Nonalcoholic Fatty Liver Disease (NAFLD)

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Outline of NAFLD Module

Obesity Epidemic

NAFLD Definition and Prevalence

NAFLD Presentation and Pathology

NAFLD Natural History

NAFLD Diagnosis

NAFLD Management

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Obesity Epidemic

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Increased Prevalence of Extreme Obesity in Children

		Prevalence:
BMI ≥ 85th percentile	Overweight	32%
BMI ≥ 95th	Obese	17%
BMI ≥ 99th	Extremely Obese	4-8%

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Freedman et al; *J Pediatr.* 2007 Jan;150(1):12-17.

NAFLD:
Definition and Prevalence

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Prevalence of NAFLD

Excess fat in the liver = Steatosis

Steatosis without alcohol = NAFLD

~ 6 million children have NAFLD

Steatosis with inflammation/fibrosis = NASH
(Nonalcoholic steatohepatitis)

~ 10-30% may develop NASH

~ 7-10% may develop
Cirrhosis and
some possibly progress to HCC

Schwimmer et al. *Pediatrics.* 2006 118; 1388.
Ascha et al. *Hepatology.* 2010; Jun;51(6):1972-8.

NAFLD Prevalence in Adults

1988 to 1994

– 46.8% of all Chronic Liver Disease cases

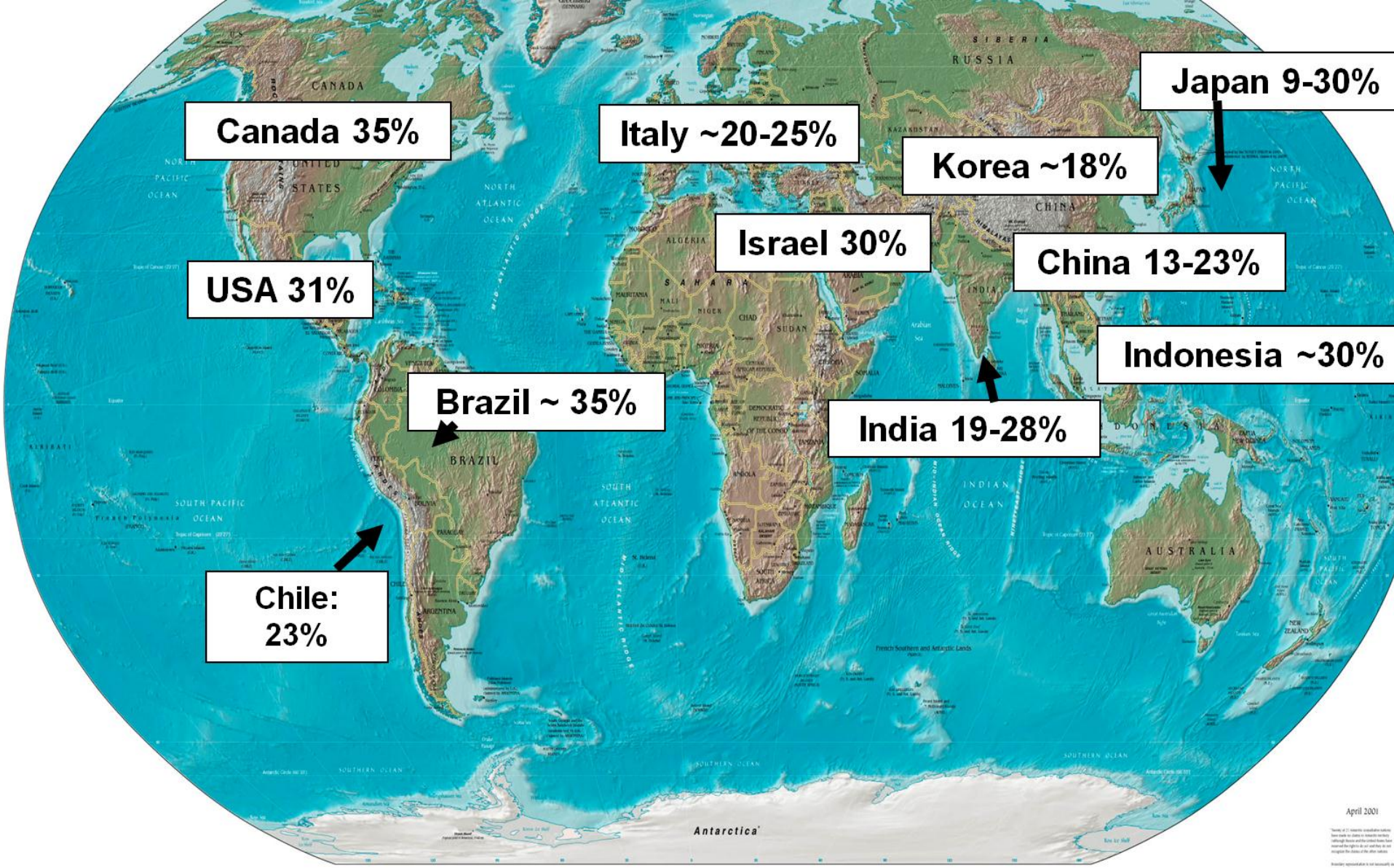
1994 to 2004

– increased to 62.84%

2005 to 2008

– to 75.1%

Younossi et al. *Clin Gastro Hepatol .* 2011;9:524.



