



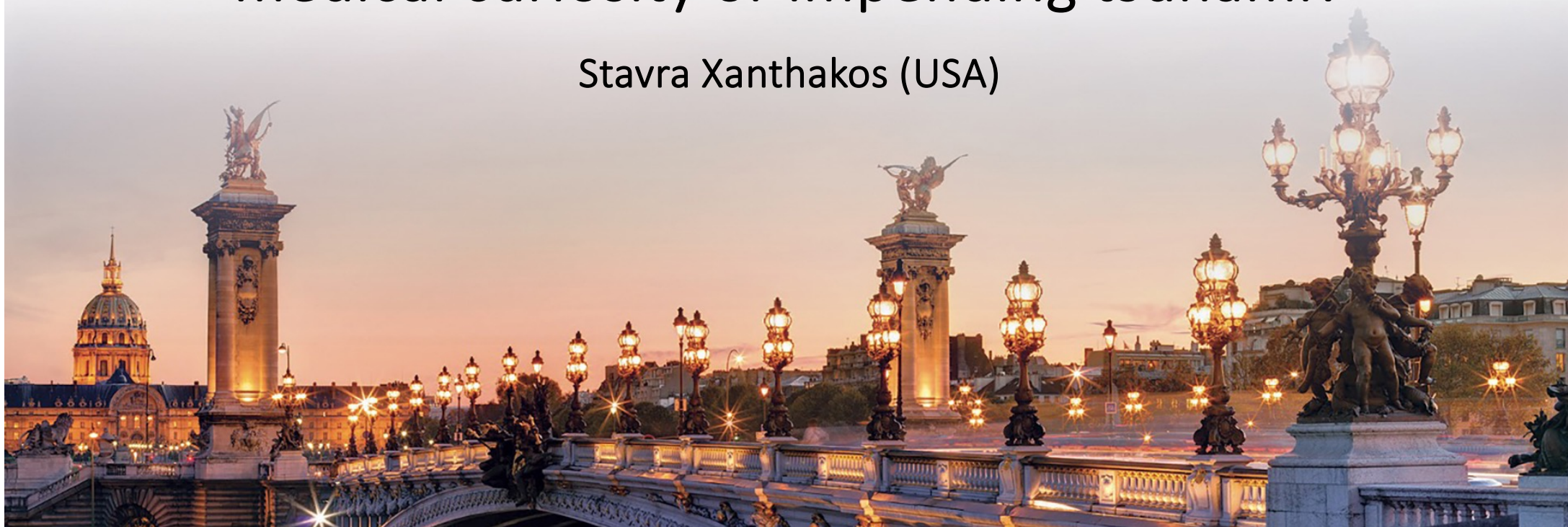
Paris
NASH
Meeting

September 7 & 8, 2023

9th edition

NAFLD in children less than 5 years old: medical curiosity or impending tsunami?

Stavra Xanthakos (USA)





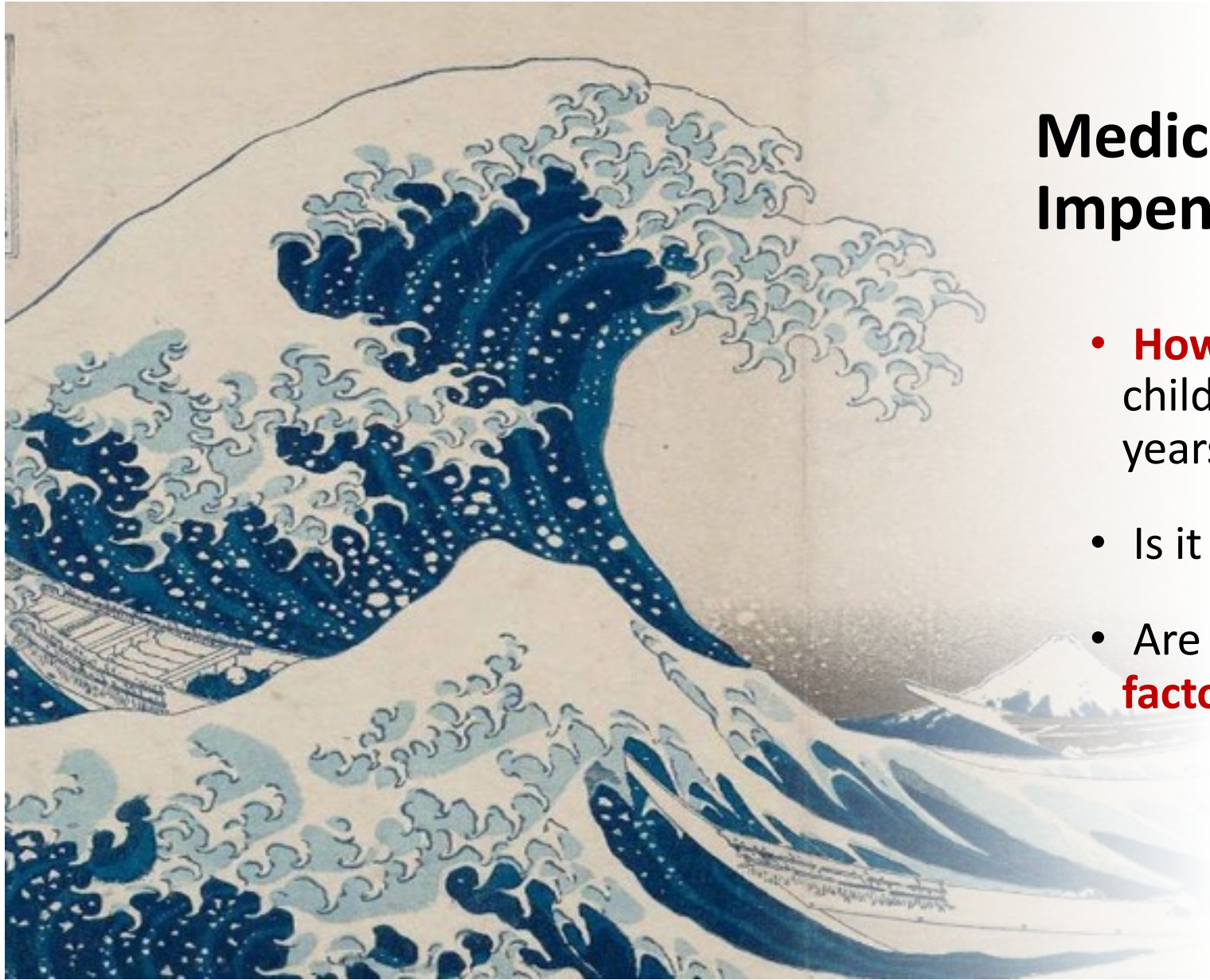
Paris
NASH
Meeting

Conflict of interest disclosure

Research Funding to Institution

- TargetRWE
- NIDDK NASH Clinical Research Network





Medical Curiosity or Impending Tsunami?

- **How common** is NAFLD in children younger than 5 years of age?
- Is it a **clinical concern**?
- Are there **early life-risk factors**?

