Nonalcoholic Fatty Liver Disease

Nutrition as cause and cure

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changing the outcome together

Disclosures

- No relevant conflicts to disclose
- I receive research funding from:
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  - TargetPharmasolutions
  - AxcellaHealth

Objectives

- **Recognize global health burden and adverse health outcomes of NAFLD**
- **Understand nutritional risk factors contributing to development of NAFLD**
- **Review evidence behind nutritional interventions for children with NAFLD**

NAFLD Terminology

≈ 10% in US Children
≈ 26-30% in obese children

Nonalcoholic Fatty Liver Disease (NAFLD)

Fatty infiltration of the liver > 5% by imaging or histology
No significant alcohol intake
No genetic or storage disease
No medications that cause steatosis

≈ 25% of children with NAFLD

NAFL (Fatty Liver)
Bland steatosis ± mild inflammation

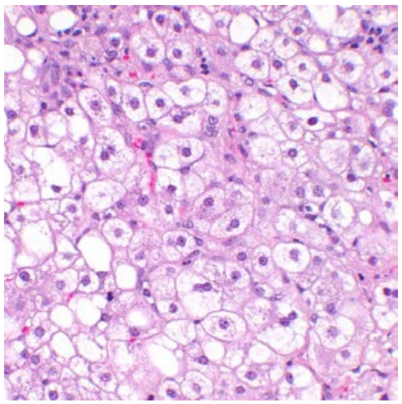
NASH (Nonalcoholic steatohepatitis)
Steatosis with inflammation + hepatocellular injury (ballooning)

Full spectrum of fibrosis possible in both NAFL and NASH

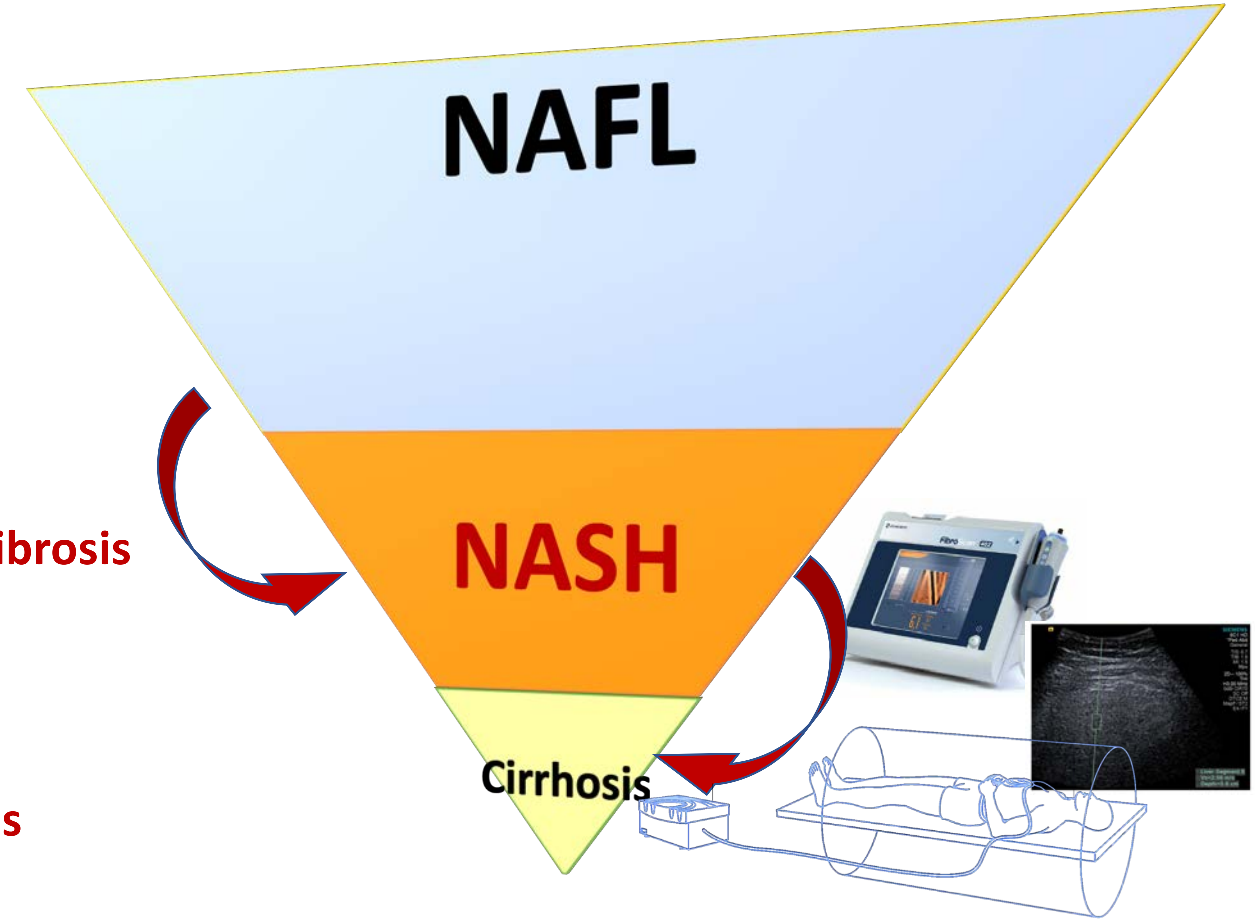
None → Mild → Moderate → Severe

Vos MB et al. JPGN 2017;64:319-334

2019: Histology still gold standard for grading and staging severity



- Patterns and staging of **early fibrosis**
- Degree and pattern
  - hepatocellular injury
  - inflammation
- **Responses to Rx/interventions**



Unique pediatric pattern: Zone 1 pattern

Classic "adult" pattern – Zone 3 centered

Steatosis

+

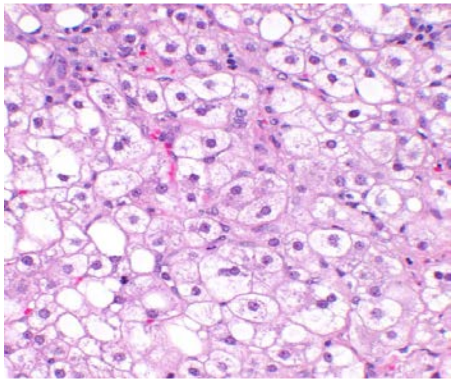
Lobular inflammation

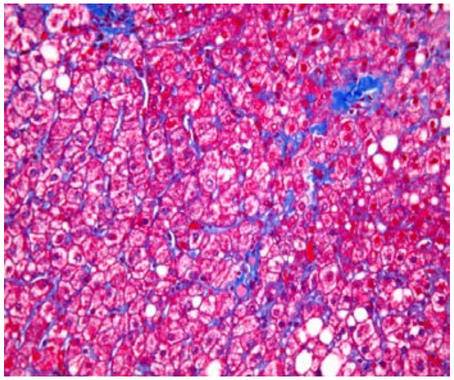
+

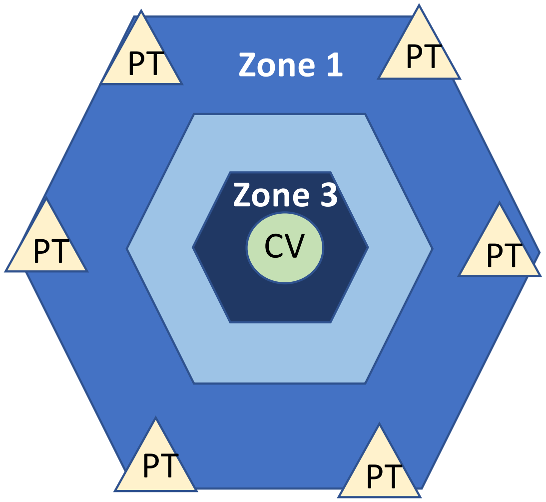
Ballooning

+/-

Perisinusoidal Fibrosis

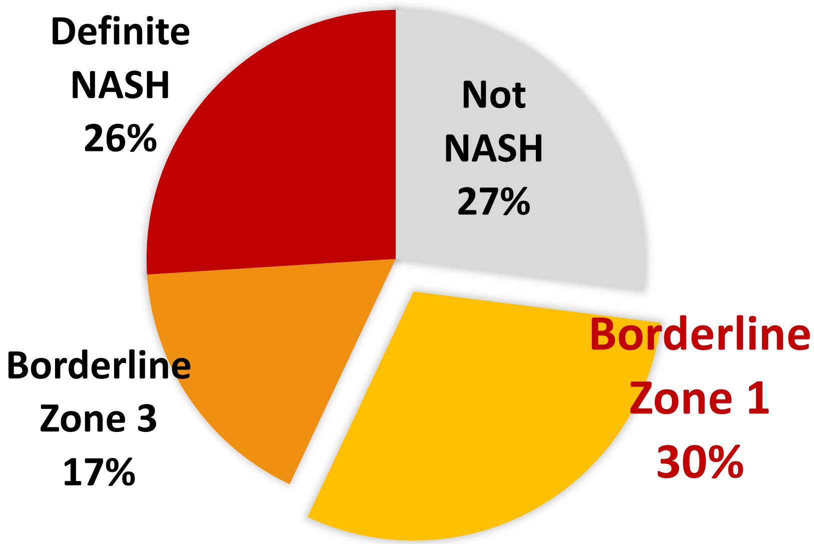


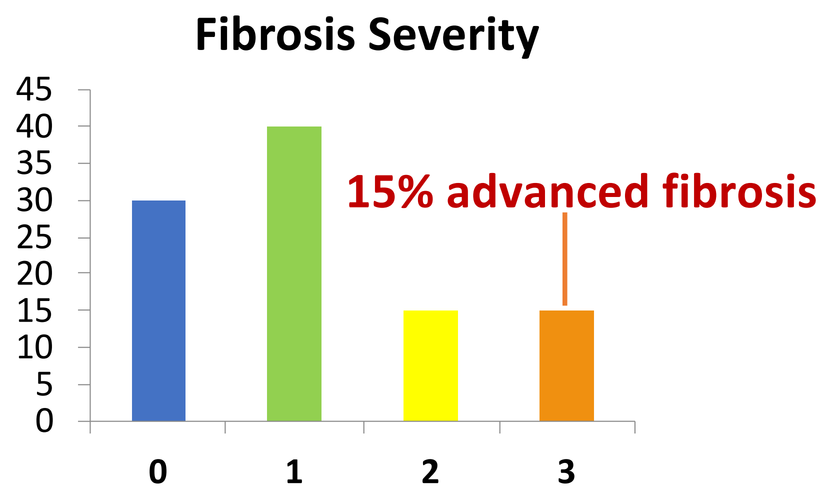




[1]Schwimmer JB. Hepatology 2005;42:641

NASH phenotypes in Children evaluated in Pediatric GI/Liver Centers (N=675 in NASH CRN)



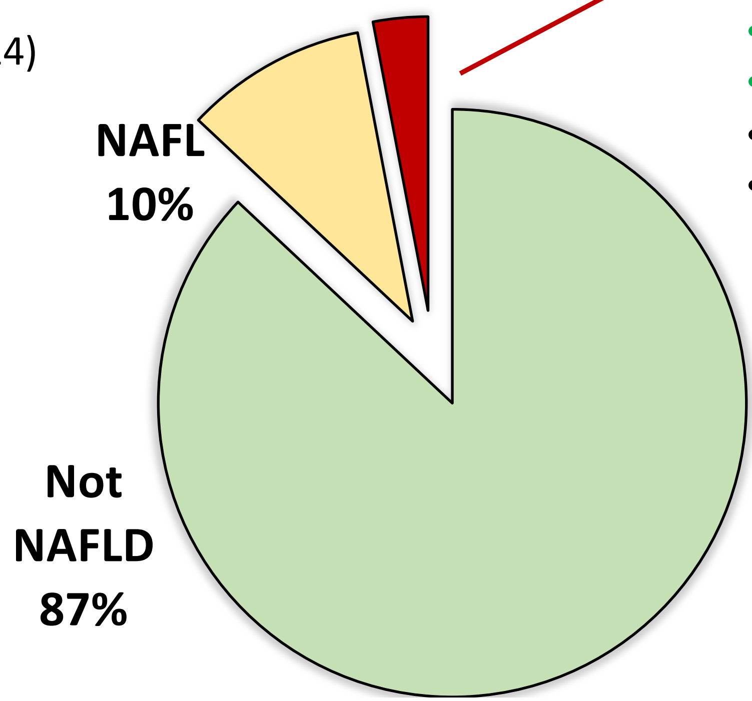


12 U.S. Centers
Mean age 12.6 years
Mean BMI 32 ± 6 kg/m^2 (z score 2.3 ± 0.4)
65% Hispanic, 28% White, non-Hispanic

[1]Newton KP et al. JAMA Pediatrics 2016

NAFLD Phenotype in Regional Pediatric Population (n=742)

2008 San Diego County autopsy study
1993-2002
Age 2-18 years (mean 14)



NASH 3% (23% of NAFLD)

- **Portal inflammation (68%)**
- **Portal Fibrosis (59%)**
- **Ballooning (18%)**
- **Perisinusoidal fibrosis (14%)**

9% ≥ stage 3 fibrosis

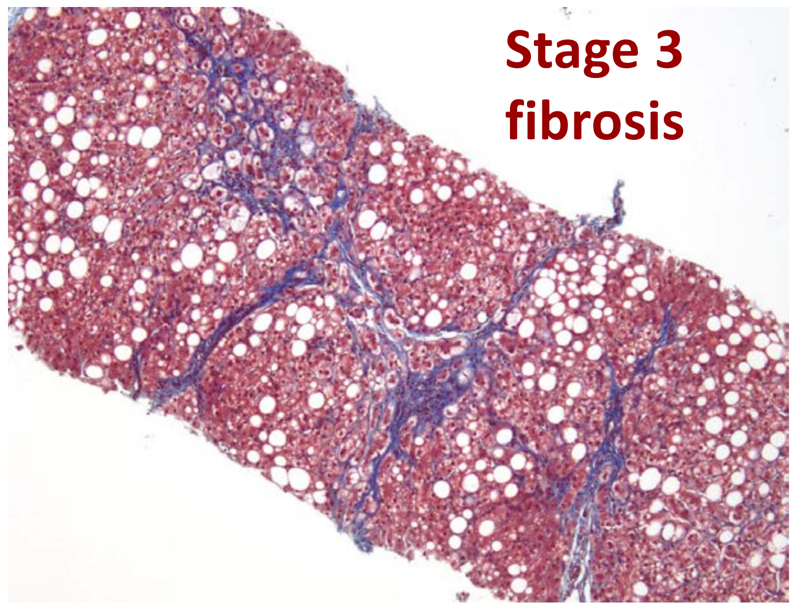
[1]Schwimmer JB. Pediatrics 2006

Some children with NASH have <u>rapid</u> progression in fibrosis with minimal to no clinical or laboratory signs

