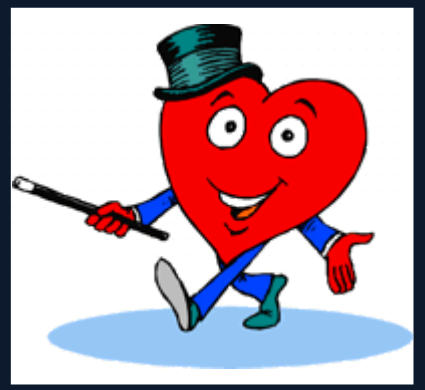
N Engl J Med 2019;381:1547-1556

Mixed Dyslipidemia:

- Pattern of ↑ TG and ↑ LDL (HDL usually ↓ or normal)
  - LDL ↑, but not enough for FH.
  - TG ↑, but usually less than in AD.
- Second most common pediatric dyslipidemia
- Often linked to lifestyle factors
- Can have a genetic predisposition
  - Some may have FH but don’t meet clinical LDL criteria.

Selective Lipid Screening: The 2008 AAP Guidelines

- Screen children 2-10 years old with **family history** of:
  - High cholesterol (Parent total chol >240mg/dL)
  - CVD (<55 years in males, <65 years in females)
  - Family history is unknown
- Screen if child has a **personal history** of:
  - Overweight or obesity
  - Hypertension
  - Tobacco use
  - Type 1 or 2 Diabetes

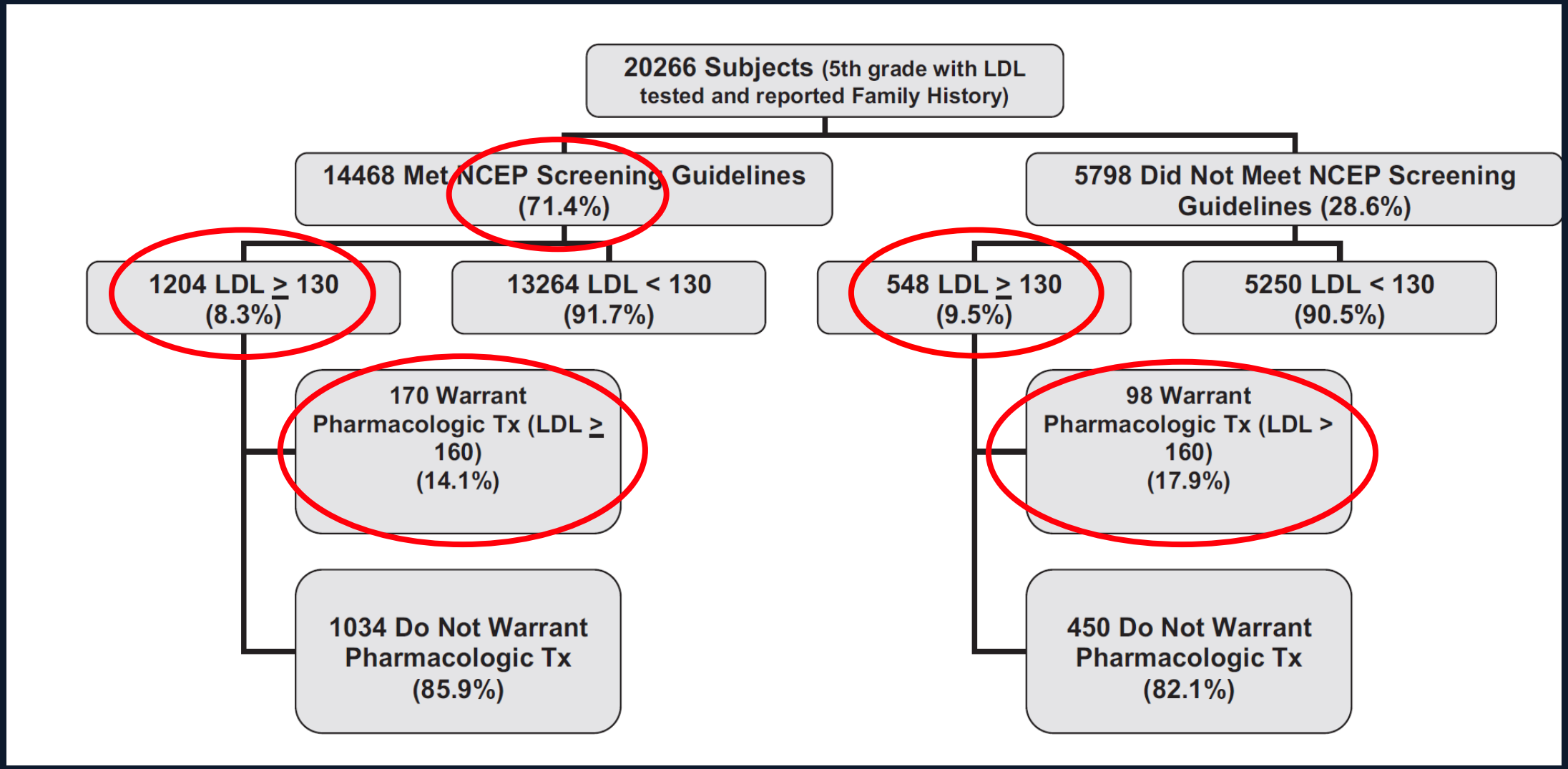


Pediatrics 2008;122:198-208.