Clark. *J Clin Gastro.* 2006:S5.
Bellentani et al. *Ann Intern Med .* 2000;132:112.
Browning et al. *Hepatology .* 2004; 40:1387.

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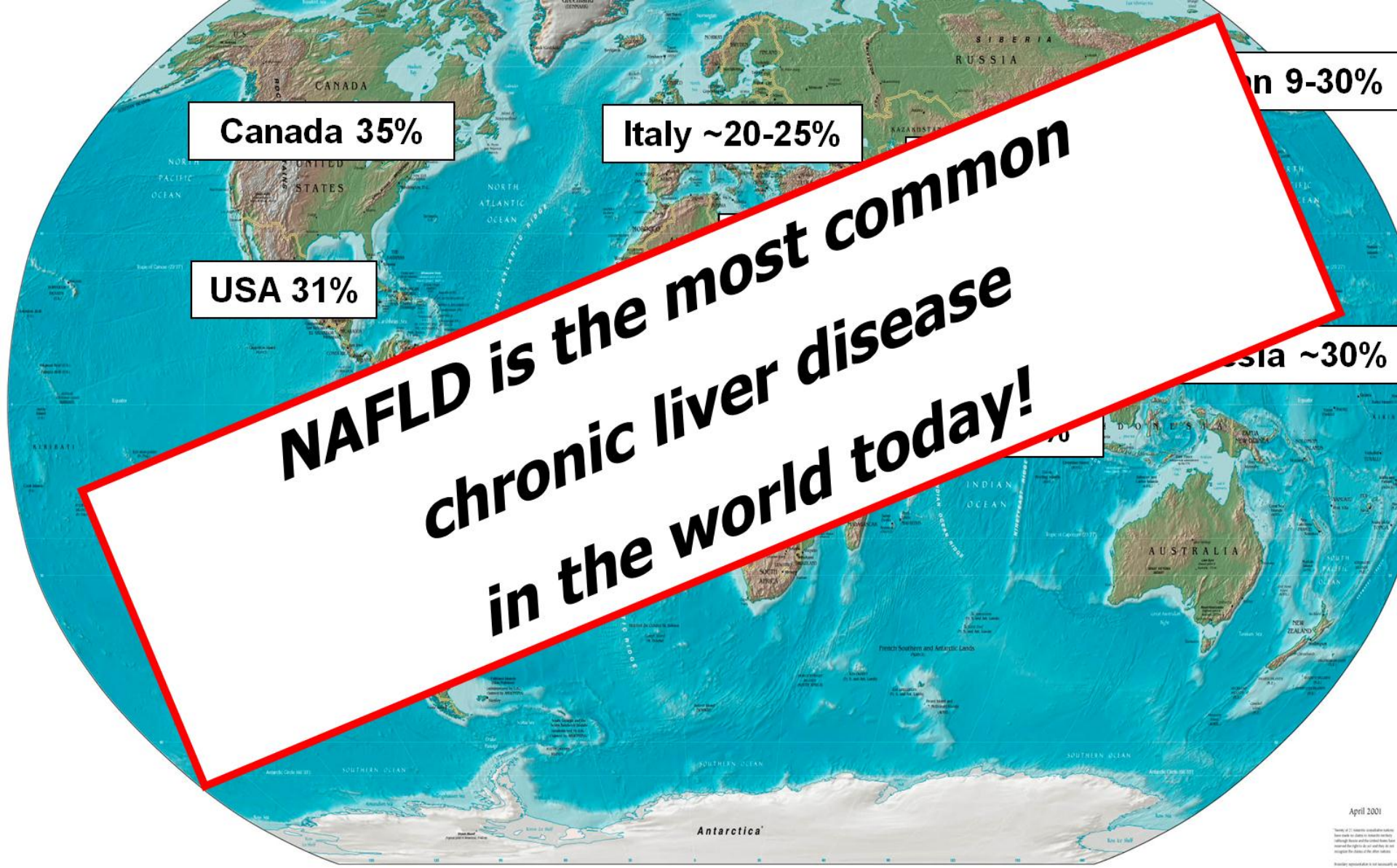

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Bellentani et al. *Ann Intern Med .* 2000;132:112.
Browning et al. *Hepatology .* 2004; 40:1387.