Age 11

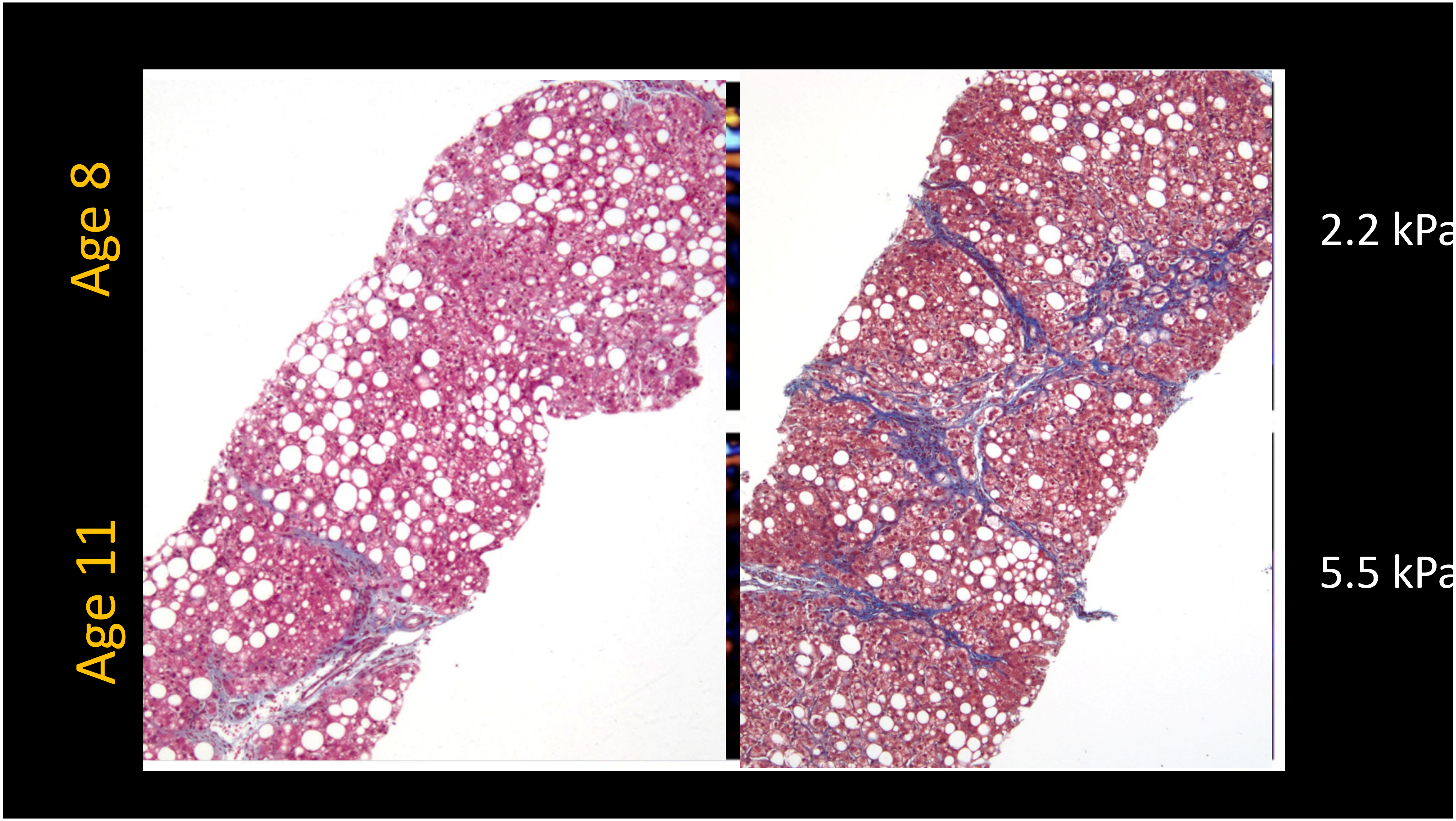
Stage 1c fibrosis

Age 16



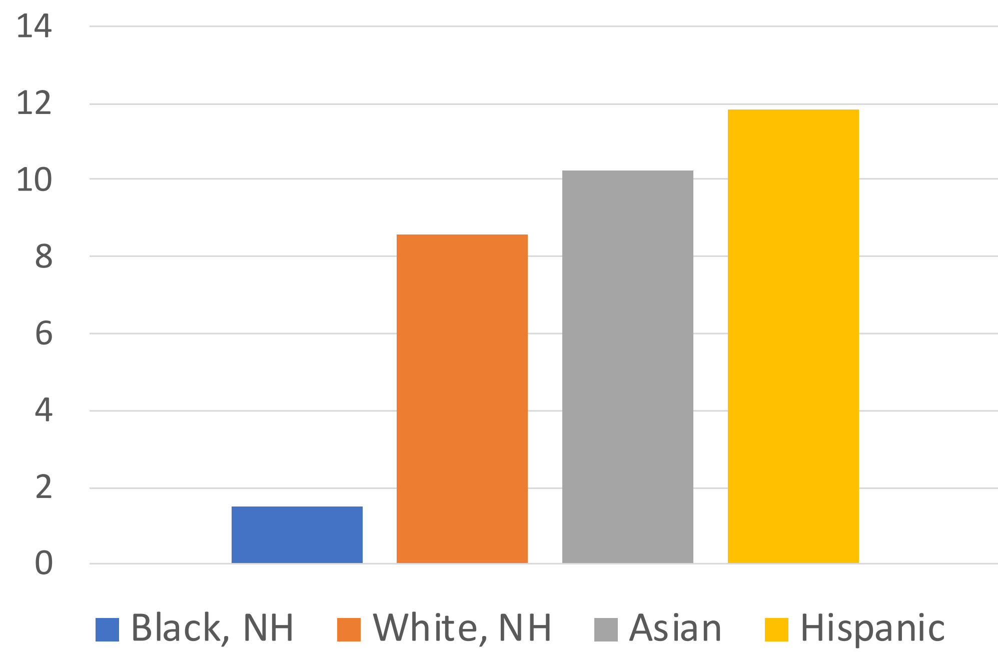
Stage 3 fibrosis

Kohli R, Xanthakos SA et al. JPGN 2009


Age 8
Age 11
2.2 kPa
5.5 kPa

Race and ethnicity influence prevalence of NAFLD

% NAFLD prevalence, San Diego autopsy study 2006



Schwimmer JB et al. Pediatrics 2006

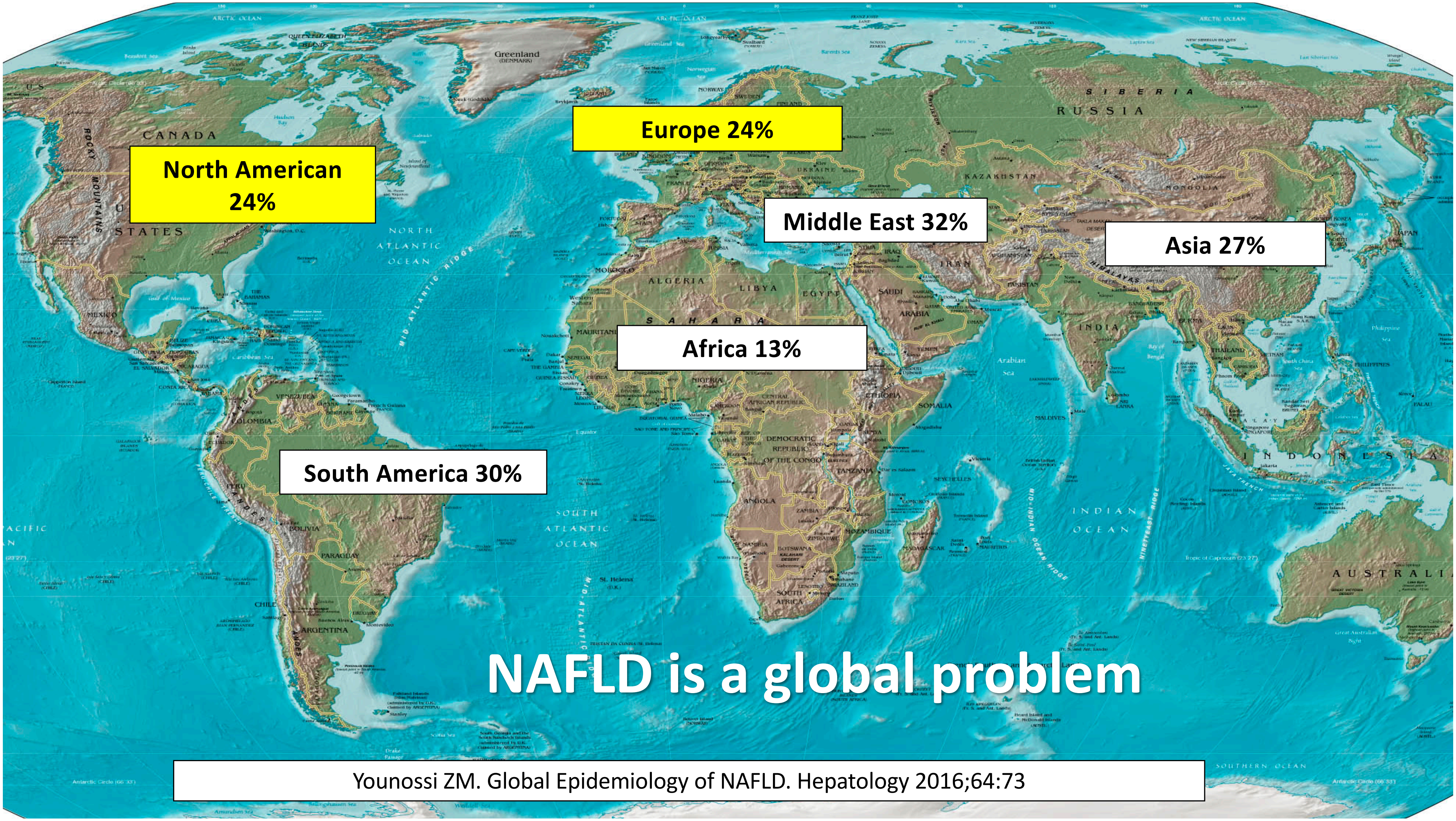
Race/ethnicity and genetic variants

- PNPLA3 G allele frequency
  - **Hispanic 0.483**
  - Caucasian 0.324
  - African-American 0.183

Characteristic	Gene
↑ hepatic steatosis	**PNPLA3** **PNPLA3** + GCKR*
↑ NAFLD activity score (NAS)	**PNPLA3** NCAN LCP1 TRAPPC9*
↓ NAS and ↓ Fibrosis	LPIN1*
↑ Fibrosis	NCAN **PNPLA3** TM6SF2 ACTR5*

Santoro N. Hepatol 2010;52:1281
Wattacheril J. J Pediatr 2017;190:100

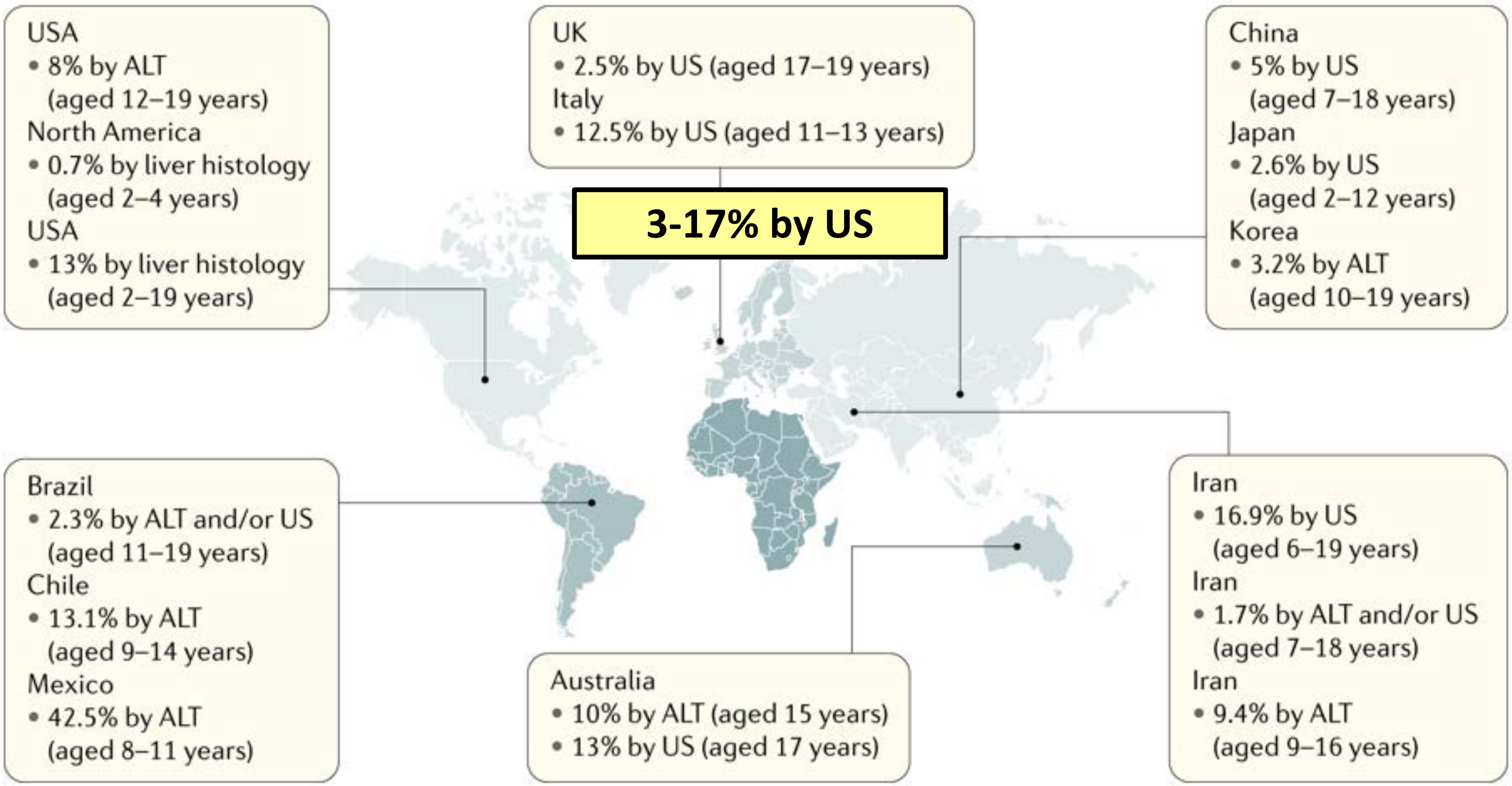
**unique to pediatric cohorts, but require validation*