All data predate 2023 nomenclature change

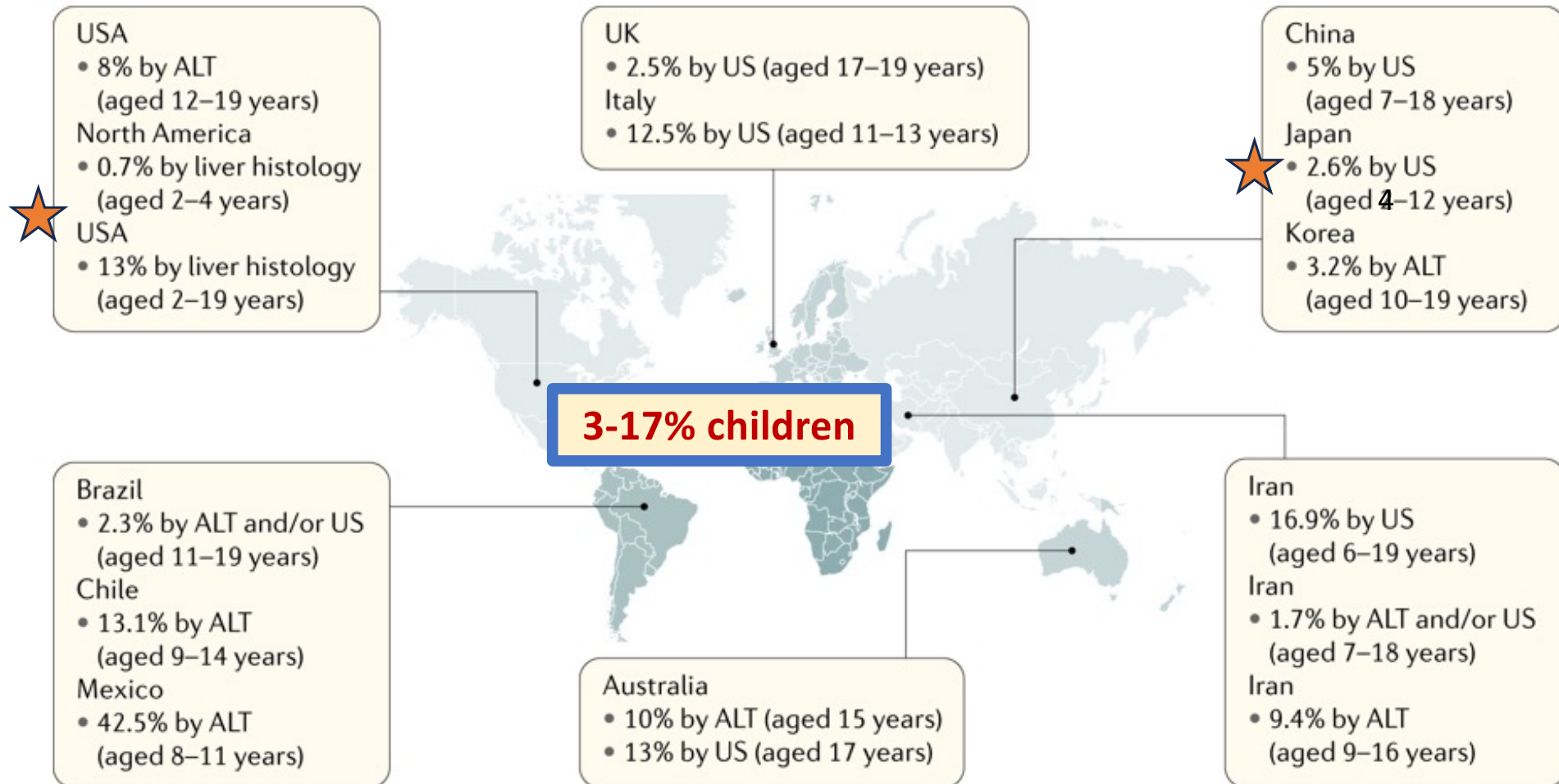


Metabolic Dysfunction-associated Steatotic Liver Disease (MASLD)

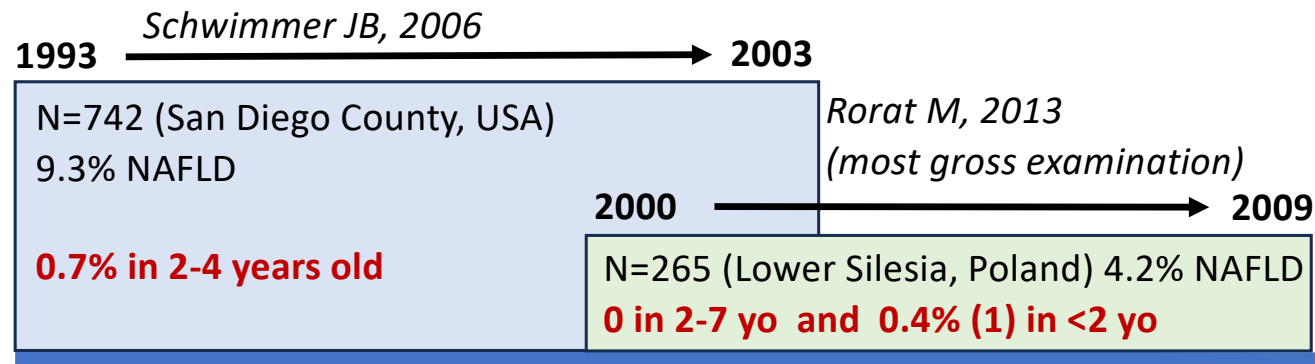
- ✓ Steatosis by imaging or biopsy (exclusion of other causes)
- ✓ ≥ 1 cardiometabolic factor

↑ ALT not required

Most epidemiology studies of NAFLD ≥ 6 years of age



Autopsy studies*: <1% in children <5 years old



?

2010-2020s

Comparable low prevalence despite:

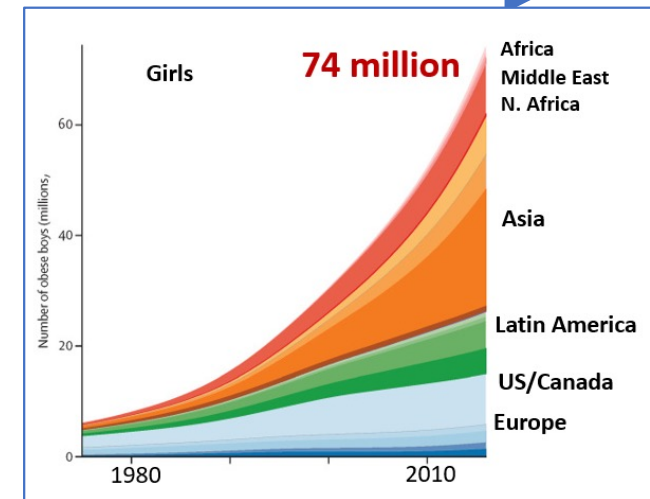
- Varied prevalence of overweight/obesity: 17% (Poland), 20% (Turkey), 42% (San Diego)
- Varied prevalence of NAFLD (4.2% to 9.3%)

No mention of severe disease in early cases

n=330 (Turkey)
6% NAFLD

0.9% in 2-4 yo

2006 → 2008
Yuksel F, 2012

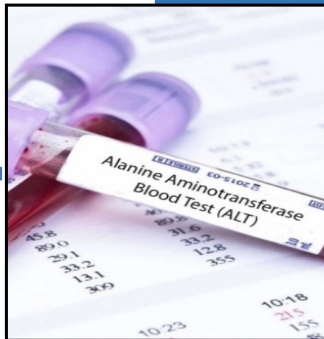


*Majority due to trauma/accidents

Prevalence: more recent studies



Incidental steatosis in children undergoing imaging for other indications



Screening for NAFLD in children with **overweight or obesity**

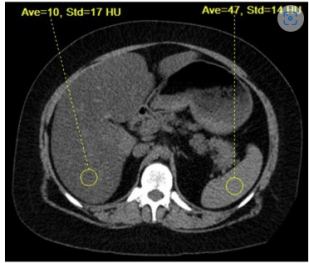
Prevalence: more recent studies



Incidental steatosis in children undergoing imaging for other indications



Screening for NAFLD in children with **overweight or obesity**



Abdominal CT exams due to trauma (Toronto, Ontario, Canada)

2004-2015, N=503 children

- Ages 1-17 years (mean 9.5 ± 4.5)
- Mean weight z-score 0.37 ± 1.05 (**no height available**)
- 17% had hepatic steatosis overall (same across sex or age quartiles)

17% prevalence in children <5.7 years of age

- Most (>87%) had **↑ ALT**
- Associated with **↑ subcutaneous adiposity**, but not visceral adiposity



Ultrasound exams at large tertiary hospital (Cincinnati, Ohio, USA)

Jan- Aug 2022, N=187 children, unselected sample

- **All < 4 years old** (median 1.1 years, IQR 2.1 years)

