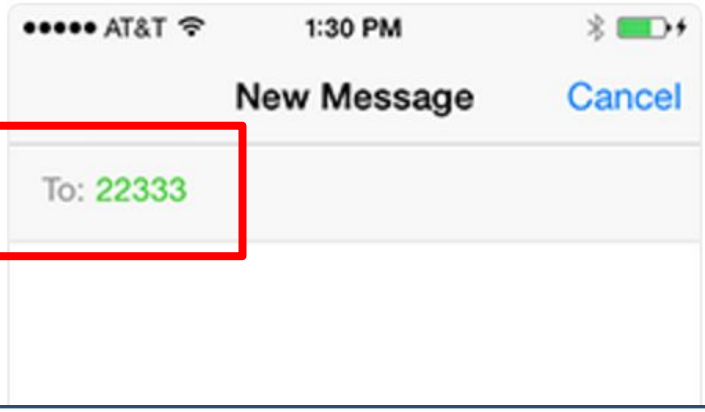

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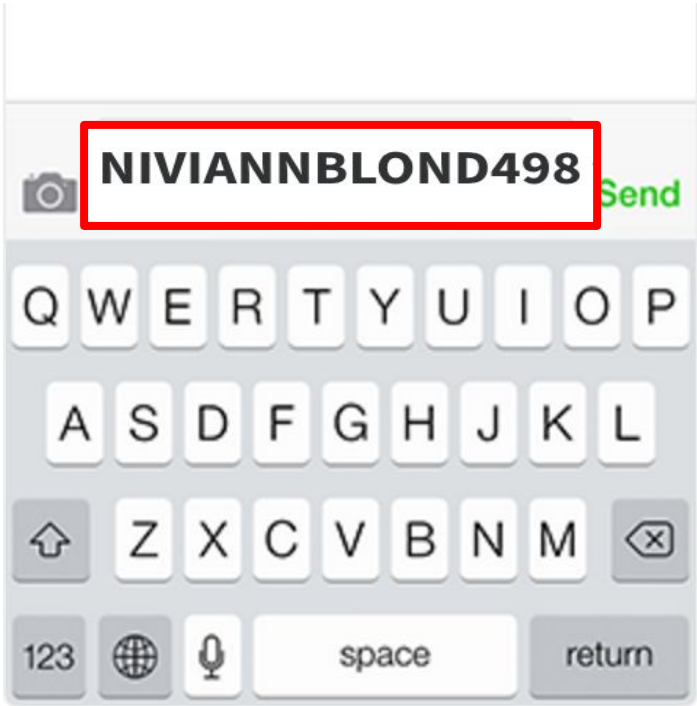

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Pediatric non-alcoholic fatty liver disease: from Takis to transplant

Niviann M. Blondet, MD

Pediatric Gastroenterology and Hepatology

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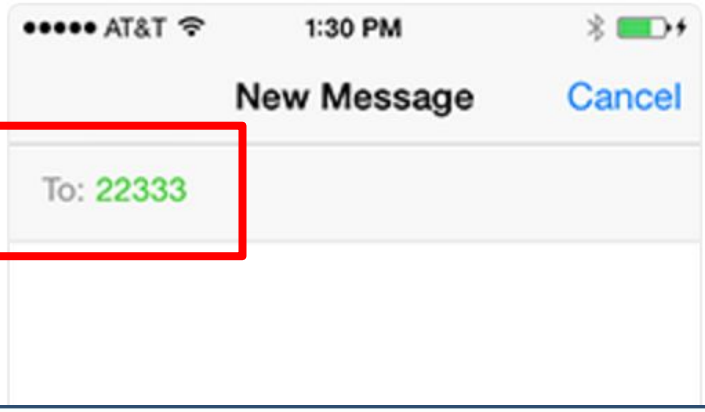
Disclosure

- There are no relevant financial relationships with commercial interests to disclose

Objectives

- Define non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)
- Discuss association to obesity and other comorbidities
- Review epidemiology and natural history
- Discuss the pathogenesis of the disease
- Review diagnostic modalities
- Discuss current treatment options



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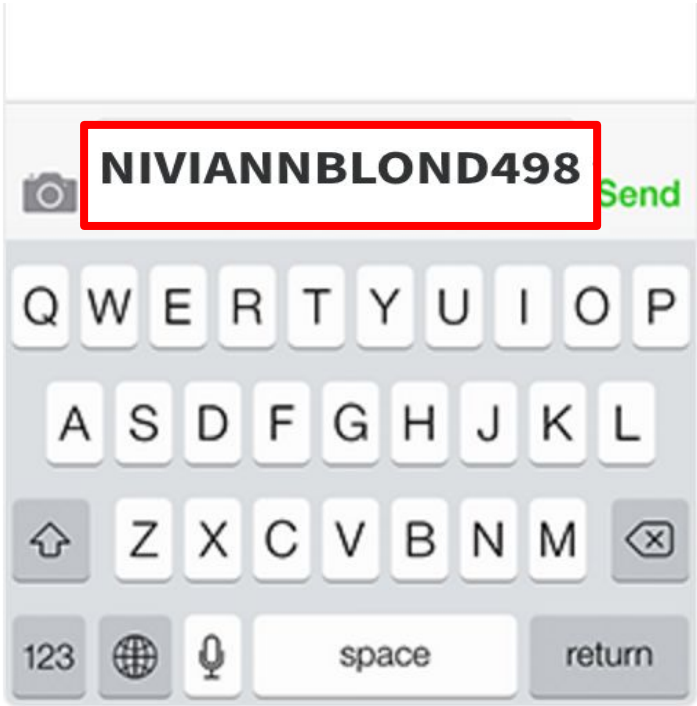