NAFLD is a global problem

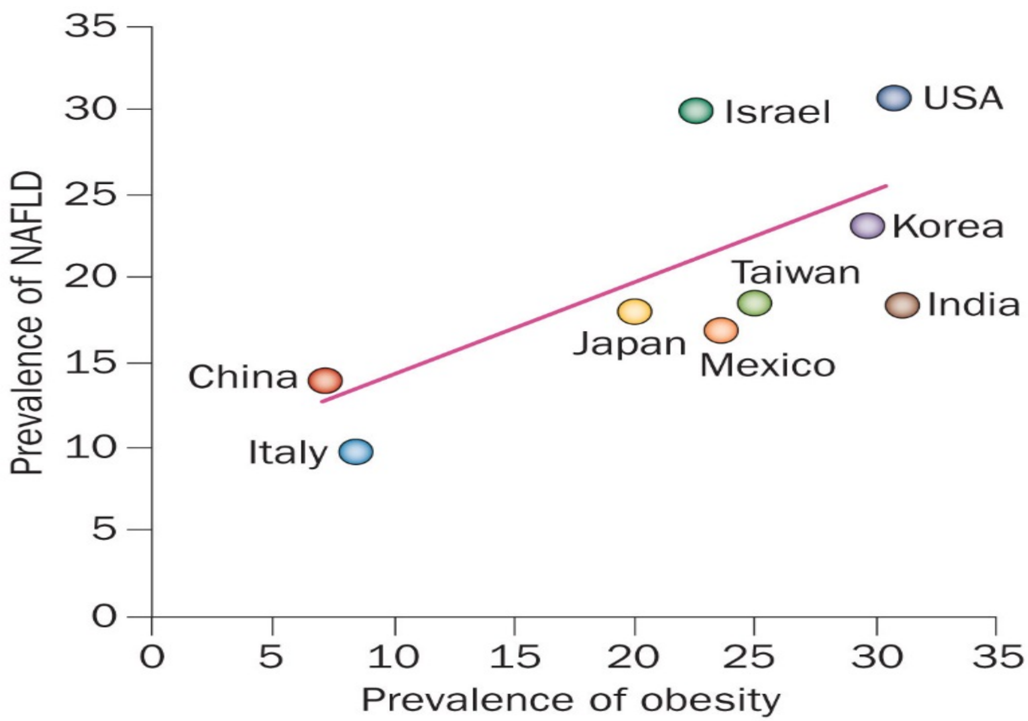
Younossi ZM. Global Epidemiology of NAFLD. Hepatology 2016;64:73

NAFLD: also a global pediatric disease



Nobili V. Nature Reviews Gastro Hepatol 2019

NAFLD prevalence correlates strongly with obesity prevalence



Meta-analysis of global epidemiology in adults:

NAFLD: 51% obese (95%CI: 42-61%)

NASH: 82% obese (95%CI: 55-94%)

Loomba, R. & Sanyal, A. J. (2013) The global NAFLD epidemic. *Nat. Rev. Gastroenterol. Hepatol.*

Younossi ZM. Hepatology 2016;64:73

Range of obesity severity in NAFLD

- **High proportion of severe obesity in patients with NASH in many clinical trials in the U.S.**
  - **Mean BMI of 33-35kg/m^2** reported in a range of pediatric and adult clinical trials in U.S.
- **Mean BMI lower in trials conducted outside of the US**
  - **Mean BMI approximately 31 kg/m^2**
  - 20% of adults in lifestyle intervention study in Cuba had BMI >35 kg/m^2 (class 2 obesity)

"Lean NAFLD" increasingly recognized

- **Adults BMI <25 kg/m^2** and **children <85th%ile**
  - More common in Asian populations (up to 19%)
  - Also seen in U.S. adults (3-7%)
- **8% prevalence in adolescents (NHANES data)**
- **Dysmetabolic phenotype**
  - **↑ age, TG, insulin resistance and ↓ HDL**
  - **Insulin resistance OR 4.2**
  - **African-American OR 0.37**

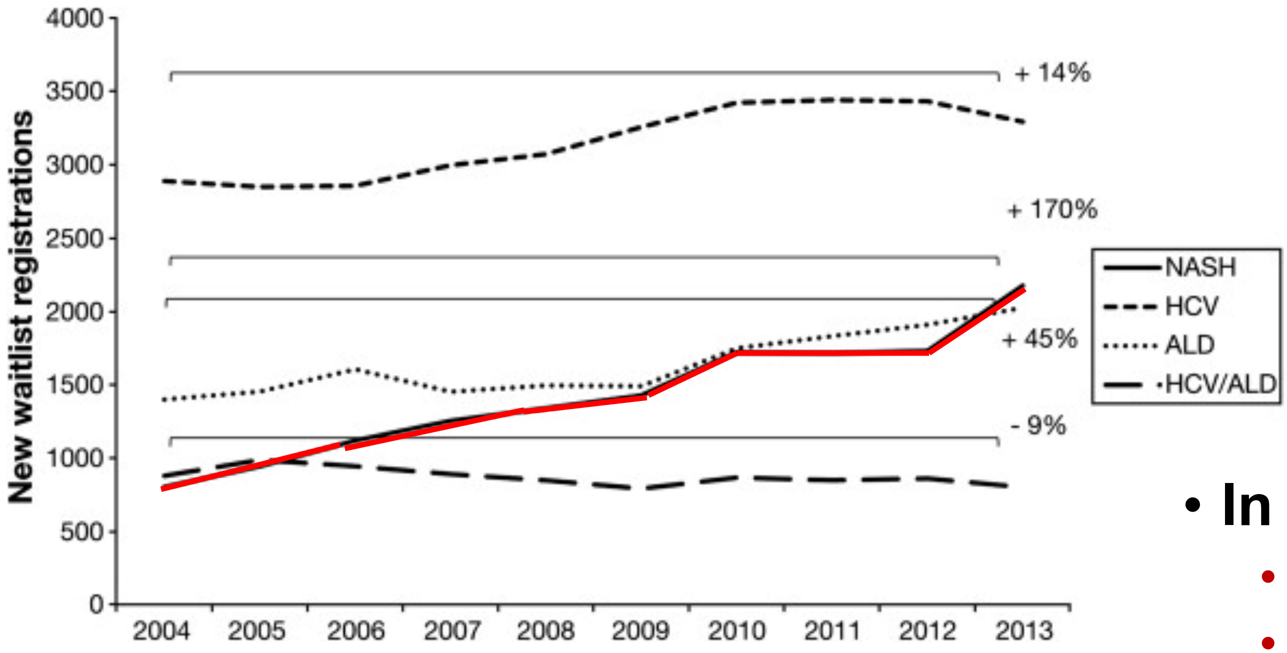
Selvakumar C. JPGN 2018;67:75

Cardiometabolic risk factors in children with NASH

Risk factor	Reported Prevalence	Phenotypic association	N (Source)
Prediabetes	23%	2x risk of NASH	675 (NASH CRN)[1]
Diabetes	6.5%	3 x risk of NASH	675 (NASH CRN)[1]
High blood pressure	36%	More severe steatosis	484 (NASH CRN) [2]
Sleep Apnea	60%	More severe fibrosis[4] 5 x risk of NASH[5] 6 x risk of significant fibrosis[5]	25 (USA, single site) [4] 65 (Italy, single site)[5]
Dyslipidemia	14% elevated LDL 51% high triglycerides	Unclear	585 (NASH CRN)[6]

[1]Newton KP et al. JAMA Pediatrics 2016; [2]Schwimmer JB et al. PLOS One 2014; [3]Korey C. J Pediatr Gastroenterol Nutr 2015; [4]Sundaram SS. J Pediatr 2014; [5]Nobili V Am J Respir Crit Care Med 2014; [6]Harlow KE J Pediatr 2018;198:76

In adults, NAFLD independently associated with ↑ CVD Morbidity & Mortality, Liver Tx



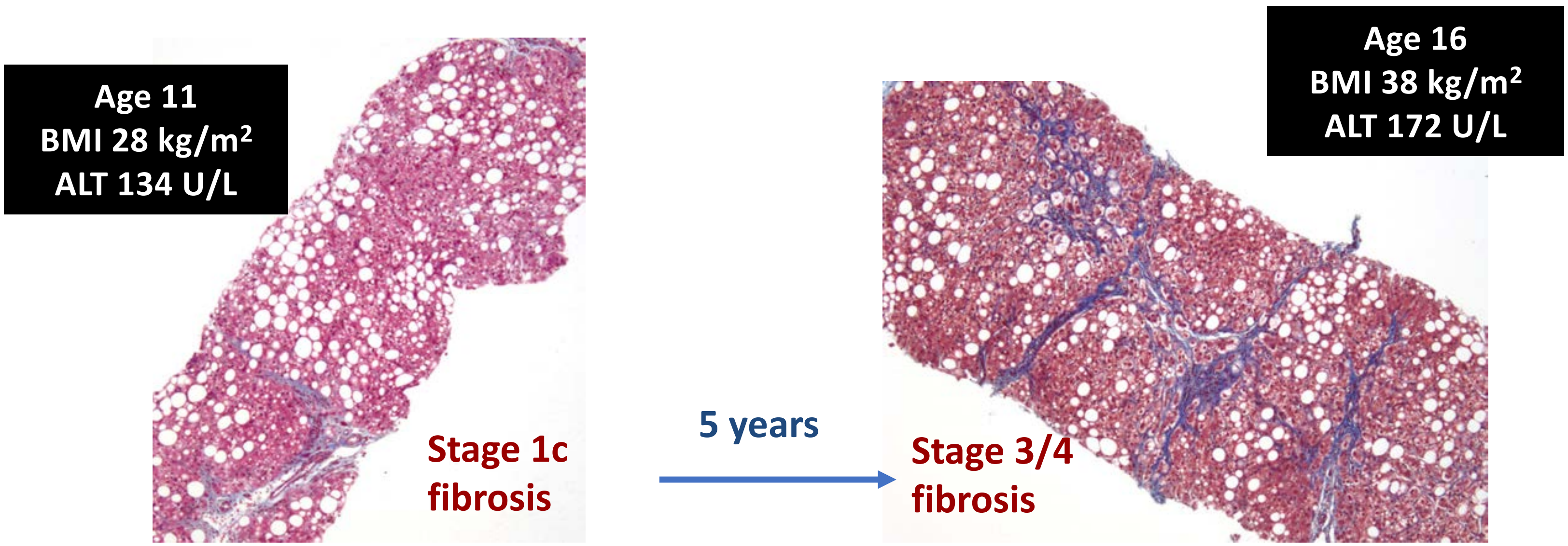
[1]Wong RJ et al. Gastroenterology 2015;
[2] Eksted et al. Hepatology 2006

- **In adults with NAFLD**
  - **4.4x HR of all cause mortality**
  - **8.2x HR of CVD mortality**

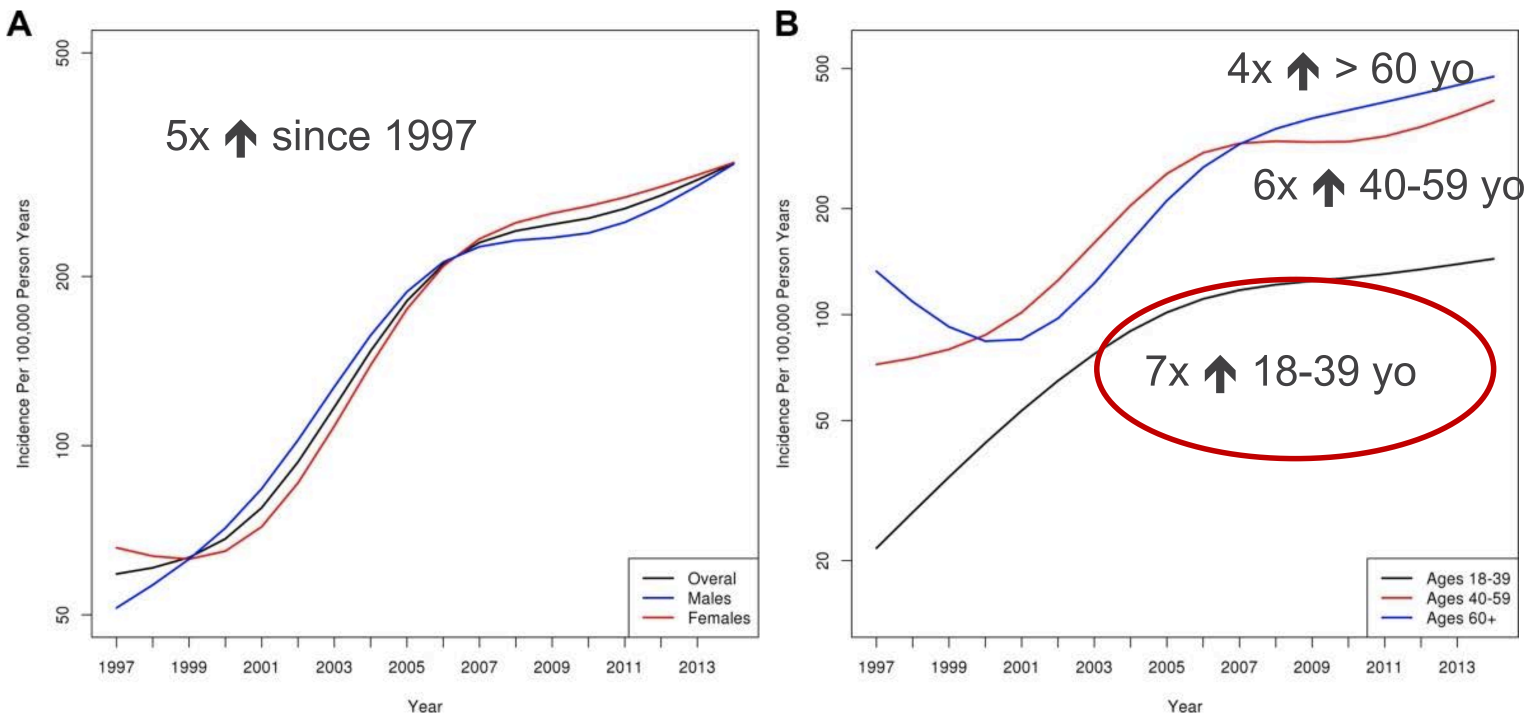
W. Am J Gastro 2008 Sep;103(9):2263-71

Long-term outcomes of children with NAFLD <u>unknown</u>

- **Hepatic outcomes:** fibrosis progression, end-stage liver disease, transplantation rate, hepatocellular carcinoma
- **Non-hepatic outcomes:** cardiovascular events, diabetes incidence and complications, all-cause and specific mortality



Increasing NAFLD Incidence (Olmsted County, MN)



Allen et al. *Hepatology*. 2018.

