Pediatric Non-Alcoholic Fatty Liver Disease: Assessment & Management

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Presented at the FCAAP FUTURE of PEDIATRIC PRACTICE 2022

Disclosures

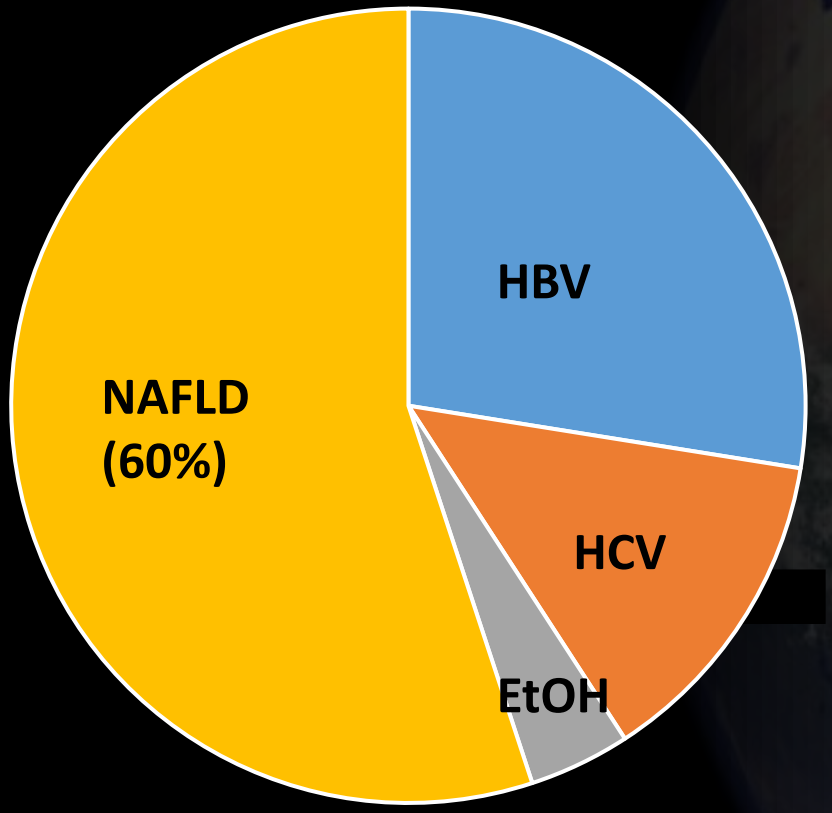
- I will be discussing unlabeled/unapproved uses of drugs in treatment of NASH in children

- I receive research funding from TargetRWE and Axcella Health, not related to the content I will discuss today.

Learning objectives

1. Review NAFLD pathogenesis, disease progression, and risk factors for disease progression in children and adolescents
2. Describe current screening and diagnosis recommendations for pediatric NAFLD and NASH.
3. Describe current treatment options for pediatric NAFLD and NASH.

NAFLD now the leading cause of chronic liver disease in the world



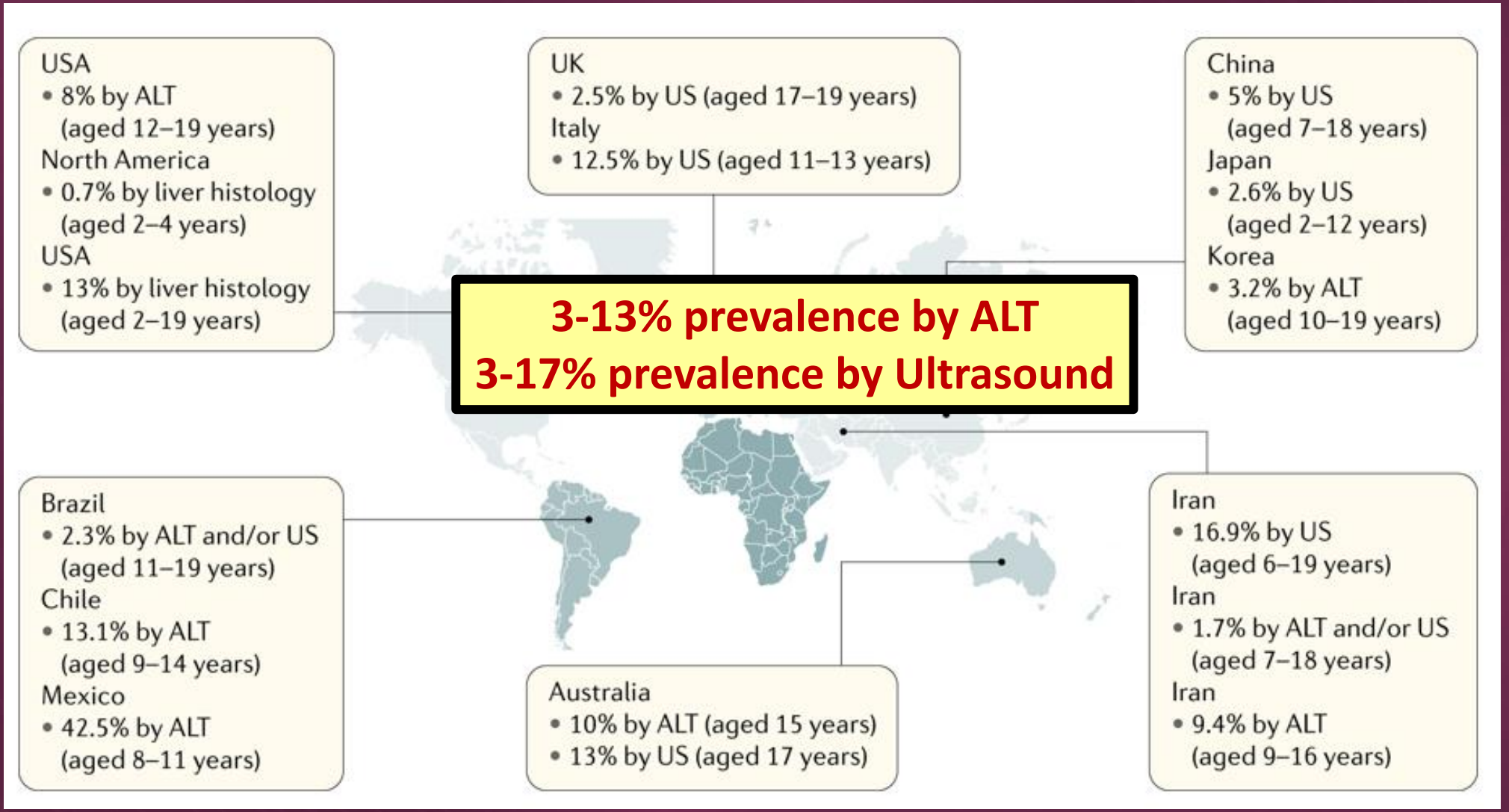
≈ 900 million NAFLD,
≈ 270 million NASH

Global Burden of Disease Study Lancet 2018:392:1789

Moon AM et al. Clin Gastroenterol Hep Aug 2019

What about NAFLD in children?

NAFLD → also prevalent in childhood

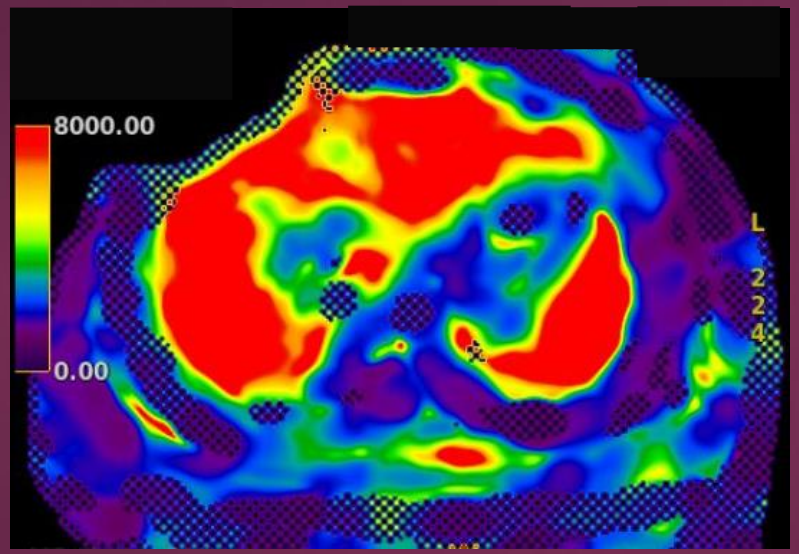


Nobili V. Nature Reviews Gastro Hepatol 2019

Mortality from all-cause cirrhosis rising most rapidly in young adults in the United States

From 2000-2019, age-adjusted death rate from all liver cirrhosis ↑26%

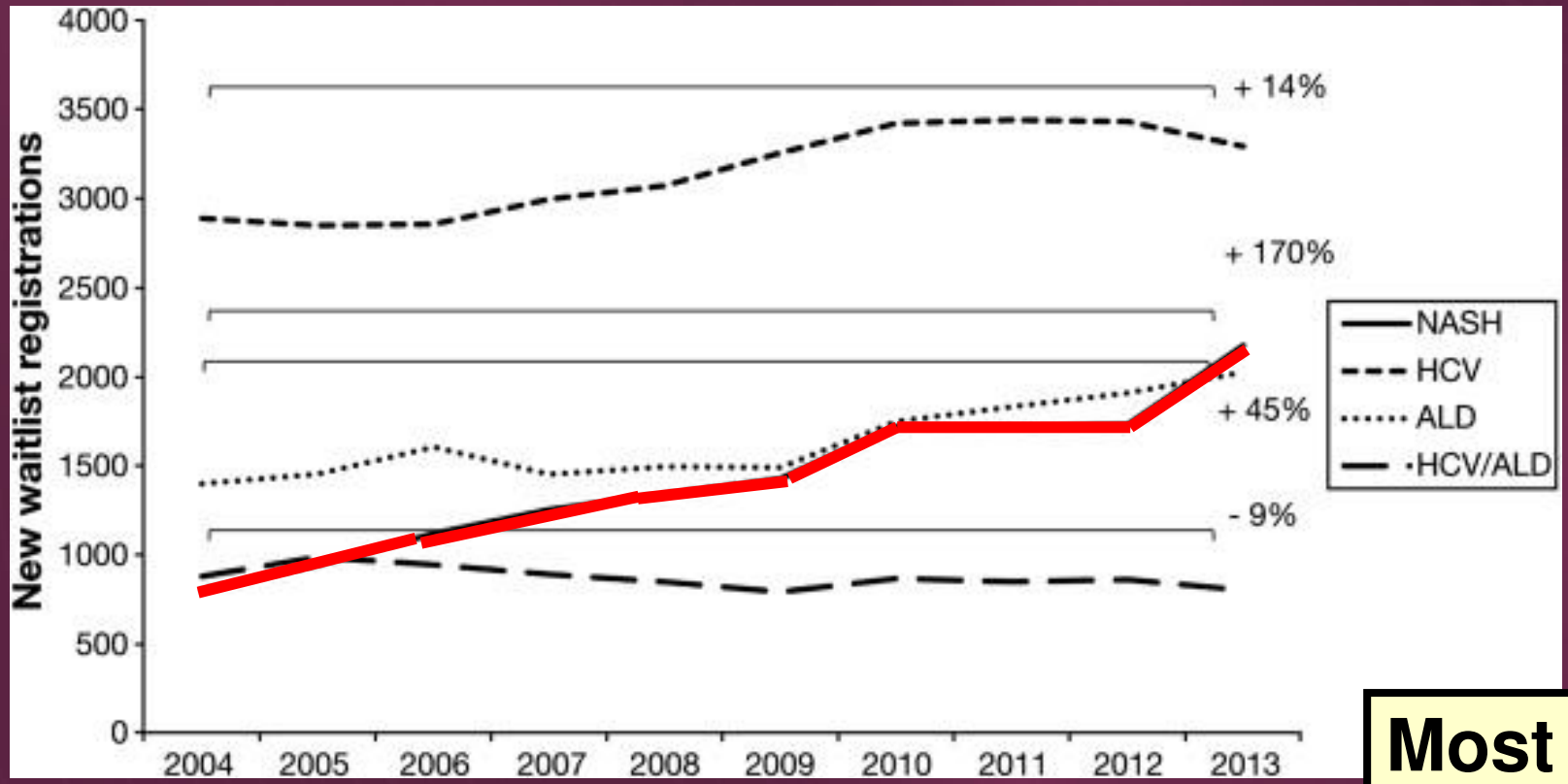
↑ 127% in millennials, 25-34 yo



MR elastogram of cirrhotic liver in 13 year old male

Moon AM. Clin Gastroenterol Aug 2019
Deaths: Leading Causes for 2017. National Vital Statistics Vol 68 (6) 2019

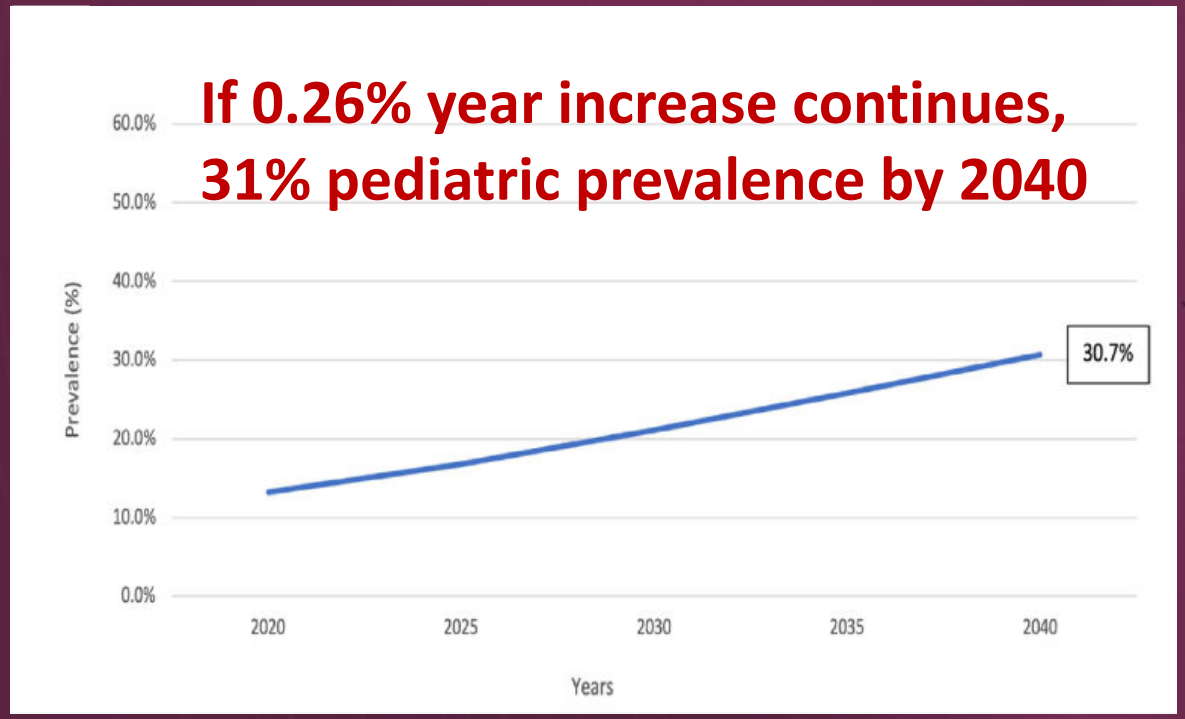
Similar ↑liver transplantation for NASH in young adults

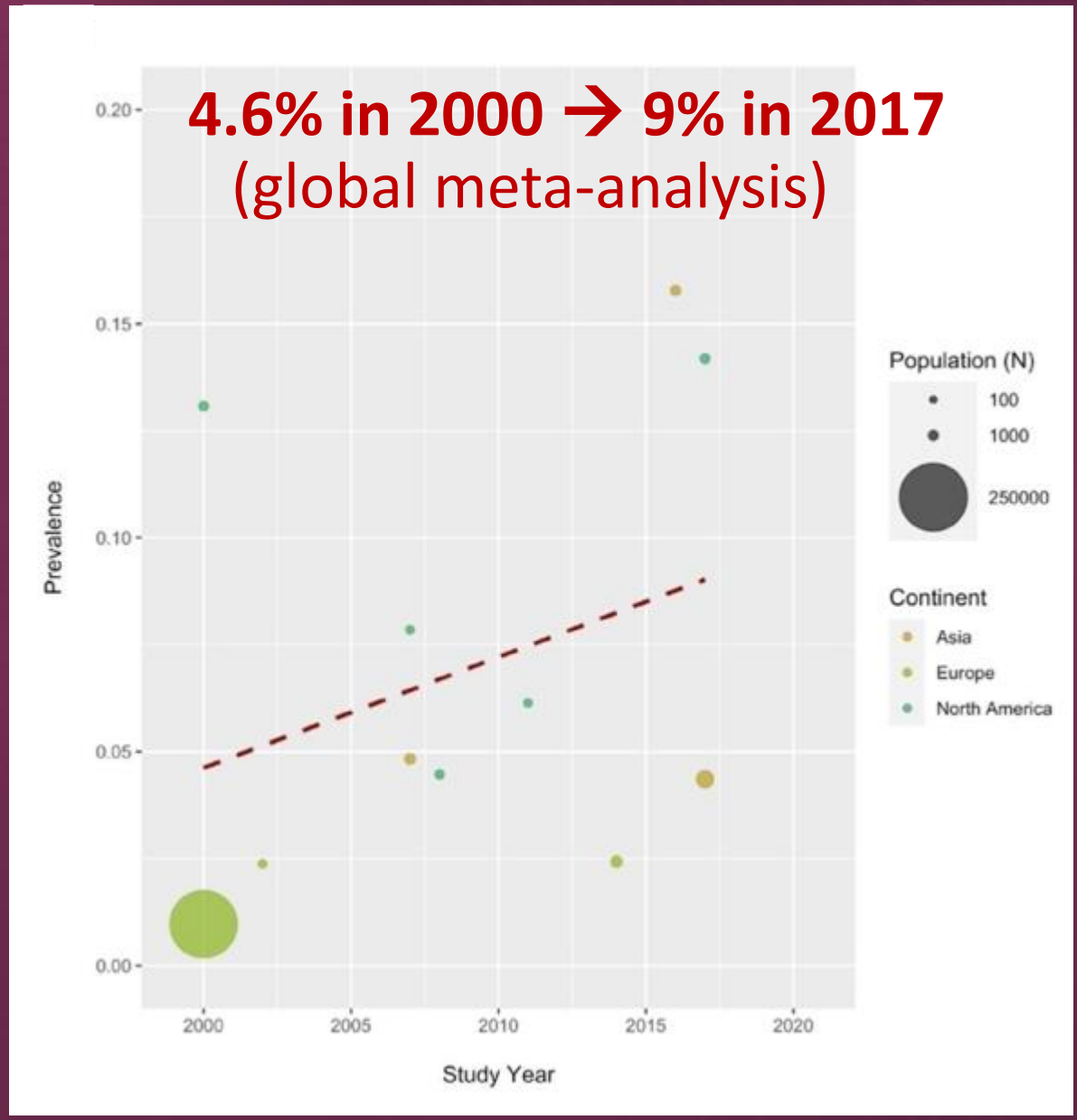


Most marked ↑ in young adults, 35-55 years old

Wong RJ et al. Gastroenterology 2015;
Eksted et al. Hepatology 2006
Shingina A. Transplantation 2019;103:140