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NAFLD:
Presentation and Pathology

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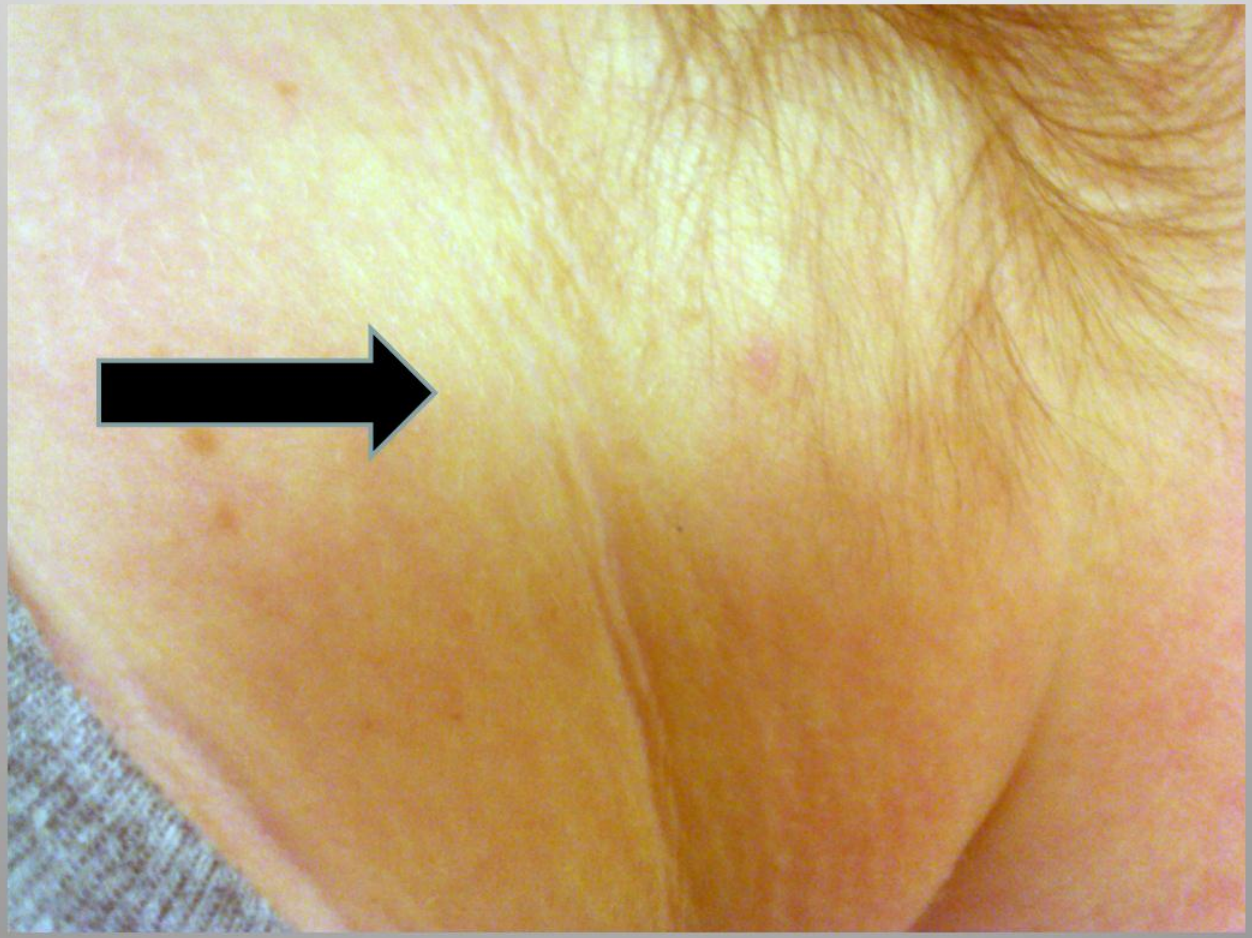
NAFLD: Signs/Symptoms

Nonspecific and often silent :

- Obesity (BMI >95% for age)
- Hepatomegaly
- RUQ discomfort
- Acanthosis nigricans
- Obesity comorbidities
  - Diabetes, Gallstones, Polycystic ovarian syndrome, Hypertension, Hyperlipidemia