Screening Recommendations

SOCIETY	YES	UNCERTAIN
American Academy of Family Physicians	X	
American Academy of Pediatrics		
National Association of Nurse Practitioners		
Endocrine Society		
American Association for the Study of Liver Diseases		
American College of Gastroenterology		
American Gastroenterological Society		
European Society for Pediatric GI, Hepatology and Nutrition		
North American Society for Pediatric GI, Hepatology and Nutrition		

All obese children

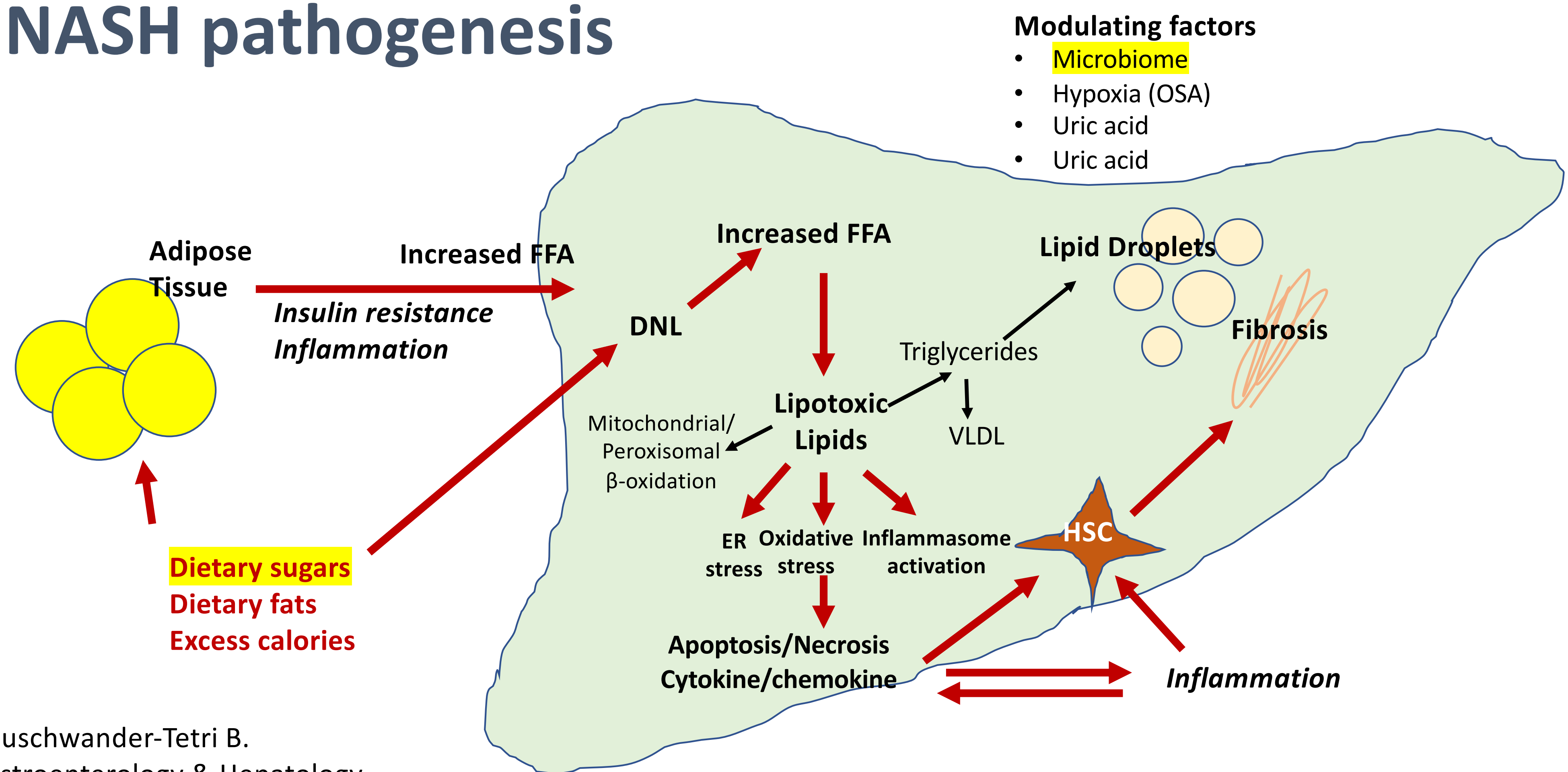
All overweight children with cardiometabolic risk factors

ALT (+/- imaging)

Start screening around age 10

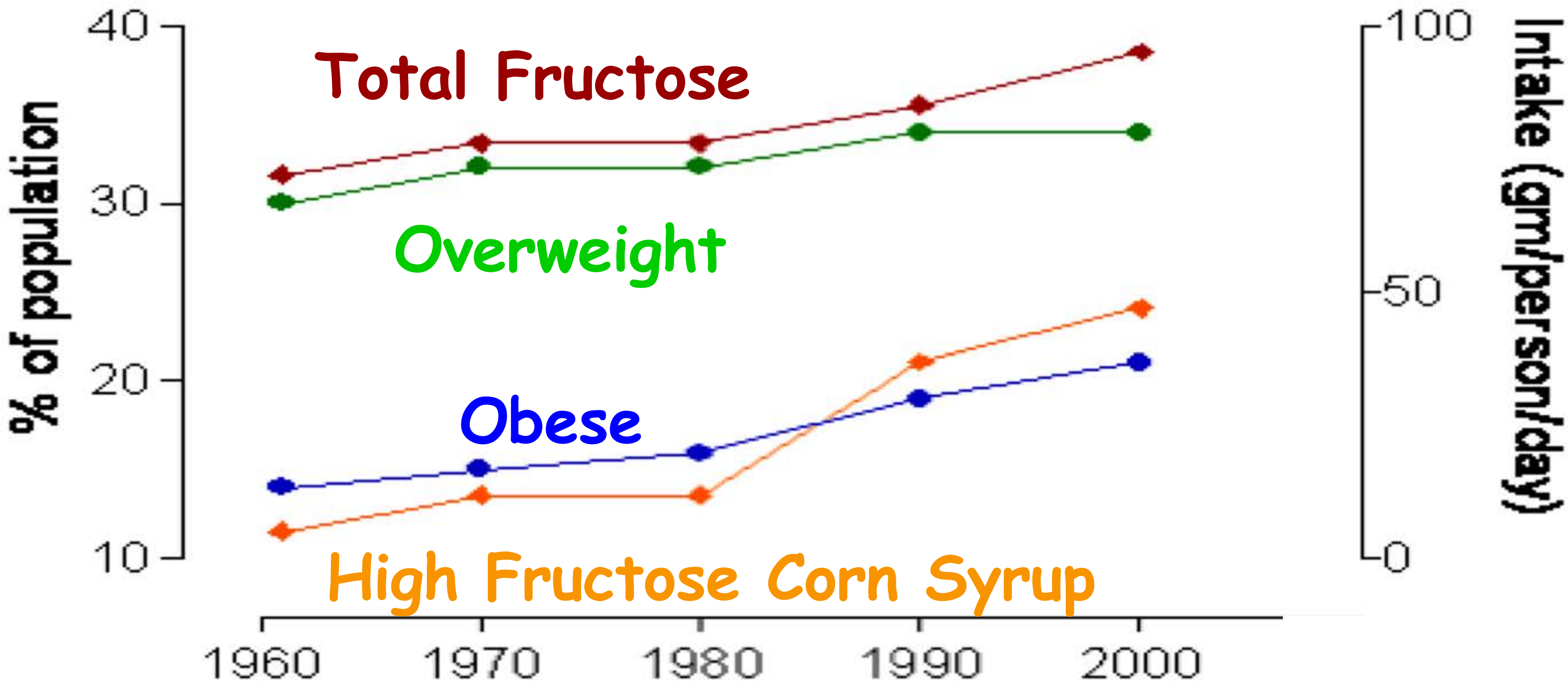
Schwimmer JB. Aliment Pharmacology & Therapeutics 2013;38:1267

NASH pathogenesis



Neuschwander-Tetri B.
Gastroenterology & Hepatology
2018;14: 582

Increase in fructose intake parallels rise in obesity



Adapted from Figure 1 in Bray et al. Am J Clin Nut 2004

Increased lifetime “load” of High Fructose Corn Syrup

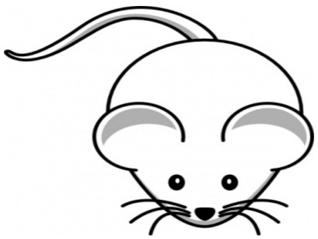
One Day	1.4 oz (40 ml)
One Week	9.8 oz (278 ml)
One Month	5.3 cups (1.25 L)
One Year	4 gallons (15 L)
Lifetime	313 gallons! (1185 L)

Increased fructose consumption associated with higher fibrosis stage in adults with NAFLD

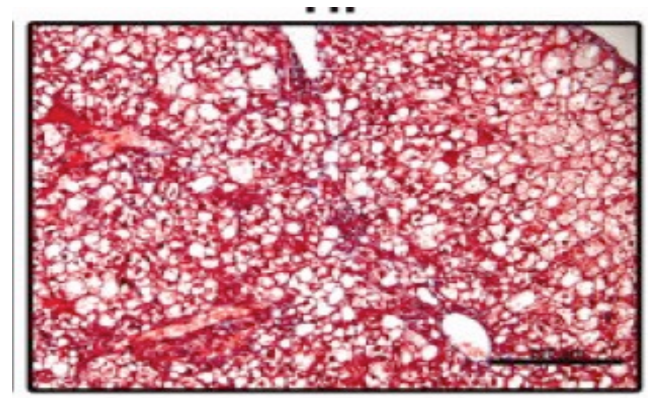
Abdelmalek M. Hepatology 2010;51:1961

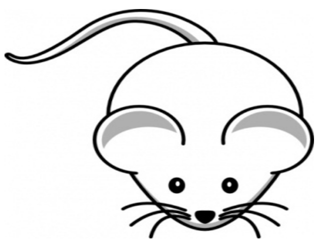
Adding fructose to high fat diet induces greater fibrosis in mouse models