Doubling in pediatric NAFLD in past 2 decades



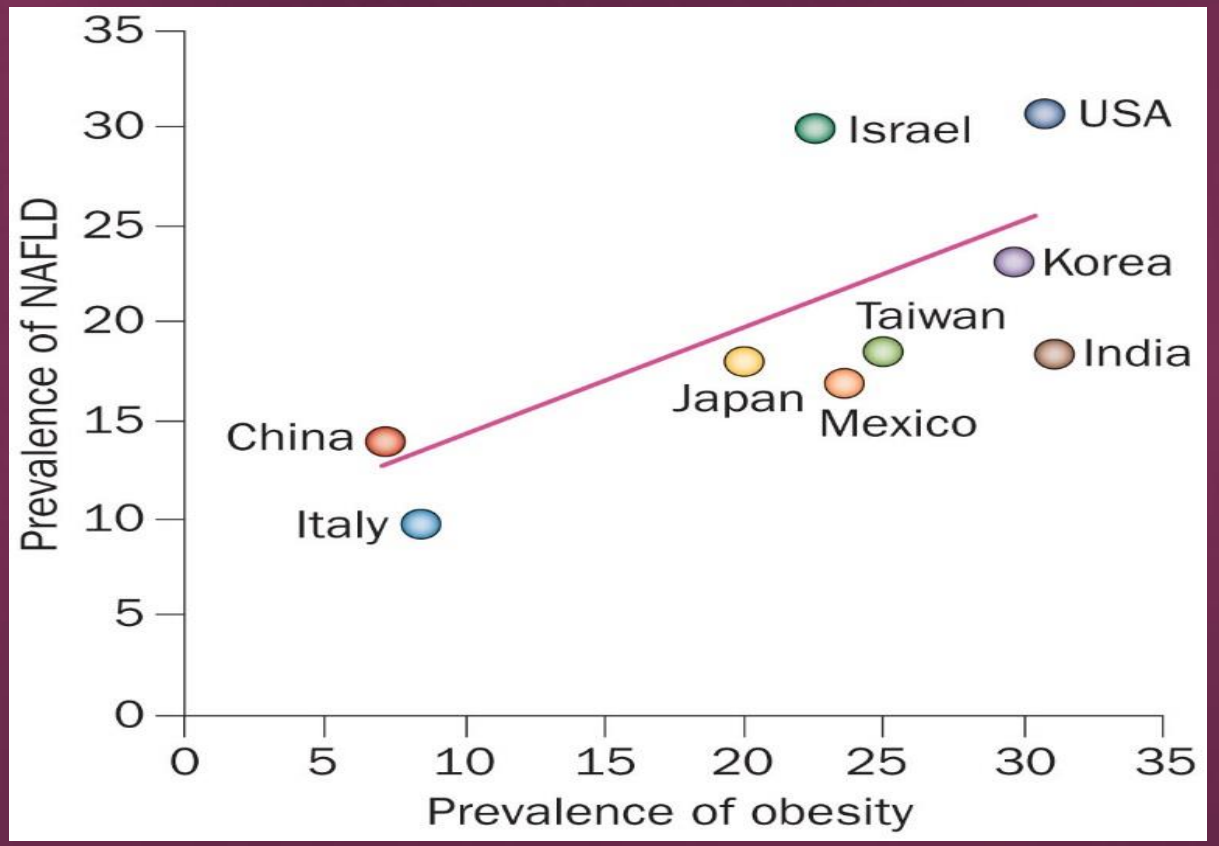


Li J. Alimentary Pharmacol & Therapeut E Pub ahead of print 6 June 2022

What environmental factors are driving this increase?

- ↑ Added sugars
- ↑ Ultraprocessed foods
- ↓ Physical activity
- ↑ Stress
- ↓ Sleep
- ↑ Endocrine disrupting chemicals

Strong association with obesity and metabolic syndrome



Loomba, R. & Sanyal, A. J. (2013) *Nat. Rev. Gastroenterol. Hepatol.*
Younossi ZM. Hepatology 2016;64:73

Early life developmental programming also may be ↑ risk of NAFLD diagnosis before age of 14 years

In nested case-control study of 5,104 children in Canada:

- **Gestational diabetes**
- **Preexisting diabetes**
- **Maternal obesity**

Soullane S. Early Human Dev 2022 Epub 2022 April 26
D01: 10.1016/j.earlhumdev.2022.105578

Earlier onset of NAFLD in very young children?

Abnormal ALT (>30 IU/L) in 1/3 (35%) of preschool children (2-6 years old) in a weight management program

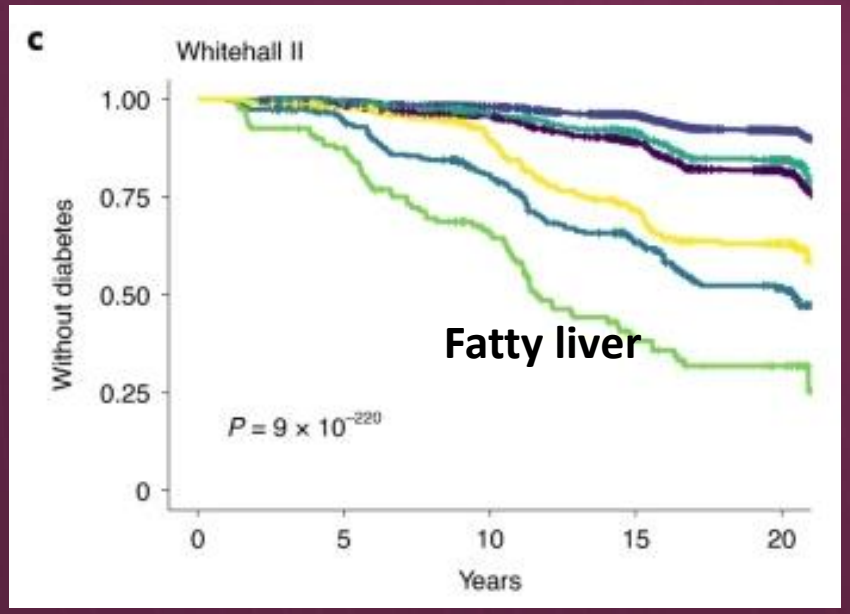
Associated with higher BMI z-score, but no other cardiometabolic risk factors

Characteristic	Total cohort n=294	ALT ≤ 30 U/L	ALT > 30 U/L N=104	P-value
Male sex %	45%	90 (47%)	41 (39%)	0.12
Hispanic ethnicity, %	19%	37 (19%)	20 (19%)	1.00
BMI z-score, median (IQR)	3.4 (2.9, 4.2)	3.2 (2.8, 3.9)	3.6 (3.0, 4.8)	0.001

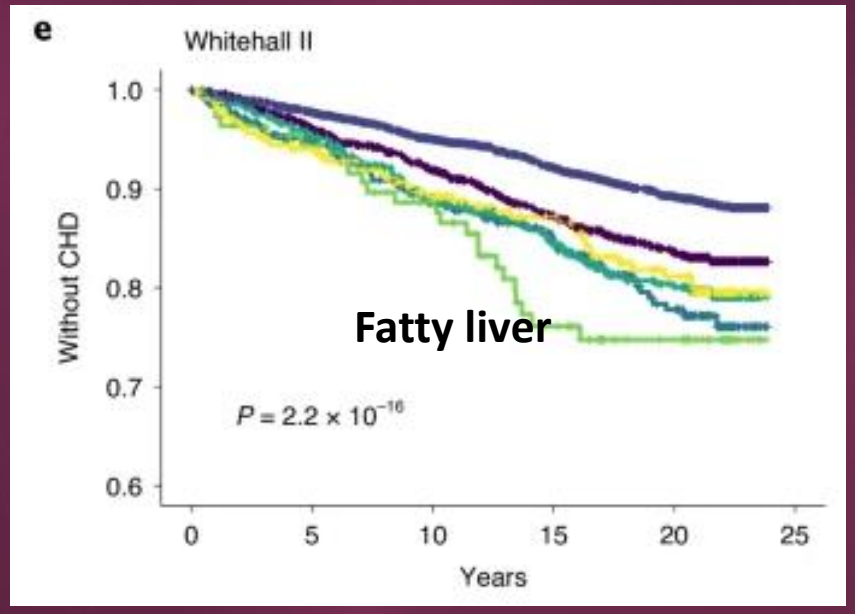
Does onset of NAFL precede development of CVD risk?

Klepper C Childhood Obesity 20 May 2022, epub ahead of print

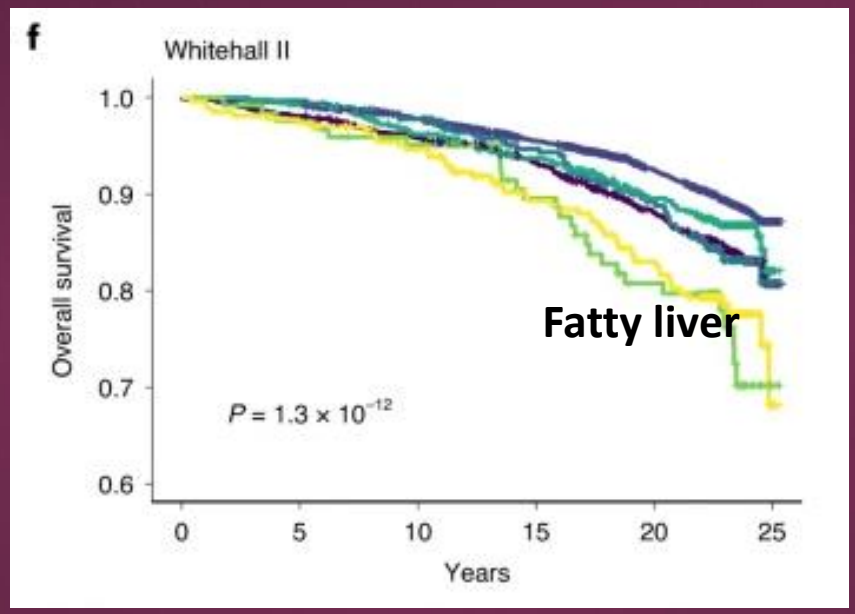
Fatty liver (MRS) in adults with prediabetes associated with ↑ risk of non-hepatic adverse outcomes



T2 Diabetes



Coronary heart disease



Mortality

Wagner R. Nature Medicine 2021;27:49

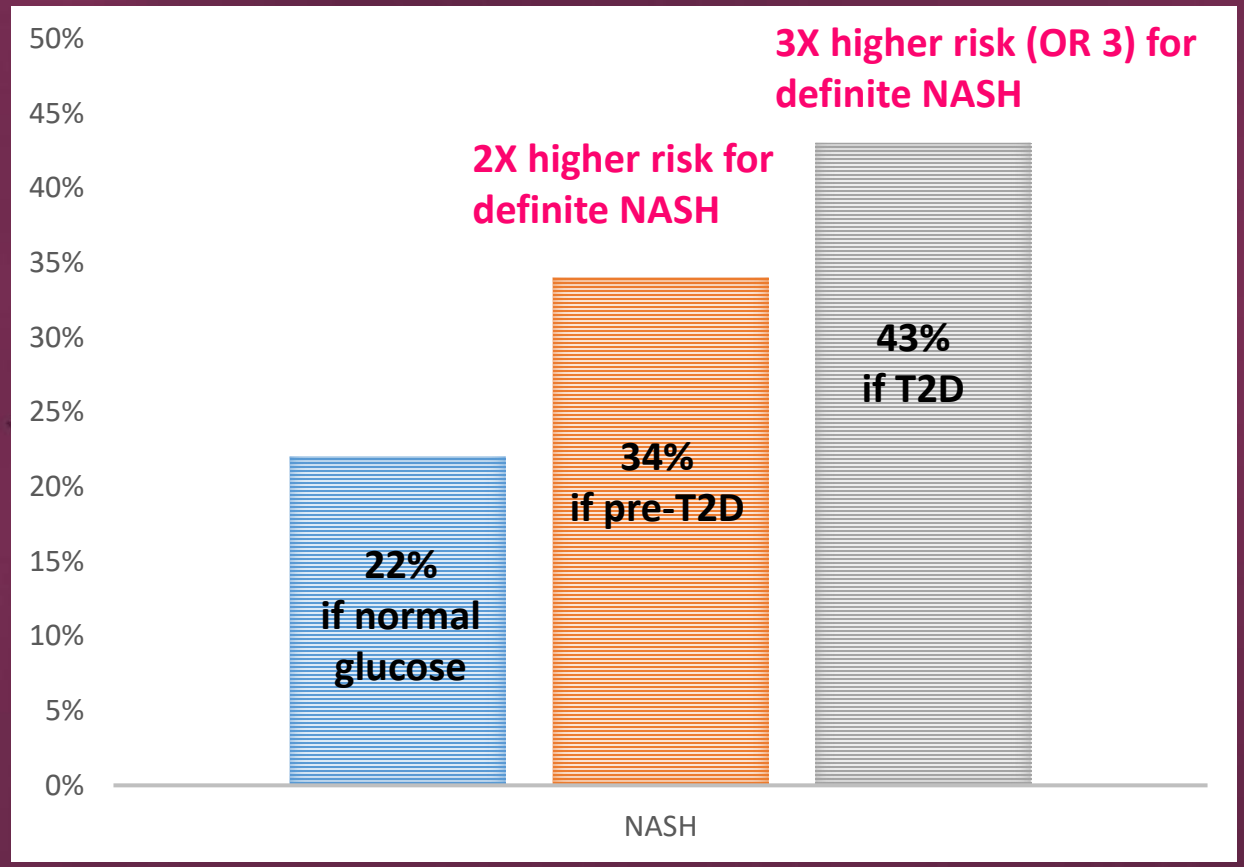
Children with NAFLD also at ↑ risk of Type 2 diabetes

675 children, biopsy-confirmed NAFLD, mean age 12, mean BMI 32.5

- **23.4% with Prediabetes**
- **6.5% with Diabetes**

In 1-2 year FU of 122 children in placebo arms of clinical trials

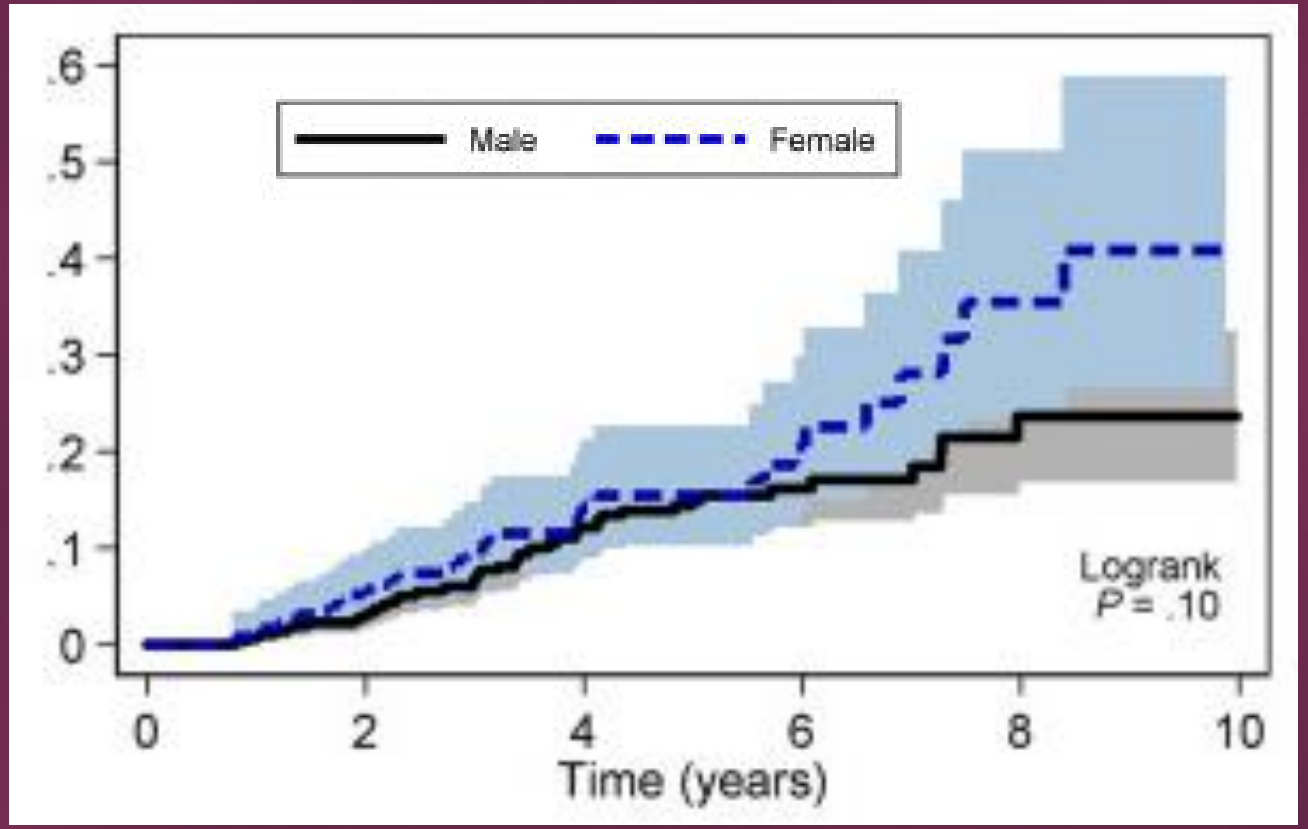
- **T2DM ↑ 2x (6% → 13%)**



Newton KP et al. JAMA Pediatrics 2016
Xanthakos et al. Gastroenterology 2020

Associated risk factors for incident T2DM in children with NAFLD

- **17% period prevalence** of T2DM over 3.8 years of FU
- Incident T2DM associated with
  - Female sex HR 1.8
  - BMI z-score HR 1.8
  - More severe liver histology
    - Steatosis grade
    - Fibrosis stage



Newton KP. Clinical Gastroenterol Hepatol 2022 epub 13 June 2022 https://doi.org/10.1016/j.cgh.2022.05.028

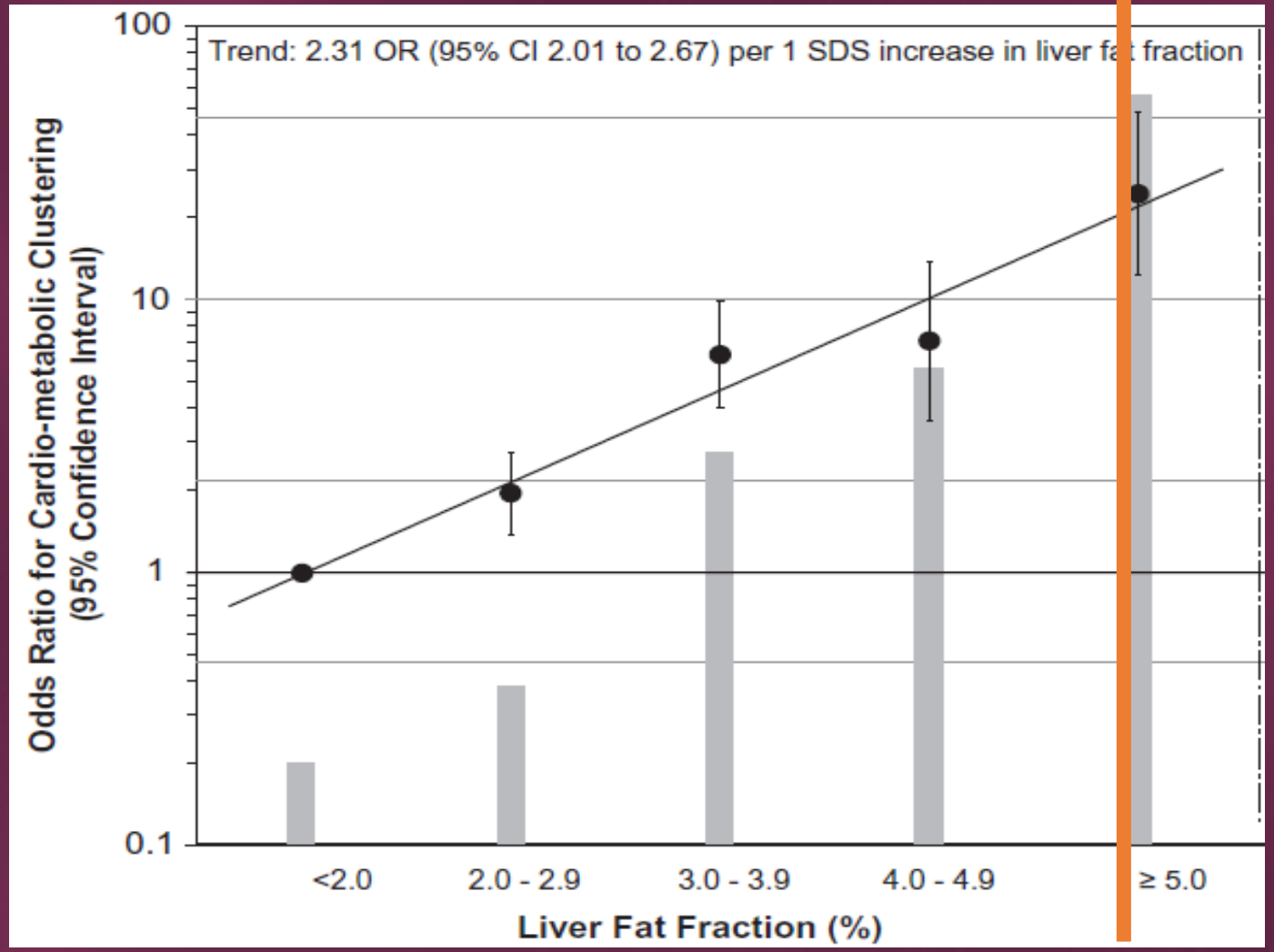
Even small ↑ hepatic fat among school age children associated with ↑ cardiometabolic risk

Population-based, prospective >3,000 children, 10-year-old

MRI-assessed **liver fat fraction**

Associated with ↑ cardiometabolic risk

- ↑ visceral fat, blood pressure,
- Dyslipidemia (↓ HDL, ↑ LDL, ↑ triglycerides)
- ↑ insulin level



Geurtsen ML et al. Hepatology 2020;72:119-29.