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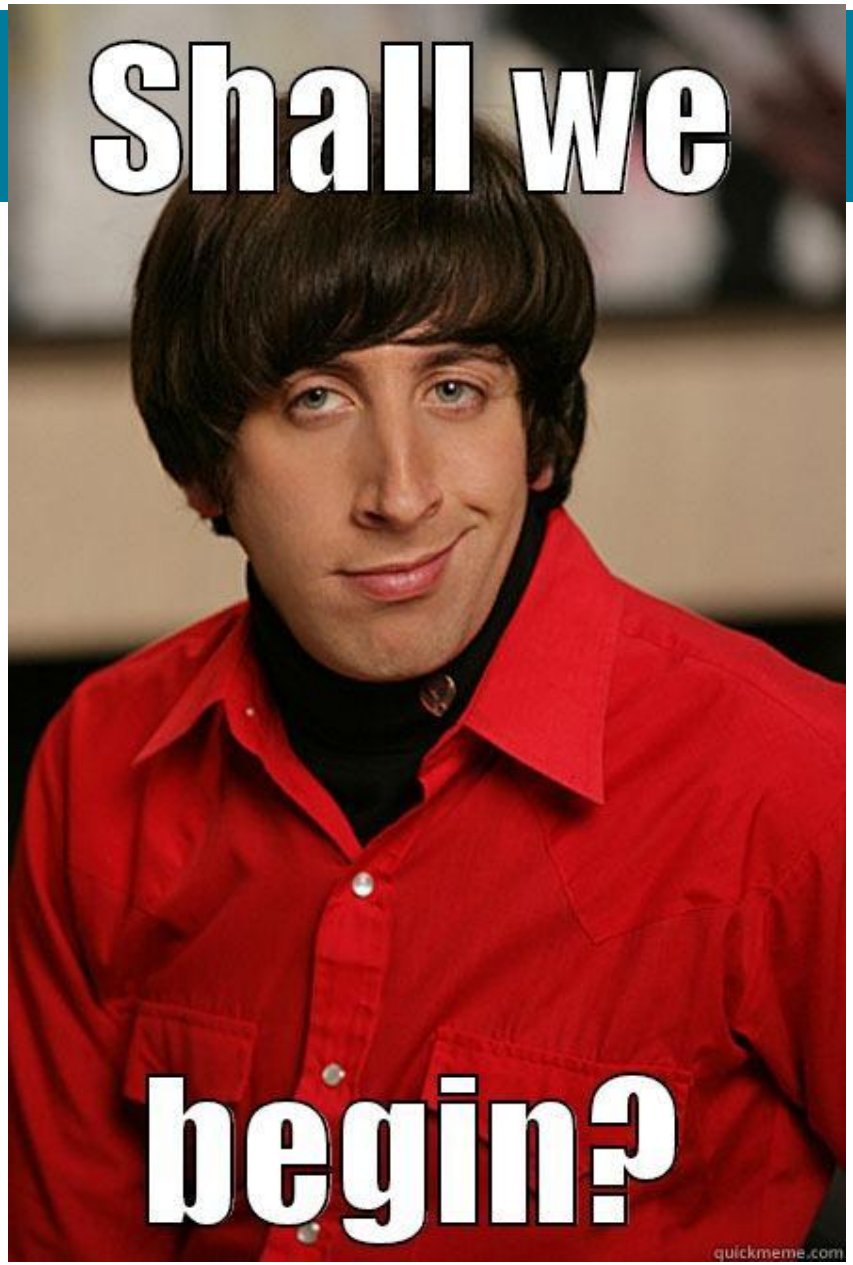
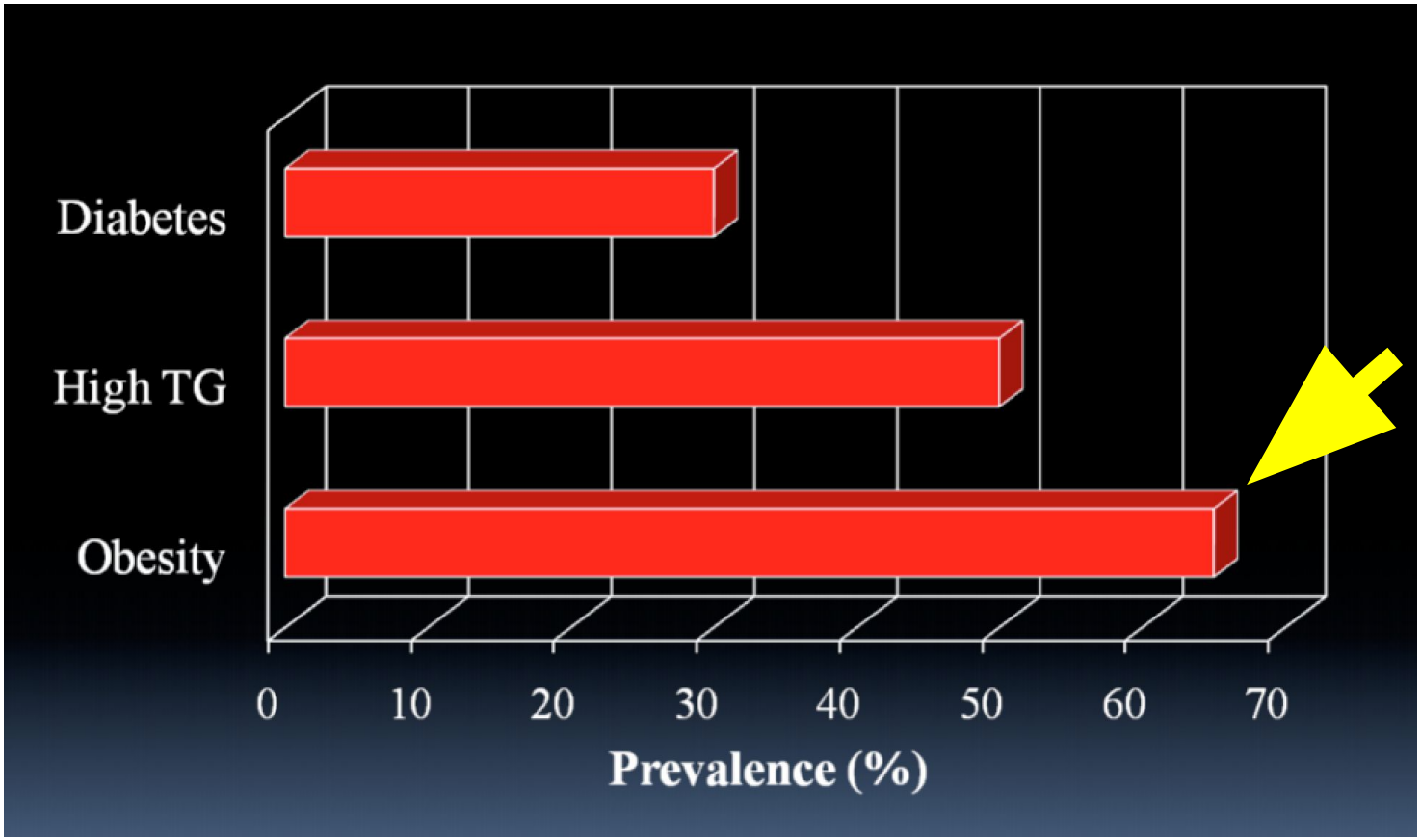

Shall we
begin?
quickmeme.com

Non-alcoholic fatty liver disease

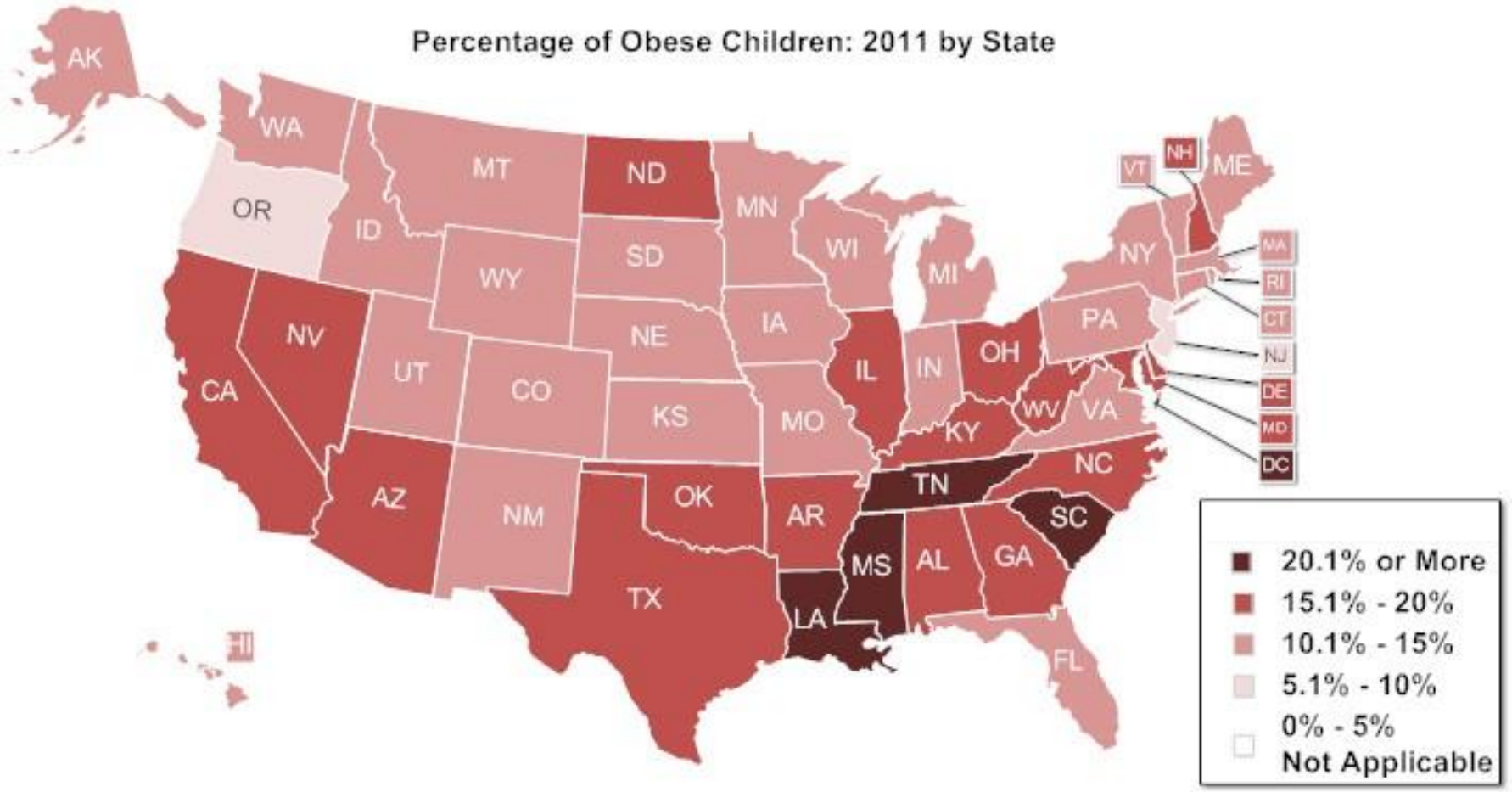
- **Spectrum** of liver disease characterized by steatosis
- Diagnosis of exclusion: liver disease not secondary to metabolic disorders, medications, infections or alcohol
- Is the hepatic component of metabolic syndrome and correlates with
  - Increased waist circumference
  - Insulin resistance
  - Lipid abnormalities

Risk factors



Yu et al. *Reviews in Gastroenterological Disorders,* 2002.

Pediatric Obesity



National Survey of Children's Health, 2011.