C57Bl/6 mice

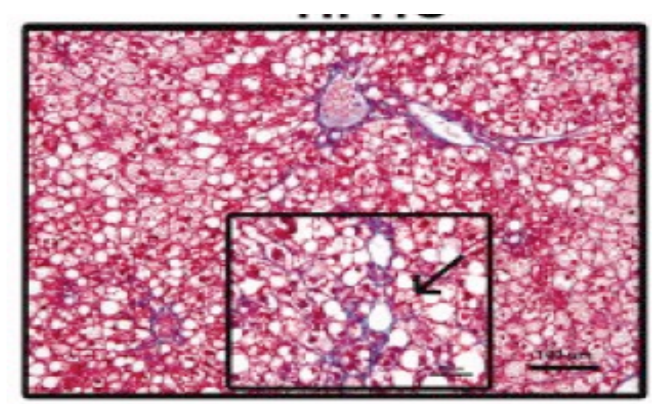


High fat diet x 16 weeks



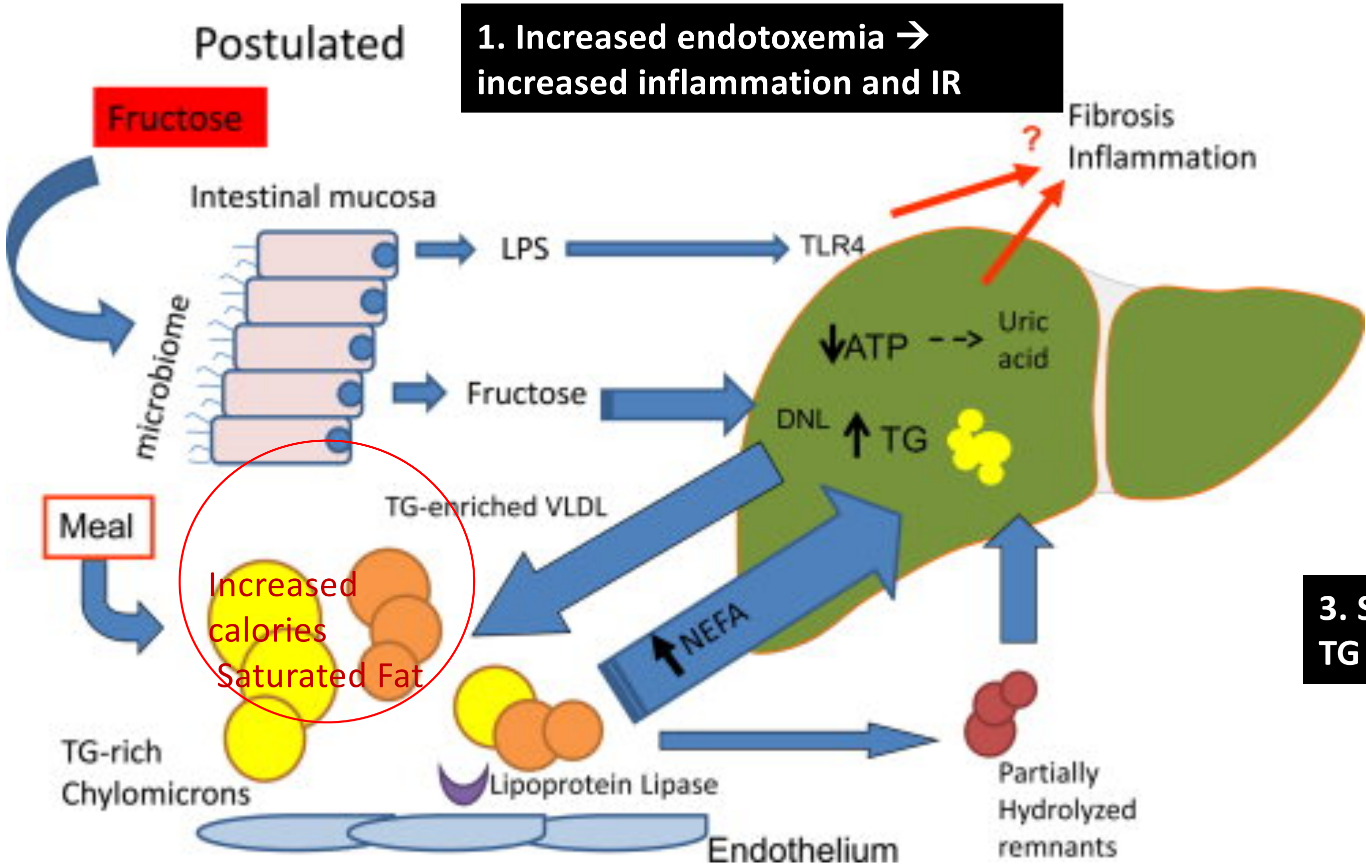


High fat + **fructose** x 16 weeks



Kohli R et al. Hepatology 2010;52:934-44

Potential mechanisms of fructose in NASH



1. Increased endotoxemia → increased inflammation and IR

2. Rapid depletion of ATP → toxic FFA, Uric Acid → HTN, ?inflammation/fibrosis

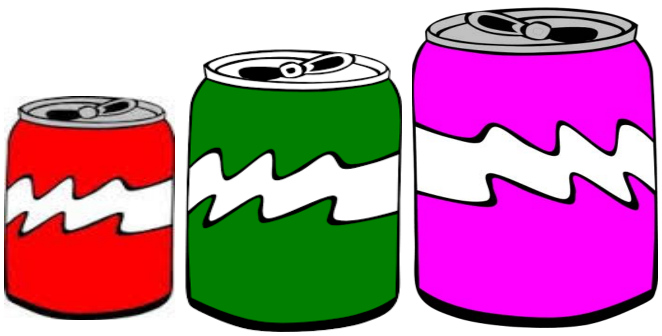
3. Stimulation of DNL → increased TG and VLDL production

Vos MB, Lavine JE. Hepatology 2013;57(6):2525

Pediatric studies also suggest link

- **Uric acid levels increased in children with NASH** vs. those with steatosis alone
  - But no difference by self-reported sweetened beverage (SSB) intake which was low overall
  - Predominantly Hispanic population using the Block Food Frequency questionnaire.
- **SSB consumption significantly correlated with ALT** level in whites and African-Americans, but not in Latinos

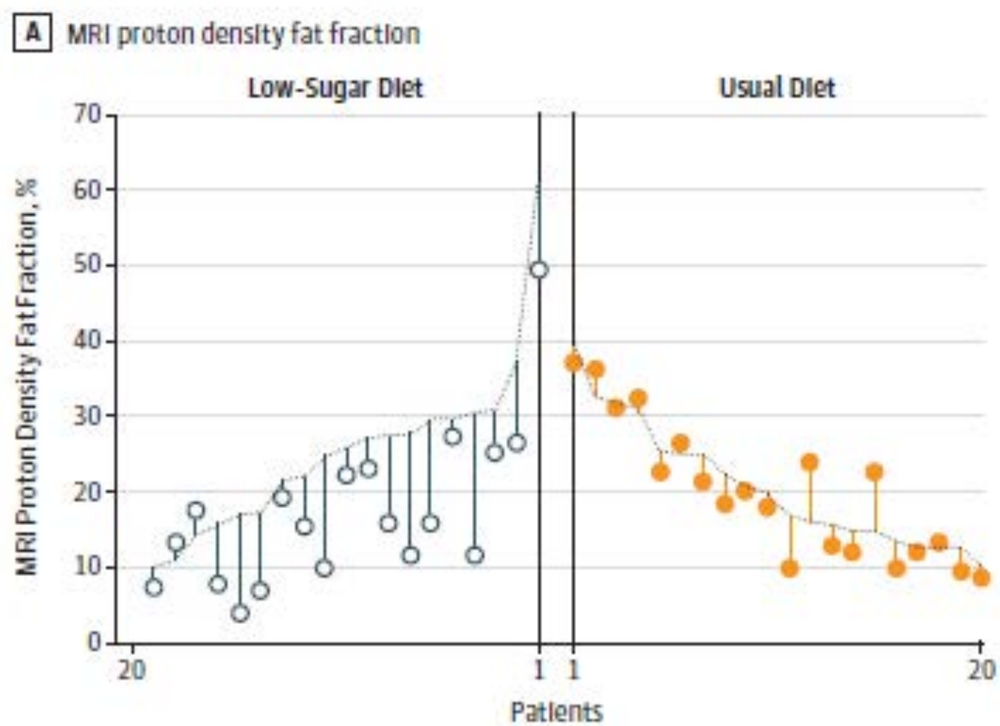
Papandreou D. Appetite 2012;59(3):939-44
Vos MB. J Pediatri Gastroenterol Nutr 2012;54:90.
Lim JS. Nat Rev Gastroenterol Hepatol 2010;7:251



Free sugar reduction improves hepatic steatosis in children

Randomized Clinical Trial

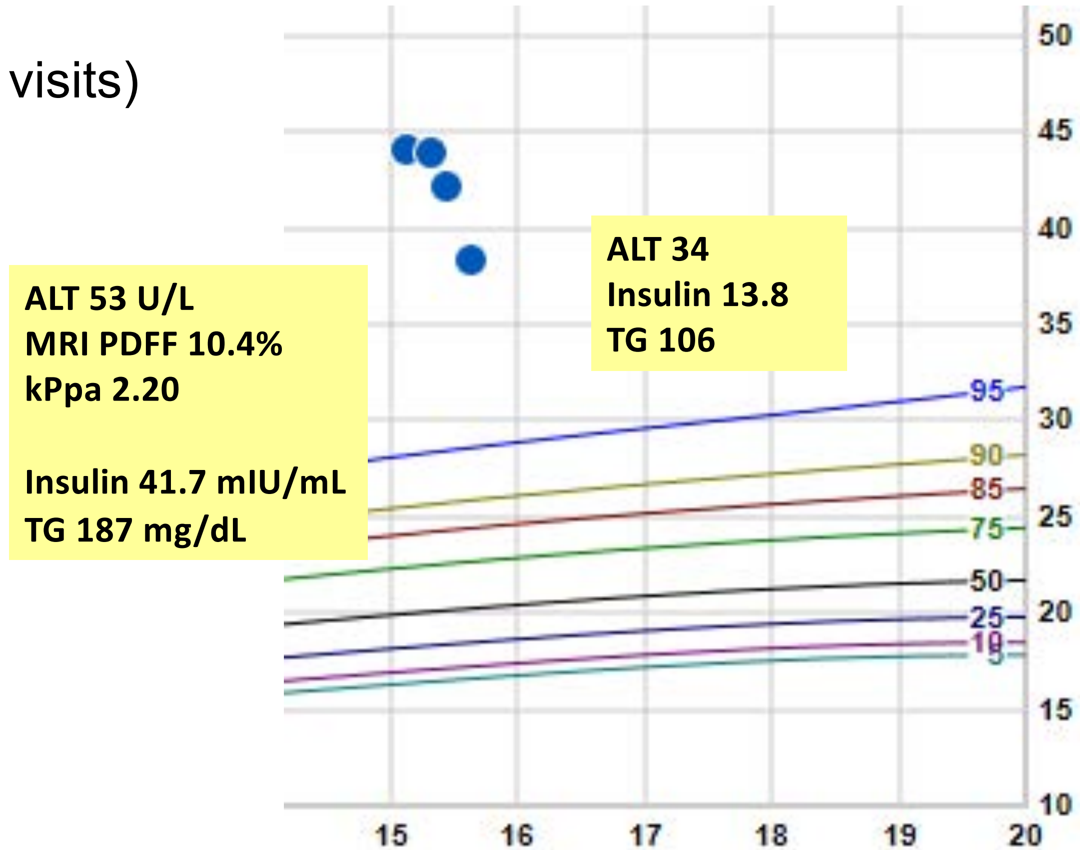
- 40 Hispanic adolescent boys with confirmed NAFLD
- Randomized to diet of low free sugar (<3% of daily calories) vs. standard diet x8 weeks
- Significantly greater ↓ in liver fat on MRI and ↓ in ALT



Schwimmer JB. JAMA 2019, JAMA. 2019;321(3):256-265Fig 2

Case: 15 year old male, initial BMI 43, presumed NAFLD (neg r/o labs)

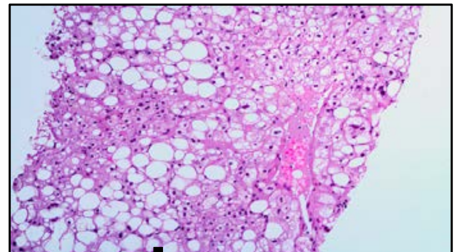
- 15 yo male followed x 6 months (2 visits)
- Cut out sugary beverages
- Increased walking, playing football
- Down 33.5 pounds in 4 months
- Follow-up BMI 38

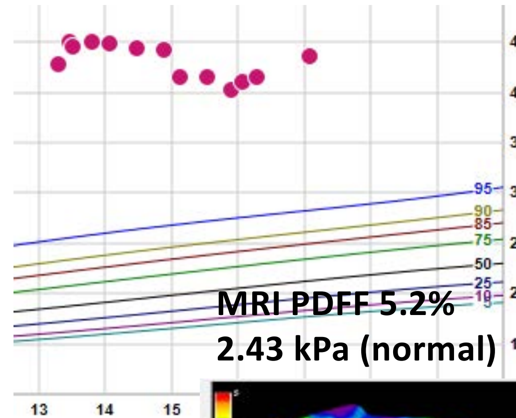


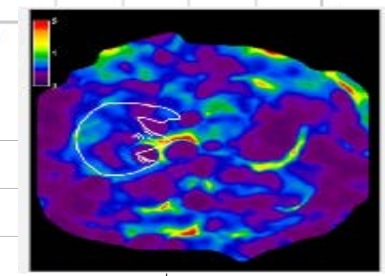
Case: 17 year old girl, BMI 45, with severe NASH

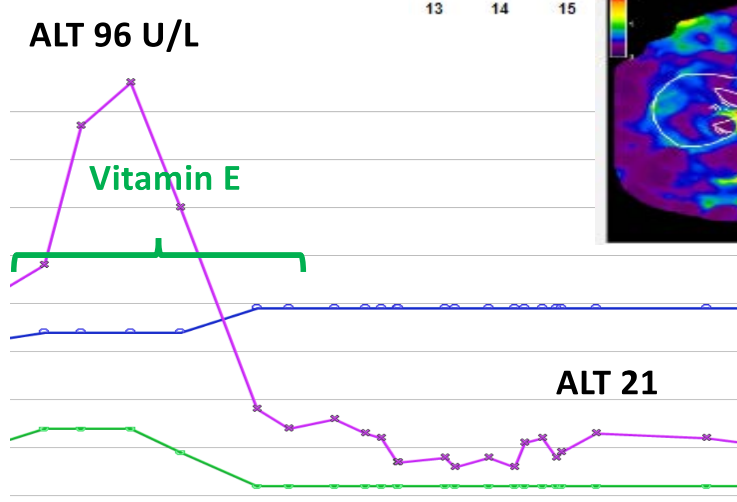
- Diagnosed at age 14
  - TG 239 mgdL
  - Insulin 56 mIU/mL
  - MRI PDFF 9.7%, stiffness 2.89 kPa
- Started on Vitamin E x 2 years (ended Aug 2015)
- Also eliminated sugary beverages and snacks

SEPT 2013: NAS 8, fibrosis 1c









Malnutrition of Obesity: Additional nutritional risk factors for NASH?

Lower intake of vitamins A, C, E, Fiber, Polyphenols and

Omega-3 fatty acids

Multiple potential mechanisms of action:

- **Reduced oxidative stress**
- **Hepatocellular protection**
- **Anti-inflammatory**
- **Epigenetic changes**
- **Intestinal Eubiosis**

Del Ben M. Br J Clin Pharmacol 2016 Feb 6 (epub)

Garcia OP. Nutrition Reviews.2009;67:559.