"Lean NAFLD" can occur in non-obese individuals

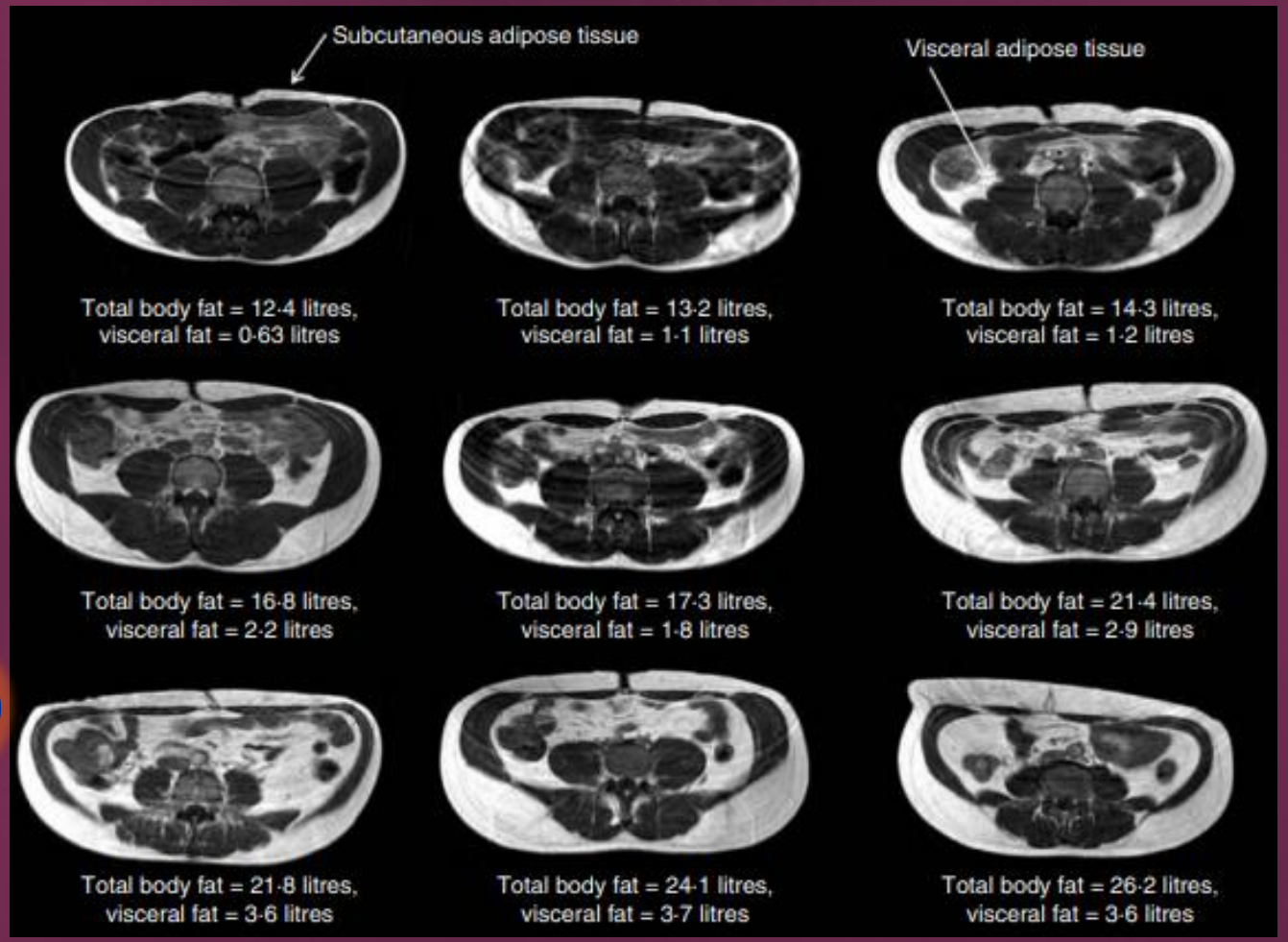
Clinical associations :

- ↑ Visceral adiposity
- ↑ Insulin resistance OR 4.2
- ↑ Triglycerides, ↓ HDL
- ↑ dietary fructose and fat intake

Prevalence

USA: 7-8% (adults/children)

Asia: 12-27%



9 Caucasian Males, all BMI 24 kg/m², visc fat 0.6-3.7L

Wei JL. Am J Gastroenterol 2015;110(9):1306
Younnossi ZM. Medicine 2012;91:319
Selvakumar C. JPGN 2018;67:75
Thomas EJ. Nutrition Research Reviews (2012), 25, 150

Should diagnostic criteria be based on metabolic dysfunction and/or obesity?

Fatty liver + ≥ 1 of following:

- **Overweight or obesity**
- **T2 diabetes**
- **2+ Metabolic risk factors**

Metabolic-dysfunction associated liver disease (MAFLD)?

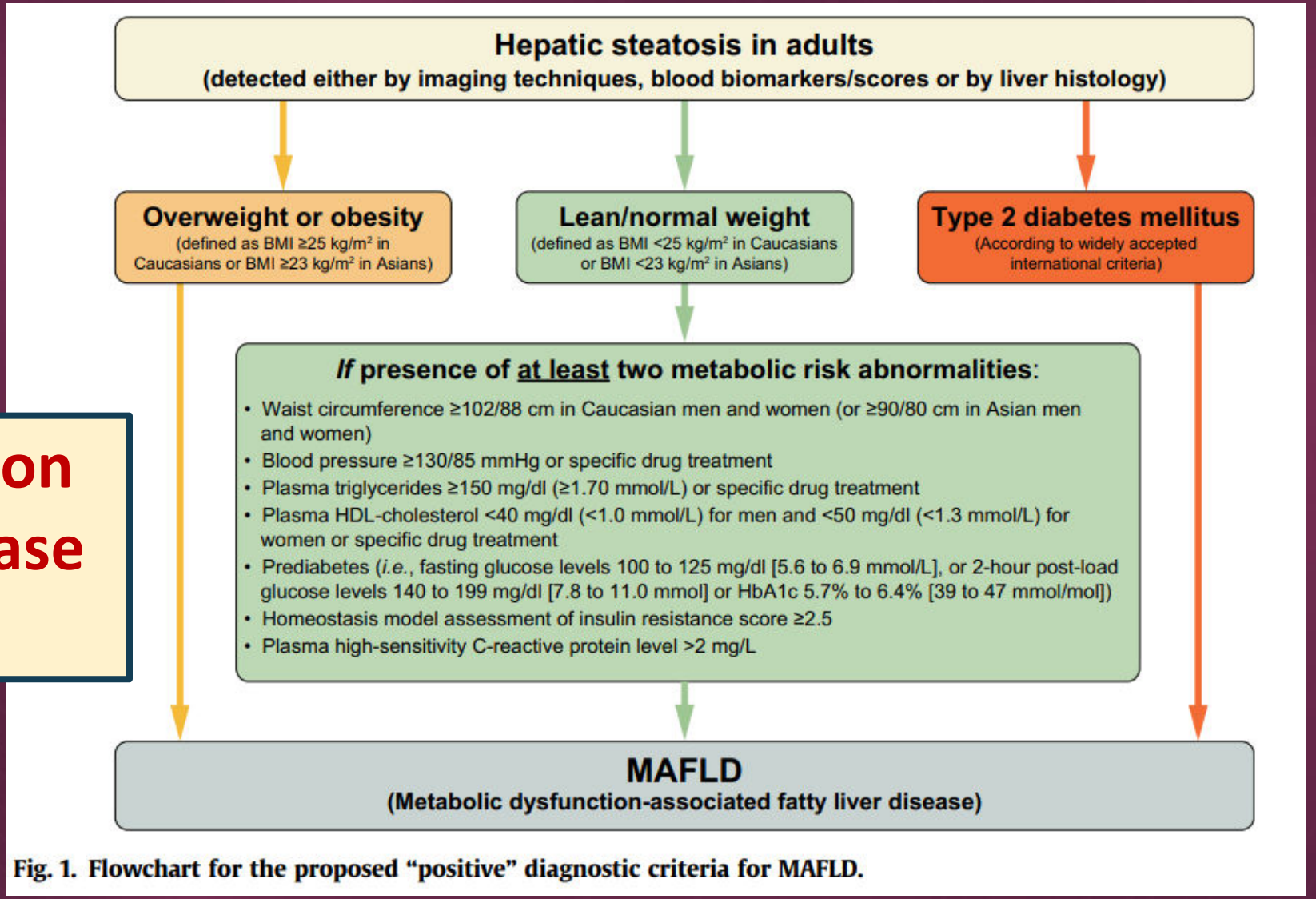


Fig. 1. Flowchart for the proposed "positive" diagnostic criteria for MAFLD.

Elsam M. Journal of Hepatology 2020;73:202

Current NAFLD Diagnosis does not require obesity or metabolic risk criteria

Nonalcoholic Fatty Liver Disease (NAFLD)

Fatty infiltration of the liver > 5% by imaging or histology

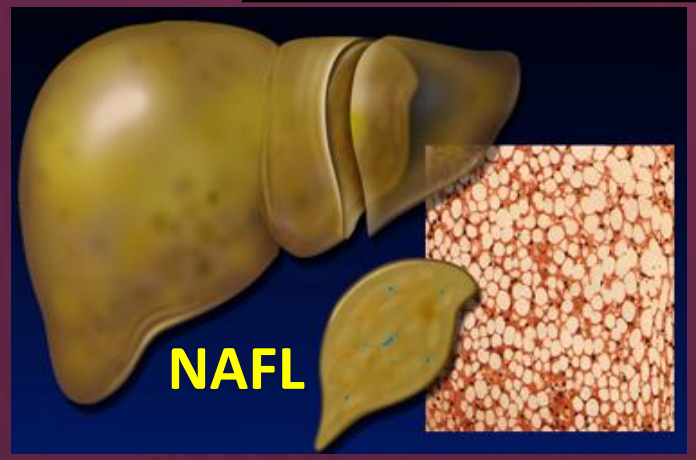
No significant alcohol intake

No viral, autoimmune, genetic or storage disease

No medications that cause steatosis

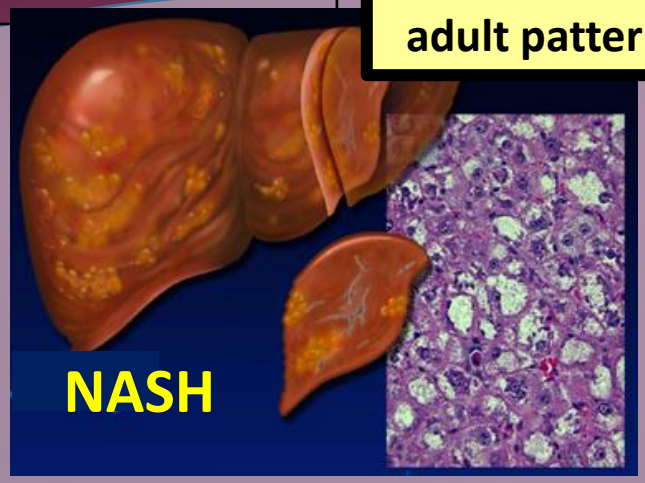
≈ 10% in US Children
≈ 26-30% in obese children

≈ 20-25% of affected children have classic adult pattern of NASH



Bland steatosis ± mild inflammation

"borderline NASH"



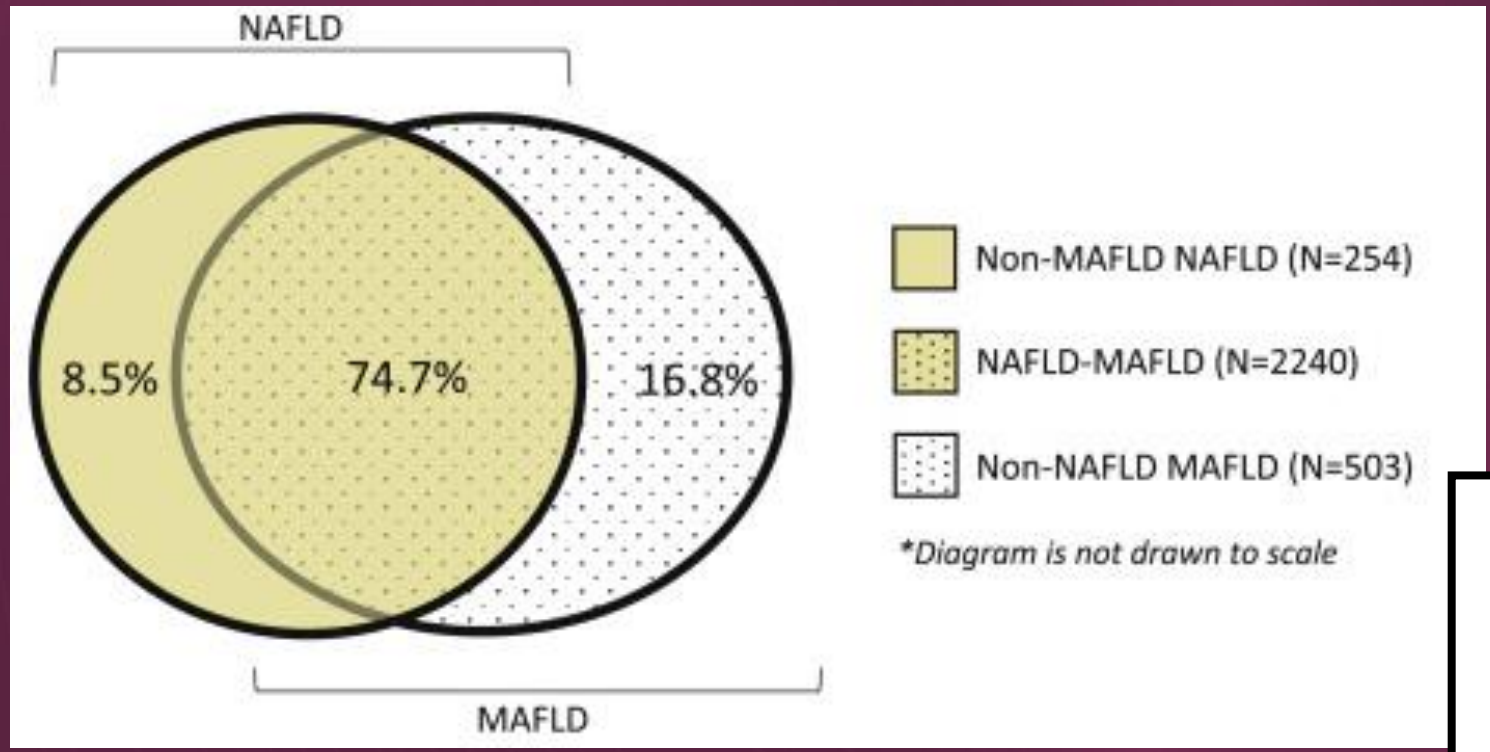
Steatosis with inflammation + hepatocellular injury (ballooning)

Full spectrum of fibrosis possible in both NAFL and NASH

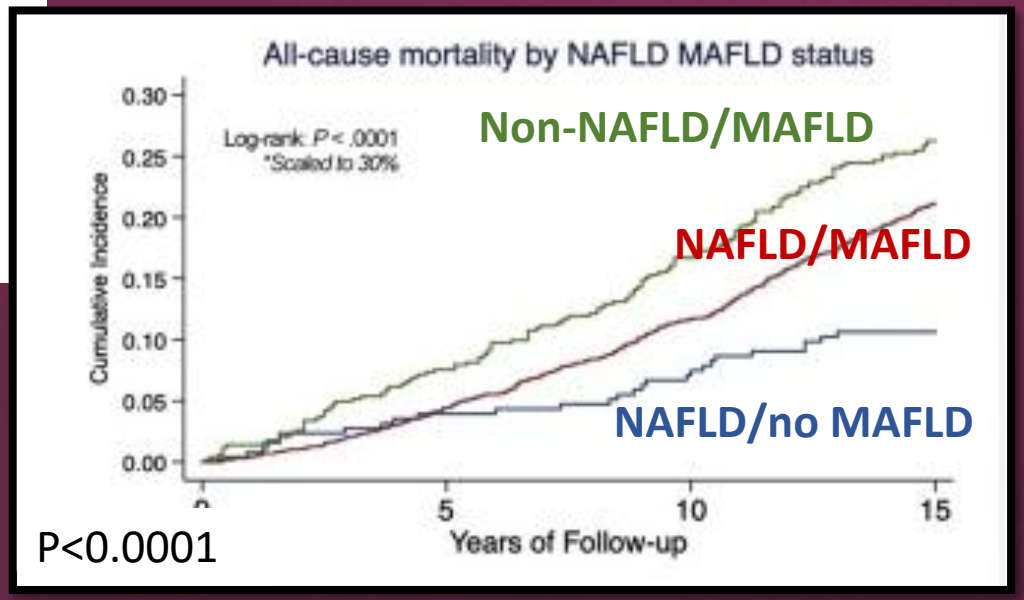
None — Mild — Moderate — Severe

≈ 10-15% have ≥F3

Both "MAFLD" and "NAFLD + metabolic risk" are associated with ↑ risk of adverse outcomes



MAFLD may co-exist with viral hepatitis, alcohol use or other liver diseases which can further worsen outcomes



Nguyen V. Clinical Gastroenterol Hepatol 2021;19:2172.