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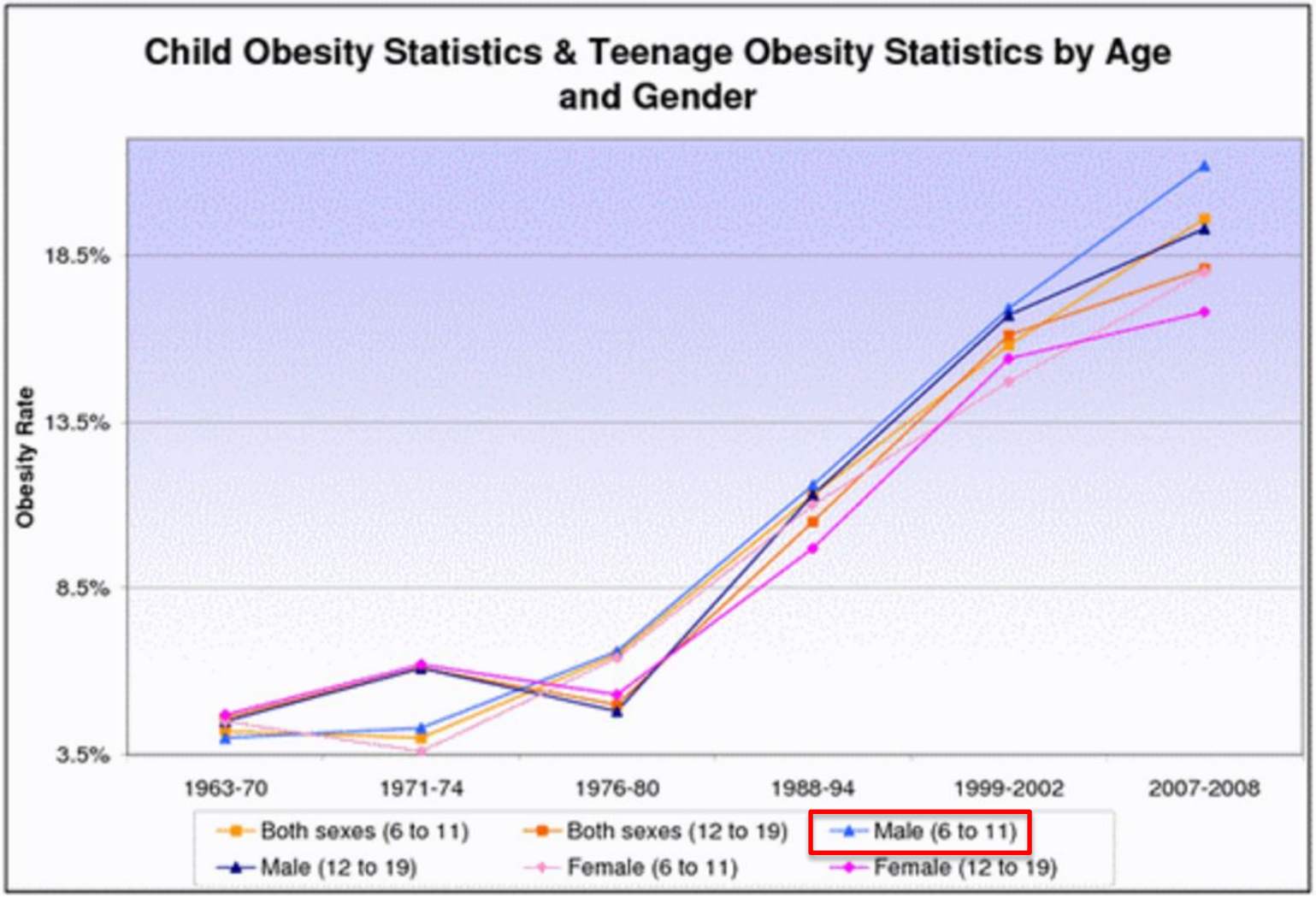
Pediatric Obesity



U.S. Department of Health and Human Services

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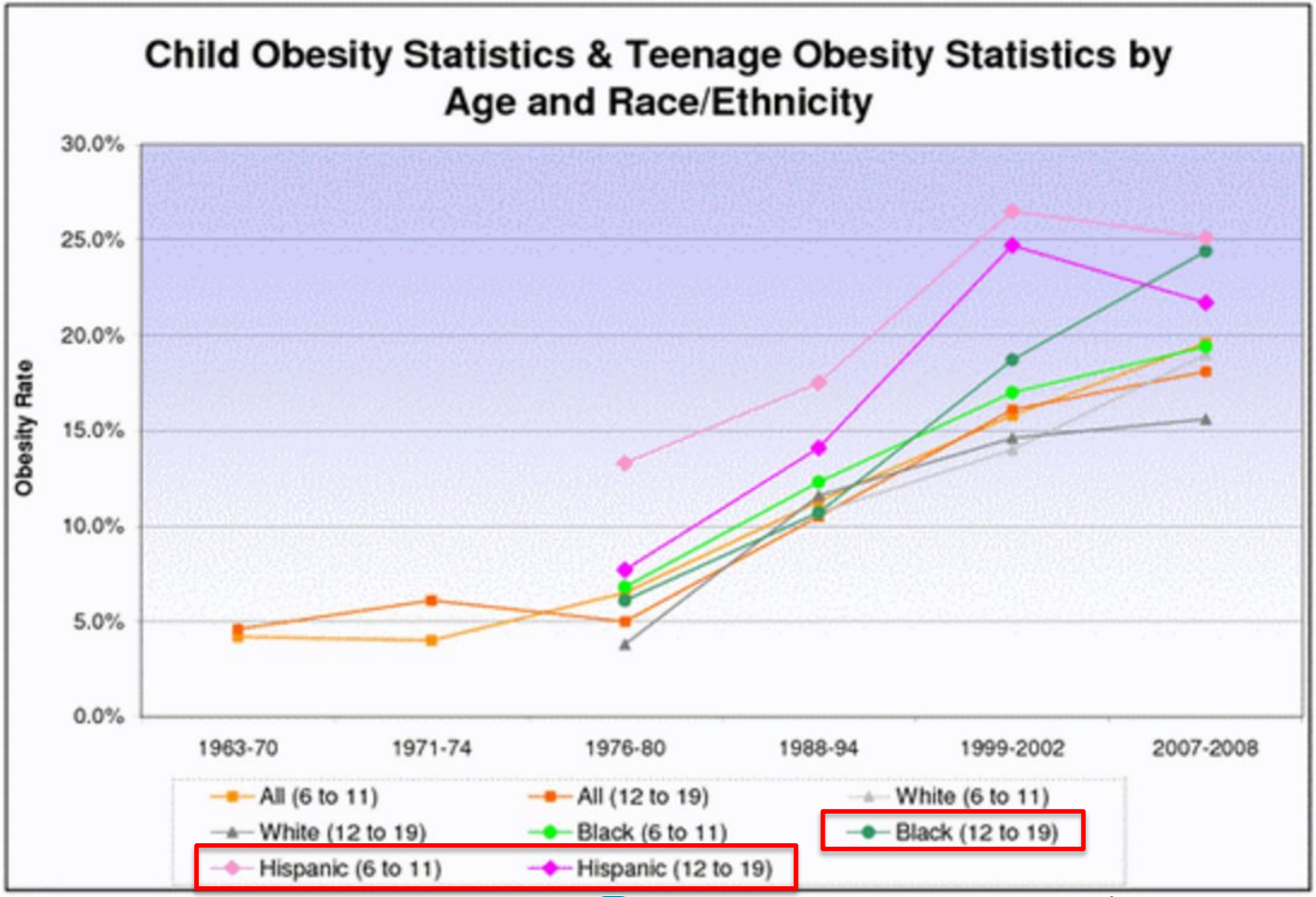
Pediatric Obesity