Acanthosis Nigricans in Neck



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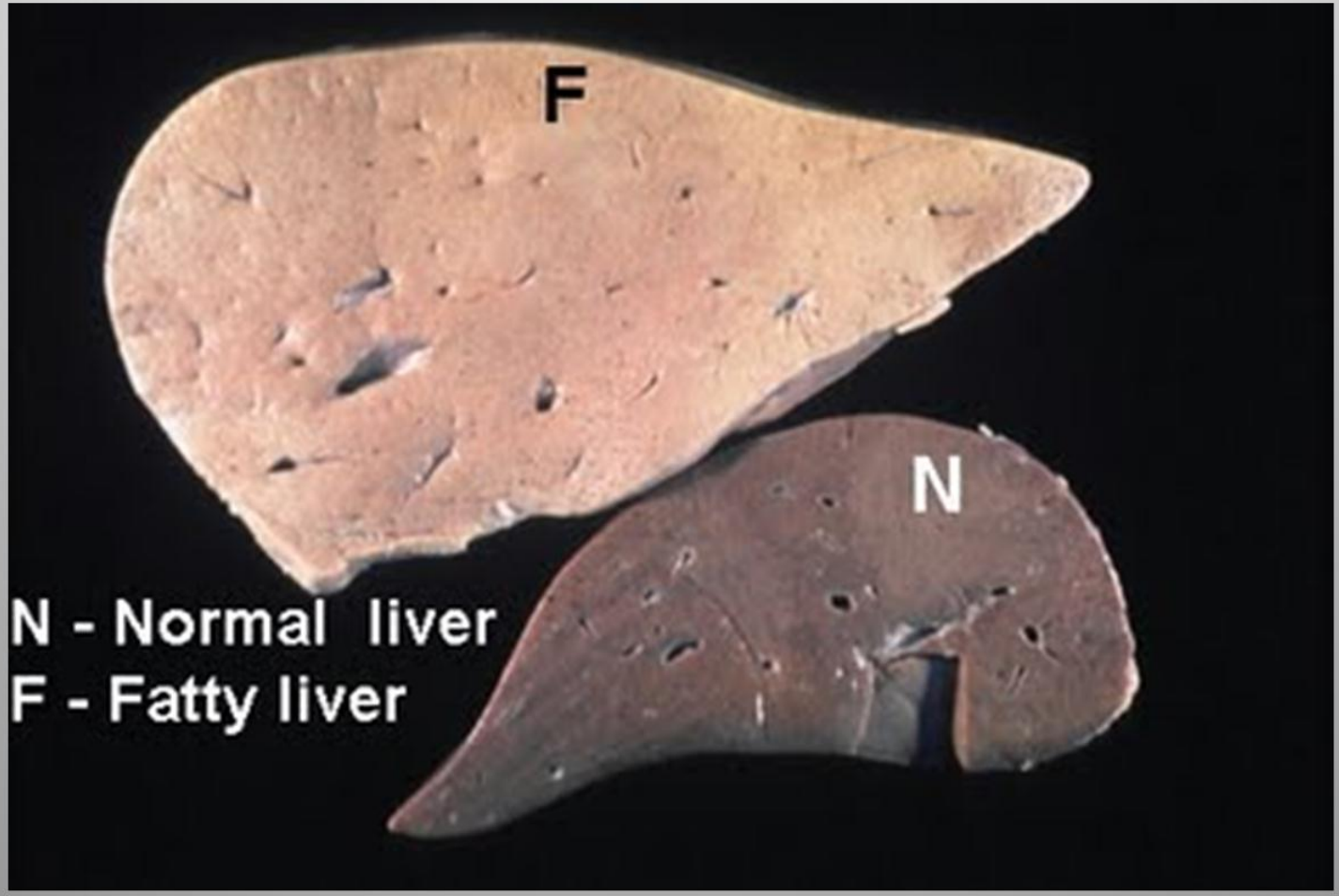
Gross Liver Morphology