Limitations to Selective Screening

- Long list of risk factors, can be stigmatizing
- Family history is often misleading!
  - Parents need to have cholesterol checked and know what it means
  - Households with limited information on relatives
  - Parents/grandparents need to be old enough to have had CVD events.
  - Widespread statin use in adults has created the “unnatural family history”

What happens when we check EVERYBODY? The WV CARDIAC Project



Pediatrics 2010;126:260-265

2011: Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

0-2 years old: no screening

2-8 years old: Fasting lipid panel for **at-risk** kids

9-11 years old: Nonfasting lipid screen for **all** kids

12-17 years old: Fasting lipid panel for **at-risk** kids

18-21 years old: Nonfasting lipid screen for **all**

Pediatrics 2011;128 (Supplement 5):S213-S256

Prevalence of Dyslipidemia in Universal and Selectively Screened Populations

Table III. Number needed to screen for universal versus targeted cholesterol screening

Outcome estimates	Universal screening	Targeted screening
Total children screened	4 100 000	1 435 000
Children with any hyperlipidemia	334 000	208 000
Children with severe hyperlipidemia	37 000	29 000
False-positives: children with dyslipidemia not diagnosed with hyperlipidemia	376 000	118 000
False-negatives: children with hyperlipidemia not diagnosed	47 000	28 000 (among positive family history only)
False-negatives: children with severe hyperlipidemia not diagnosed	5000	4000 (among positive family history only)
Postdietary treatment: children with any hyperlipidemia	301 000	187 000
Postdietary treatment: children with severe hyperlipidemia	33 000	26 000
Number needed to screen to identify		
Any hyperlipidemia	12	7
Severe hyperlipidemia	111	49

8.3% with some dyslipidemia

0.9% with severe dyslipidemia

J Pediatr 2018;196:201-7.

Childhood Cholesterol Predicts Adult CV events

Table 2. Hazard Ratios for Adult Cardiovascular Events According to Childhood, Adult, or Childhood plus Adult Risk Scores.*

Variable	Hazard Ratio (95% CI)†	
	Fatal Event	Fatal or Nonfatal Event
Childhood risk factor		
Youth smoking: yes vs. no	1.61 (1.21–2.13)	1.70 (1.49–1.93)
z Score for body-mass index	1.44 (1.33–1.57)	1.45 (1.38–1.53)‡
z Score for systolic blood pressure	1.34 (1.19–1.50)	1.33 (1.24–1.42)
z Score for ln(triglycerides)	1.50 (1.33–1.70)	1.45 (1.34–1.56)
z Score for total cholesterol level	1.30 (1.14–1.47)	1.31 (1.22–1.42)
Combined-risk z score§	2.71 (2.23–3.29)	2.75 (2.48–3.06)‡

N Engl J Med 2022;386:1877-1888.

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First-line treatment for all dyslipidemia: Lifestyle Changes

Turku STRIP study

Intervention:
Individualized dietary counseling ≥ 2x/year starting at 6 months old.

- Reduce saturated fat, cholesterol, and salt
- Increase whole grains, fruits, veggies

- **Intervention group has:**
- Lower LDL cholesterol
- Lower blood pressure
- Less obesity
- Improved insulin sensitivity and less metabolic syndrome
- Enhanced endothelial function
- No adverse effect on brain development

Circulation 2015;131(7):605-13.

Quick Lifestyle Advice (for all ages!)

1. Listen to your body (eat when you're hungry, stop when you're full)
2. Cut out sugar sweetened beverages
3. Eat a high-protein breakfast
4. Water, water, water
5. Screens off while eating
6. Screens have a bedtime, too
7. *MOVE:* something is better than nothing

Dx: Atherogenic Dyslipidemia

Second-line treatment options

- Omega-3 FA or icosapent ethyl – consider if TG > 400.
- Over the counter minipills, liquids commonly discussed as treatment options.
  - More kid-friendly than capsules but more $$
  - Not regulated by FDA, DHA+EPA content often unreliable
- OTC DHA+EPA gummies are basically useless (sugar >> DHA+EPA)

Pediatrics 2011;128 (Supplement 5):S213-S256

Dx: Atherogenic Dyslipidemia

Third-line treatment options for TG > 500mg/dL

- Immediate goal with TG at this level is prevention of pancreatitis
- Guidelines advise pediatric use be restricted to dyslipidemia specialists

  Fenofibrate most common agent used. *Not* FDA-approved for TG reduction in pediatrics

- Generally used with Rx Omega 3 FA in children with genetic dyslipidemias

Pediatrics 2011;128 (Supplement 5):S213-S256

Diagnosis: FH

One evidence-based approach to treatment.