U.S. Department of Health and Human Services

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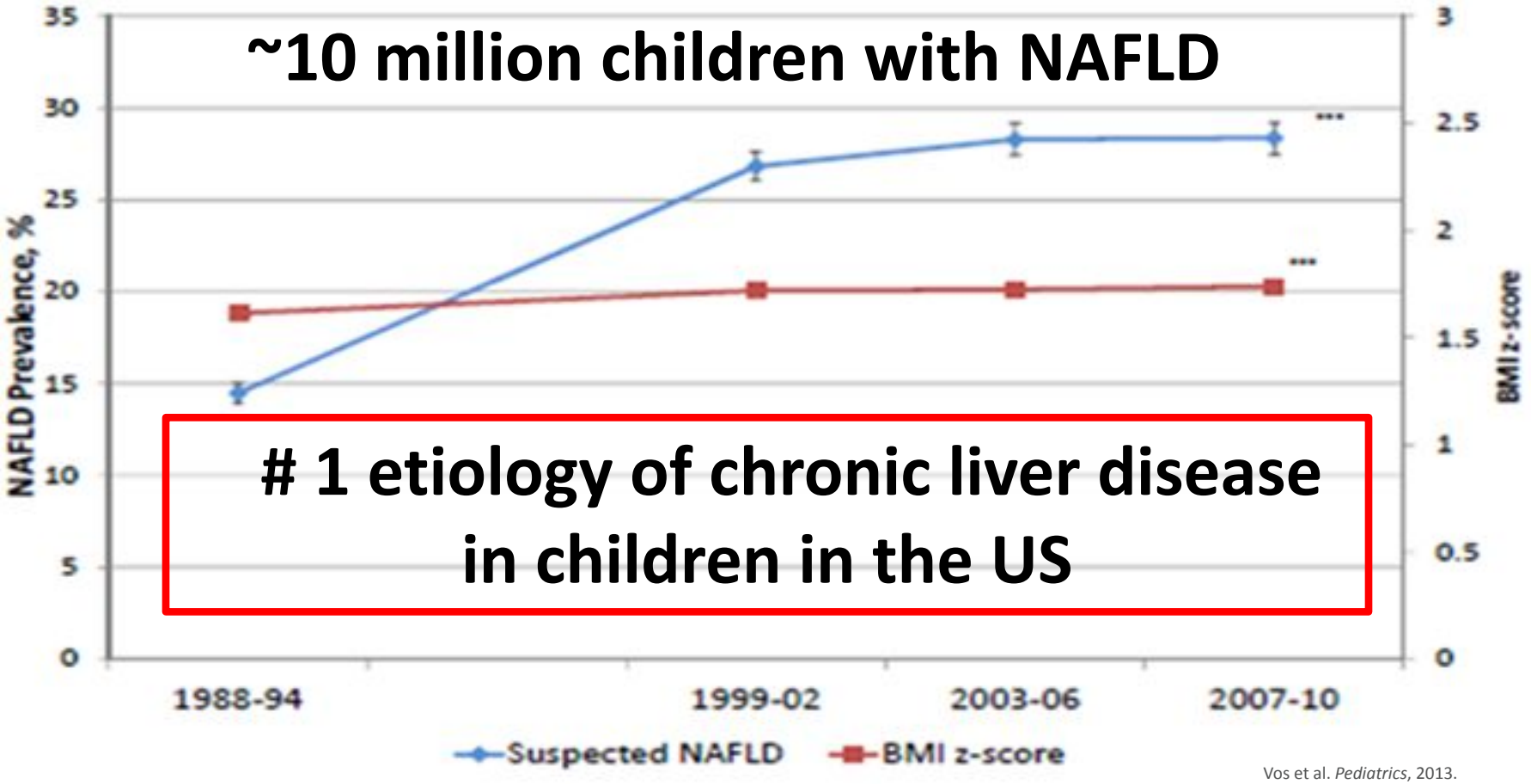
Pediatric NAFLD



Vos et al. *Pediatrics*, 2013.

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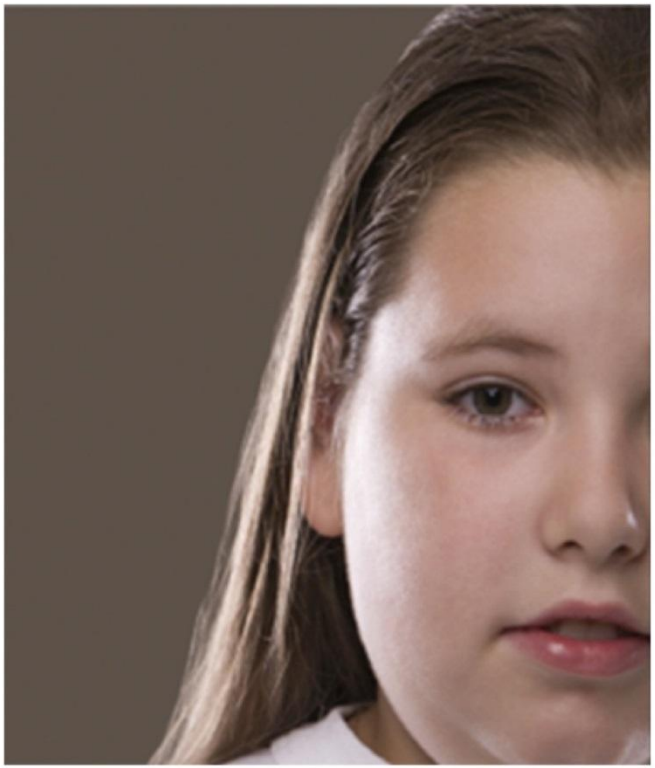
NAFLD – Prevalence in Children



- 2-4 years - 0.7%
- 15-19 - 17.3%
- Obese children by ALT elevation - 29-38%

Welsh JA et al. *J. Pediatr* 2013;162 (3):496-500e1. Schwimmer JB et al. *Pediatrics* 2006;118(4):1388-93.
Louthan MV et al. *J Pediatr Gastroenterol Nutr* 2005;41(4):426-9.
Strauss RS et al. *J Pediatr* 2000;136(6):727-33. Rehm JL et. *J Pediatr* 2014;165(2):e1.
Patton HM et al. *J Pediatr Gastroenterol Nutr* 2006;43:413-427.

NAFLD – Prevalence in Children

Continued

- 11-22 years - 4-fold increased risk for Hispanic children
- 10.2% in Asian children
- 8.6% in white children
- 1.5% in black children

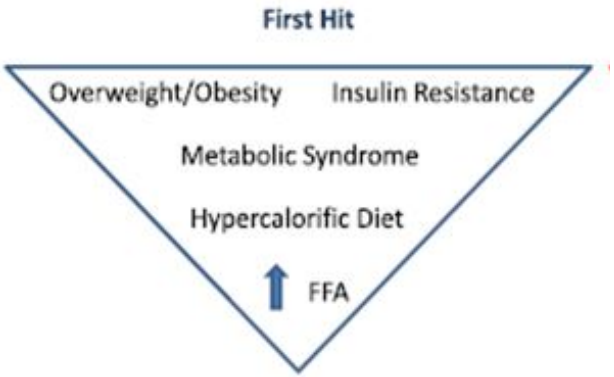
Welsh JA et al. *J. Pediatr* 2013;162 (3):496-500e1. Schwimmer JB et al. *Pediatrics* 2006;118(4):1388-93.
Louthan MV et al. *J Pediatr Gastroenterol Nutr* 2005;41(4):4.
Strauss RS et al. *J Pediatr* 2000;136(6):727-33. Rehm JL et. *J Pediatr* 2014;165(2):e1.
Patton HM et al. *J Pediatr Gastroenterol Nutr* 2006;43:413-427.

Pathogenesis

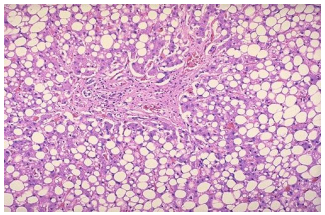
- Defects at multiple levels tip the metabolic balance towards hepatic fat accumulation
  - Excessive substrate supply to the liver: **high carbohydrate/fructose-based diets** promote *de novo* lipogenesis

- The expanded liver fatty acid pool leads to increased mitochondrial and peroxisomal beta-oxidation, which produces reactive oxygen species
  - Promotes a local pro-inflammatory state leading to release of pro-inflammatory cytokines and progressive liver injury