Vitamin E alpha tocopherol (++)

- **800 IU/day of vitamin E** vs. placebo x 96 weeks in 247 adults with biopsy-confirmed NASH
  - Greater improvement (**43%** vs. 19% in placebo, p=0.001) in NASH activity and e greater resolution of NASH (**36%** vs. 21%, p=0.05)
  - Similar signal in children (**58%** vs, 28%, p=0.006)
- **Caveats:** Potential health risks associated with high dose vitamin E in other studies
  - Increased all cause mortality
  - Increased prostate cancer risk

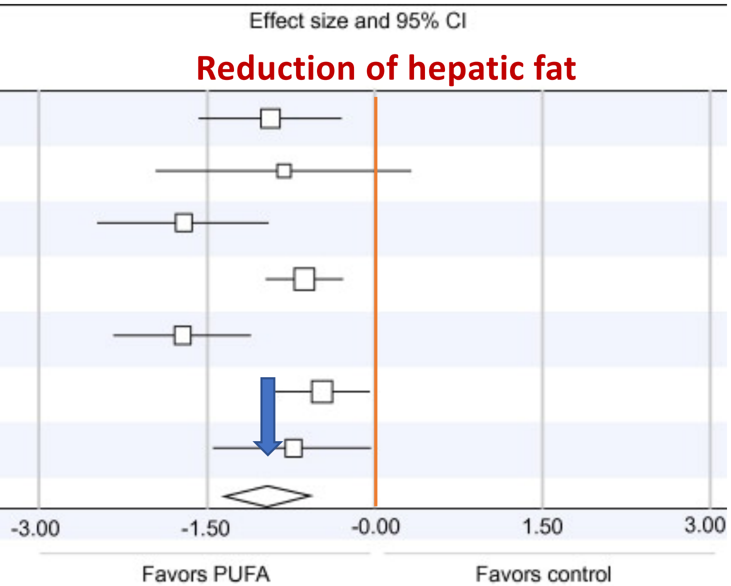
Sanyal AJ. NEJM 2010;362:1675.

Lavine J. JAMA 2011;305:1659

Polyunsaturated fatty acid supplementation (+)?

- Systematic meta-analysis of 9 studies (5 RCTs) with 355 adults

Authors, year [Ref.]	Effect size Hedge's g	Effect size 95% CI	*p*
Capanni *et al.*, 2006 [45]	-0.938	-1.559, -0.316	0.003
Sofi *et al.*, 2010 [53]	-0.811	-1.948, 0.326	0.162
Spadaro *et al.*, 2008 [54]	-1.709	-2.460, -0.958	0.000
Zhu *et al.*, 2008 [48]	-0.626	-0.971, -0.281	0.000
Cussons *et al.*, 2009 [56]	-1.718	-2.326, -1.109	0.000
Tanaka *et al.*, 2008 [47]	-0.476	-0.894, -0.058	0.026
Chen *et al.*, 2008 [55]	-0.731	-1.441, -0.021	0.043
	-0.965	-1.348, -0.582	0.000



- Optimal dose unknown (**median 4g/day**: 0.8 – 13.7 g/day)
  - Only one study used highly purified N-3 omega fatty acids

Parker HM, J of Hepatology 2012;56:944-51

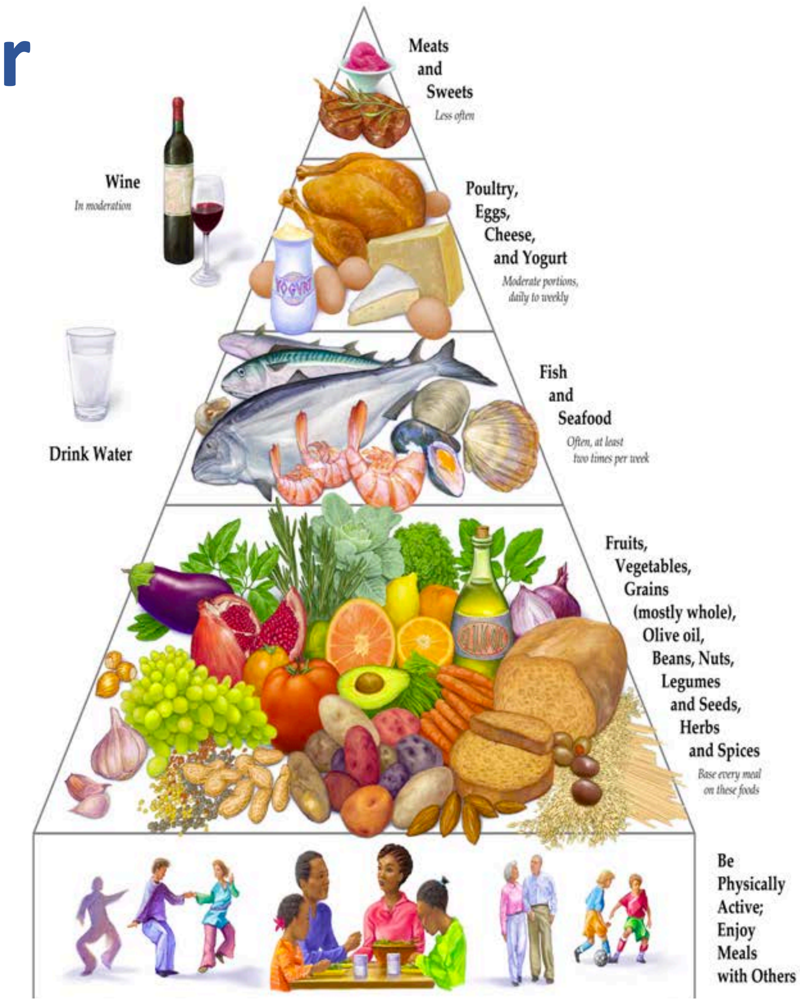
Supplements with unclear benefit

- **Vitamin C (1 gram per day)**
  - 2 RCTs with combination treatment (vitamin E or atorvastatin) improved steatosis – unable to isolate effect of vitamin C.
- **Vitamin D (high doses x 4-6 months)**
  - Small RCT and open label study – no significant differences in LFTs, steatosis, histology
- **Carnitine (500 mg po BID – 2000 gm daily)**
  - RCT of 2000 mg daily improved ALT and histology
- **Silymarin** (polyphenol) – most studies given with vitamin E
- **Reservatrol** (polyphenol)
  - 2 short term RCTs (3 months) suggest improvement in ALT and possibly hepatic steatosis
  - 2 other studies raise doubts

Del Ben M. Br J Clin Pharmacol 2016 Feb 6 (epub)

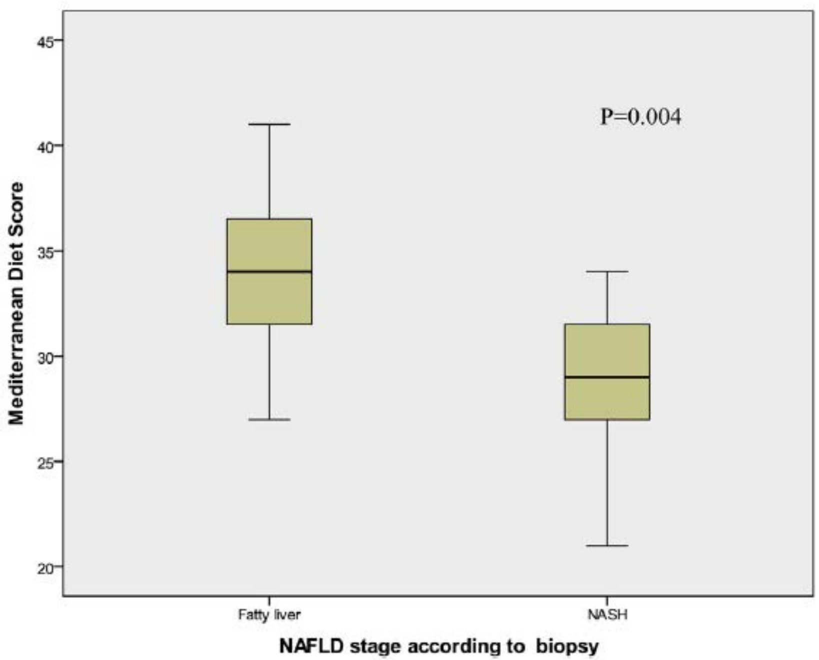
Fruits and vegetables matter

- Mediterranean diet associated with **lower risk of obesity, cardiometabolic disease, including NAFLD**
- ↓ **Mediterranean diet** associated with:
  - ↑ Sonographic **NAFLD** (OR 5.43) and **insulin resistance** (OR 2.45) in 243 obese children
  - ↑ **Liver fibrosis** (OR 2.58) in 100 children with biopsy-confirmed NAFLD



Della Corte C. Nutrition 2017;39:8

↑Mediterranean Diet Score associated with ↓NAFLD Severity in adults



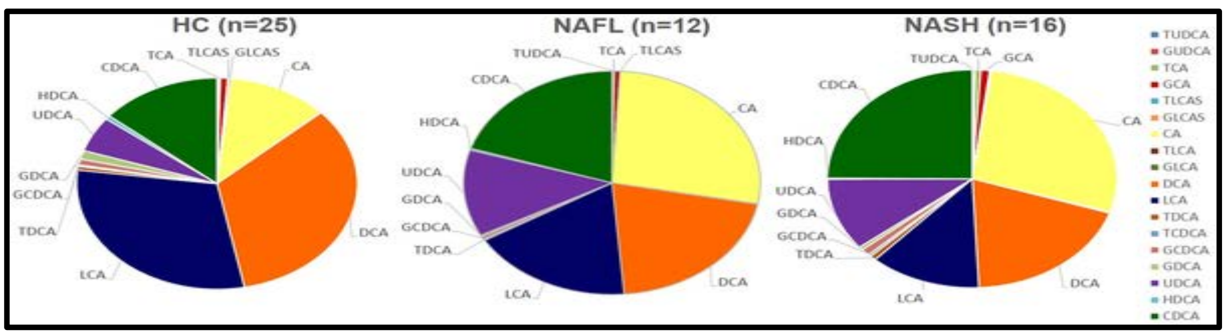
- 73 adults: recent biopsy NAFLD
- 58 matched healthy controls
- No diabetes
- Habitual diet assessed using FFQ
- Mediterranean Diet Score calculated

Kontogianni MD, Clinical Nutrition 2014;33:678, Fig 1

Diet influences Intestinal Microbiome

- Varying microbiome profiles in NAFLD, NASH compared to healthy controls → “dysbiosis”
  - Increase intestinal permeability
  - Increased portal LPS, alcohol, VOCs → TLR activation, inflammatory cytokines → hepatotoxicity
  - Altered bile acid composition and FXR modulation

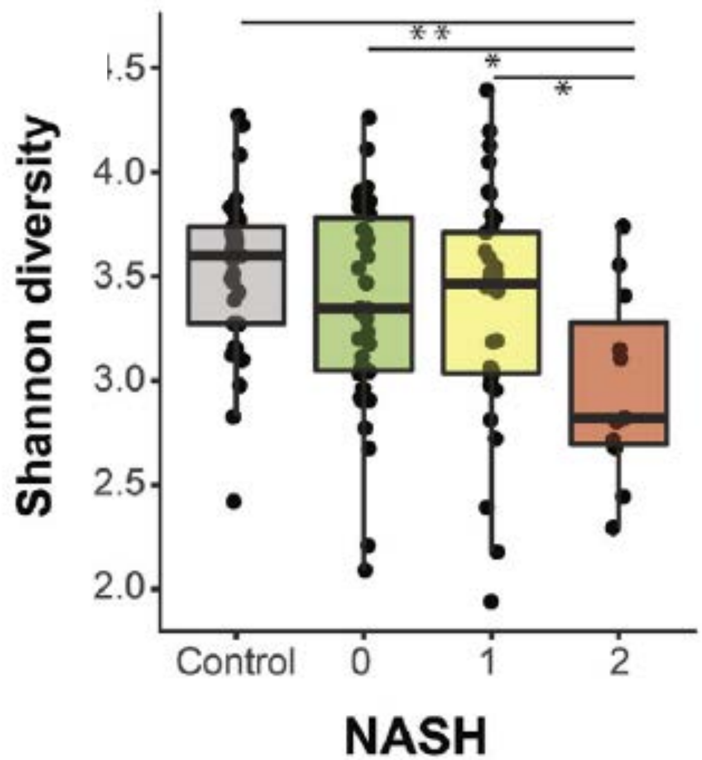
Higher total fecal BA, CA and CDCA in NASH



Mouzaki M. PLOS ONE 2016
Zhu L. Gut Microbiome and NAFLD. 2015;77:245
Del Chierico F. Hepatology 2016

Children with NAFLD also have intestinal dysbiosis

- 87 children with confirmed NAFLD and 37 obese controls with no NAFLD
- Children with NAFLD had:
  - **Lower fecal microbial diversity** compared to controls (p=.02)
  - **NASH had lowest diversity** vs. NAFLD and HC (p=.001)
  - High **Prevotella copri → more severe fibrosis** (p=.04)
  - **Genes for LPS biosynthesis enriched in NASH** (p<.001)



Schwimmer JB. Gastroenterology 2019;157:1109, Fig 2B

Breastfeeding and lower NAFLD Risk?