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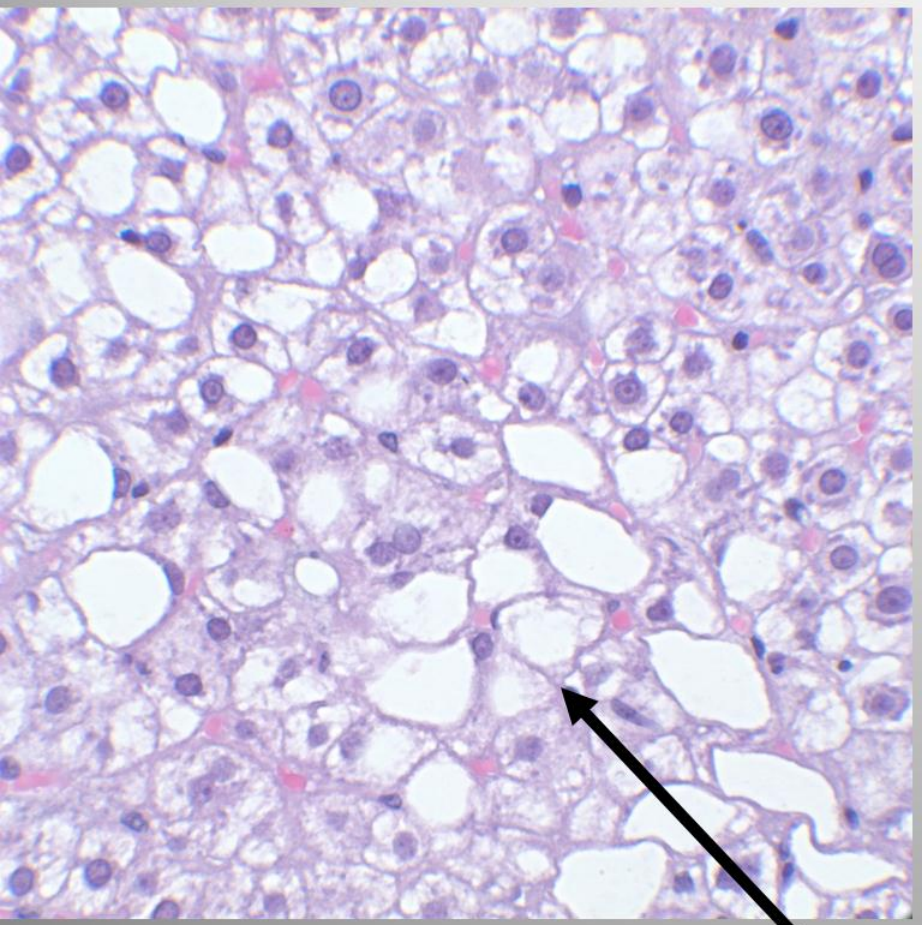
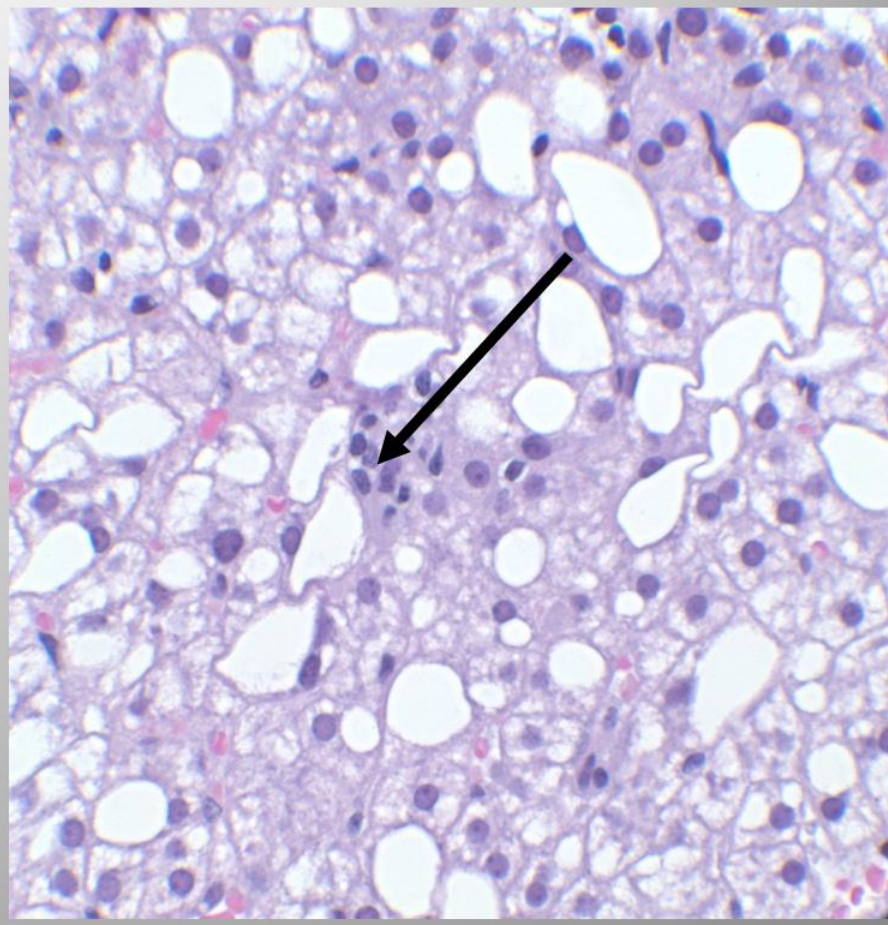
NASH Histology