Two-Hit Hypothesis

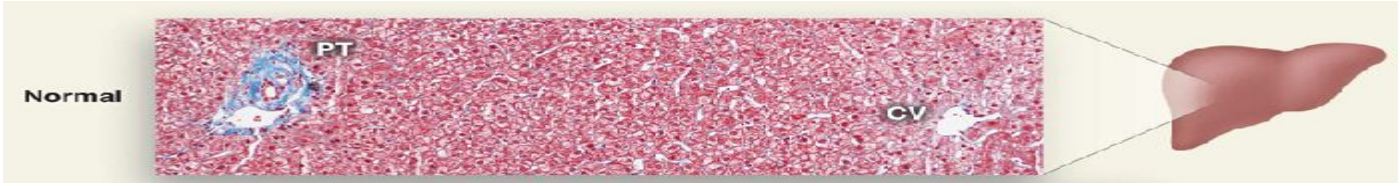


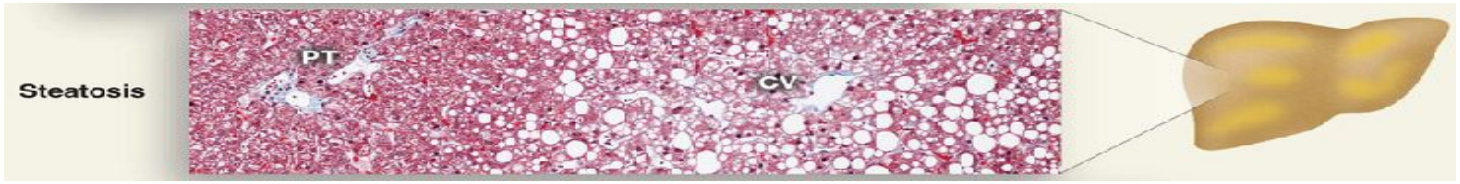
"bland" steatosis ⟷

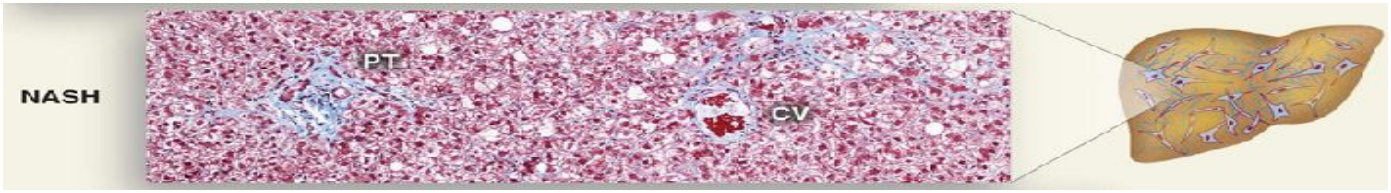


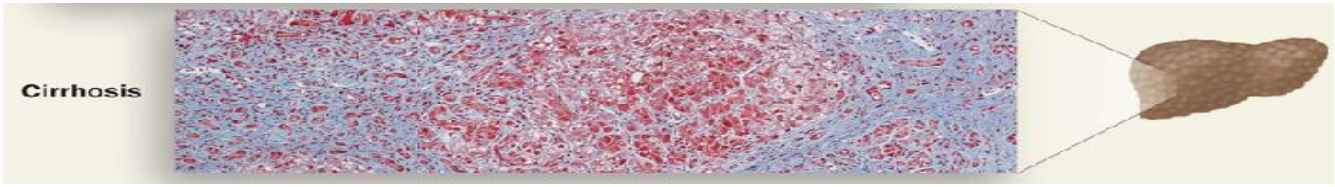
Giorgio V et al. *Pediatrics* 2013.

Spectrum of disease









Natural History

- Not well understood but, in general:
  - Steatosis tends to follow a benign course
  - NASH with fibrosis has increased liver-related morbidity and mortality

- In a study of children with NAFLD with fibrosis on diagnosis (mean age 13 y/o), repeat liver biopsy when compared to baseline (mean 28 months) showed [1]
  - No change in fibrosis in 8
  - Worsening fibrosis in 7
  - Improved fibrosis in 3… all **lost weight**!!!

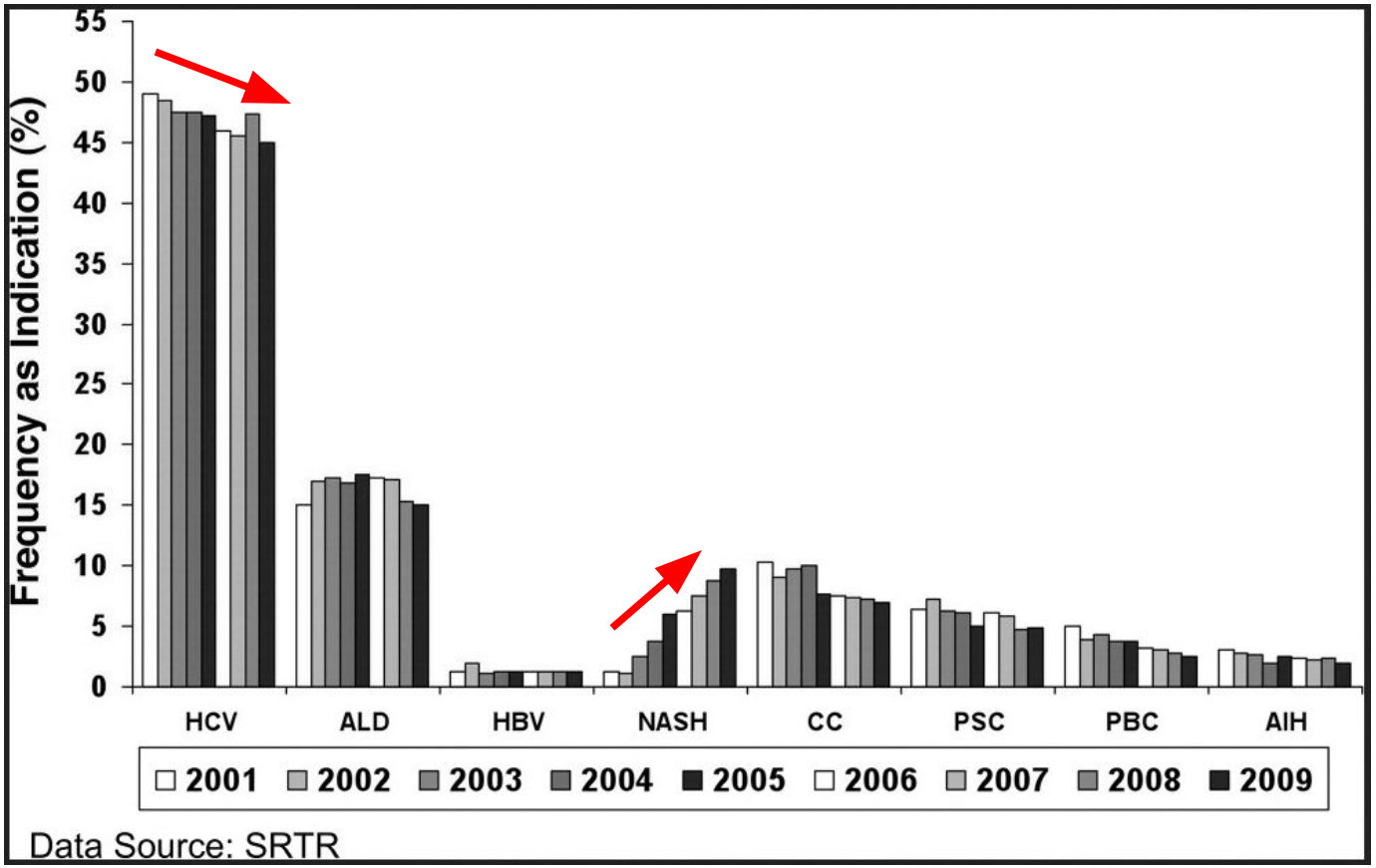
- There are case reports of rapid progression to cirrhosis[2]

[1] Molleston JP et al. *Am J Gastro*, 2002.
[2] Kader HH et al. *Clin Gastroenterol Hepatol,* 2008.

Natural History

- NAFLD-related liver disease is currently the most rapidly increasing indication for liver transplant in adults in the US
- It is anticipated that NAFLD-related liver disease will become the leading indication for liver transplant in adults by 2030
- For patients needing transplant there are two problems:
  - lower MELD than other etiologies of liver disease
  - presence of comorbidities: post-transplant outcomes are worse in patients with metabolic syndrome components

Liver transplantation in adults



Charlton et al. *Gastroenterol*, 2011.