Screening and Diagnosis of NAFLD and NASH in Children

ALT most widely used biomarker for NAFLD

- *Biological norms in healthy, non-overweight children <30 U/L*

ALT 25.8 U/L for BOYS
ALT 22.1 U/L for GIRLS

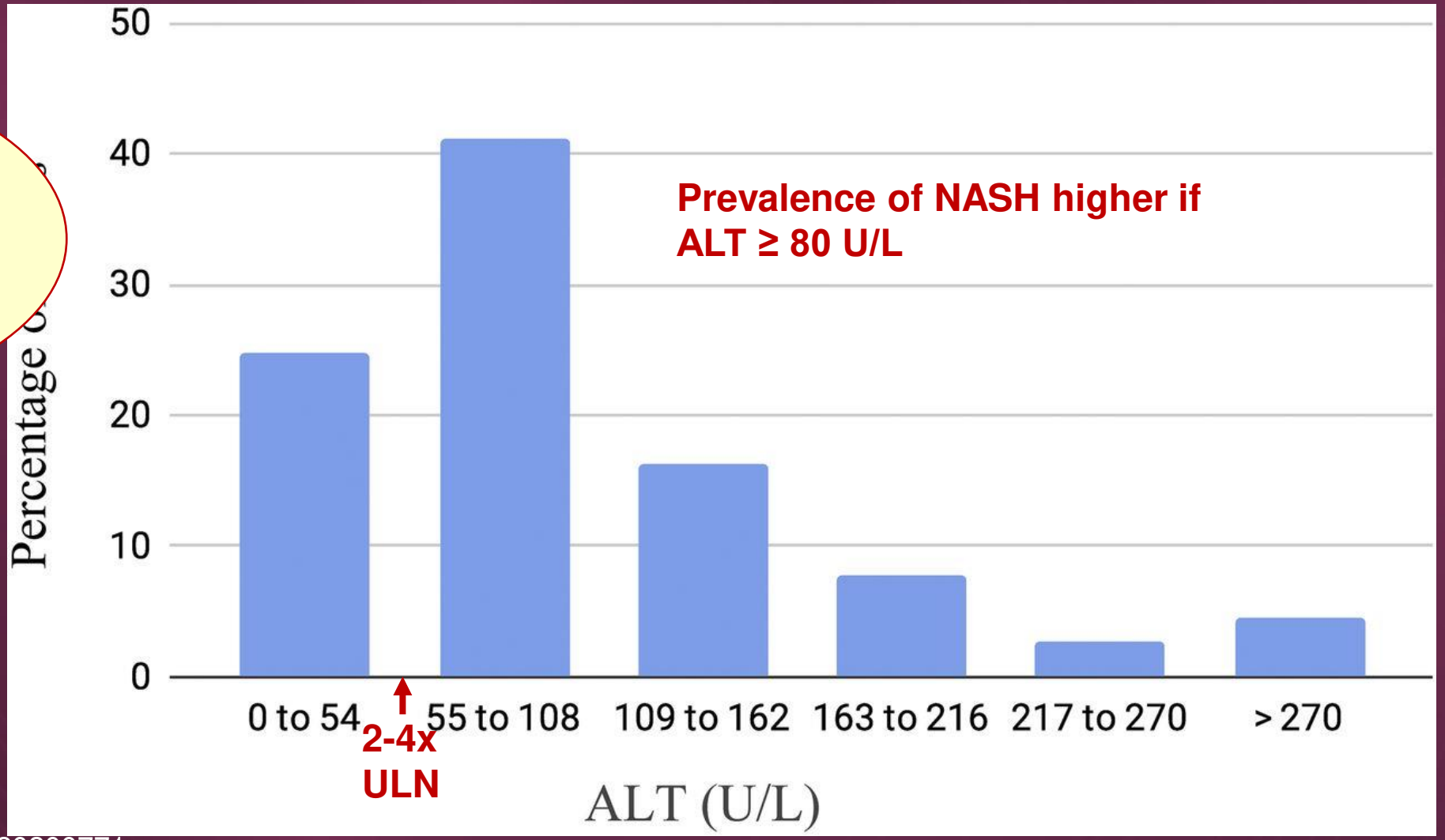
- *But for detection of NASH, most guidelines propose*

ALT > 2x ULN (45-50 U/L)

Loomba R, Clin Gastro Hep 2008; 6(11):1243-8
Schwimmer JB. Gastroenterology 2010;138:1357
Vos MB. JPGN 2017;64: 319.
Styne DM. J Clin Endocrinol Metab 2017;102:709
Vajro P. JPGN 2012;54:700
Barlow SE. Pediatrics 2007;120:S164

Majority of children (75%) with NAFLD have elevated ALT > 2 x ULN

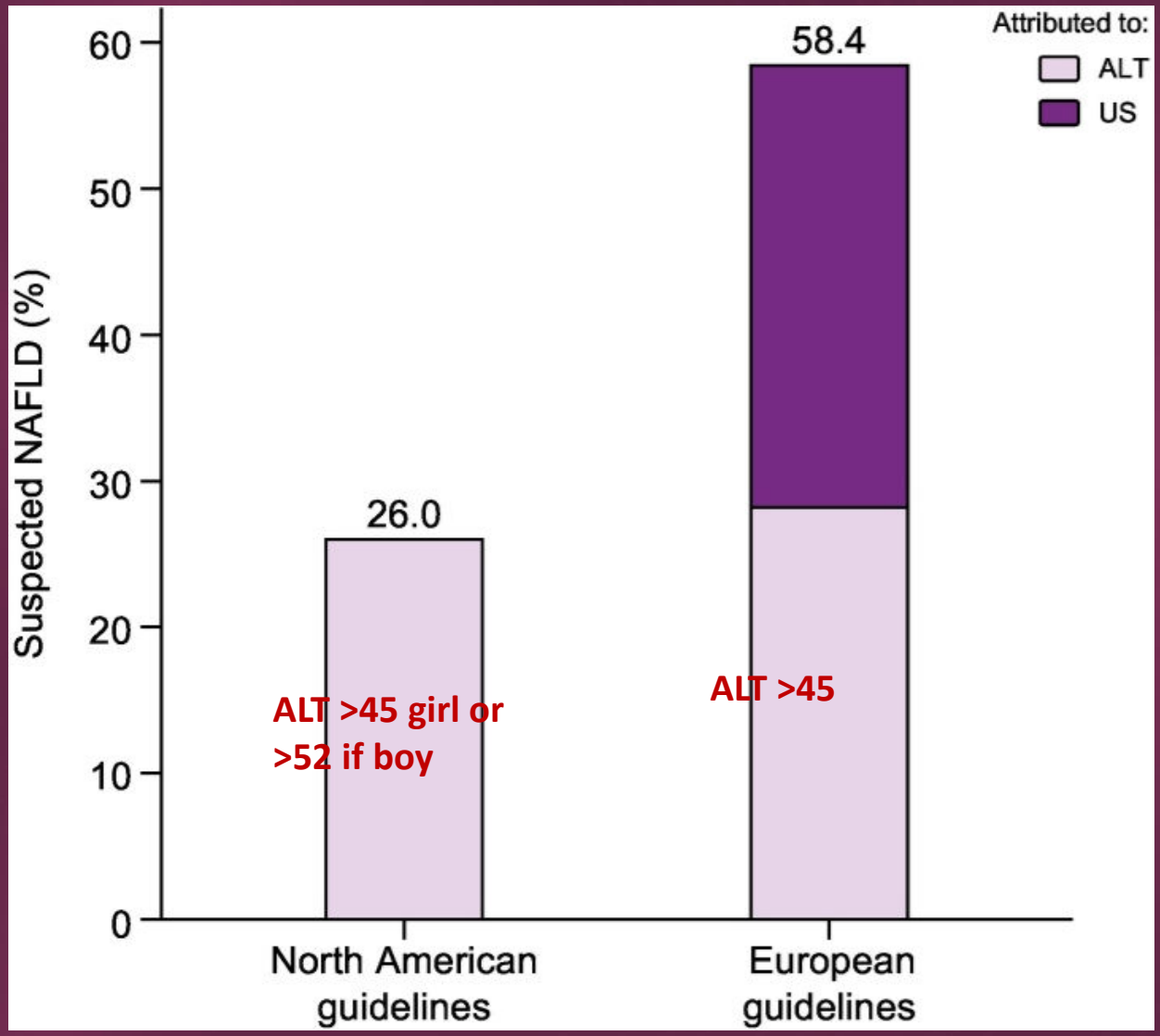
But ALT can be **normal or mildly** elevated, with NASH, fibrosis or cirrhosis



Sahota AK et al. Pediatrics 2020;146:e20200771

Adding imaging to diagnosis increases detection of NAFLD

% with NAFLD diagnosis



Ezaizi Y. JHEP Reports 2019:1:259

When to refer to Pediatric Gastroenterology/Hepatology for evaluation of other causes

RED FLAG Signs or symptoms (acute or advanced liver disease)

- abdominal pain, GI bleeding, ↑ INR, jaundice or ↑direct bilirubin, splenomegaly, firm or enlarged liver, ↓platelets or WBC, chronic fatigue, chronic elevated liver enzymes (>2 years) or rapidly rising liver enzymes

Initial ALT ≥ 80 U/L (recheck in 1-2 weeks, and get CBC, PT/INR)

- Higher likelihood of having NASH

Liver aminotransferase levels not improving or worsening after 3-6 months of lifestyle counseling, for evaluation for other causes

- Viral hepatitis, autoimmune hepatitis
- Storage diseases, inborn errors in metabolism
- Alcohol use (in older teens)
- Medication toxicity

Vos MB. JPGN 2017;64: 319.

Exclusionary testing for reference

Condition	Testing
Viral hepatitis	Hepatitis B, C serologies (Hepatitis A, EBV, CMV if indicated)
Autoimmune hepatitis	Autoantibodies: ANA, ASMA, ALKM autoantibodies, serum IgG, possibly liver biopsy
Alpha-1 antitrypsin	Phenotype
Hemochromatosis	Serum iron, total iron binding capacity, ferritin (genetic testing if indicated)
Wilson disease	Serum ceruloplasmin, 24 hour urine copper, (genetic testing if indicated, possibly liver biopsy)
Celiac disease	Serum tissue transglutaminase antibody, total IgA
Medication toxicity	valproic acid, methotrexate, corticosteroids, valproic acid, HAART
Alcohol use	Adolescents ≥ 12 years of age
Hypothyroidism	TSH, free T4
Gallbladder disease/Liver mass	Abdominal US to rule out gallbladder disease, hepatic masses, etc. **(NOTE: normal US does not exclude NAFLD)**
Genetic and metabolic disorders, esp in very young or not obese	Fatty acid oxidation, lysosomal acid lipase deficiency, lipodystrophies, abeta-hypobeta lipoproteinemia, mitochondrial or peroxisomal disorders (may require liver biopsy)

Vos MB. JPGN 2017;64: 319

Alternative causes of liver disease – how common are they among children with presumed NAFLD?

Two center study (Cincinnati Children's and Yale)

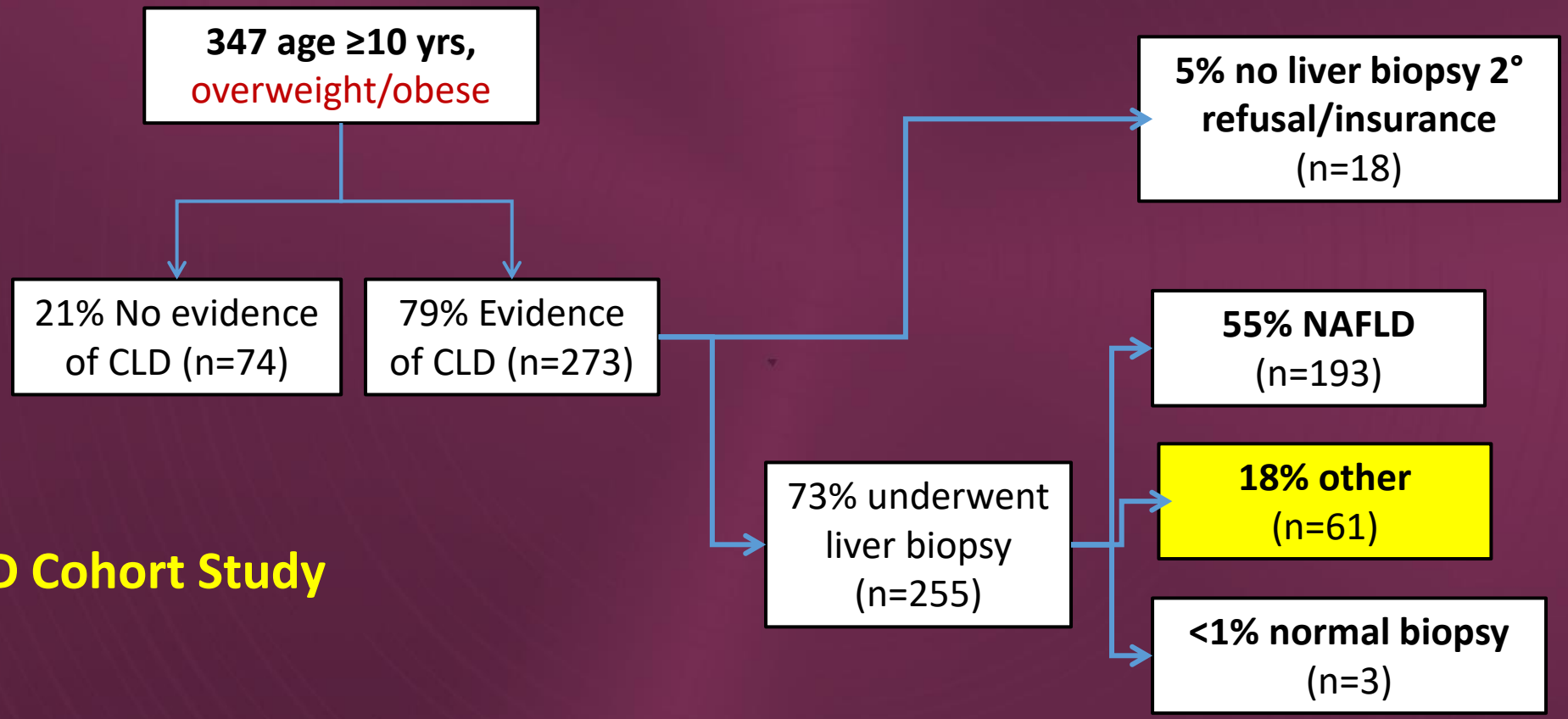
Out of 900 children with overweight and obesity (median age 13, 63% male, 26% Hispanic):

Only 19 (2%) were found to have alternate causes

- **11 with treatment-requiring hypothyroidism**
- 3 with celiac disease
- 3 with A1AT deficiency
- 1 with Hemophagocytic Lymphohistiocytosis

Yodoshi T. Pediatrics 2021;147(4):e202009829

But this may vary by region:



UCSD Cohort Study

Schwimmer JB. Alimentary Pharmacol Therapeutics

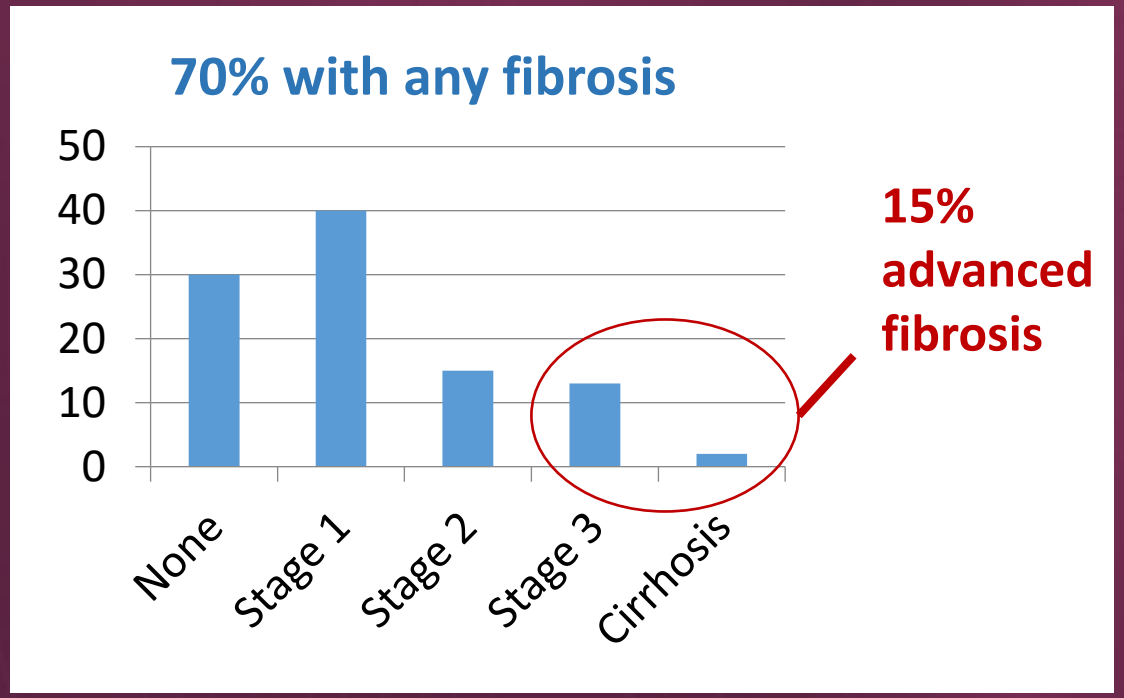
If no other etiologies of CLD*:

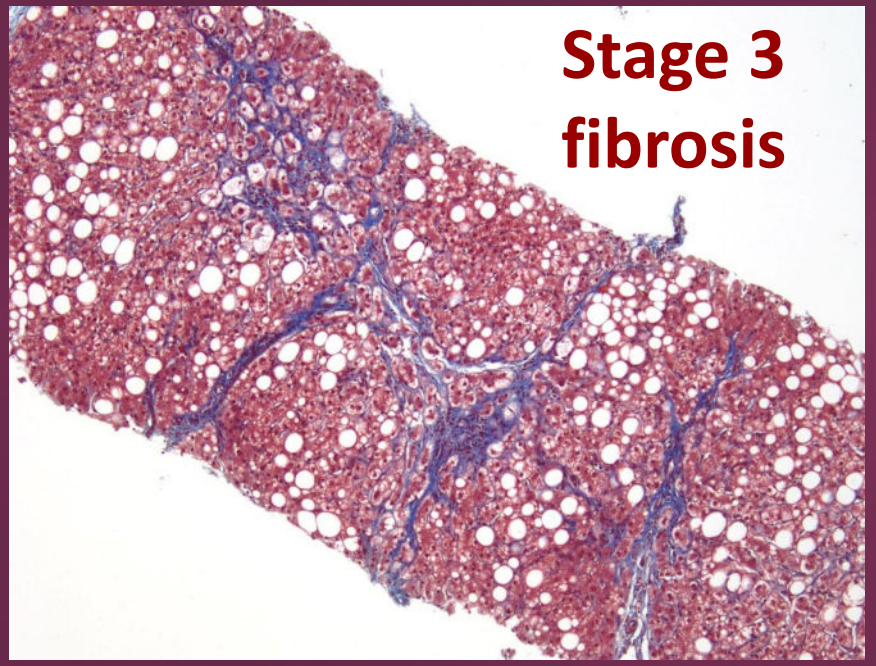
PRESUMED DIAGNOSIS

Nonalcoholic fatty liver disease

*sometimes NAFLD can co-exist with other diseases, such as hepatitis C, autoimmune liver disease, cholelithiasis

High prevalence of fibrosis in children at diagnosis in NASH CRN cohort



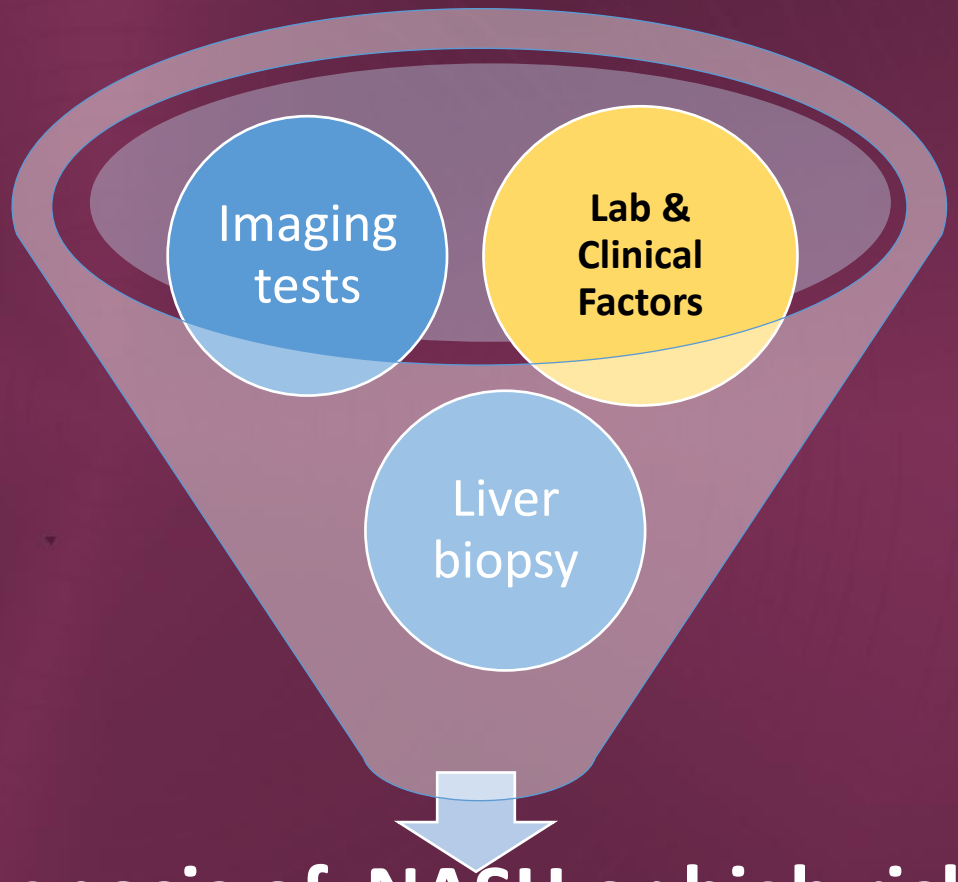


675 children from 12 USA sites, mean age 13 years, mean BMI 32, z score 2.3

NASH Clinical Research Network

Newton KP. JAMA Pediatrics 2016:170: e161971

How can we identify children at greater risk of severe liver disease or adverse outcomes?