- Retrospective analysis of 191 children in Italy with biopsy-confirmed NAFLD
- 48% of cohort had been breastfed a median of 8 months during infancy
- For each month of breast-feeding in infancy, decreased odds of NASH (OR 0.70, 95% CI 0.001 to 0.87) and fibrosis (OR 0.86, exact 95% CI 0.75 to 0.98)
  - Adjusted for age, waist circumference, gestational age and neonatal weight
- Requires further validation in larger, prospective studies

Nobili V. Arch Dis Child 2009 Oct;94(10):801-5

Additional Environmental Factors

- **Post infancy diet**
  - High fructose intake
  - Processed foods (emulsifiers and additives)
  - Low fiber intake
- **Medications**
  - Antibiotics
  - Antacids

> - **Alter intestinal microbiota composition and diversity**
> - **Impair functional properties of mucus barrier**
> - **Metabolized to other byproducts with systemic effects on metabolism**

Commonly found in 6 main food categories consumed in large quantities by many children

- **Baked goods (bread, biscuits, cakes)**
- Fat-based spreads (**nut butters**, margarine)
- Mayonnaises and salad dressings
- **Ice creams and other dairy desserts**
- **Confectionary (Caramels, toffees, chocolates)**
- **Beverages (soft drinks,** wine, spirits)

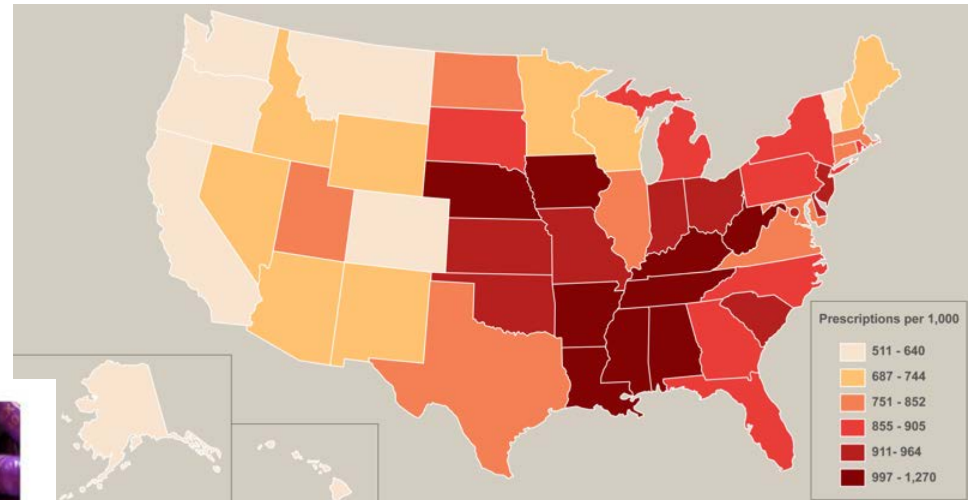
Challenges in translating experimental findings to human populations

- **Actual amounts ingested in diet difficult to quantify**
  - physiologic not pharmacologic doses
- **Additive or synergistic effects?**
- Ingested in **emulsion (humans) vs. in isolation** (most animal and in vitro studies)
- **Many but not all destroyed via digestion**

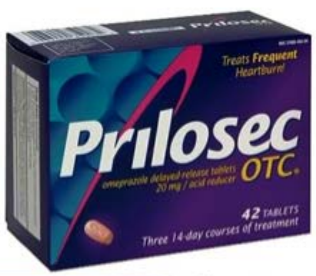
Halmos EP. Aliment Pharmacol Ther 2019;49:41

Additional Environmental Factors: Medications

- **Antibiotics**
- **Antacids**

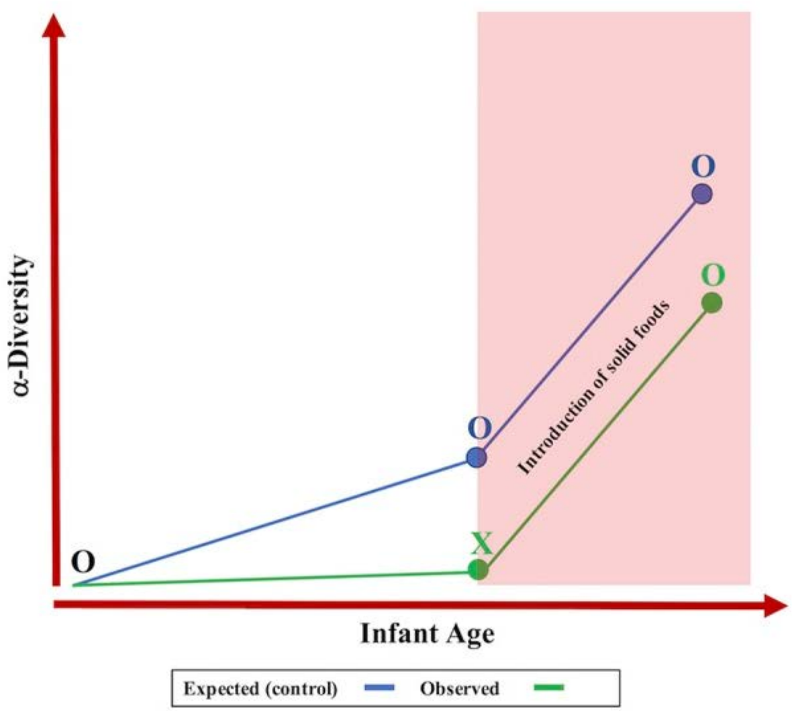


Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People™


270 million antibiotic prescriptions per year in US

Long-term impact of PPIs in children not clear



- In adults, PPI usage associated with
  - Reduced microbial diversity and dysbiosis
  - Increased risk of C. Difficile infection
  - Increased SIBO

Imhann F. Gut 2016;65:740

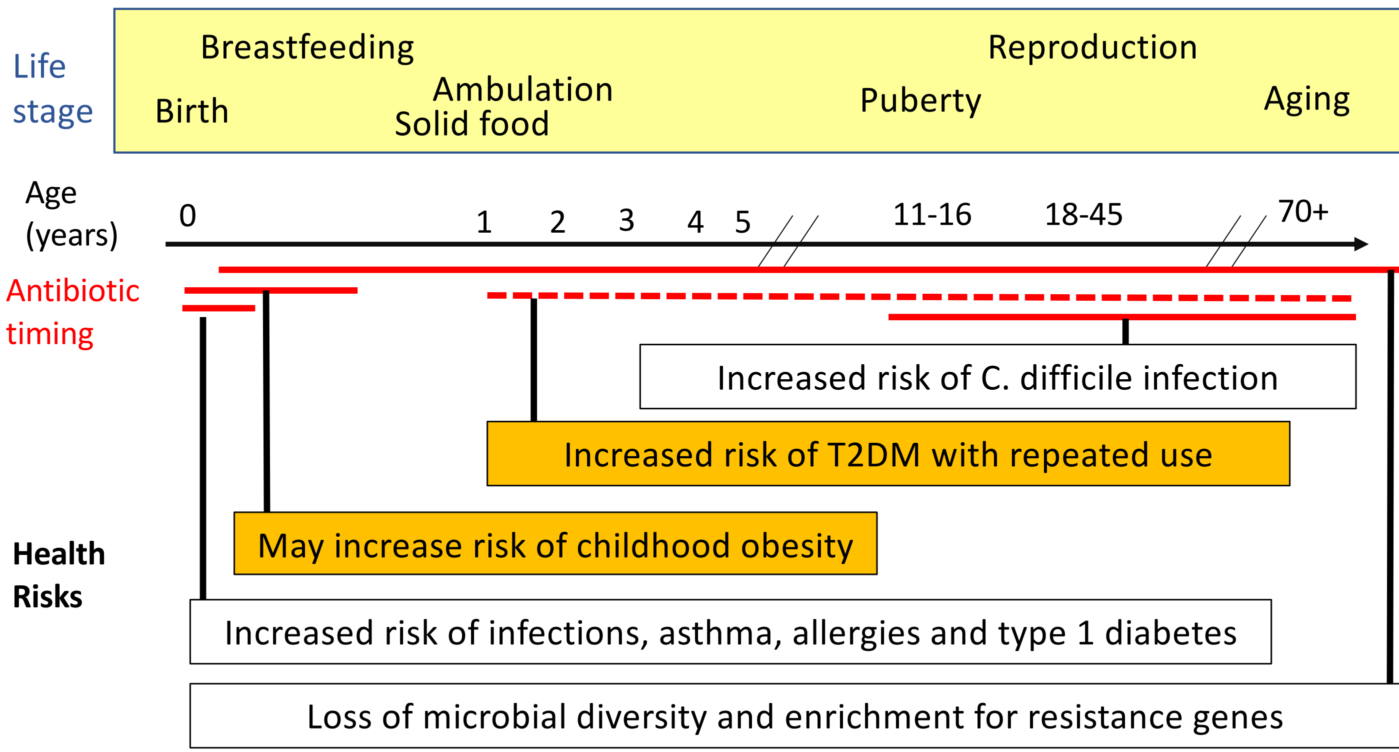
Lombardo L. Clin Gastro Hepatol 2010

What is the effect of early use of PPIs in infants and children on the microbiome and related diseases, like NAFLD?

We don't know

Drall K. Front Cell Infect Microbiol 2018;8:430

Antibiotics: Timing and Frequency Matter



Adapted from Langdon A. Genome Medicine 2016;8:39

Lifestyle intervention: first line therapy for NAFLD

- **Goals: ↓ substrate and ↑ energy expenditure**
  - ↓ high sugar, refined high carbohydrate foods and drinks
  - ↑ fruits and vegetables (more whole foods)
  - ↑ physical activity
- **But routine counseling effective in only minority of adults**
  - **10-20 % NASH resolution** in placebo arms of clinical trials in adults

AASLD NAFLD guidelines 2018
NASPGHAN NAFLD guidelines 2017

Weight loss very effective

- Lifestyle interventions
  - At least 7-10% weight loss associated with highest rates of improvement/resolution
  - **>10% weight loss associated with 90% resolution of NASH in 293 adults in a lifestyle intervention study**
    - **But only achieved by 13%**
- Bariatric surgery even more effective in adults
  - **75-85% resolution of NASH**
  - But no controlled studies
  - Durability unknown

Lifestyle modification is challenging

- **NASH typically silent for years** –until end-stage liver disease develops
- Often **little incentive to change behaviors**
- High proportion of **severe obesity**
  - More difficult to reverse through lifestyle alone
- Comprehensive weight management treatment is **resource intensive and expensive** and places **economic stress** on publicly and privately funded health systems

Common Barriers in Clinical Practice

- Lack of clinician time, training, treatment options or interest
- Inadequate reimbursement
- Lack of multidisciplinary support services
- Lack of institutional funding for support services

Family or Patient Barriers

- Low motivation and/or concern
- Socioeconomic barriers

Routine lifestyle counseling in children with NAFLD
modest but positive outcomes in some

- 122 children in NASH CRN trials 2005-2015
- Standard lifestyle counseling q3 months + placebo
- 52 or 96 weeks duration
- **29% NASH resolution (52% resolved NASH or improved fibrosis)**

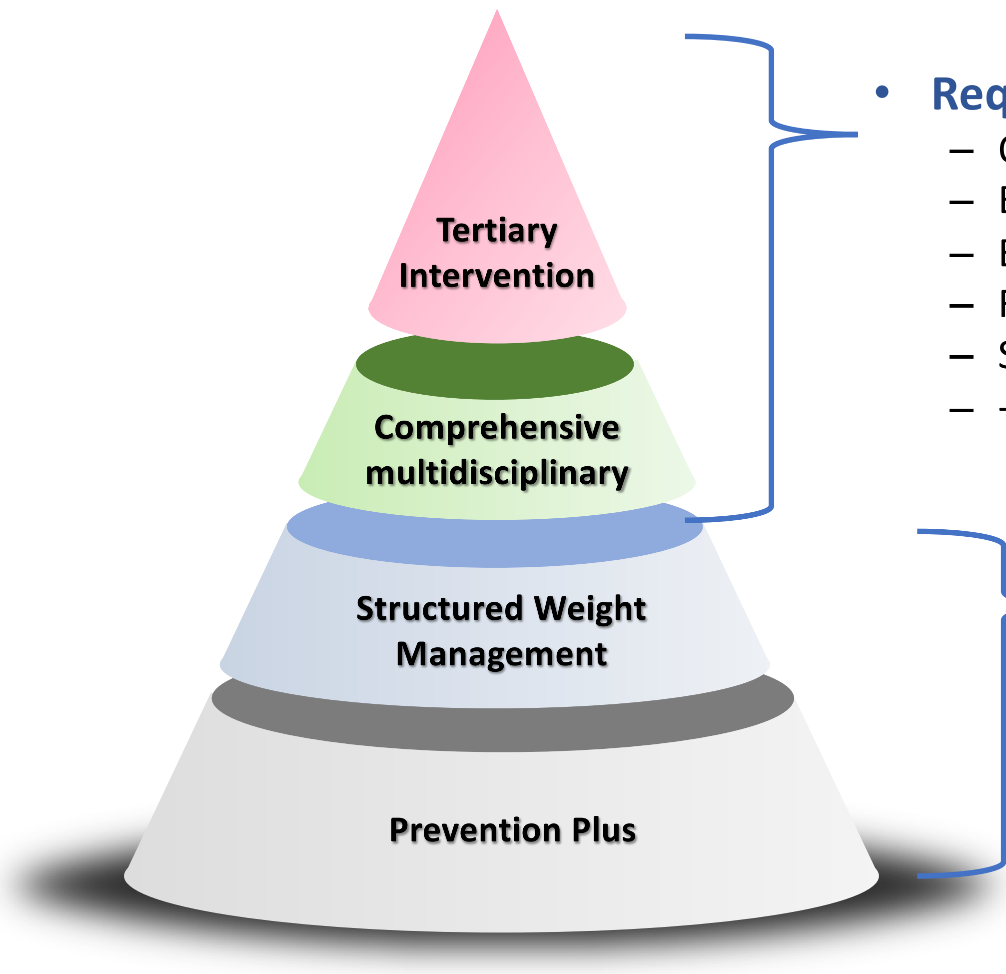
Only 3 resolved NAFLD!