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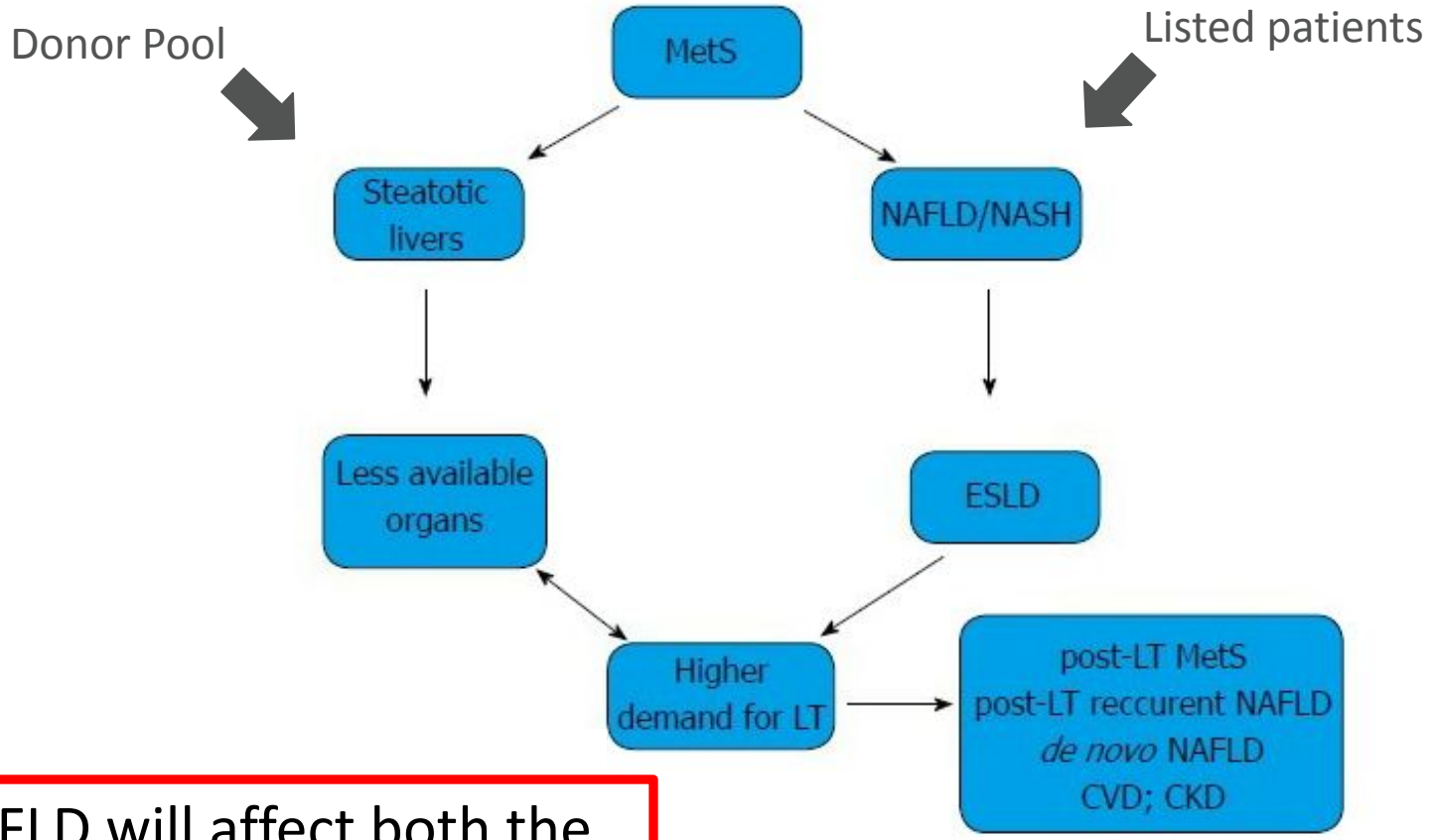
Other implications



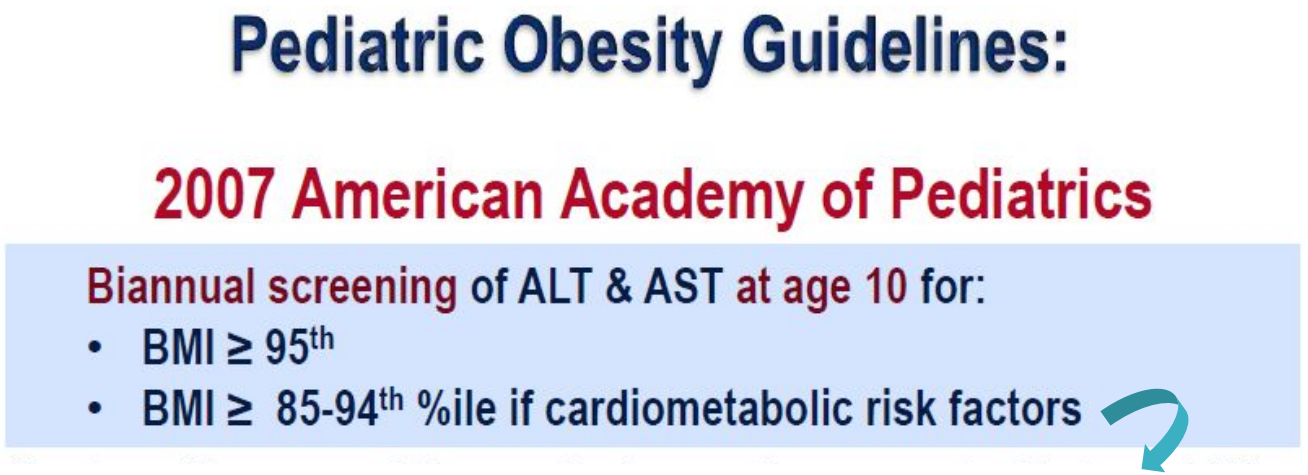
Mikolasevic et al. *World J Gastroenterol*, 2018

NAFLD will affect both the **demand** and the **supply** of available organs

Early diagnosis = early intervention

Diagnosis

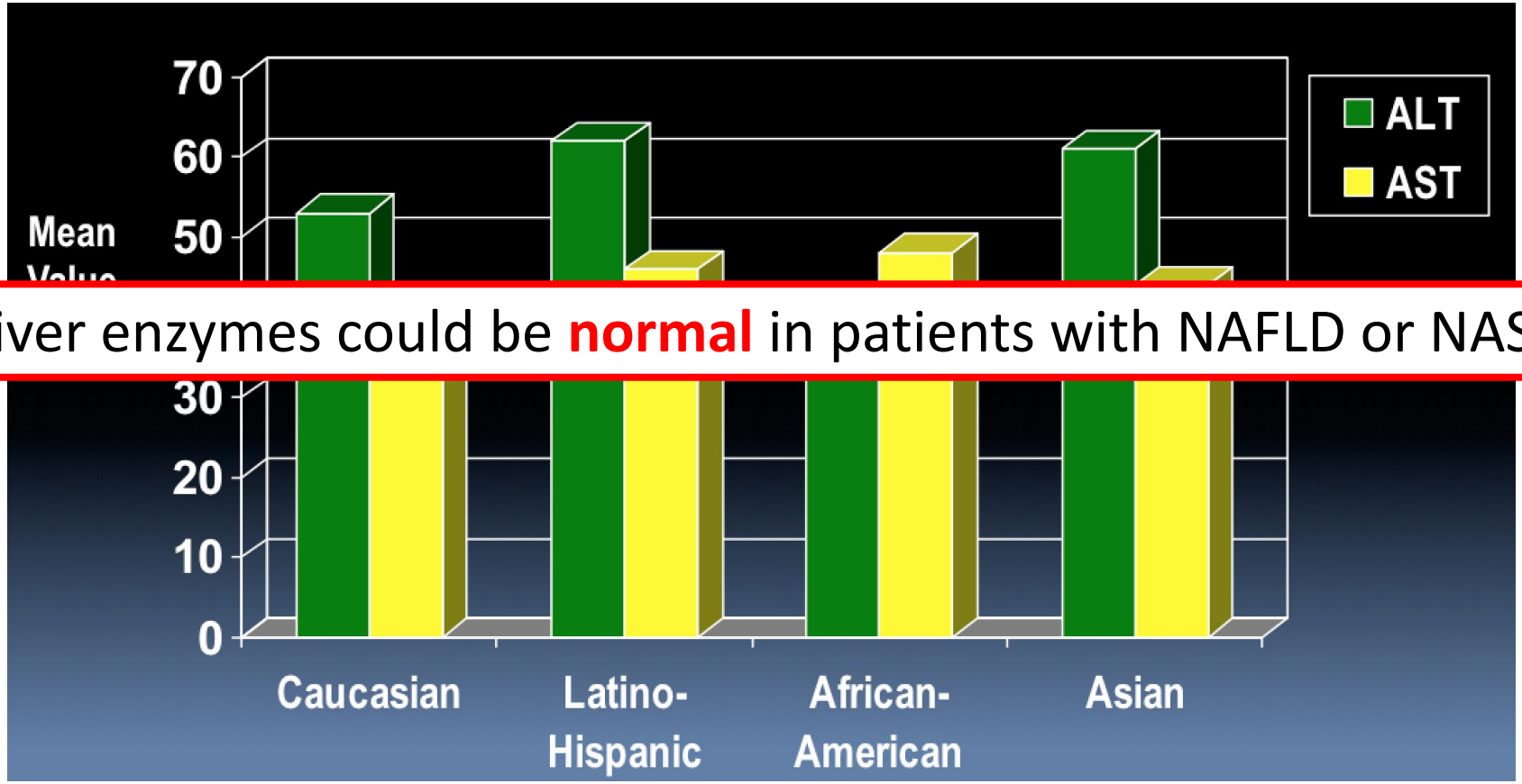
- Elevation of the ALT/AST is the most common laboratory abnormality seen in NAFLD



Risk factors: central adiposity, IR, dyslipidemia, OSA, family history

As per NASPGHAN guidelines: suspect if ALT is ≥2 times the ULN (ALT **>50 for boys** and **>44 for girls**)