8% prevalence by ↑ Hepatorenal Index >1.75

- 6% prevalence in < 2 years old

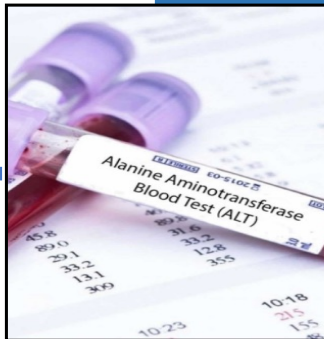
14% prevalence of qualitative steatosis

Higher prevalence if overweight/obese: 19% vs. 5%

Prevalence: more recent studies



Incidental steatosis in children undergoing imaging for other indications

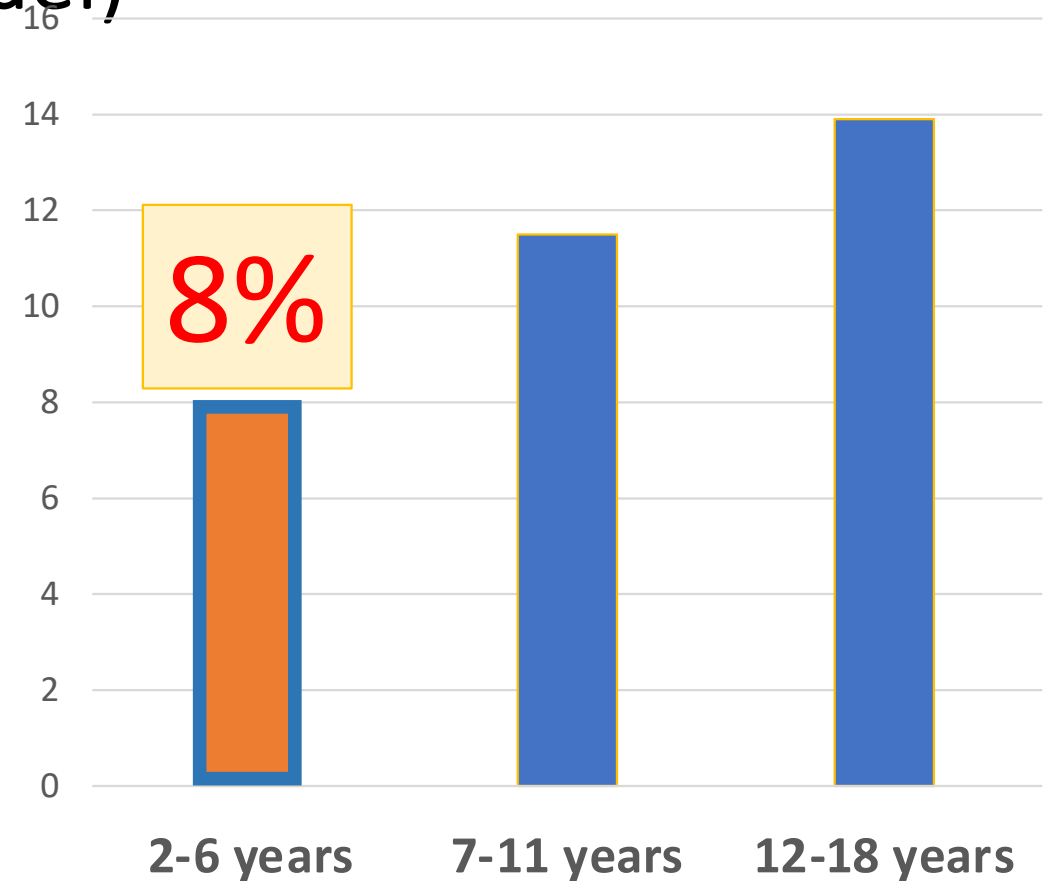


Screening for NAFLD in children with **overweight or obesity**



↑ ALT prevalence: Children with overweight and obesity in health maintenance organization (Israel)

- 2015-2017
- 63,766 children with overweight and obesity, 2-18 years old
 - Excluded celiac, HBV, HCV, CF and Wilson disease
 - 12,250 were 2-6 years old
- 12.7% overall had ALT >30 U/L





Children with overweight in primary care (Rome, Italy)

2011-2012: n=597 overweight or obese children, ages 2-6 years,
seen at 13 primary care practices

219 had ultrasound screening

31% liver steatosis by ultrasound

Mild 88%

Moderate 12%

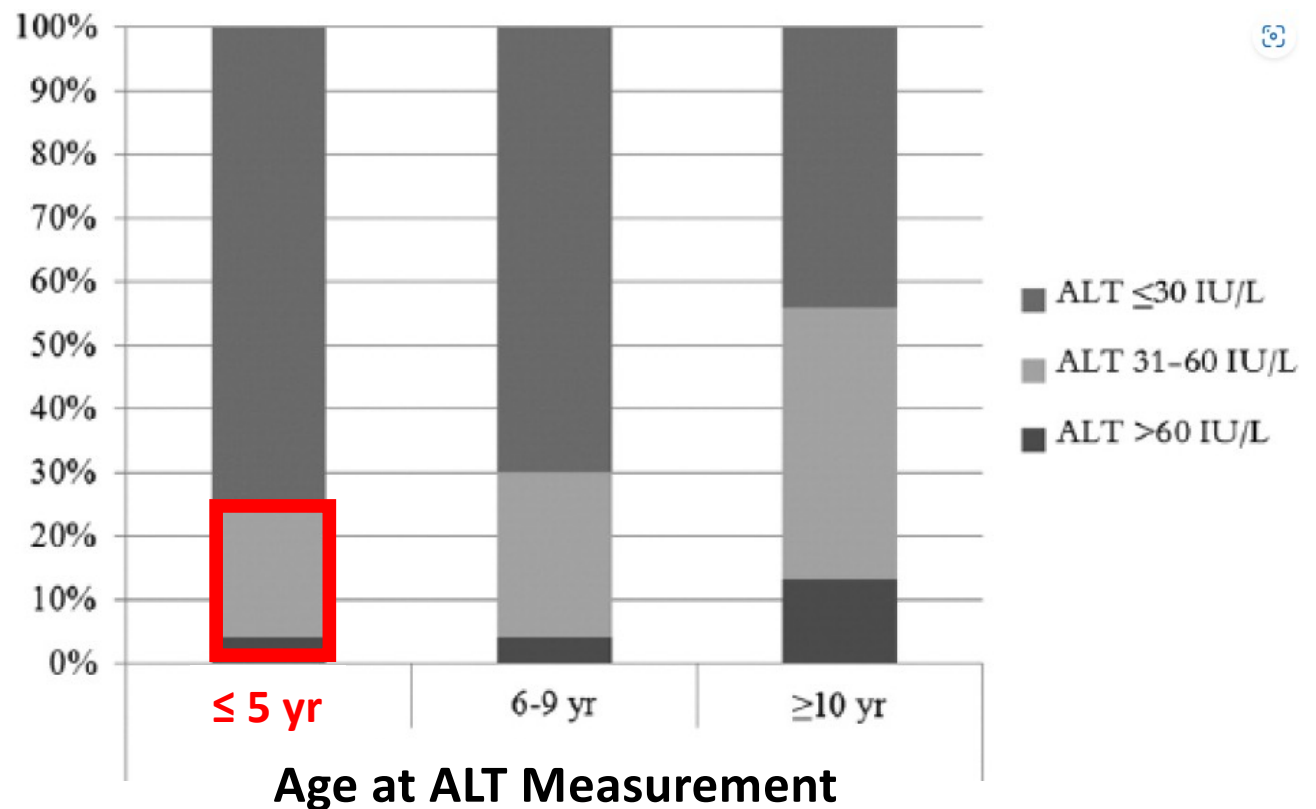
- Insulin resistance in 33%
- Hypertension in 13%
- Dyslipidemia in 25%



↑ ALT prevalence: **pediatric weight management program** (Chicago, USA)

- 2007-2010
- Tertiary program,
n=73/284, 2-5 years old
 - primarily Hispanic,
 - severe obesity