Diagnosis of NASH or high risk of adverse outcomes

Clinical characteristics associated with more severe disease

- Markers of more advanced liver disease
  - ↑ ALT, GGT elevation
  - ↓ platelet counts
- Metabolic risk factors
  - Abdominal obesity
  - Higher serum triglycerides
  - Insulin resistance and prediabetes/Type 2 diabetes mellitus
- Advancing Age? Peri and post pubertal in some analyses
- Race/ethnicity (genetic polymorphisms, e.g. PNPLA3)
  - Hispanic or Indigenous American > White or Asian> Black

Current proposed pediatric fibrosis prediction algorithms perform poorly

		Formula	Detection
AST to ALT Ratio	AAR	AST (U/L)/ALT (U/L)	F0 vs F1-F4
AST to Platelet Ratio	APRI	[AST (U/L)/AST 40 U/L as ULN]/platelet number x 100	F0-1 vs. F2-4
Paediatric NAFLD Fibrosis Index	PFNI	Model including age, waist circumference, triglycerides	F0 vs F1-F4
Paediatric NAFLD Fibrosis Score	PNFS	Model including ALT, alkaline phosphatase, platelets, GGT	F0-2 vs. F3-4
Fibrosis-4	FIB-4	(age × AST)/(platelet count × √ALT)	F0 vs F1-F4

In validation study in children: AUROC only 0.51- 0.67

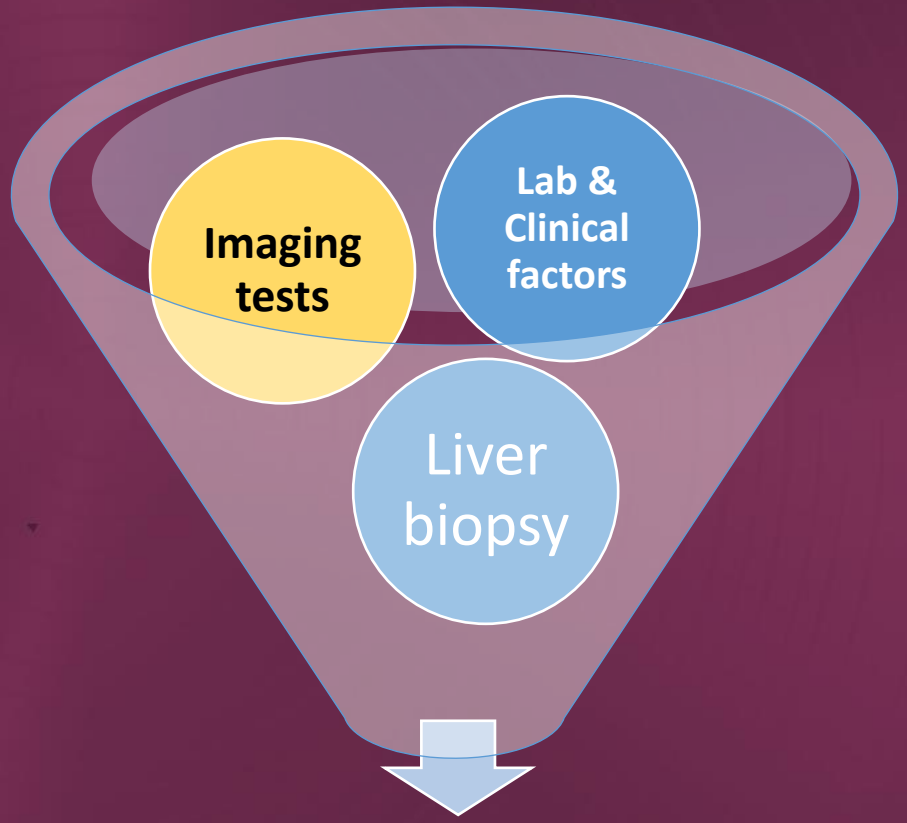
Jackson J. Journal Paediatrics and Child Health 2018;54:172

Several fibrosis scores perform well in adults

Test		Formula
NAFLD Fibrosis Score	NFS	Age, BMI, IFG/diabetes, AST, ALT, albumin, platelets
FibroTest/FibroSure		α2 macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, age, gender
Enhanced Liver Fibrosis	ELF	hyaluronic acid, aminoterminal propeptide of type III collagen, and TIMP1
Fatty Liver Index	FLI	Waist circumference, BMI, TG, GGT
Fibrosis-4	FIB-4	(age × AST)/(platelet count × √ALT)

But not sufficiently validated in children

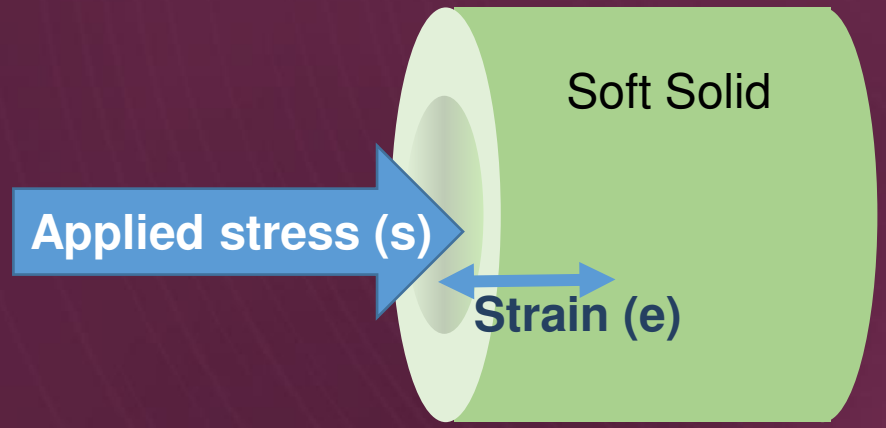
What about imaging?



Elastography: measures tissue elasticity

Basic principles

- Induce transient mechanical stress of target tissue by external or internal forces
- Measure speed of the induced tissue movement (strain) or wave propagation
- Quantify tissue elastic properties from the measured displacement of tissues



Stiffer tissues move less (lower strain) after induced stress

↓

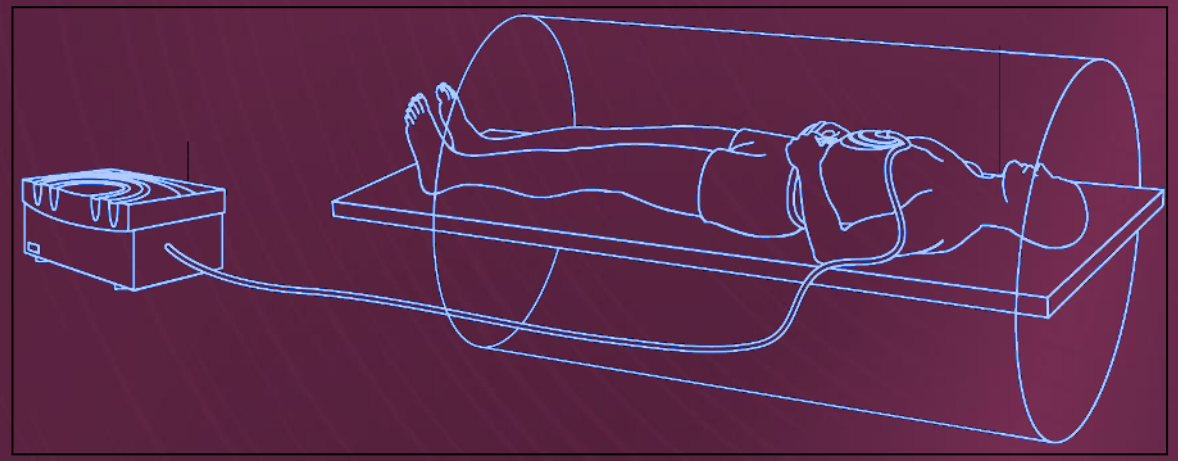
Faster wave propagation through the tissue which is measured by the device

Ultrasound (US) and Magnetic Resonance (MR) Elastography Options

Ultrasound (US)-based elastography:

- Transient Elastography (TE)
- Acoustic Radiation Force Imaging (ARFI)
- Shear Wave Elastography(SWE)

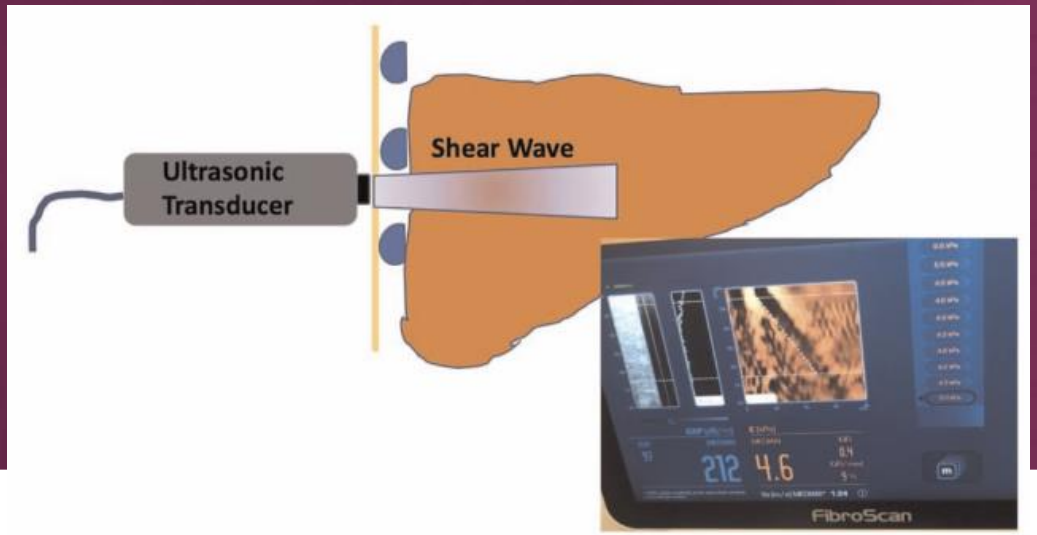
MR elastography (MRE)



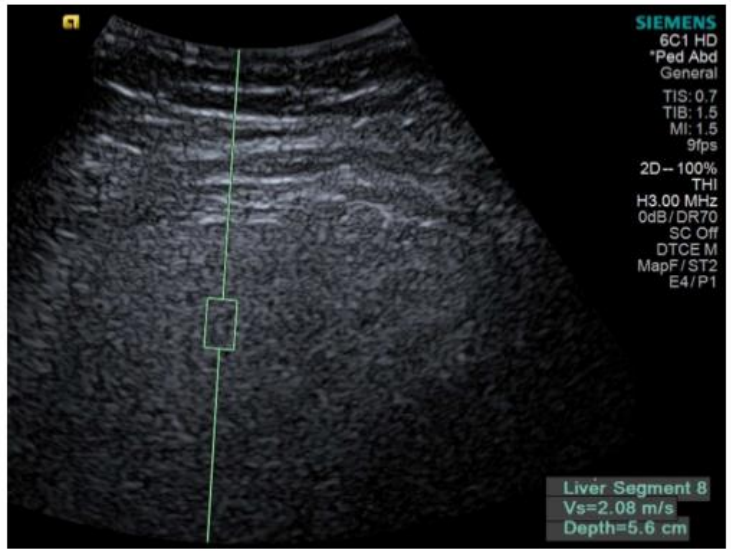
US device with integrated ARFI technology

VCTE device

Transient Elastography



US-shear wave elastography



PROs	• **Painless and fast** • **Point of Care** • **Samples > liver area than biopsy** • **Less expensive vs. MRI** • **Can assess steatosis severity (CAP score, only with M and XL probes)**	• **Includes ultrasound image** • **Not affected by ascites** • **Samples greater area than TE** • **Less expensive than MRI**
CONS	• **Limited by severe obesity** • **Not accurate if ascites** • **Only right lobe**	• **Less accurate with rising obesity** • **Smaller liver area sampled** (vs. MRE) • **Not point of care test**
FDA	• S, M probes approved for children	• Some vendors approved

Banc-Husu A. JPGN 2021:73:141

Caveats of US-based elastography in Pediatric NAFLD

Not validated in large, multicenter cohorts

- **No validated accuracy in pediatric severe obesity** (more severe pediatric obesity in USA)
- **No well-validated pediatric cut-offs** for varying degrees of fibrosis and steatosis in pediatric NAFLD

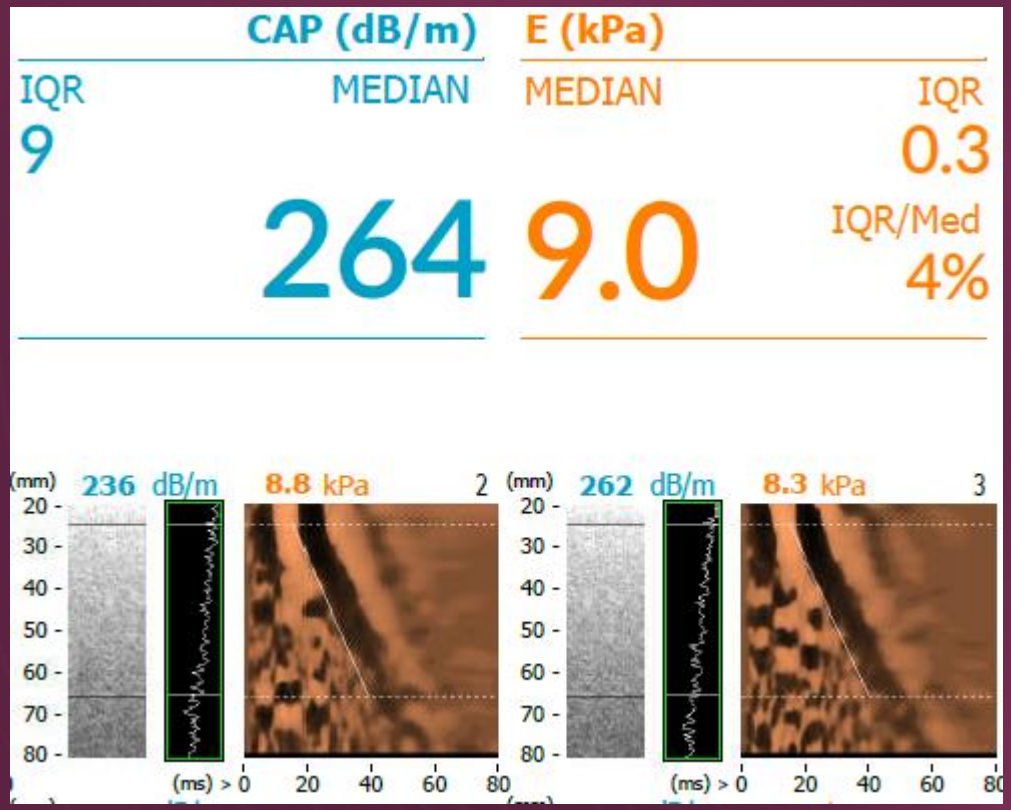
Mean CAP (SD) scores	No steatosis CAP	Mild/Moderate Steatosis CAP	Severe Steatosis CAP	≥F3 Fibrosis kPa
Desai 2016, 69 children (n=14 with NAFLD)	**Mean 198 ± 37**	**Mean 265 ± 53**	**Mean 313 ± 25**	**9** (Nobili 2008)
Eddowes 2019, 404 adults NAFLD, M and XL probes	mean 250	>302 (mild) or >331 (mod)	>337	**9.7**

No longitudinal correlation data with disease progression and outcomes

Desai N et al. J Pediatric 2016;173:160;
Eddowes P et al. Gastroenterol 2019;156:1717
Nobili V et al. Hepatolo 2008:48:442

Example of Fibroscan with good correlation with biopsy

Male, age 8, BMI 38 (z=2.82, 180% of the 95th%ile), ALT 118, AST 69, GGT 86

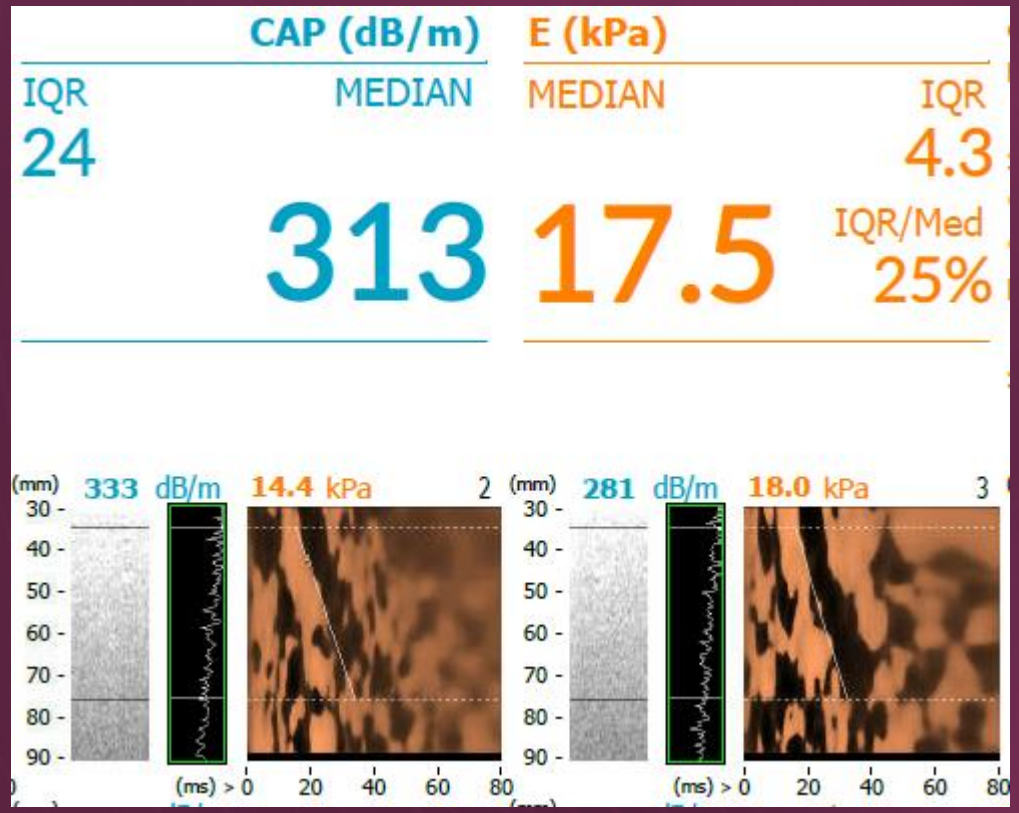


Biopsy: consistent with NASH, adv fibrosis

- **Steatosis 40-50% (Moderate)**
- **Mild ballooning and lobular inflammation**
- **Advanced fibrosis (early stage 3)**
  mild portal/periportal with delicate early bridging