Ballooning Degeneration

Foci of lobular inflammation

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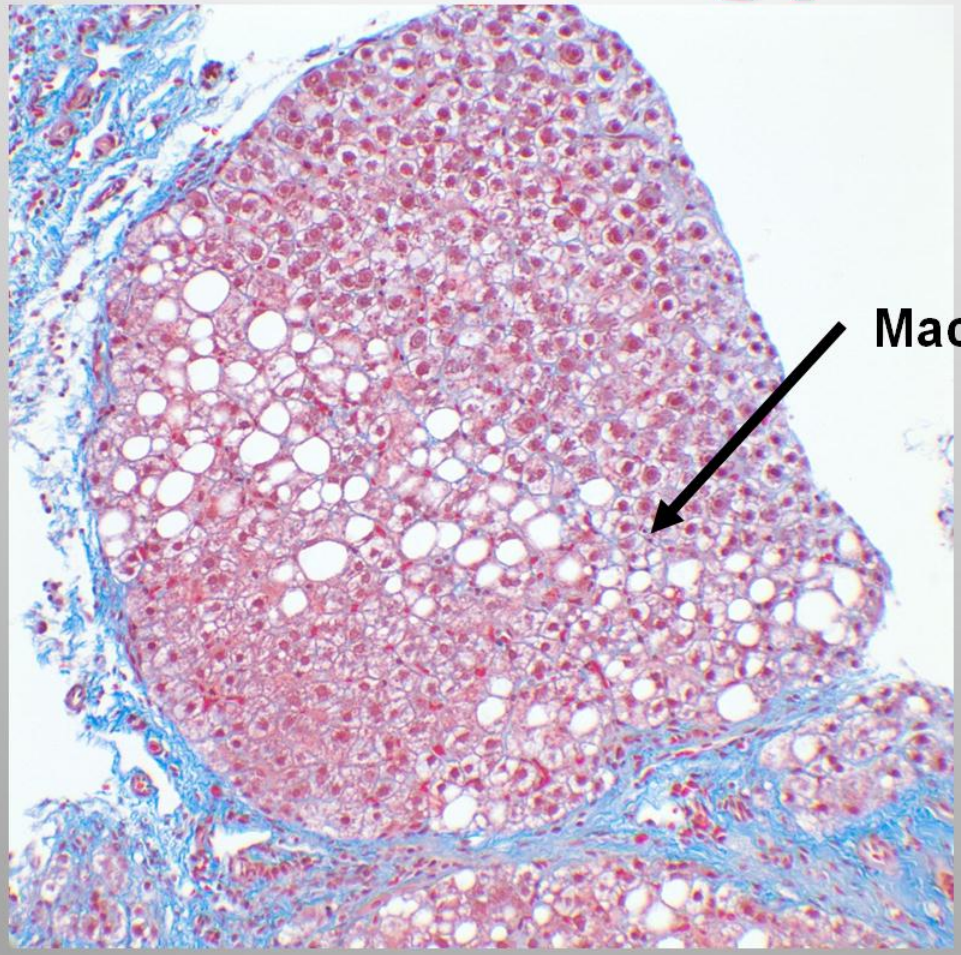
NASH Histology-Fibrosis



Trichrome stain (blue) highlighting fibrosis

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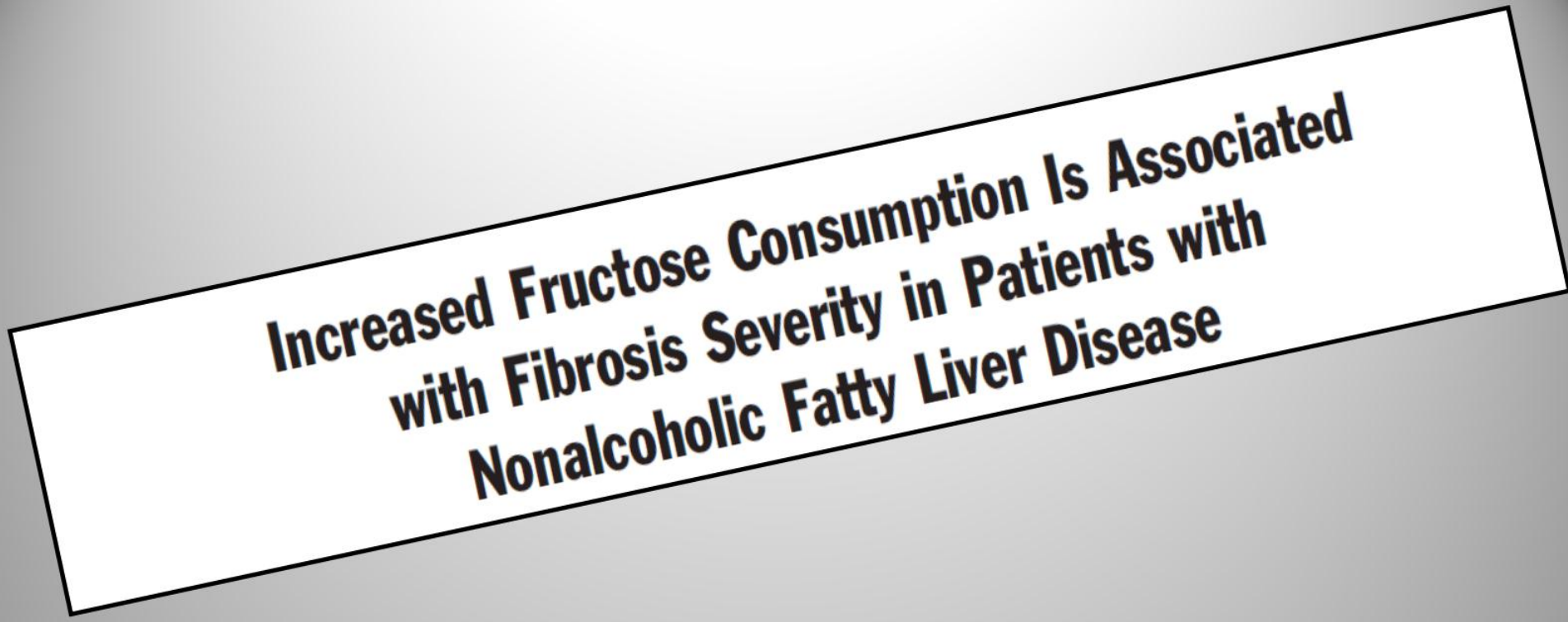