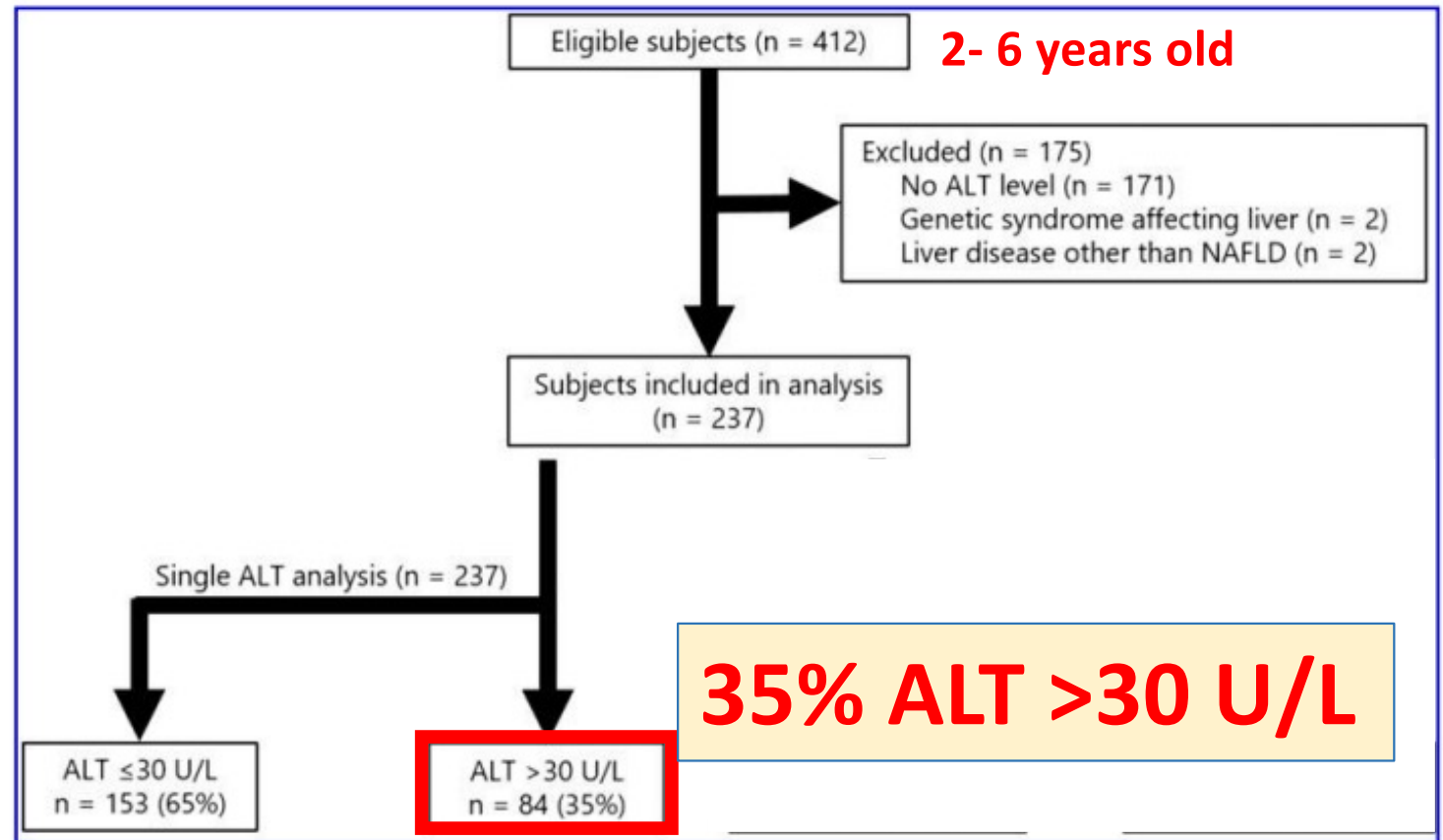
26% ALT>30 U/L





↑ ALT prevalence: **pediatric weight management program 2010-2020** (Cincinnati)

- CV risk factors did not differ between those +/- ↑ALT (predates onset of CV risk?)
- Only 7% had evaluation for other causes



Summary of reported prevalence in children <5 years old: imperfect estimates

Autopsy
(1993-2009)

- <1% (Regional studies)

Incidental imaging
(2006-2022)

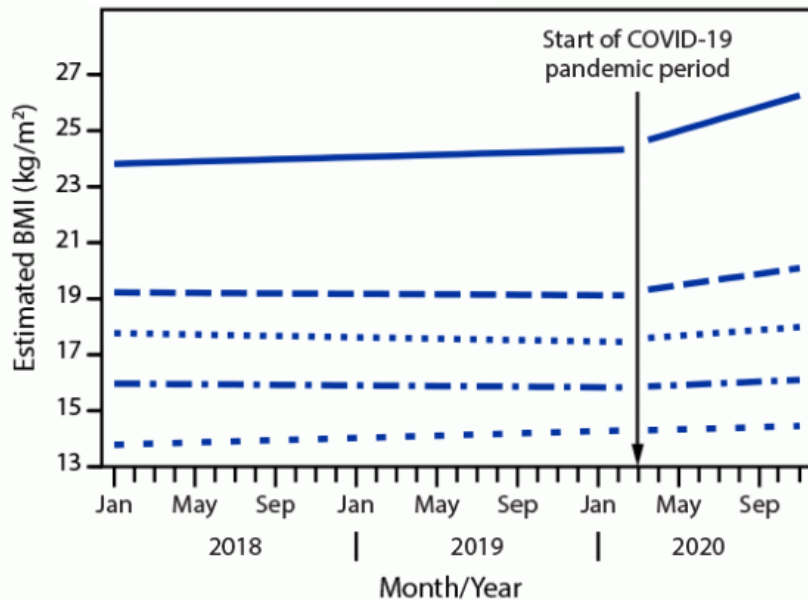
- 8-17% by CT or US (Single center studies)

**Overweight/
Obesity**
(2010-2020)

- 31% by US (Regional)
- 8-35% by ALT (Single center, 1 population-based)

Effects of COVID Pandemic ...

3-5 year olds



thebmj

NEWS

Montreal
Cite this as: *BMJ* 2021;374:n2332
<http://dx.doi.org/10.1136/bmj.n2332>
Published: 21 September 2021

Obesity in US children increased at an unprecedented rate during the pandemic

Owen Dyer

The proportion of US children who are overweight or obese, which has climbed steadily for years, surged to unprecedented levels during the pandemic, according to new figures from the Centers for Disease Control and Prevention (CDC).¹

The four new states with over 35% obesity are Delaware, Iowa, Ohio, and Texas. They join Alabama, Arkansas, Indiana, Kansas, Kentucky, Louisiana, Michigan, Mississippi, Oklahoma, South Carolina, Tennessee, and West Virginia.

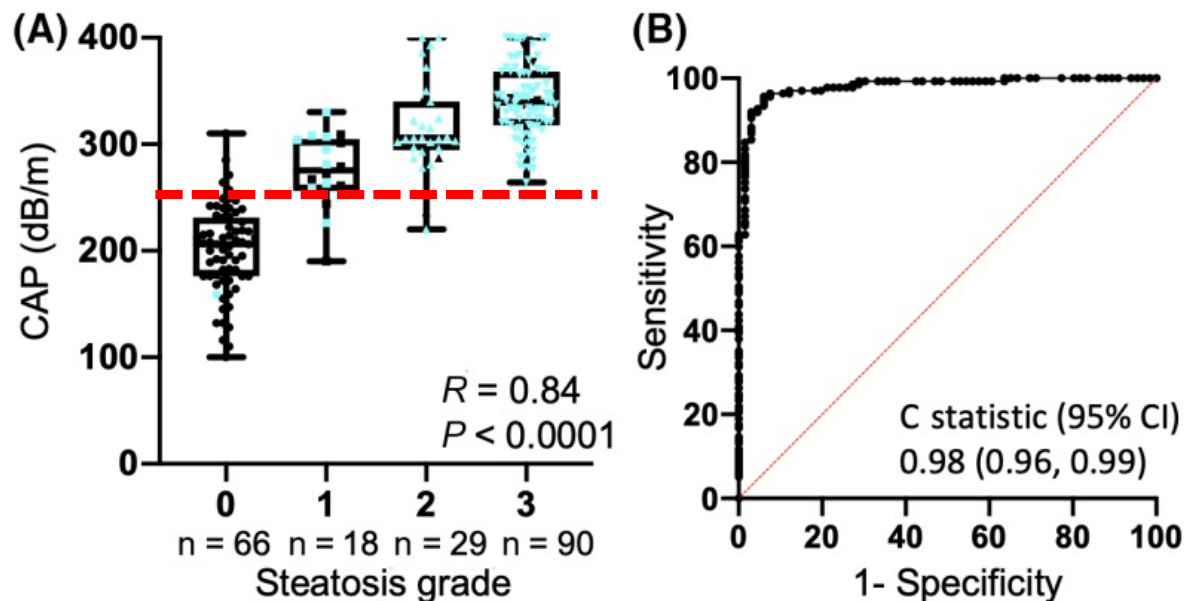
Lange SJ, et al. MMWR Morb Mortal Wkly Rep 2021.

↑pediatric obesity in
USA: 19.3 → 22.4%
in 1 year

Limitations of current screening

- **ALT** – inexpensive, but normal in $\approx 25\%$ of children with steatosis
 - **MRI-PDFF** – most accurate but expensive, sedation in very young
 - **Ultrasound**- not sensitive for lower ranges of steatosis
 - **VCTE – relatively inexpensive, point of care**
- Feasibility?**
Validity?