36% progressed in NASH or worsened in fibrosis

5% → incident T2DM
(>300 fold expected rate/PY)

NASH CRN data, presented at AASLD October 2017

Pediatric Weight Management: Staged Approach

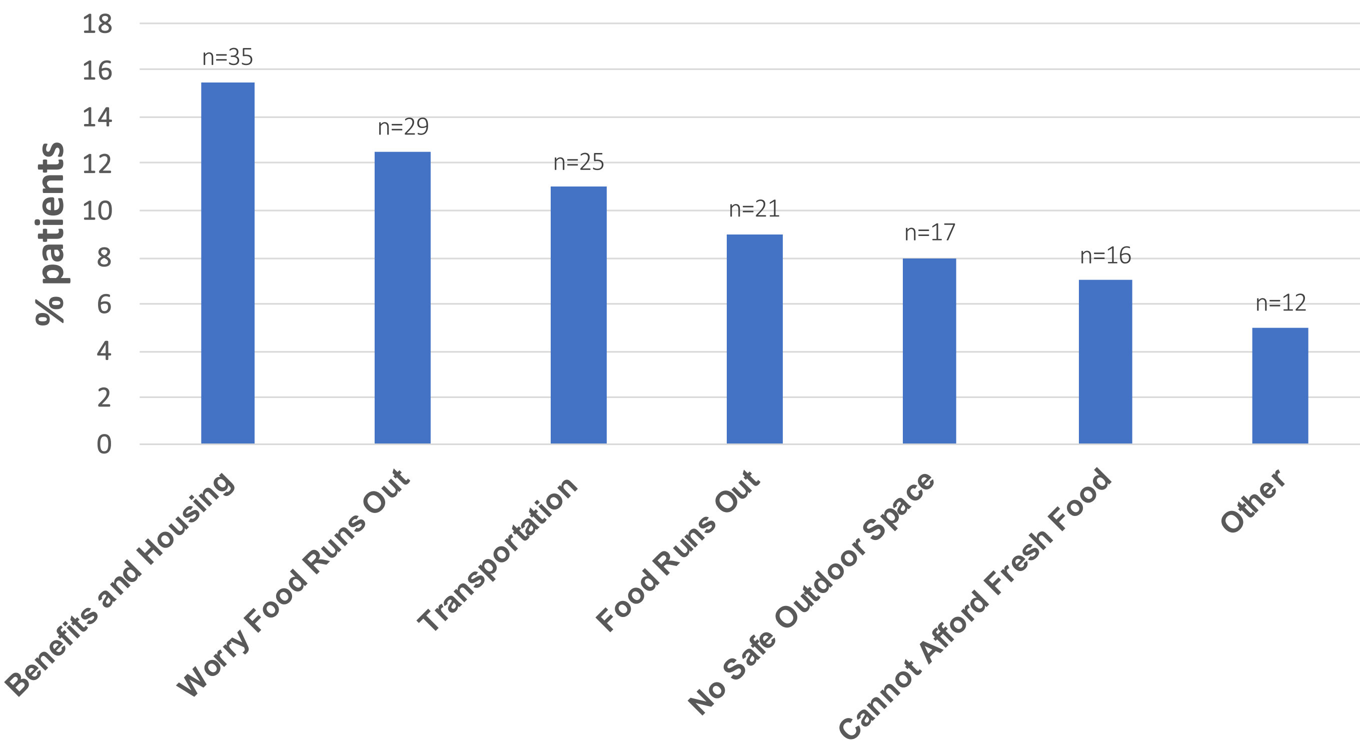


- **Require additional multidisciplinary support**
  - Obesity medicine experts
  - Behavior modification experts
  - Exercise physiologist
  - RDs with obesity management training
  - Social Work
  - +/- Medications, Bariatric Surgery

- **Feasible in most clinics**
  - MD, APRN, PA
  - Nurse
  - **RD**
  - **Social worker helpful**

Spear BA. Pediatrics 2007:120:S254.

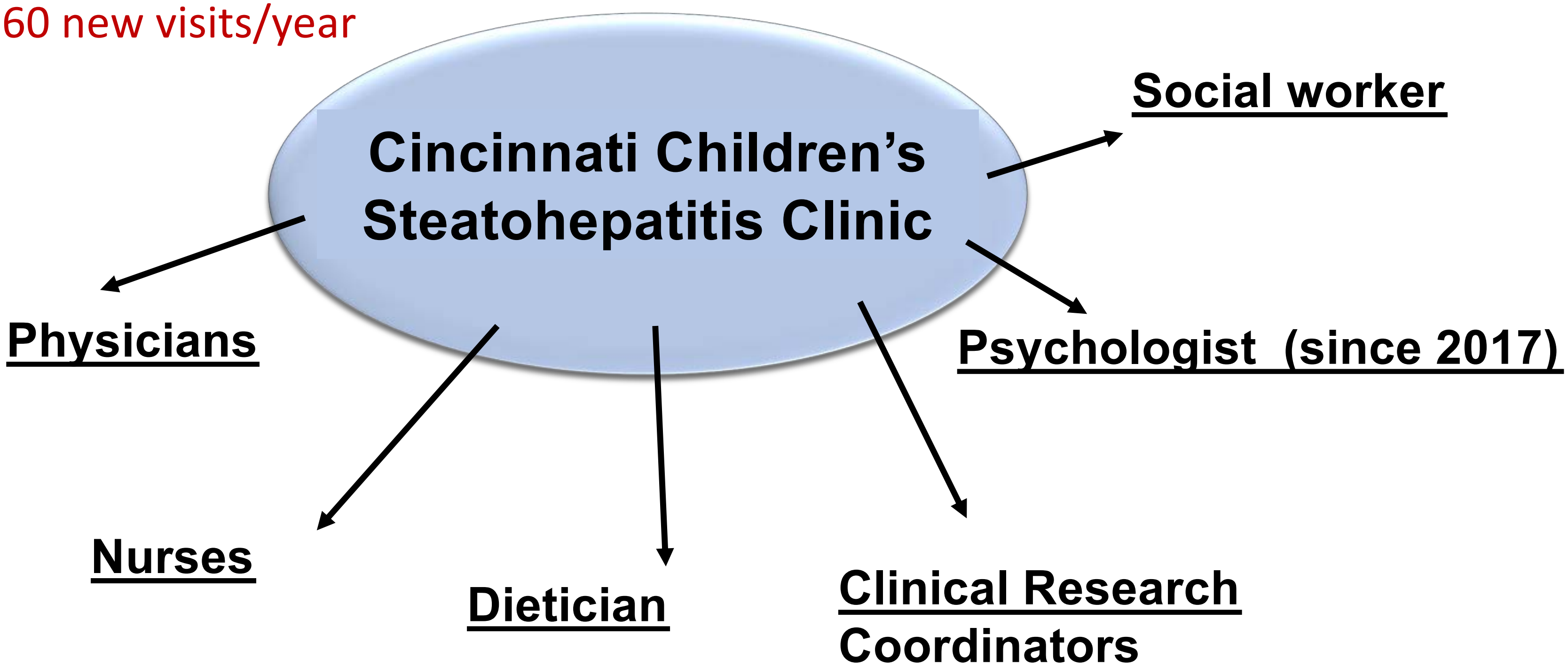
One third of patients in our NAFLD clinic (n=233) report ≥ 1 Socio-Economic Barrier



Orkin S et al. Submitted to AASLD.

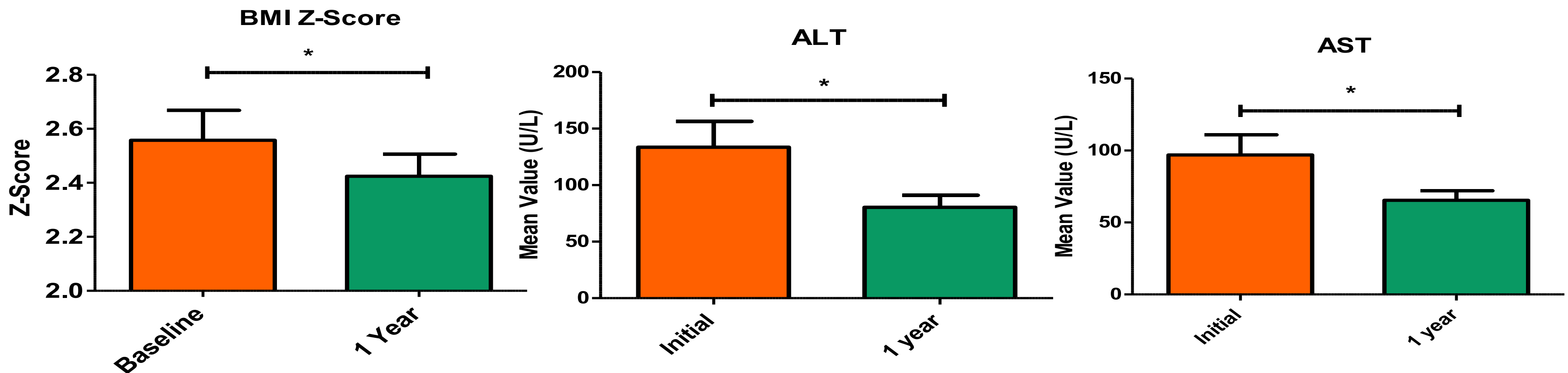
Cincinnati Children's NAFLD Clinic: a "stage 2 program"

- Over 1000 children seen since 2010
- About 160 new visits/year



Cincinnati Steatohepatitis Center:

Significant reduction in BMI, ALT and AST **(*p<0.05).**



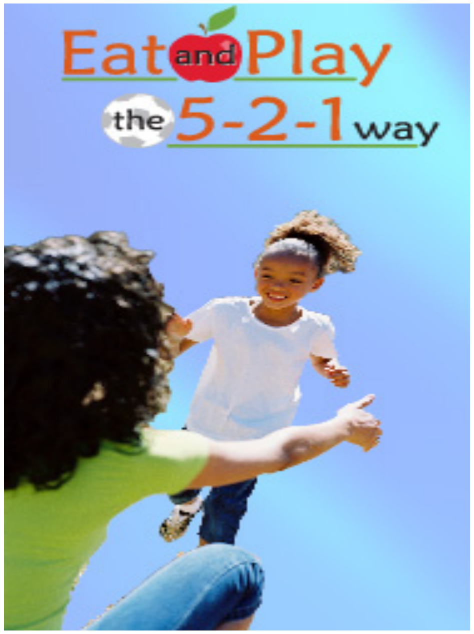
Only~50% return for 1 year follow-up

Those with liver biopsy more likely to return

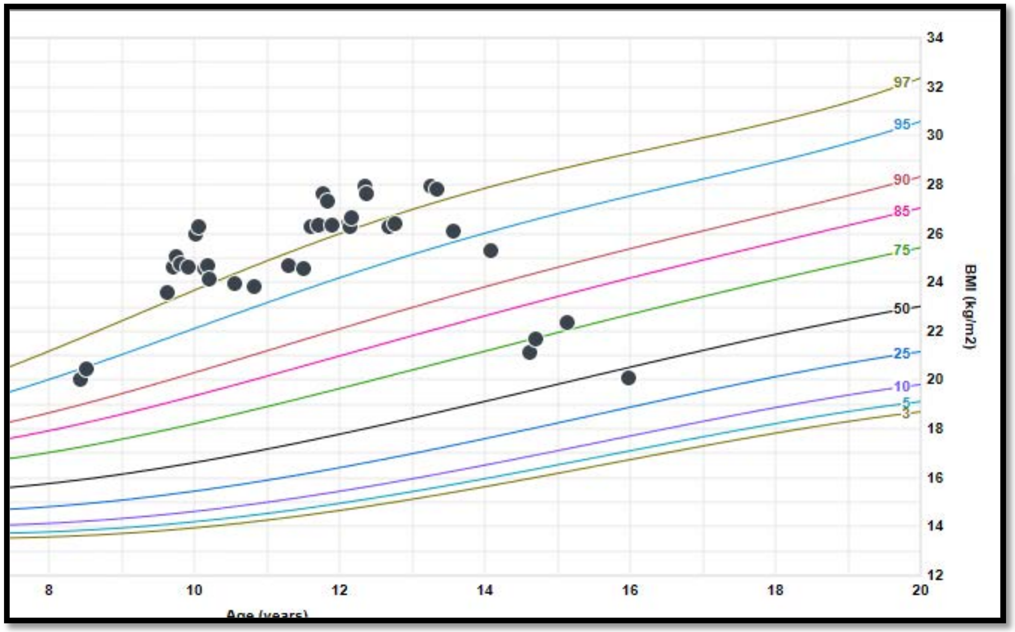
Kohli R, Xanthakos S; JPGN 2013;57:119

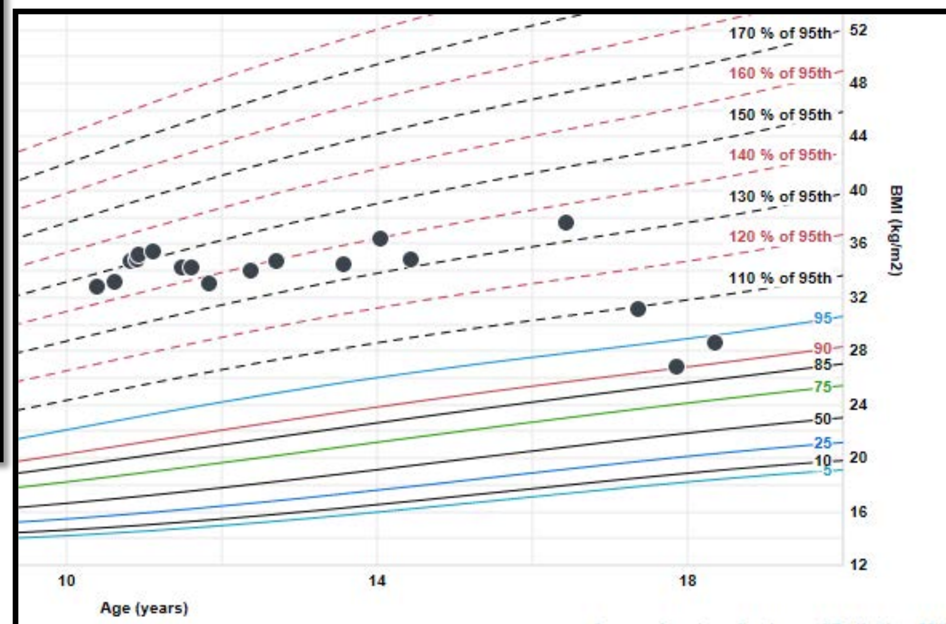
NASH-Focused Lifestyle advice

- **Diet:**
  - **Decrease/avoid sugar sweetened foods/drinks**
  - **Reduce take out/fast food meals**
- **Increase fruits and vegetables, whole foods**
- **Activity:**
  - **Increase physical activity 1 hr/day**
  - **Reduce screen time < 2 hs/day**
- **Avoid other hepatotoxins**
  - **Alcohol for teens/young adults**
  - **Immunize for Hepatitis A and B**



Lifestyle interventions can be dramatically success!





Summary: Modifiable environmental factors very important in NAFLD/NASH

- **Dietary factors very important in NAFLD/NASH**
  - Excess calories clearly a key driver in promoting steatosis
  - Specific dietary factors may increase risk of NASH
    - Intestinal dysbiosis x genetic susceptibility
- **More high quality clinical trials (RCT) needed**
  - to determine role of specific diets and supplements in treating NAFLD/NASH

Further research critical:

- **Inconsistent results of pilot studies of specific diets or supplements in NASH**:
  - Probiotics: If yes, which ones? (VSL#3, lactobacillus)
  - Omega -3 PUFAs? (DHA)
  - Low fructose vs. low carb vs. low fat vs. low calorie? Is weight loss the key driver?
  - Vitamin E - further validation, dosing, safety?
- **Impact of genetic variation on outcomes:**
  - One single nutrient or drug unlikely to work for all
- **Influence of environmental toxins and endocrine disruptors?**
  - BPA, flame retardants, heavy metals, in utero exposures

Questions?