NIH-NASH Clinical Research Network Study

Adults drinking >7 servings of fructose rich beverages /week (sodas, kool-aid etc) had more severe fibrosis

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Abdelmalek et al. *Hepatology* . 2010;51:1961-1971.

A Common Variant in the Patatin-Like Phospholipase 3 Gene (*PNPLA3*) Is Associated with Fatty Liver Disease in Obese Children and Adolescents

The occurrence of the G allele of a lipid metabolism gene, PNPLA3, increased the risk of severe NAFLD

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Santoro et al. *Hepatology.* 2010 ;52(4):1281-90.
Lin. *Journal of Pediatrics.* 2011 158:740.

NAFLD: Natural History

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Natural History

Adults: 420 adults

NASH subjects had liver related death as 3rd leading cause vs. 13th in general population

- Increased heart related complications
- 5% developed cirrhosis

Pediatrics: 63 children

Retrospective study with small sample size

Needs further study

Feldstein et al. *Gut.* 2009; 58: 1538-44.

Adams et al. *Gastro*. 2005;129:113-121.

Long-Term Follow-up of Patients With NAFLD and Elevated Liver Enzymes

(HEPATOLOGY 2006;44:865-873.)

Mattias Ekstedt,[1] Lennart E. Franzén,[2] Ulrik L. Mathiesen,[3] Lars Thorelius,[4] Marika Holmqvist,[5] Göran Bodemar,[1] and Stergios Kechagias[6]

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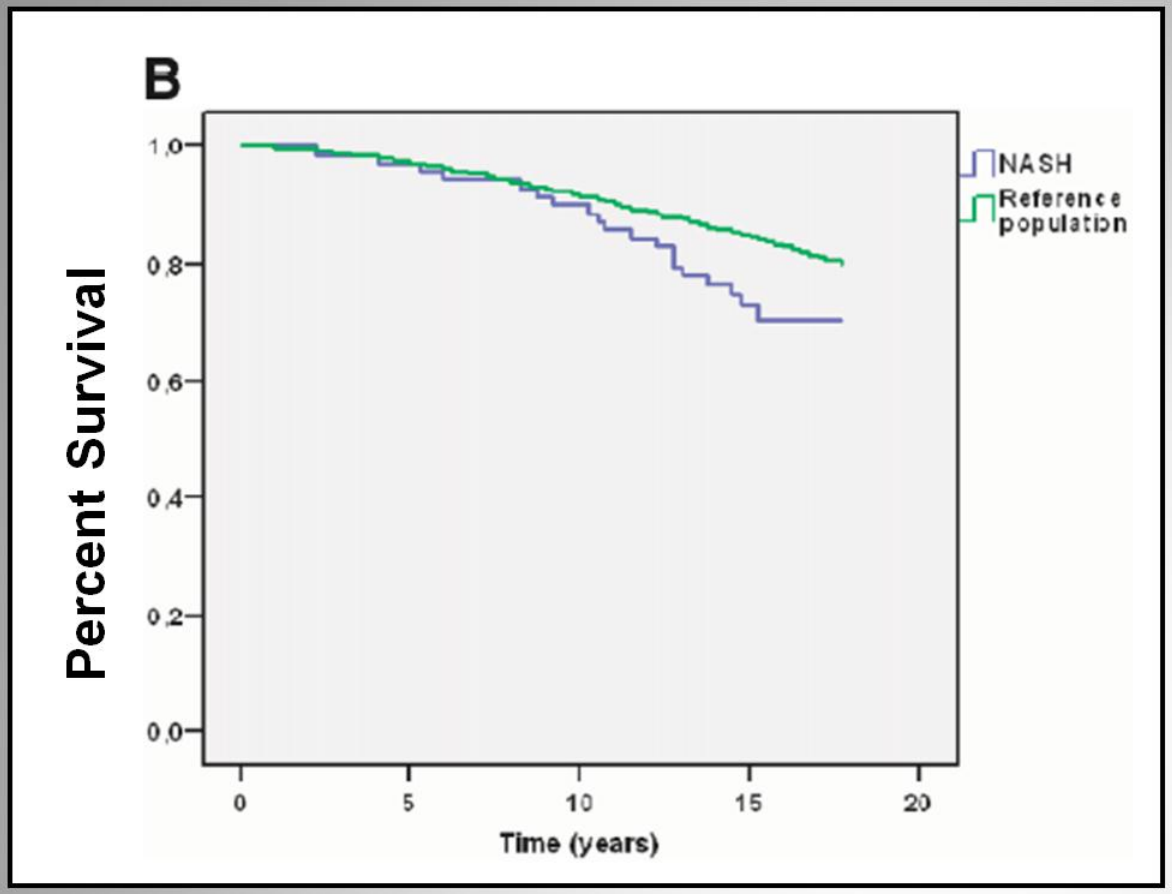