Fibroscan® CAP scores in children with chronic liver disease evaluated in hepatology clinic (Colorado, USA)

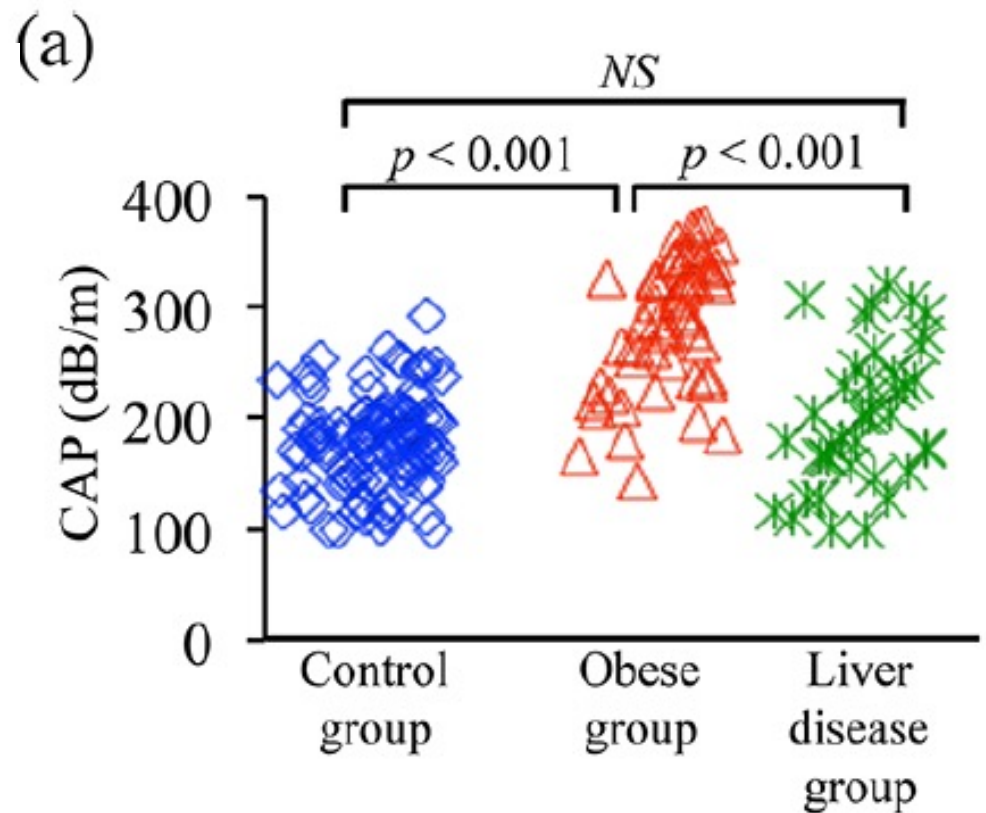
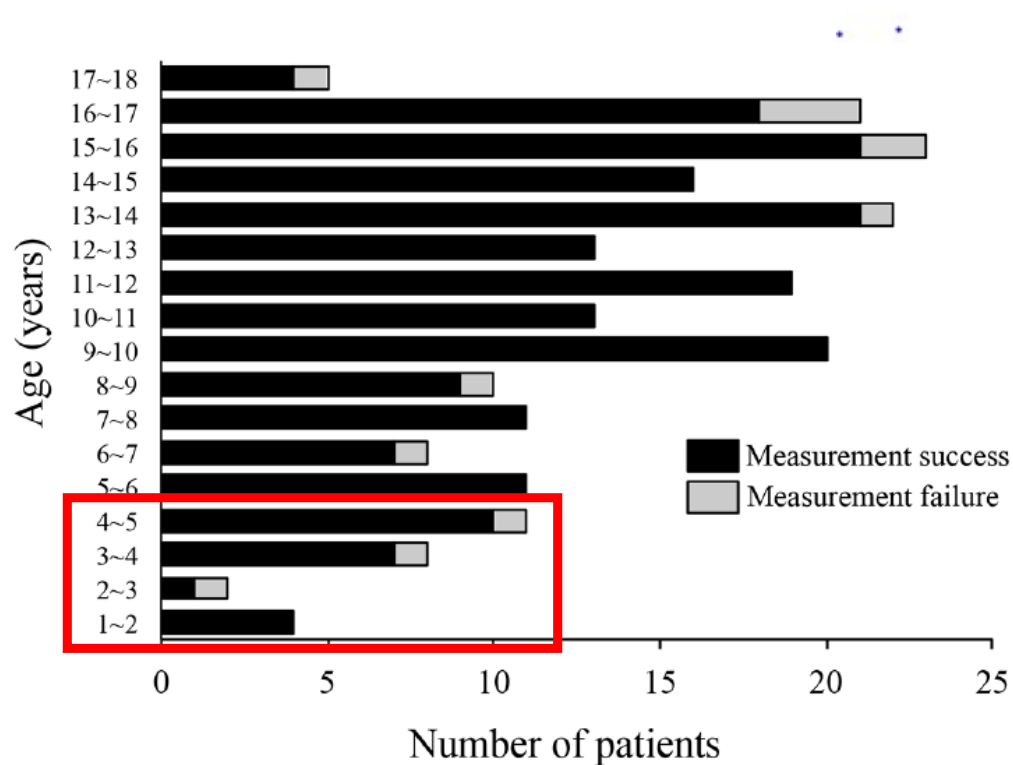


116 NAFLD (biopsy)
90 non-NAFLD disease
Mean age 13.7 ± 3.7

**CAP ≥ 259 dB/m detected
steatosis \geq grade 1**

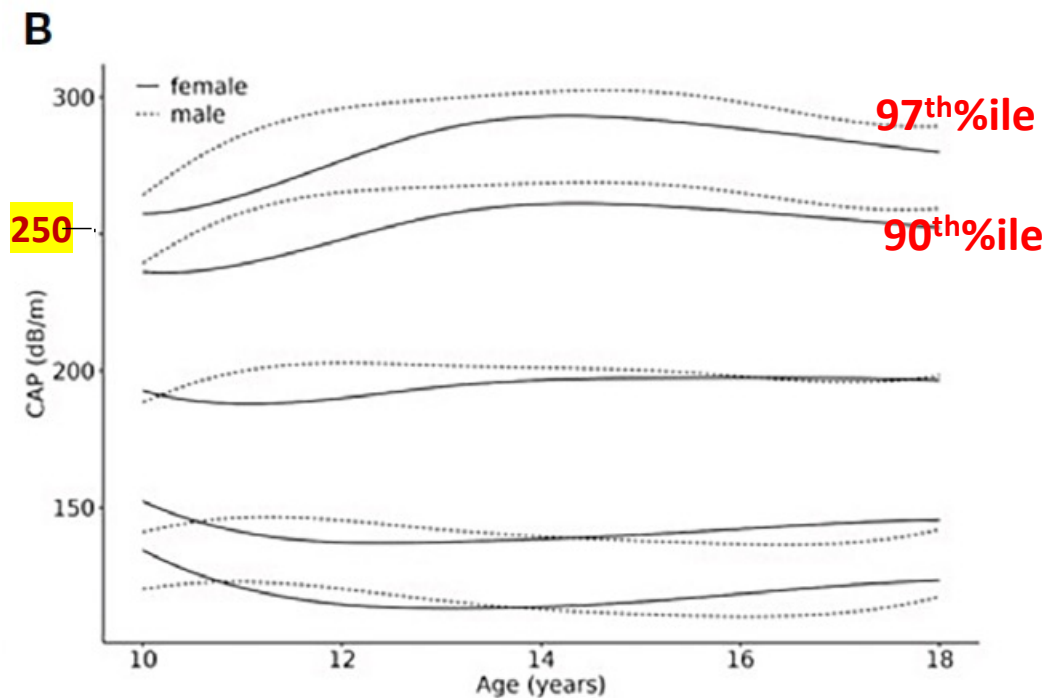
sens 94%, spec 91%,
PPV 97%, NPV 91%

VCTE feasible in young children <5 years old



Reported CAP ranges in healthy normal BMI range children

	Range of CAP scores	Median CAP
12-19 year olds (NHANES) N=462 Ramirez-Velez, 2022	150 – 245 dB/m (10 th – 90 th %iles)	199 dB/m