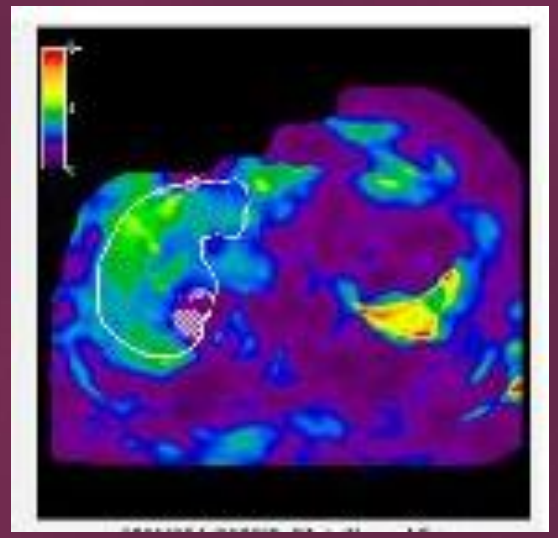
Example of Fibroscan with poor correlation with MRI and biopsy

14 yo male, BMI 53 (z 2.99, 205% of 95th%ile) , ALT 146, AST 82, GGT 34



Biopsy: consistent with NASH, mild fibrosis

- **Steatosis >66% (Severe)**
- **Moderate ballooning + lobular inflammation**
- **Fibrosis 1c (mild) portal/periportal**



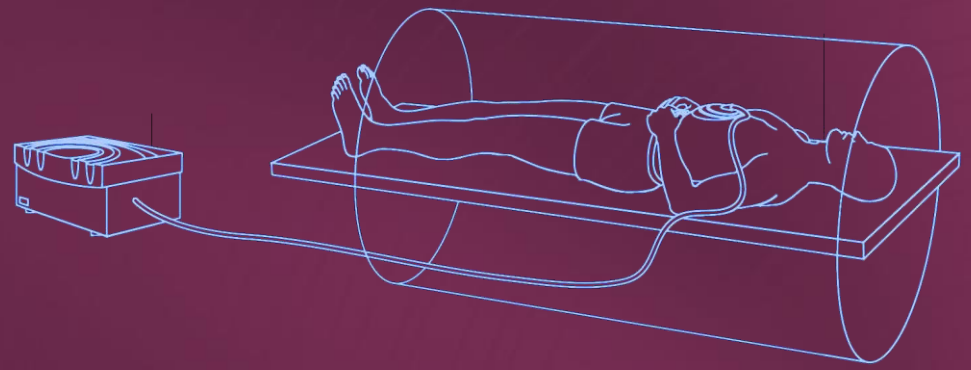
MRI elastography and PDFF

Fat fraction 34%

Stiffness mild ↑ 3 kPa

(not c/w cirrhosis)

MRI: Pros and Cons

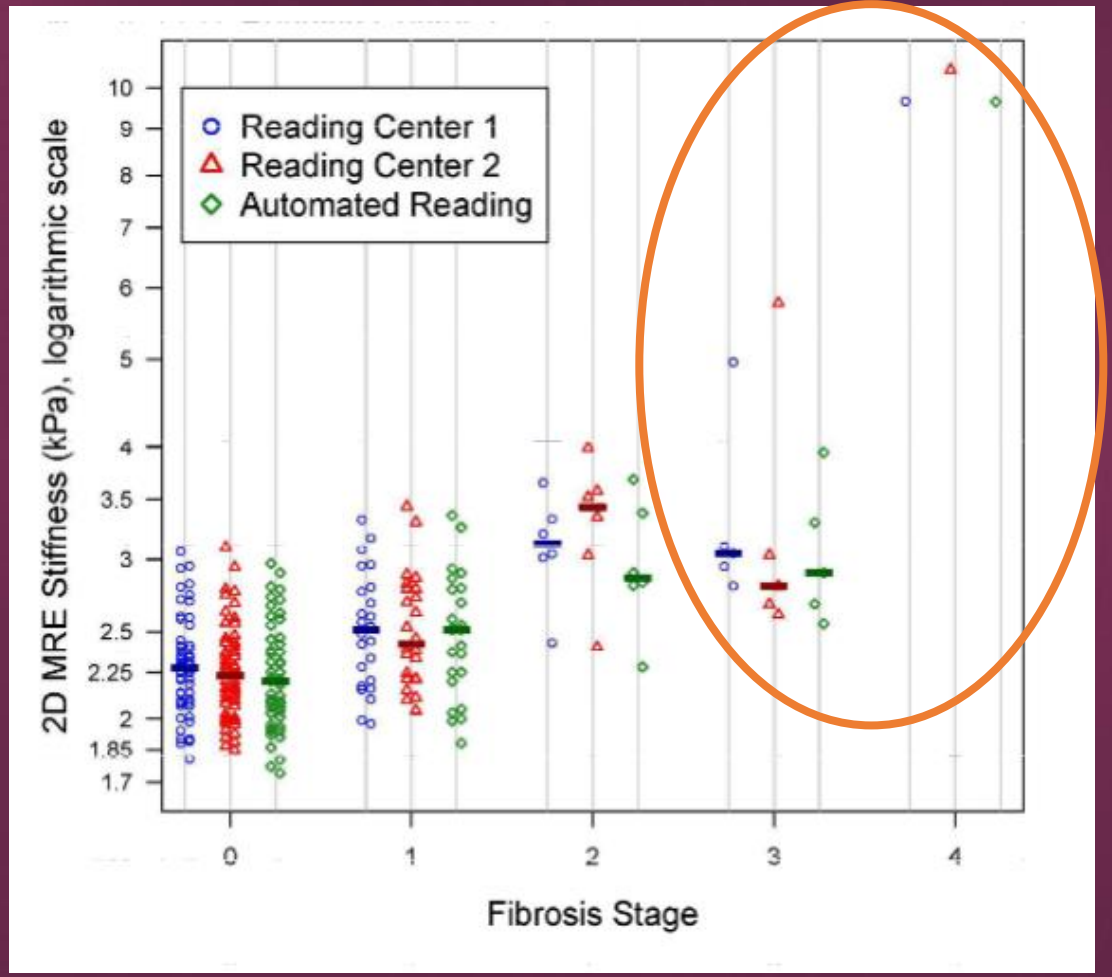


Pros

- Greater accuracy (90%) for advanced fibrosis
- Quantifies liver steatosis and liver/spleen volume
- Assess large area of liver
- 15 min, no IV needed
- Low failure rate (<5% usual)
- Performs better in severely obese
- Normative data available in nonobese children

Cons

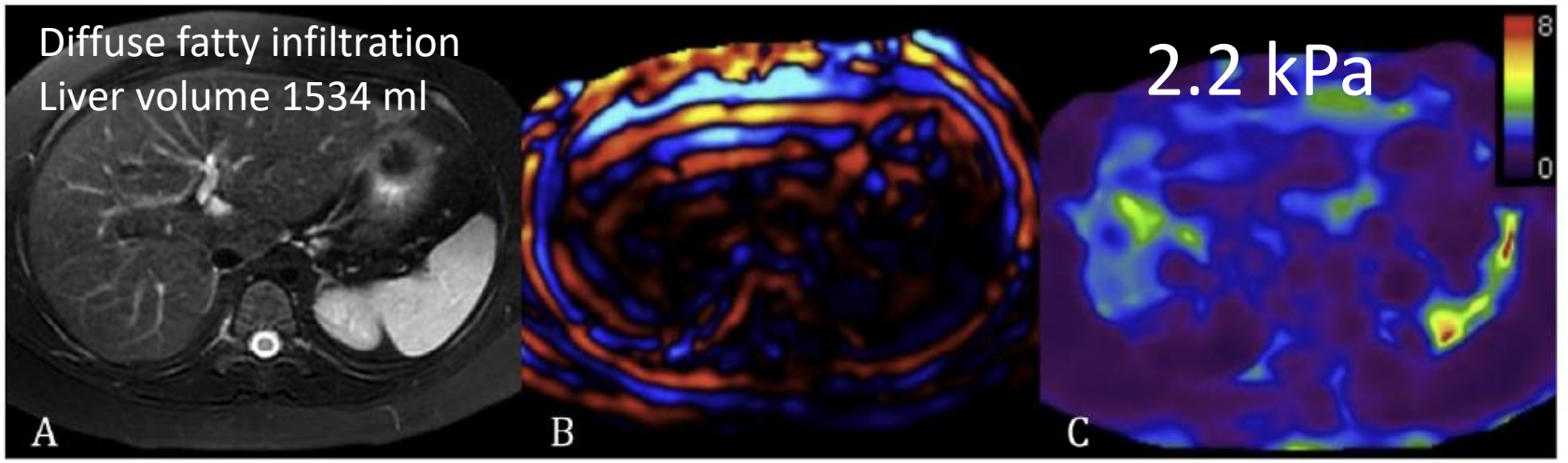
- Expensive
- Sedation for very young (<6 years)
- Not Point of Care
- Lower accuracy for discriminating between no vs. lower degrees of fibrosis