ALT/AST in NAFLD



Liver enzymes could be **normal** in patients with NAFLD or NASH

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Labs do not rule out NAFLD…

- Not every obese patient with elevated liver enzymes has NAFLD
  …and not every patient that has NAFLD is obese
- Elevated ALT/AST also seen in:
  - Hepatitis A, B, C
  - Wilson disease
  - Autoimmune hepatitis*
  - α-1 antitrypsin deficiency
  - Hemochromatosis
  - Drug-induced liver injury

Every patient with elevated liver enzymes should be evaluated by a hepatologist

Imaging

- Ultrasound
- Computed Tomography
- Magnetic resonance and spectroscopy
- Transient elastography

Ultrasound

- Sensitivity of ultrasound varies by the amount of fat
  - With >30% fatty infiltration, sensitivity is 80%
  - With 10-19% fatty infiltration, sensitivity is 55%
- Sensitivity and specificity of ultrasound decrease due to the presence of morbid obesity
- **Not** recommended as a screening tool for NAFLD

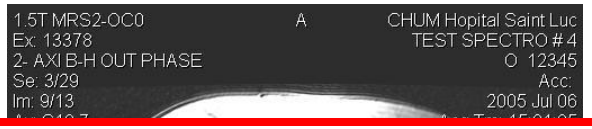
Imaging

Computed Tomography

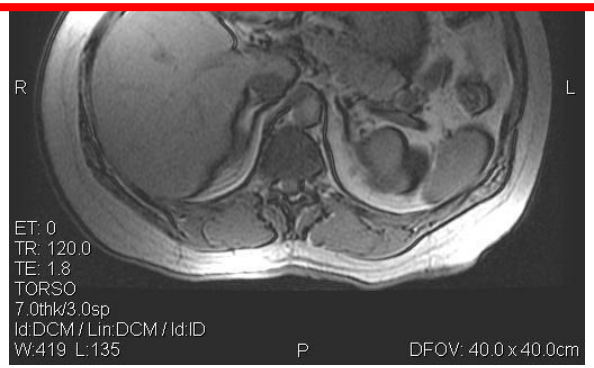
- Is 43-95% sensitive and 90% specific for detecting liver fat
- These values are decreased if the fatty liver content is

Magnetic Resonance

- MRI or MRS
- 80-90% sensitive and >90% specific for liver fat



Fatty infiltration can be seen in Hepatitis C and Wilsons disease



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Transient elastography

Fibroscan

- Measures the velocity of a shear wave created by a vibratory source as it travels through the liver
- The velocity of the wave correlates with tissue stiffness: the wave travels faster through denser, fibrotic tissue

Reference values for children have not been established

Liver Biopsy

- Gold standard to diagnose NAFLD
  - It is the only way to differentiate between NAFLD and NASH or stage fibrosis
- Imaging nor bloodwork able to stage the degree of fibrosis
  - 15% of children with NAFLD have stage 3 fibrosis or higher at diagnosis[1]
- Timing of biopsy not well established

If you have an issue, you need some tissue

[1] Schwimmer et al. *PLoS One*, 2014.

Diagnostic Approach

Benefits

Liver Biopsy
- ☑ Differentiates NAFL from NASH
- ☑ Excludes other liver diseases
- ☑ Clinical reference for diagnosis

Serum Biomarkers
- ☑ Non-invasive
- ☑ Cheap

Imaging Modalities
- ☑ Non-invasive
- ☑ Imaging of entire liver
- ☑ Can exclude certain conditions
- ☑ Cost varies

Limitations

Liver Biopsy
- ☑ Invasive
- ☑ Samples a small fraction of the liver

Serum Biomarkers
- ☑ Often have low sensitivity/specificity
- ☑ Some remain to be validated

Imaging Modalities
- ☑ U/S has low sensitivity/specificity
- ☑ CT exposes to radiation
- ☑ MRI/MRS: diagnostic cutoffs unclear

Management

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NASPGHAN clinical practice guidelines

Treatment options in pediatric NAFLD

Lifestyle changes	• Avoidance of sugar-sweetened beverages • Consumption of healthy, well balanced diet • Moderate- to high-intensity exercise daily • Less than 2 hour/day of screen time

Weight loss!

Many retrospective and prospective studies in children and adults identify weight loss as the backbone for the treatment of NAFLD

Other interventions	• Bariatric surgery can be considered in select individuals with NAFLD and other comorbidities

Vos et al. *JPGN*, 2017.

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What do our children eat?

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What do our children eat?

Total calories = about 600

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What do our children eat?

Dietary intervention should start with **NORMALIZING** carbohydrate and sugar intake

Medications

Metformin

- Schwimmer et al[1]
  - Open-label phase 2 clinical trial in non-diabetic children and adolescents with biopsy proven NASH
  - 10 obese children treated with Metformin 500 mg BID for 24 weeks
  - Findings:
    - ALT improved from 184 to 98 U/L
    - Liver fat by MRS improved from 30 to 23%

- Nobili et al[2]
  - Open label 24 month observational study with Metformin 500 mg TID compared to control group (lifestyle modification)
  - 57 subjects 9-18 y/o with biopsy proven NAFLD
  - Findings: Metformin was **not** more effective than lifestyle modification

[1] Schwimmer JB. *Aliment Pharmacol Ther*, 2005.
[2] Nobili V et al. *Clin Ther*, 2008.

TONIC Study

- Pediatric randomized, double-blind, placebo-controlled clinical trial comparing vitamin E, metformin and placebo
- 173 patients (aged 8-17 years) with biopsy-confirmed NAFLD
- Patients received daily dosing of 800 IU of vitamin E, 1000 mg of metformin or placebo for 96 weeks
- Findings:
  - **Neither vitamin E nor metformin was superior to placebo** in attaining sustained reduction in ALT level
  - Compared with placebo, vitamin E showed improvement on hepatic ballooning; however, neither therapy demonstrated significant improvements in other histological features compared to placebo

Lavine et al. *JAMA*, 2011.

Other medications

- Neither vitamin C, fish oil, probiotics, lipid lowering agents (clofibrate, gemfibrozil) nor ursodeoxycholic acid have shown benefit in lowering liver enzymes or improve histology

Bariatric Surgery

- A 2010 Cochrane meta-analysis of bariatric surgery concluded that "the lack of scientifically sound evidence precludes any recommendation to support or reject bariatric surgery to treat patients with NAFLD"[1]
- May be considered for **selected** adolescents

Reference	Lower BMI criteria:	Higher BMI criteria:
Inge *et al.* (2004)[7]	BMI ≥ 40 kg/m^2 with: Type 2 diabetes Obstructive sleep apnoea Pseudotumor cerebri	BMI ≥ 50 kg/m^2 with: Hypertension Dyslipidaemias NASH Venous stasis disease Quality of life impairment
Pratt *et al.* (2009)[9]	BMI ≥ 35 kg/m^2 with comorbidities associated with greater short-term morbidity: Type 2 diabetes Severe steatohepatitis Pseudotumor cerebri Moderate-to-severe obstructive sleep apnoea	BMI ≥ 40 kg/m^2 with comorbidities associated with long-term morbidity (not specified)
Michalsky *et al.* (2012)[8]	BMI ≥ 35 kg/m^2 with major comorbidities: Type 2 diabetes Severe steatohepatitis Pseudotumor cerebri Moderate-to-severe obstructive sleep apnoea (apnoea-hypopnea index ≥ 15)	BMI ≥ 40 kg/m^2 and other comorbidities: Hypertension Insulin resistance Glucose intolerance Impaired quality of life Dyslipidaemia
Nobili *et al.* (2015)[1*]	BMI >97% percentile (or >40 kg/m^2) with major comorbidities: Type 2 diabetes mellitus Moderate to severe sleep apnoea Pseudotumor cerebri NASH with significant fibrosis (Ishak score ≥1)	BMI >97% percentile (or >50 kg/m^2) with other mild comorbidities: Hypertension Insulin resistance Glucose intolerance Substantially impaired quality of life Dyslipidaemia Milder sleep apnoea

Xanthakos et al. *Nat Rev Gastroenterol Hepatol*, 2015.

[1] Chavez-Tapia et al. *Cochrane Database Syst Rev*, 2010.

What "works"?