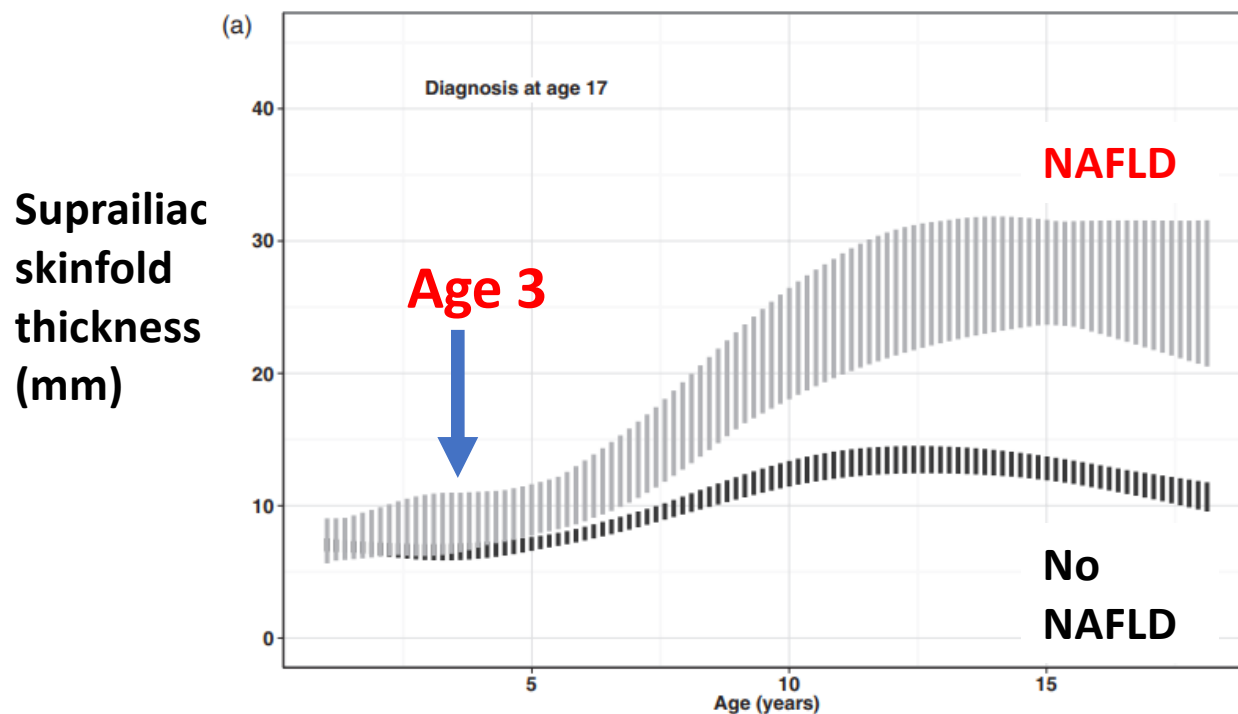
N=482, Healthy children age 10-18, BMI z score 3rd-97th%ile
Brunnert *Frontiers Endocrinol* 2022



Medical Curiosity or Impending Tsunami?

- How common is NAFLD in children younger than 5 years of age?
- Is it a **clinical concern?**
 - ❖ Autopsy studies **no severe fibrosis** in <5 year old cases
 - ❖ No longitudinal cohort studies, but...

Increased adiposity by age 3 associated with greater risk of NAFLD by age 17



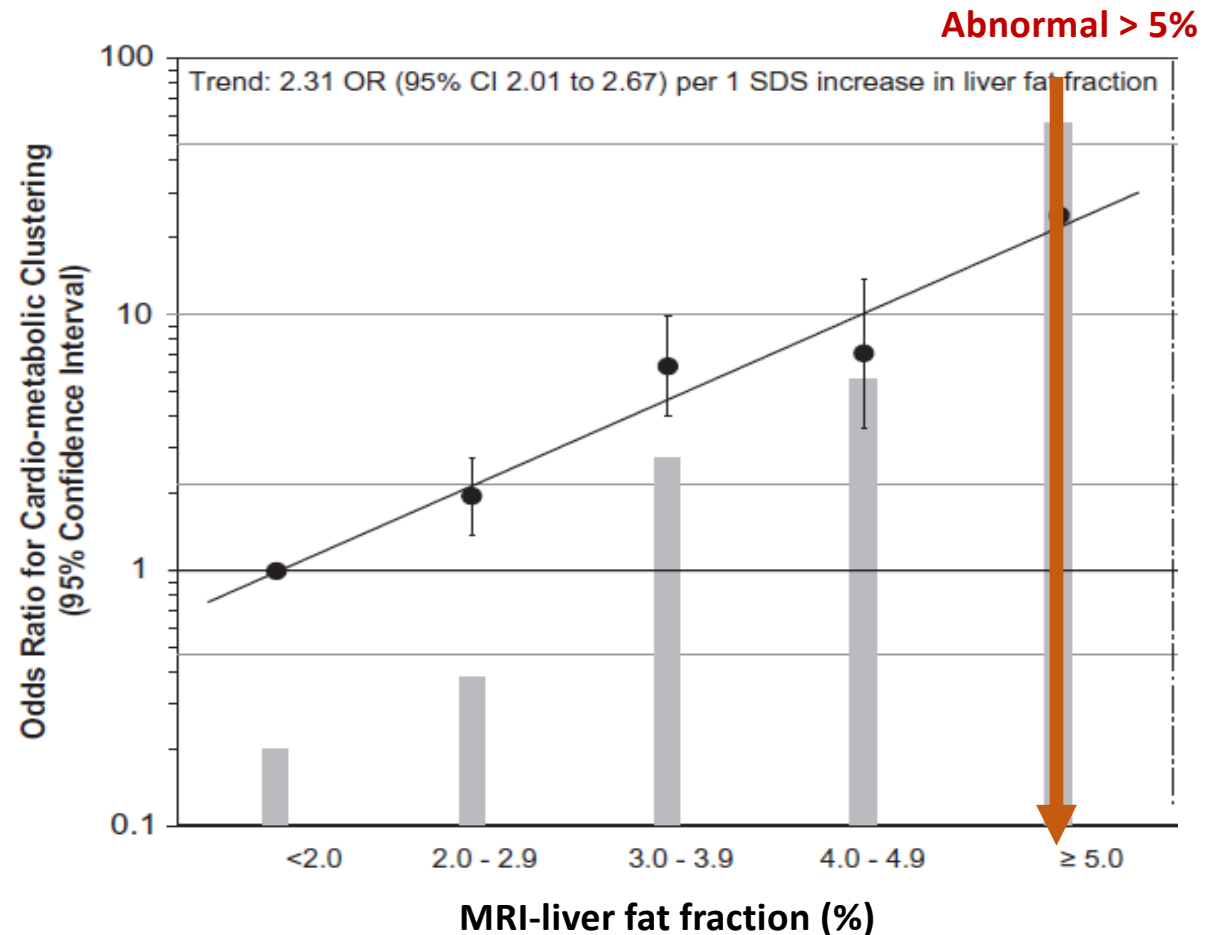
- ↑ risk of NAFLD (US)
- ↑ sonographic severity of steatosis

Even small ↑ hepatic fat among school age children associated with ↑ cardiometabolic risk

Population-based prospective cohort study in 3,170 10-year-old children

Subclinical increases in MRI-liver fat associated with:

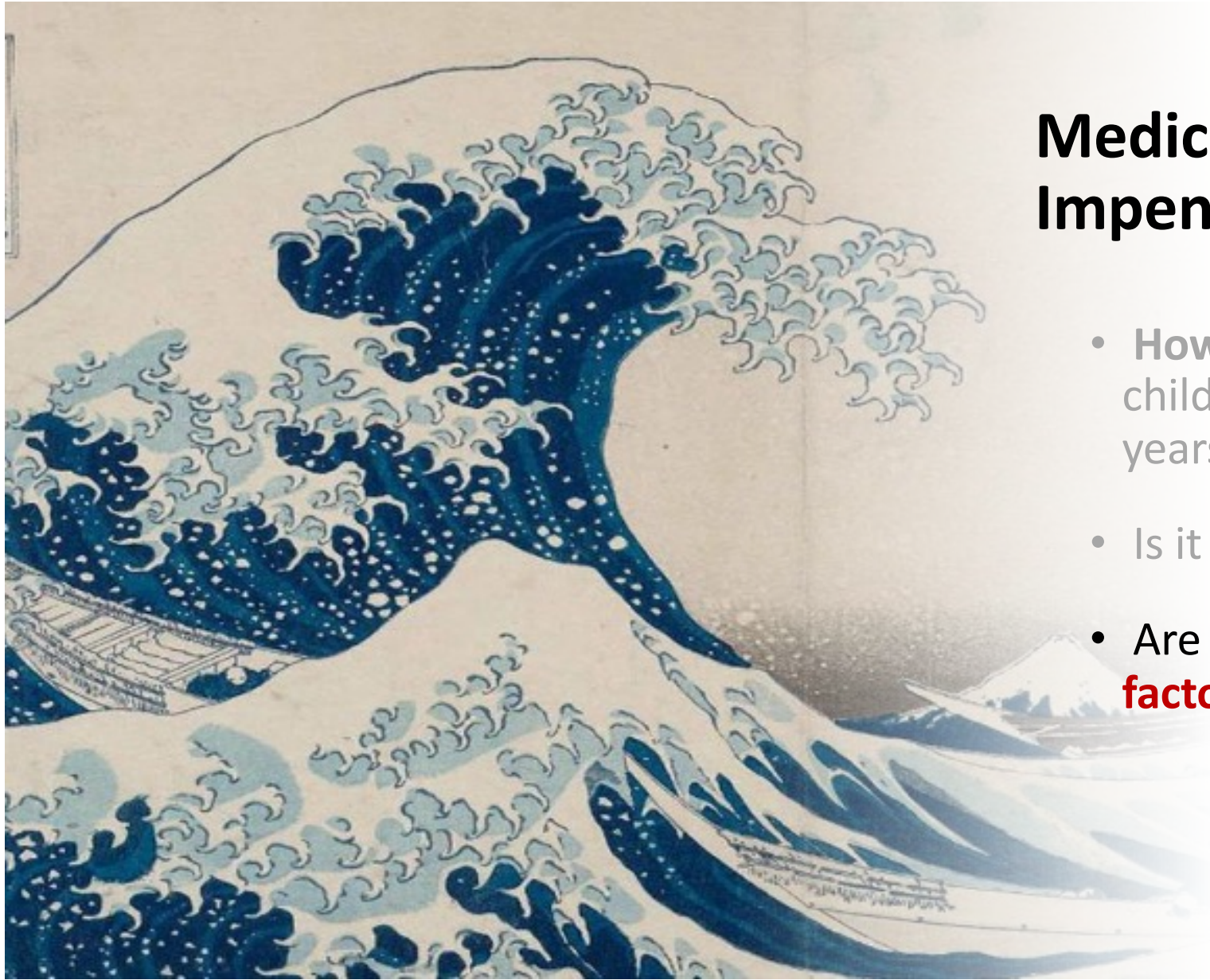
↑ visceral fat mass, blood pressure, triglycerides, insulin levels and ↓ HDL



Geurtsen ML, Santos S, Felix JF, et al. Liver Fat and Cardiometabolic Risk Factors Among School-Age Children. Hepatology 2020;72:119-29.

Increase in **fasting insulin age 3-6 associated with increased risk of T2DM** in adulthood

- **Longitudinal CV risk in Young Finns Study (n=2,478)**
 - Enrolled 3-18 years at baseline
 - Assessed for T2DM in adulthood (mean age 39.6 years)
- Among 3-6 year olds, **1 SD ↑ fasting insulin → 2-fold ↑ RR for T2DM in adulthood**
 - adjusted for BMI and parental history of T2DM



Medical Curiosity or Impending Tsunami?

- How common is NAFLD in children younger than 5 years of age?
- Is it a clinical concern?
- Are there **early life-risk factors**?



Alternate genetic causes of hepatic steatosis may be more common in young children

- In some single center studies, up to 50% of children <10 years of age with biopsy-proven steatosis had alternate cause
- **Higher index of suspicion for inborn errors of metabolism** (monogenetic causes) if:
 - Younger age
 - Normal anthropometric measurements (normal BMI, no visceral adiposity)
 - + family history
 - Other systems involved (neurodevelopmental delay, seizures)
 - Consanguinity of parents

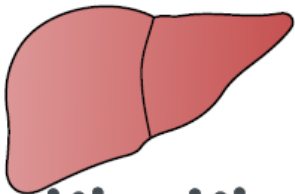
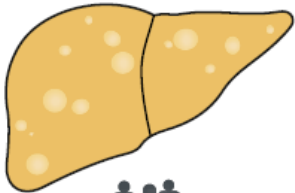
Nur Karhan A Pediatr Gastroenterol. Hepatol Nutr 2021;24:518

Mogahed EA. Eur J pediatr 2020;1799:719

Maternal obesity independent risk factor for confirmed NAFLD in children < 25 years of age

Hagstrom H. Journal of Hepatology 2021;75:1042

Biopsy-proven
NAFLD, Sweden,
1998-2016



**Supported by systematic
review (8 studies)**

Quarter I. Clinical gastroenterol Hepatol 2022;20:740

Endocrine disrupting chemical (EDC) exposure across the lifespan (ubiquitous, bioaccumulate)

- **Oral, dermal or inhalation:** food, drinking water, household dust, personal care or consumer products
- **Infants and young children at higher risk for EDC exposure**
 - Breastfeeding
 - More hand-to-mouth activity
 - Higher contact with soil and dust
 - Increased dietary intake per unit body mass



EDCs can mimic endogenous hormones and bind to membrane or nuclear receptors altering signal transduction

- Thyroid homeostasis
- Estrogenic & androgenic hormones
- Metabolism
- Fat storage
- Bone development
- Immune system