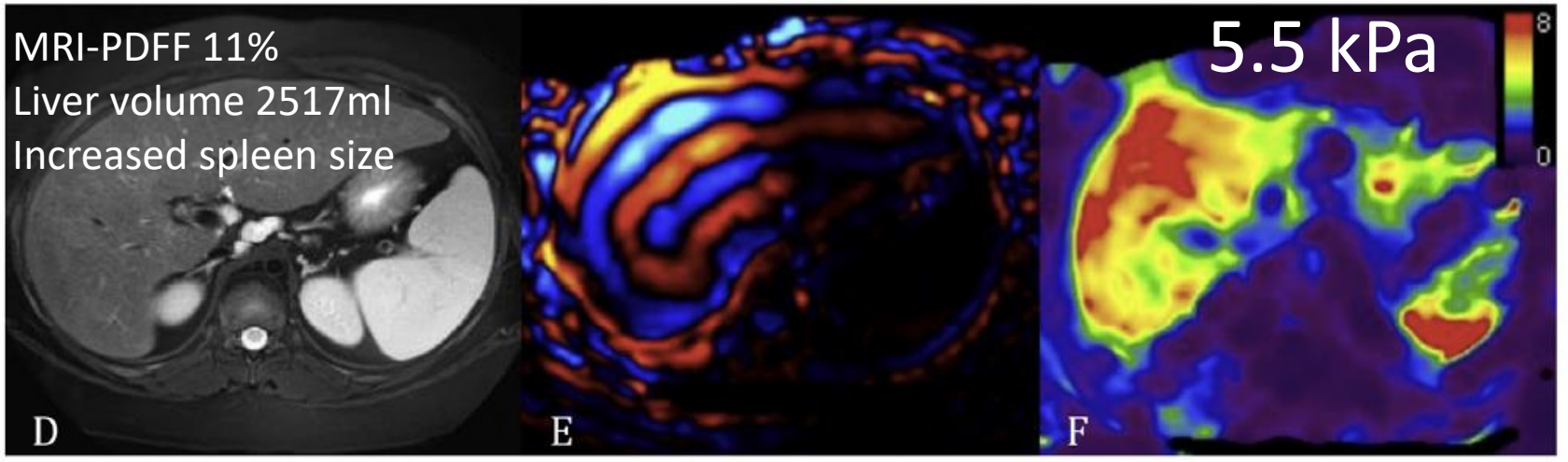


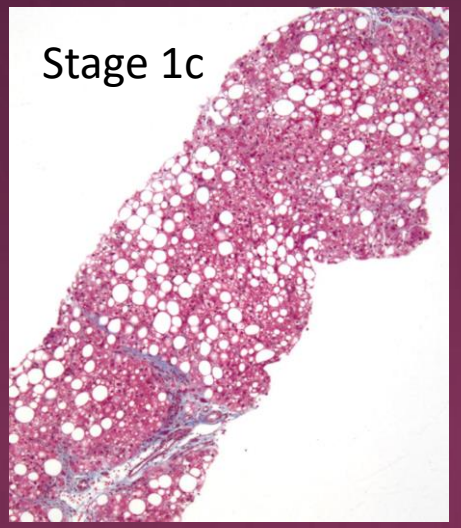
Schwimmer JB et al. Hepatology 2017

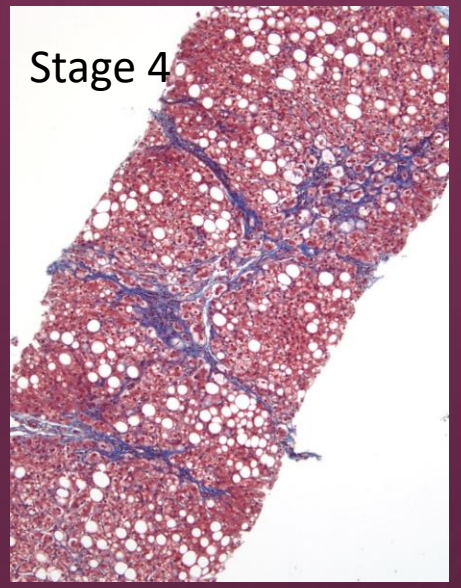
Xanthakos et al. Hepatology 2017

Elastography can be helpful to detect progression in fibrosis

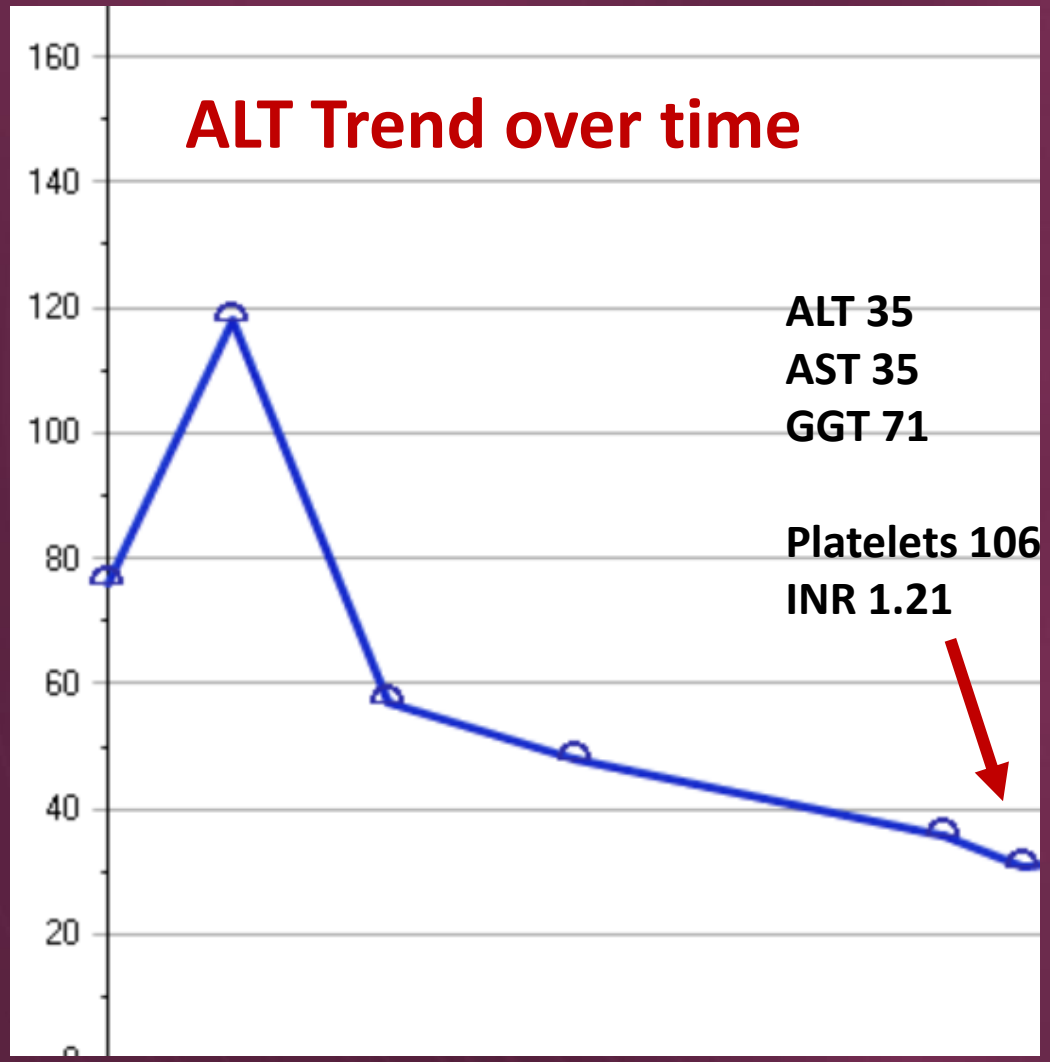


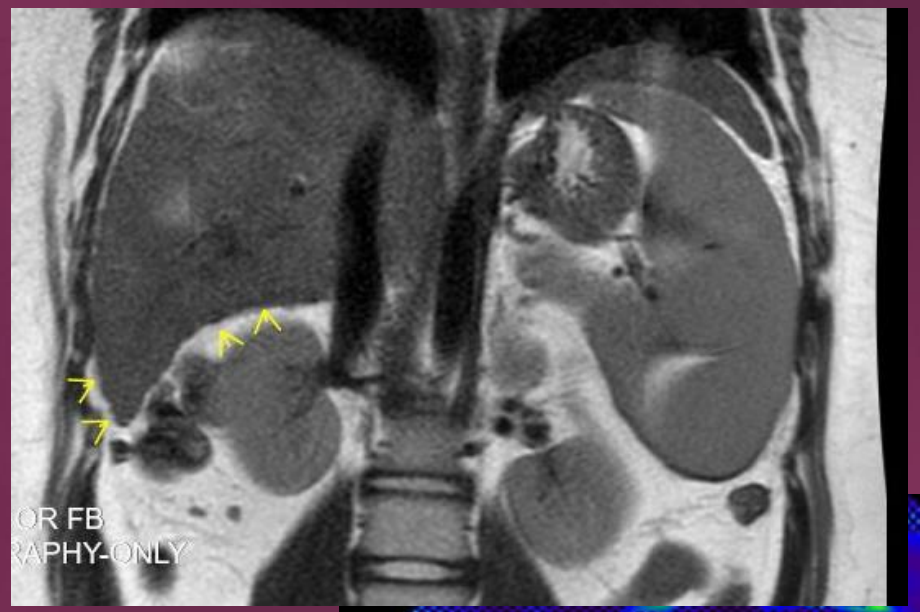




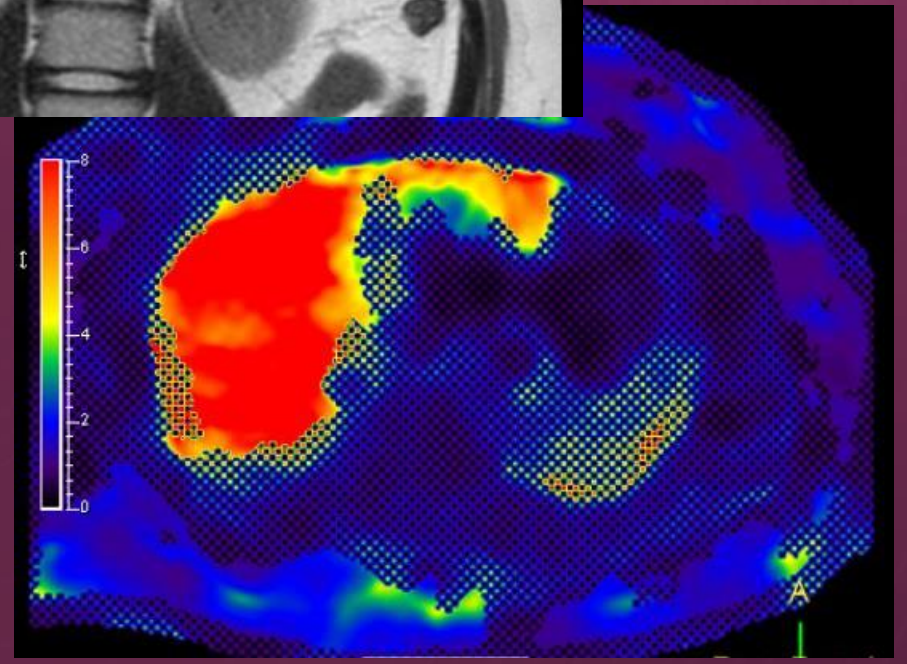


Caution: liver enzymes can normalize once cirrhosis develops



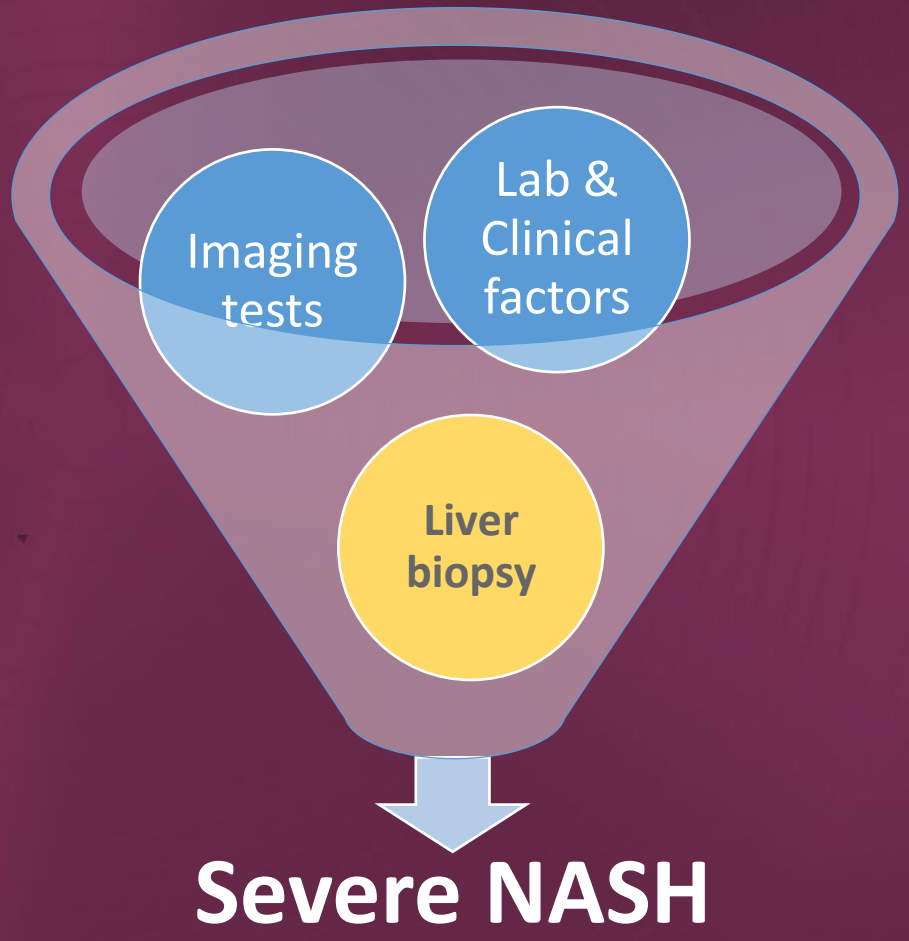


Nodular liver
Splenomegaly
on MRI



Stiffness 7.94
kPa

What is the role of liver biopsy?



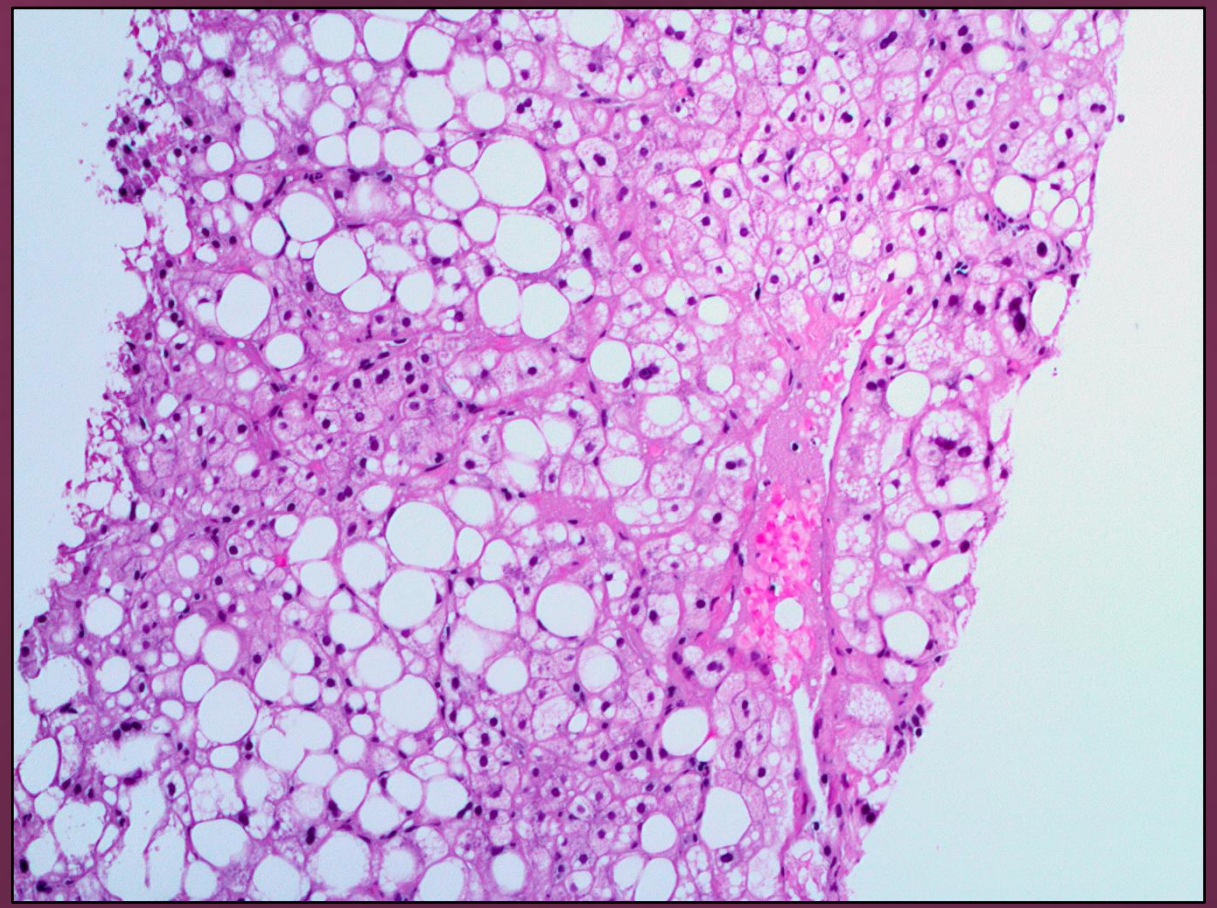
To biopsy or not to biopsy? No universal consensus

PROS

- Only way to diagnosis NASH and detect earlier stages of fibrosis
- Rule out other liver diseases like autoimmune hepatitis
- Can guide escalation to more aggressive Rx, e.g. bariatric surgery or clinical trials

CONS

- Sampling error
- Invasive and expensive
- Risks:
  - common mild pain
  - rarely bleeding or injury to other organs (<1:100)
  - extremely low risk death (1:10,000 adults)



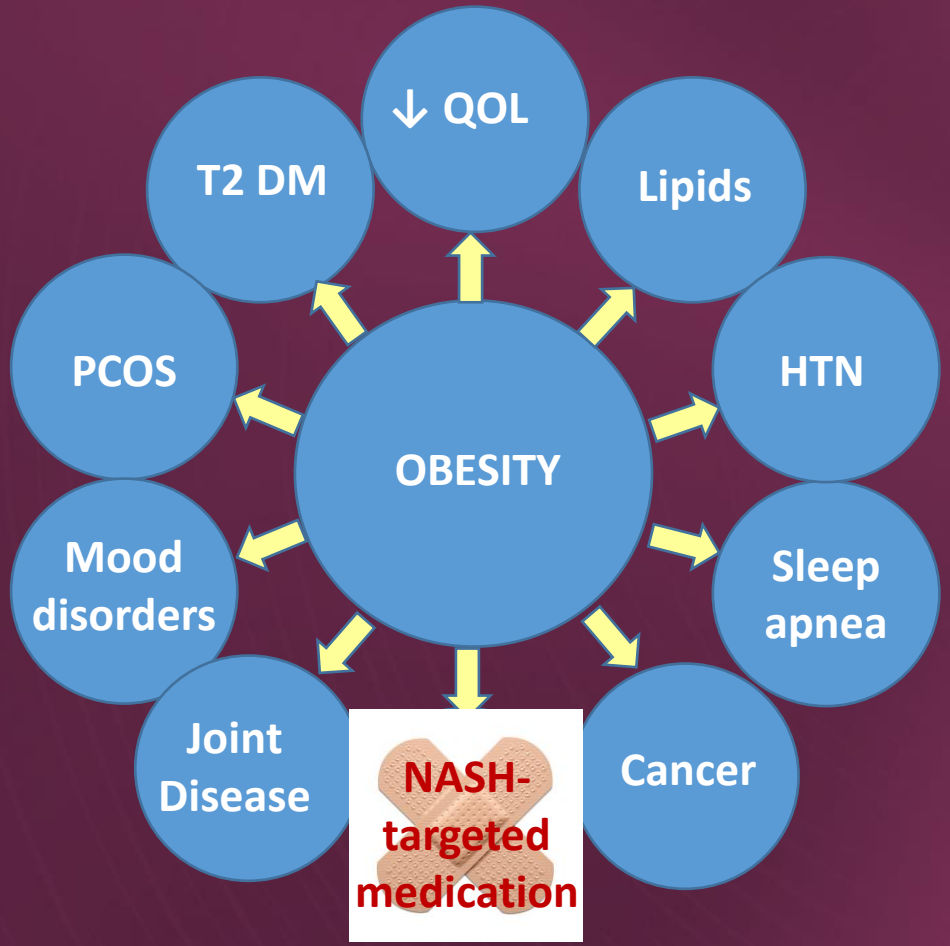
- Ballooned (swollen) liver cells
- Inflammation (↑white blood cells)

Treatment options for children with NAFLD

Management is Clinically Challenging

- **Typically clinically silent**
- Treatment **requires lifestyle changes** to improve weight status
- But patients often **feel fine** and have **little incentive to change**
- **No approved pharmacotherapy** options

Important to maintain a holistic approach to treating NASH in children and adults



A treatment that improves liver histology, but doesn't address root cause and associated conditions may not improve key clinical outcomes of

- **Mortality**
- **Quality of Life**

Clinical trial secondary endpoints:

- Cardiometabolic endpoints
- Anthropometric measures
- Liver-related outcomes
- Mortality

The optimal treatment would:

Lifestyle intervention: first line therapy for NAFLD

General principles the same

- ↓ high sugar, refined sweetened foods and drinks
- ↑ fruits and vegetables
- ↑ physical activity (more research needed!)
- Reduce take out/fast food and ultra-processed foods
- Reduce screen time

Avoid hepatotoxins (alcohol, medications) and **HBV, HAV vaccination**

Weight loss helps ↑ weight loss = ↑ NASH resolution

In adults, among those with ≥ 10% weight loss = 90% with resolution of NASH

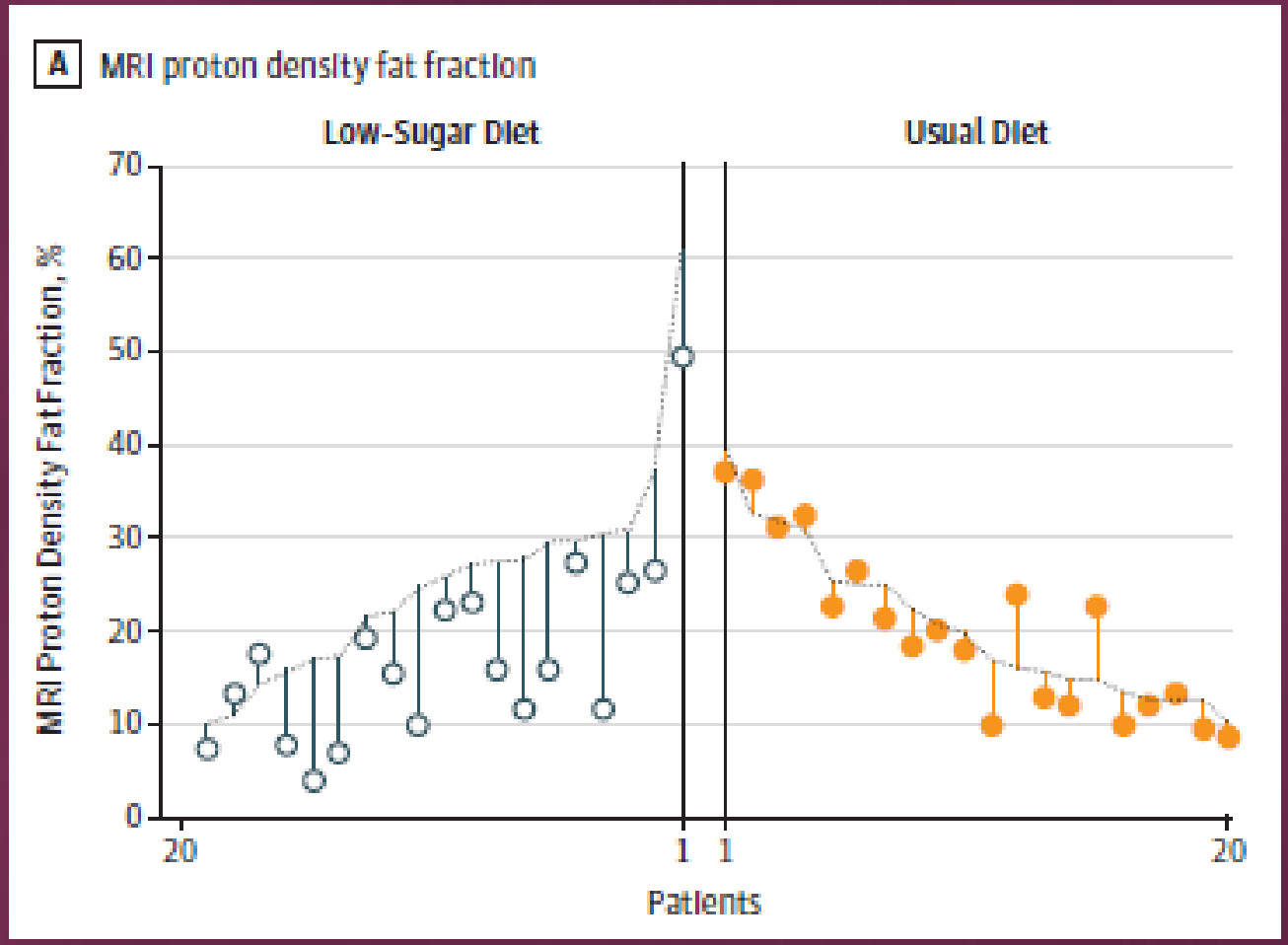
In children, for each -0.25↓ BMIz, ↑ OR 2.08 of NASH resolution

AASLD NAFLD guidelines 2018
NASPGHAN NAFLD guidelines 2017

Free sugar reduction ↓hepatic steatosis

Pediatric Randomized Clinical Trial

- 40 Hispanic adolescent boys with confirmed NAFLD
- Randomized to diet of low free sugar (<3% of daily calories) vs. standard diet **x 8 weeks**
- **Greater ↓ in liver fat on MRI (-6.2% , p<.001)** and **↓ in ALT**
- **Weight loss -2kg mean difference,** p=.002



Schwimmer JB. JAMA 2019;321(3):256

Lifestyle counseling outcomes in pediatric clinical trials

- 122 children in NASH CRN trials 2005-2015
- Standard lifestyle counseling q3 months + placebo x 52 or 96 weeks
- **52% resolved NASH and/or improved fibrosis (20% achieved both)**

Only 3 resolved NAFLD

36% progressed in NASH or in fibrosis

8% → incident T2DM (>300 fold expected rate/PY)

Xanthakos et al. Gastroenterology 2020:159:1731

Variables associated with worsening fibrosis and/or NASH:

Adolescent age, higher waist circumference, ALT, AST, total and LDL cholesterol at baseline

↑ALT, HbA1C and GGT.

Incident diabetes (OR 16.9), diabetes at any visit (OR 9.08)

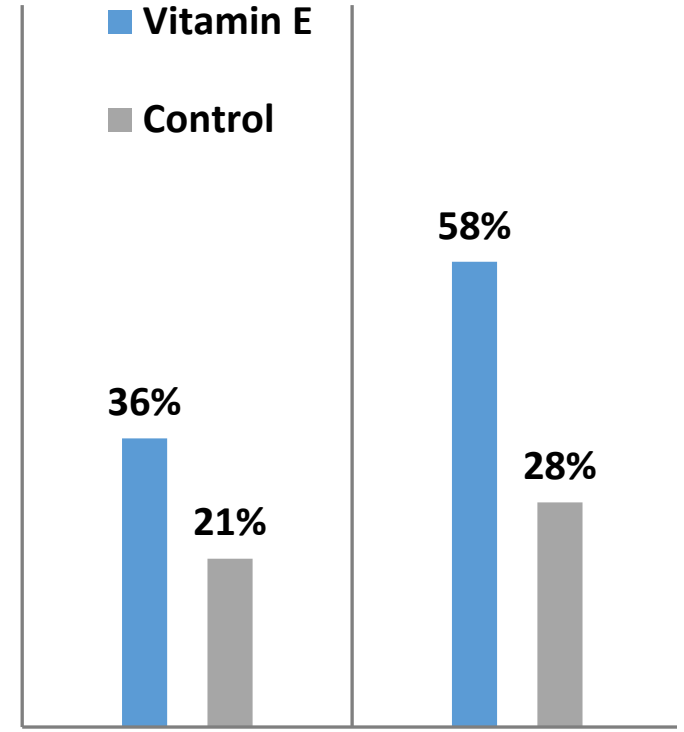
Xanthakos et al. Gastroenterology 2020:159:1731

High Dose-Vitamin E in children and adults

Natural form (α-tocopherol)
nondiabetic adults and children

- **Children (≥ 8 years)**: 400 IU po BID (35-50 x RDA)
- **Adults:** 800 IU po daily

No effect on fibrosis in any trial



Sanyal AJ. NEJM 2010 Lavine J. JAMA 2011

[1] Bril Diabetes Care 2019

Vitamin E remains controversial in children

Caveats

- **Secondary analysis in pediatric trial (N of 39 with NASH in trial)**
  - Predominantly due to reduced ballooning
  - **No effect on steatosis, inflammation or fibrosis**

- **↑ CV events, mortality, prostate cancer risk in adults on high dose vitamin E?**
  - Not seen in 2 year NASH CRN studies
  - But not studied in patients with type 2 DM

- **If using it, recommend biopsy pre- and post-treatment to stage disease severity and response**

Lavine J. JAMA 2011;305:1659

What about non-liver targeted therapies?