1. Rule out secondary causes: thyroid, medications, diet
2. Lifestyle therapy for 3-6 months reasonable.
3. Pre-treatment labs: TSH, AST, ALT, CK, HgbA1c, repeat lipids
4. First line agent: statin
   - Pravastatin, rosuvastatin, pitavastatin approved 8+ yrs
   - Atorvastatin, simvastatin, fluvastatin, lovastatin approved boys 10+ yrs, postmenarchal females
   - Start with lowest dose.
5. After 2 months: AST, ALT, FLP. Generally treat to LDL < 130.
   - Once on stable dose, FLP, AST, ALT q 6 months

Eur Heart J. 2015;36:2425-2437 and personal practice.

Diagnosis: FH

One evidence-based approach to treatment.

6. Screen potentially affected family members, refer if needed!
7. Pregnancy risk considerations (when applicable)
   - FDA recommended "X" warning be removed in 2021, still advise "most pregnant patients should stop taking statins".
   - What I do: counsel and recommend contraception but I do not require it. Educate.
8. Referral to specialist appropriate when:
   - LDL > 500 mg/dL at any time, or >130 mg/dL on treatment
   - Any question of statin intolerance
   - Clinician is not comfortable diagnosing FH or prescribing statins

Eur Heart J. 2015;36:2425-2437 and personal practice.

What about high LDL that's not FH?

Need for statin therapy depends on **degree of LDL elevation** and **presence of other risk factors**.

High Risk

- Kawasaki (with aneurysms)
- Type 1 or 2 diabetes
- End-stage kidney disease
- Solid organ transplant recipient
- Stem cell transplant survivor

Can manifest *overt coronary artery disease* before 30 years old

Moderate Risk

- Elevated Lipoprotein (a)
- Hypertension
- Cancer survivor (chest radiation)
- BMI ≥ 120% of 95%ile
- Coarctation of the aorta
- CKD stages 1-4

Can manifest *significantly accelerated atherosclerosis* before 30 years old

Circulation 2019;139:e603-e634.

Elevated LDL: WHEN to treat

<u>LDL >190</u> with no risk factors (this is FH!).

<u>LDL 160-189</u> with:

- + Family history (this is FH!) OR
- 1 high-level risk factor OR
- At least 2 moderate-level risk factors

<u>LDL 130-159</u> with:

- 2 high level risk factors OR
- 1 high level + two moderate risk factors OR
- Clinical evidence of CV disease

The vast majority of children treated with a statin have LDL ≥ 160 after lifestyle treatment has been maximized.

Circulation 2019;139:e603-e634.

Take-Home Point #1

The purpose of cholesterol screening in childhood is to IDENTIFY and TREAT children with GENETIC dyslipidemia that predisposes them to premature heart disease.

www.thefhfoundation.org

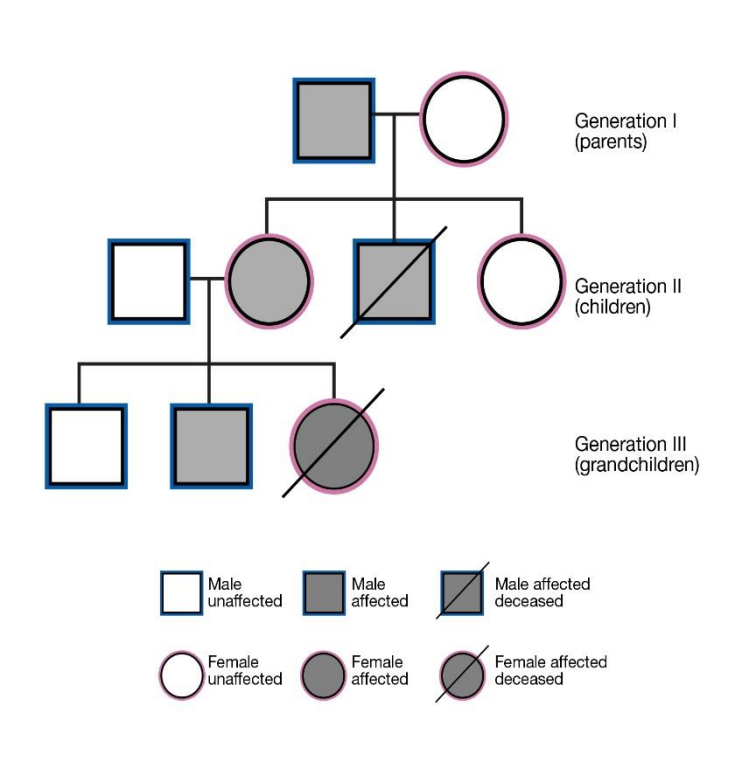
Take-Home Point #2

The kids who have dyslipidemia due to obesity are not the kids who need lipid lowering medications. *Usually*.

Please note:
Pediatric obesity is unfortunately so common that kids with genetic dyslipidemia may also have obesity.

Take-Home Point #3

If you do not check for dyslipidemia, I guarantee you will miss it.



- By diagnosing the *child*, you can diagnose the *family*.
- The life you save may not be your (pediatric) patient's.