1. Patient needs to be **motivated**
2. Family needs to be **committed**

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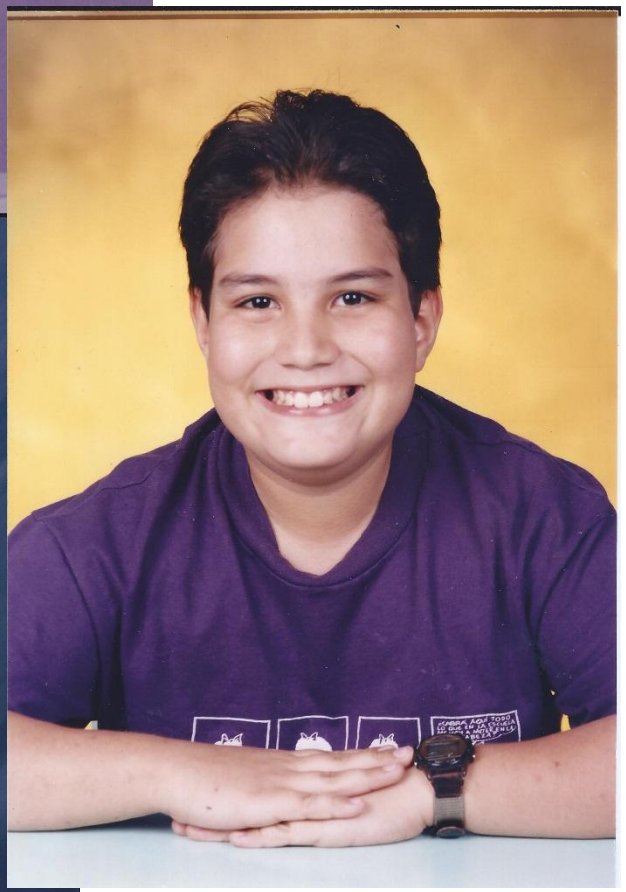
Once Upon a time...



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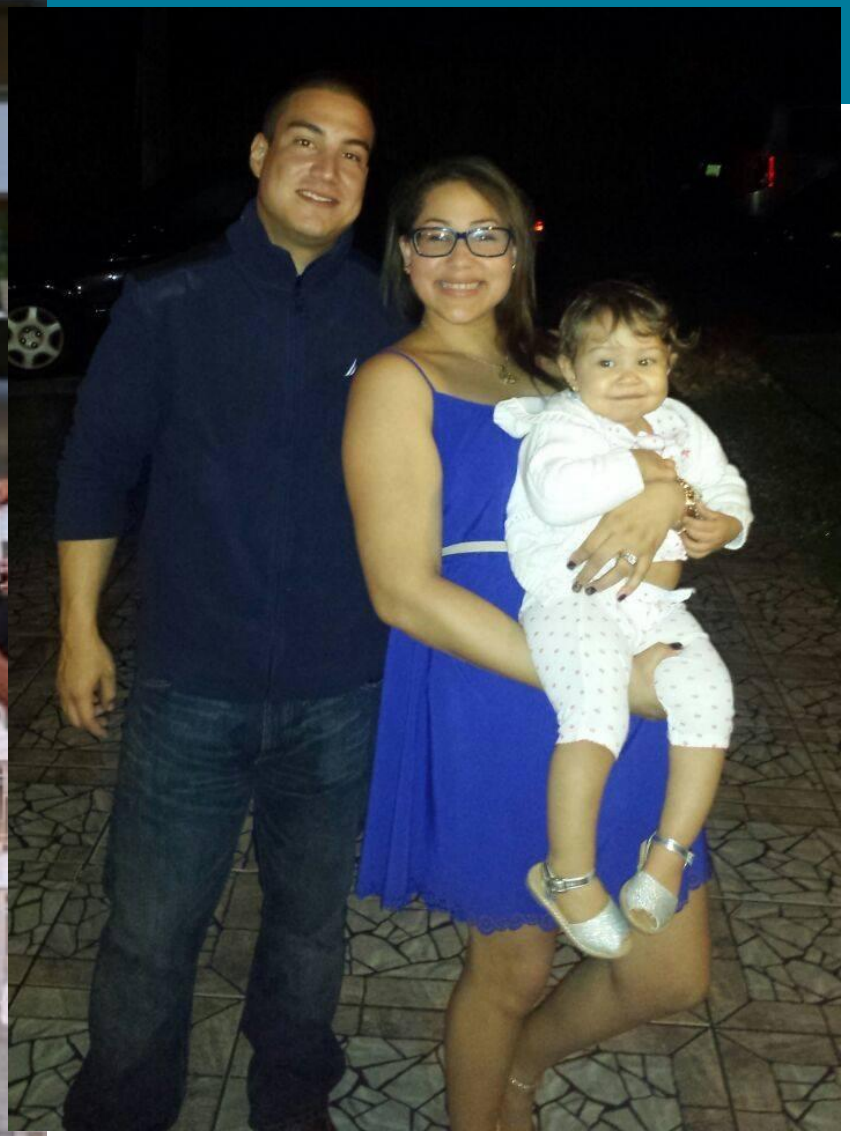

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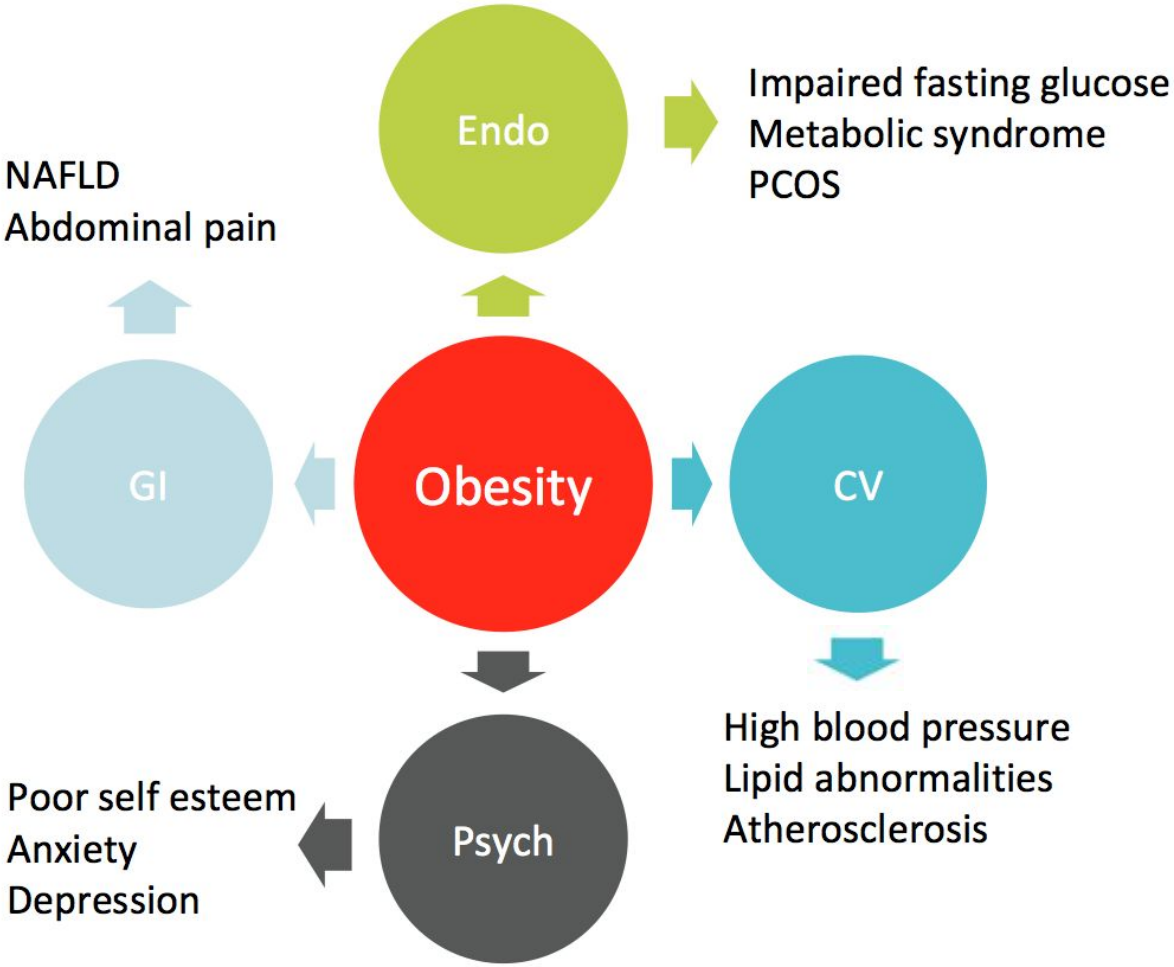
Multidisciplinary approach



Fatty liver clinic at Seattle Children's

- Team includes:
  - Hepatology
  - Endocrinology
  - Dietitian
  - Athletic Trainer
  - Psychologist

- New referrals- "suspected fatty liver"

Conclusions

- NAFLD is the most common cause of chronic liver disease in children in the US
- Progression of disease is very variable
  - Bland steatosis is relatively benign, but NASH has significant morbidity/mortality risk
- Sustained gradual weight loss and exercise are the hallmark therapies
- A multidisciplinary approach greatly benefits children that suffer from NAFLD

Questions?

Thank you!

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