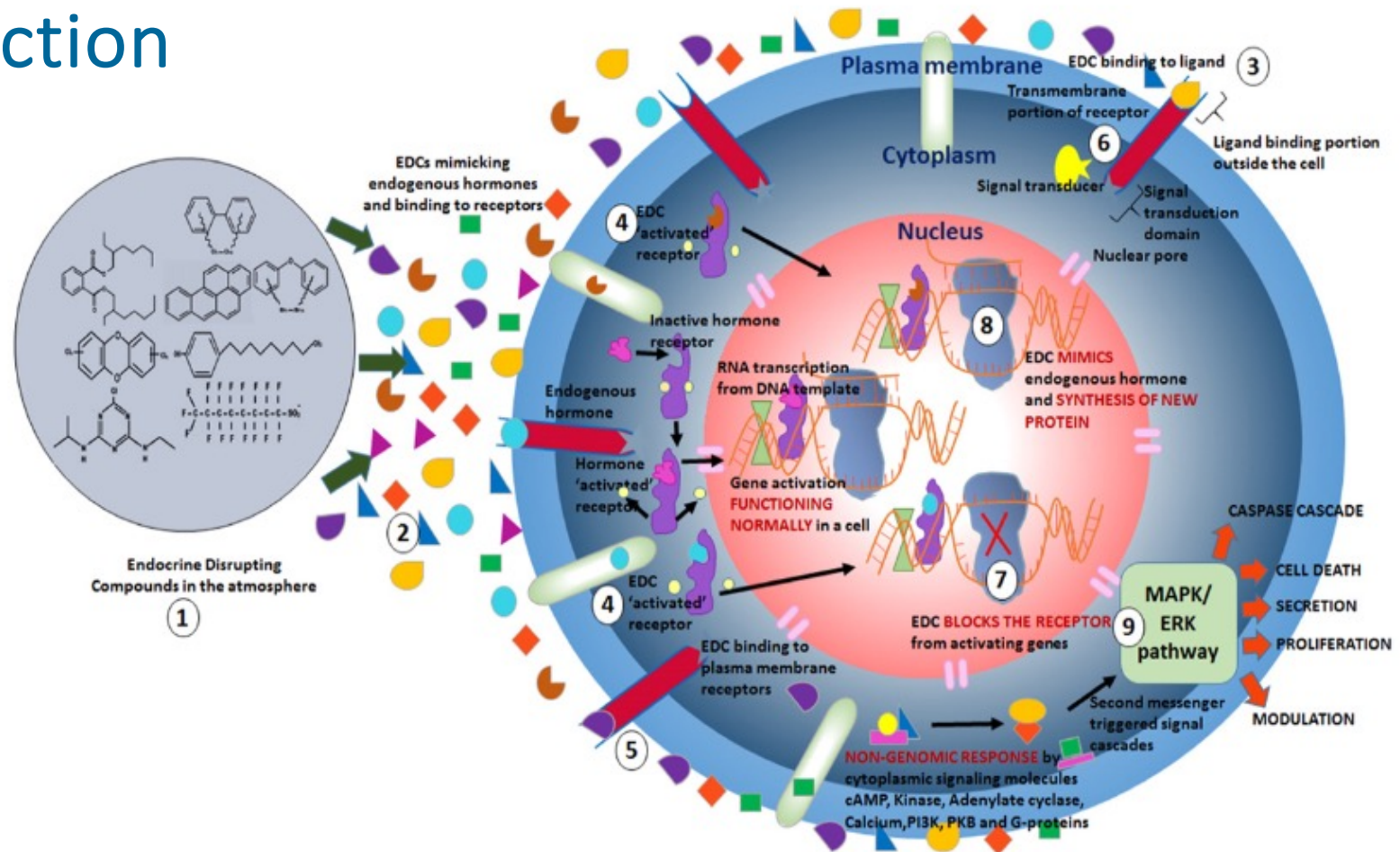
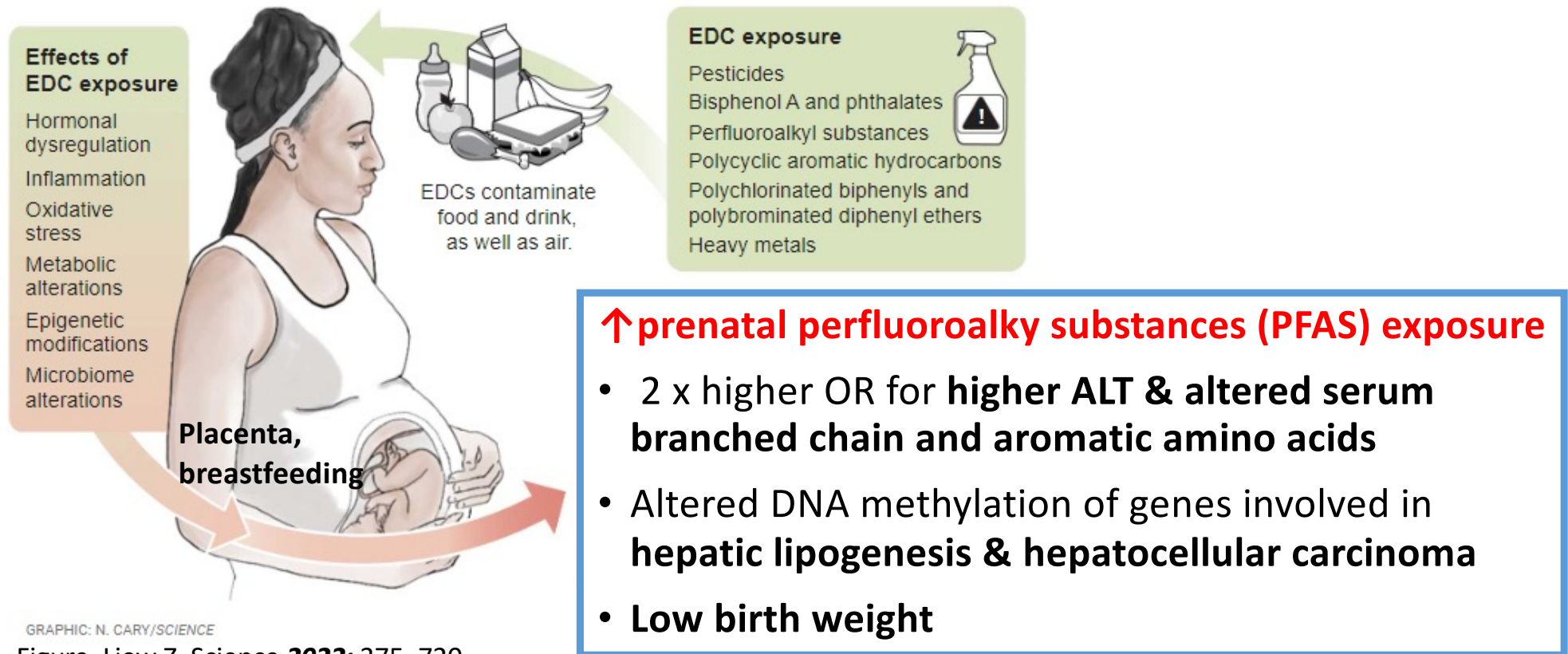


Fig 5. Annamalai J. Environment International 2015;76:78

Prenatal exposure to EDC increases risk in offspring



GRAPHIC: N. CARY/SCIENCE

Figure. Liew Z. Science **2022**; 375, 720

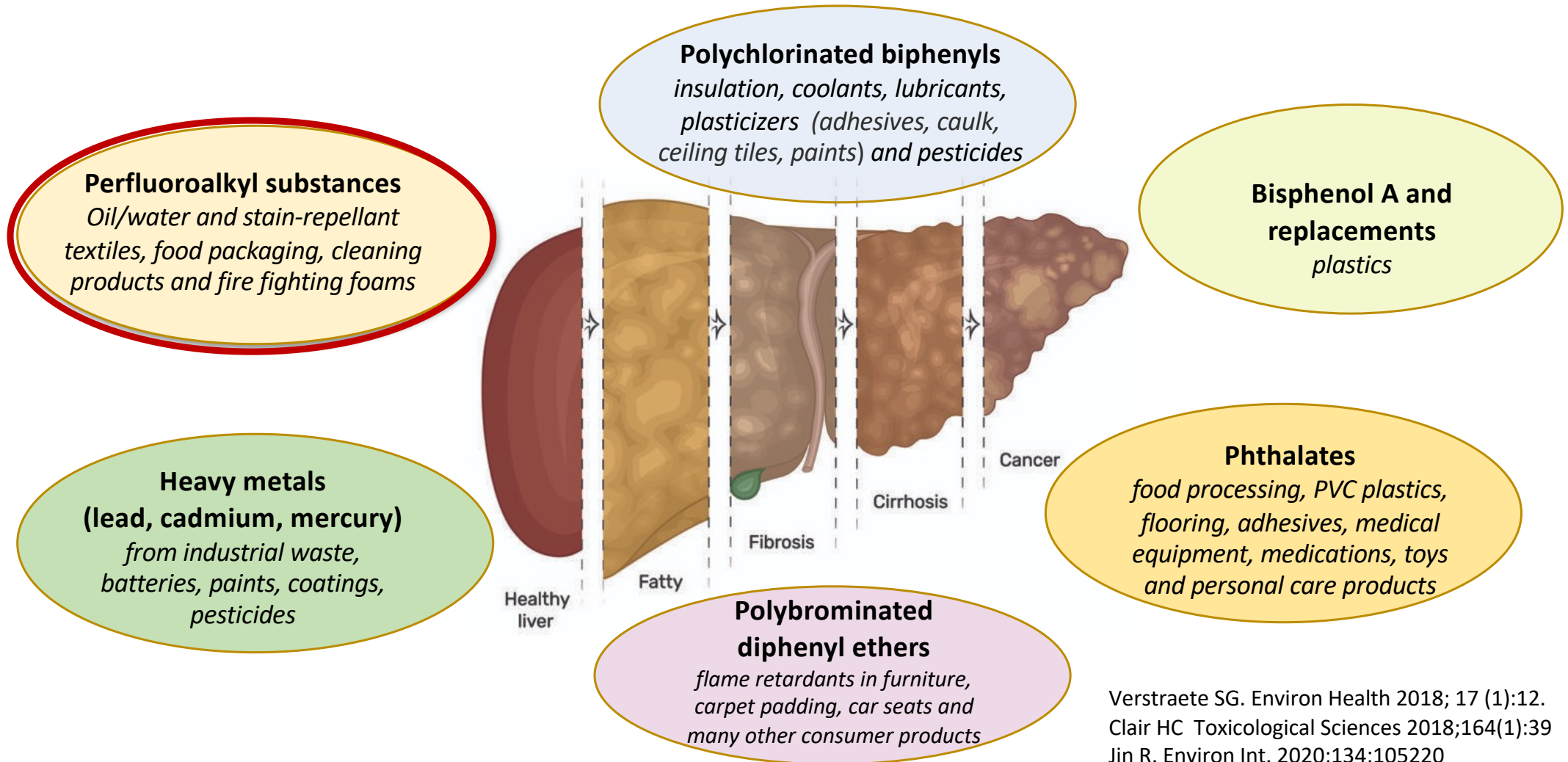
Padula M. Environ Health Perspect 2023

Stratakis N. Hepatology 2020.

Kingsley SL. Environ Res 2017;158:174-8.

Lin H. J Cancer 2018;9:2116-22.

Multiple EDCs of concern in NAFLD pathogenesis



Verstraete SG. Environ Health 2018; 17 (1):12.
Clair HC Toxicological Sciences 2018;164(1):39
Jin R. Environ Int. 2020;134:105220

Summary

- Limited data **suggest comparable prevalence of NAFLD in children < 5 yrs old** (8-17% all, 35% if overweight/obesity)
- No direct studies but **indirect data suggestive of ↑adverse outcomes** later in life
- **Maternal, genetic and environmental risk factors** likely contributing to early onset of NAFLD/MASLD