Manage metabolic syndrome

- **Diabetes medications**
- Dyslipidemia medications
- Hypertensive medications

- **Pioglitazone**
- **GLP-1 receptor agonists**

Pioglitazone (off-label) for adults (18 years +)

Dose: 45 mg/day x 18-36 months

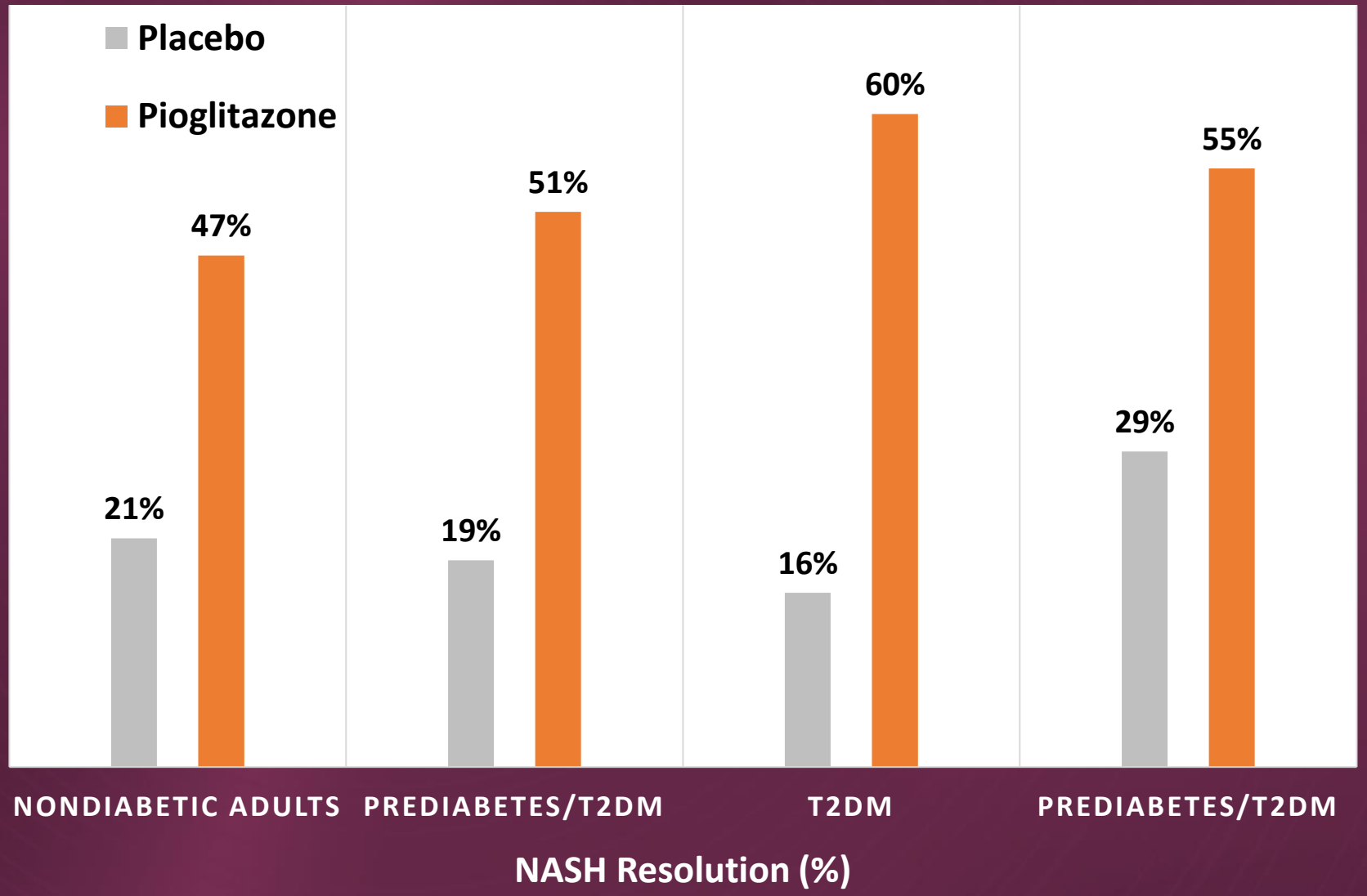
Higher NASH resolution

Also **improvement in fibrosis**

Mean 2.5kg weight gain

Limitations:

- weight gain
- loss of bone density in women
- bladder cancer?



Sanyal AJ. NEJM 2010;362:1675
Cusi K. Ann Intern Med 2016;165:305
Bril F. Clin Gastro Hepatol 2018;16:558

Phase 2 multicenter LEAN study: liraglutide (GLP1 RA)

1.8mg daily x 48 weeks

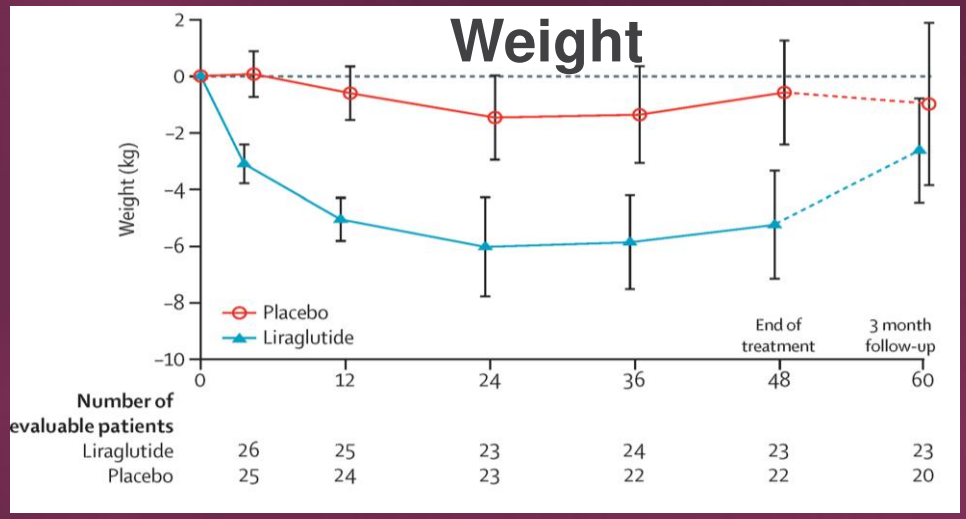
- **↑Resolution of NASH 39% vs. 9% in Placebo (p<0.05)**
  - RR 4.3 (95% CI: 1-18, p = 0.02)

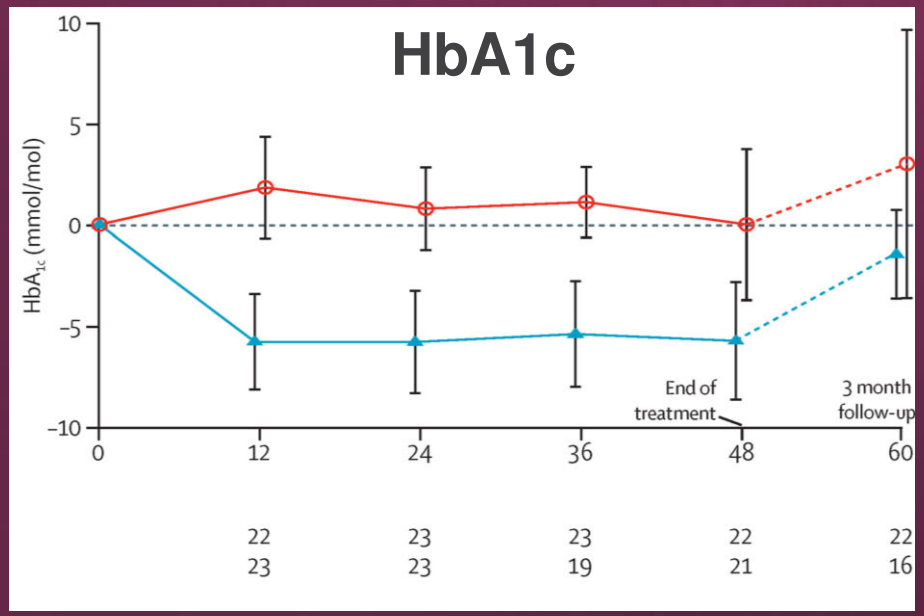
Mainly GI side effects

- 81% vs. 65% PBO (diarrhea)

Limitations:

- Small cohort (n=52)





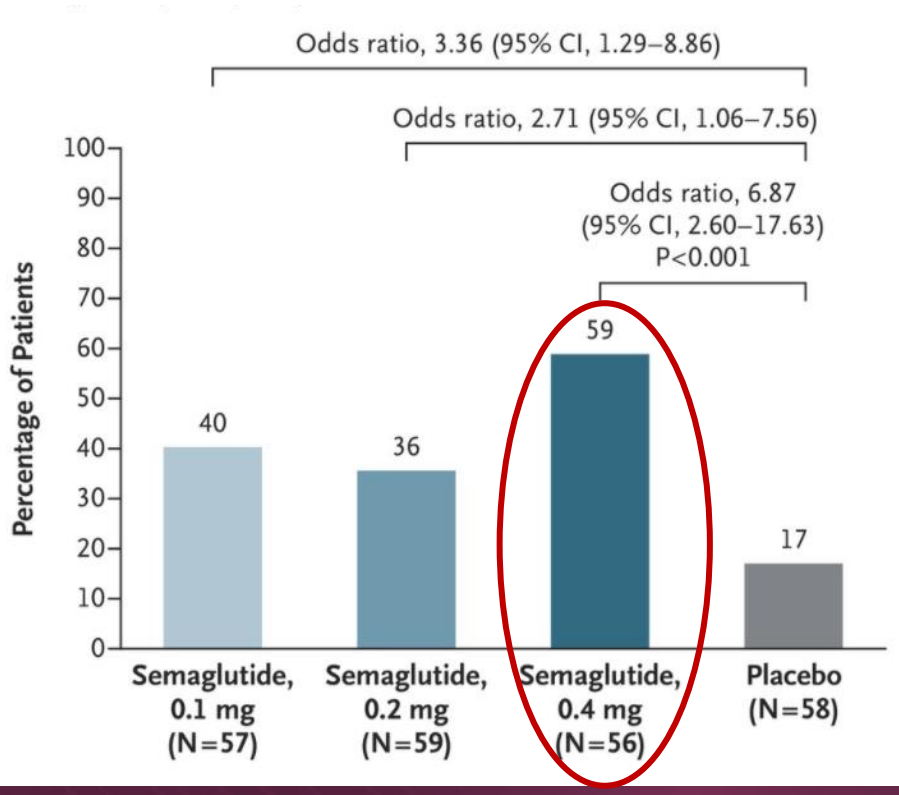
Armstrong MJ. Lancet 2016;387(10019):679

Phase 2B: semaglutide (GLP1 RA)

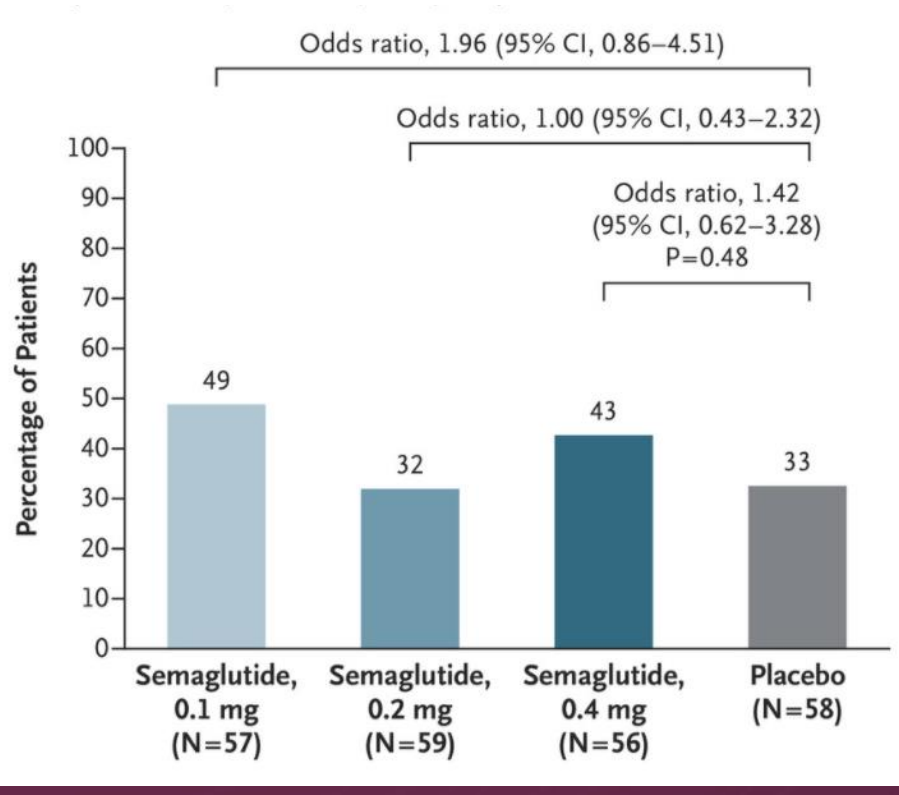
320 adults, 18-75 years, **NASH, with F1-F3 fibrosis, +/- T2DM**

0.1mg, 0.2mg, 0.4mg vs PBO once daily SC x 72 weeks

Resolution of NASH – no worsening fibrosis (primary endpoint)



Improving Fibrosis – no worsening NASH (secondary endpoint)



Newsome PN. NEJM 2021;384:1113

Liraglutide approved for treatment of children with T2DM (10+ yrs)

Other GLP1 also used off-label in older adolescents with T2DM

- Dulaglutide once weekly S.C.
- Semaglutide once weekly S.C.
- Semaglutide daily oral

Caveats:

- **None studied in dedicated pediatric trials with histologic NASH outcomes**
- **Common GI side effects:** nausea, diarrhea, vomiting, decreased appetitie
- **Uncommon to rare concerns:** medullary thyroid cancer, pancreatitis, hypoglycemia , acute kidney injury, hypersensitivity
- Avoid in pregnancy or if concurrent use of SSRI

Liraglutide FDA-approved for treatment of obesity in adolescents (12 years+) 12/04/2020

Eligible:

- Weight ≥60kg and BMI %ile that corresponds to 30 kg/m2 in adulthood

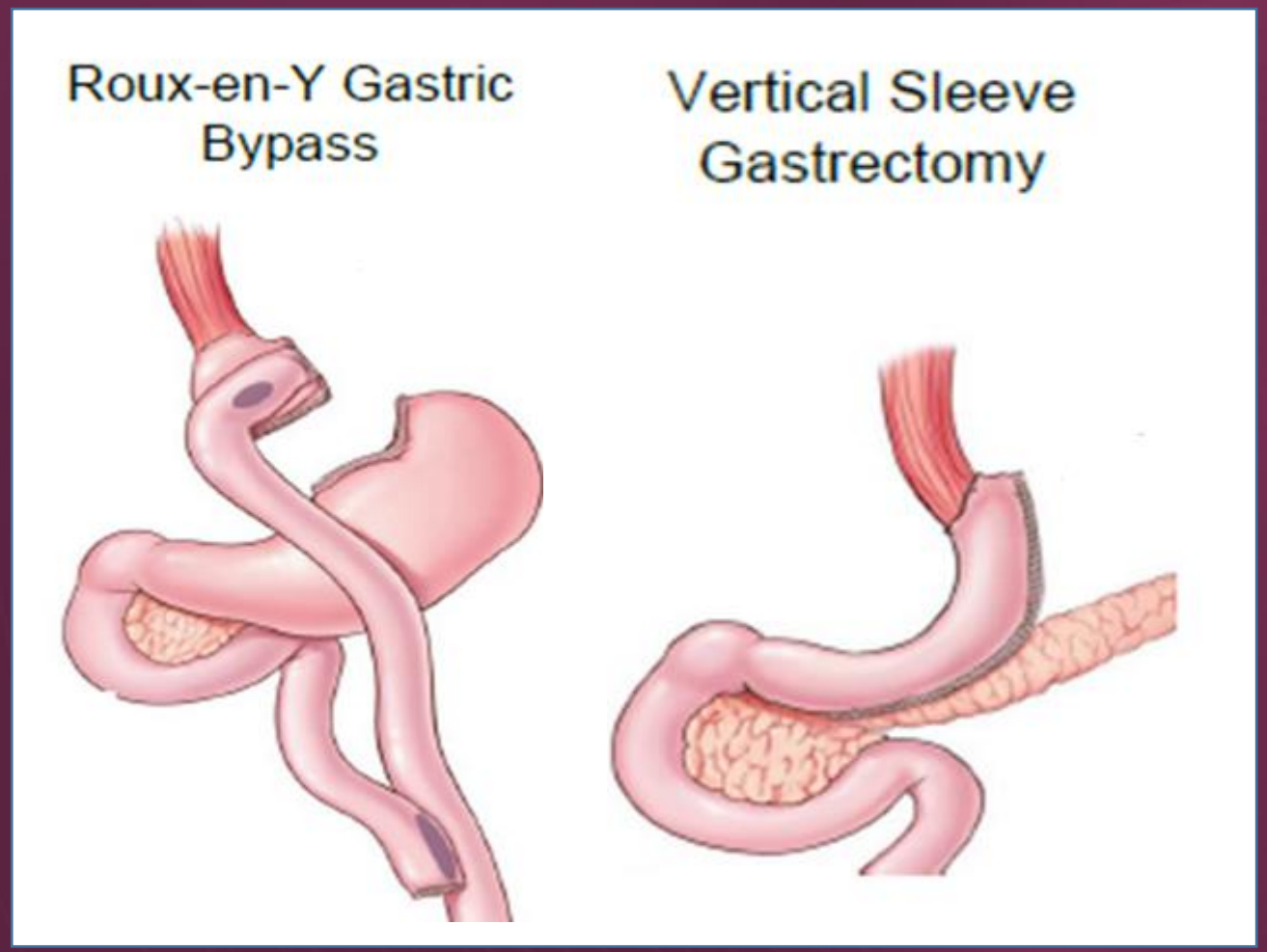
Dosing:

- Subcutaneously with multi dose pen
- Start 0.6mg /day, ↑ by 0.6 mg weekly to 3mg once daily
- Monitor for GI side effects
- Continue only if weight loss > 4% at 16 weeks

Caveats:

- **Expensive**
- **Adherence to daily injections may be lower in adolescents**

Laparoscopic Bariatric Metabolic Procedures if severe obesity



Highly effective

- **≈85% NASH resolution in meta-analyses**

Not widely scale-able?

- Accessibility (cost/centers)
- Currently limited to severe obesity and NASH
- Safety considerations
  - Surgical
  - Nutritional

Summary: If biopsy-confirmed NASH with fibrosis (esp F3), consider adjunctive pharmacotherapy (+lifestyle)

2018 AASLD Practice Guidance recommends liver biopsy **before any pharmacotherapy**! (Clinical trials may also require staging)

Population	Pharmacotherapy options
Confirmed NASH ± fibrosis	High dose vitamin E (1-2 year trial) • 8-18 years: 400 IU po BID • If 18+ years: 800 IU po once daily
≥ 18 years with NASH with fibrosis	Pioglitazone (off-label) 45 mg/day Transition to adult hepatologist for clinical trial access

Take home points

Children with NAFLD are at higher risk of T2DM and cardiometabolic disease

Screening can identify at-risk children with NASH or early-onset of fibrosis who may need more intensive interventions or follow-up for progressive disease

No currently approved medications for NASH, but current GLP1 medications approved for T2DM or obesity may be helpful in interim in children with NAFLD who meet clinical criteria for use