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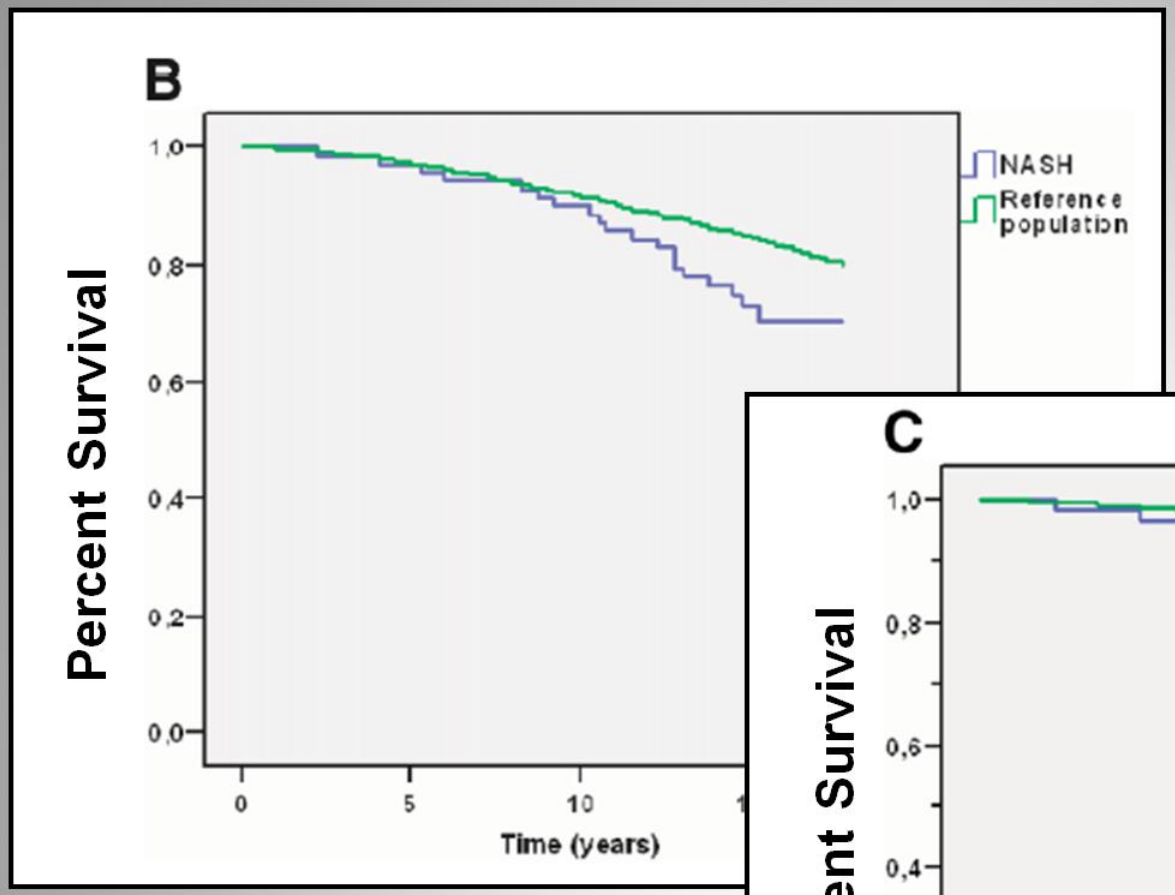

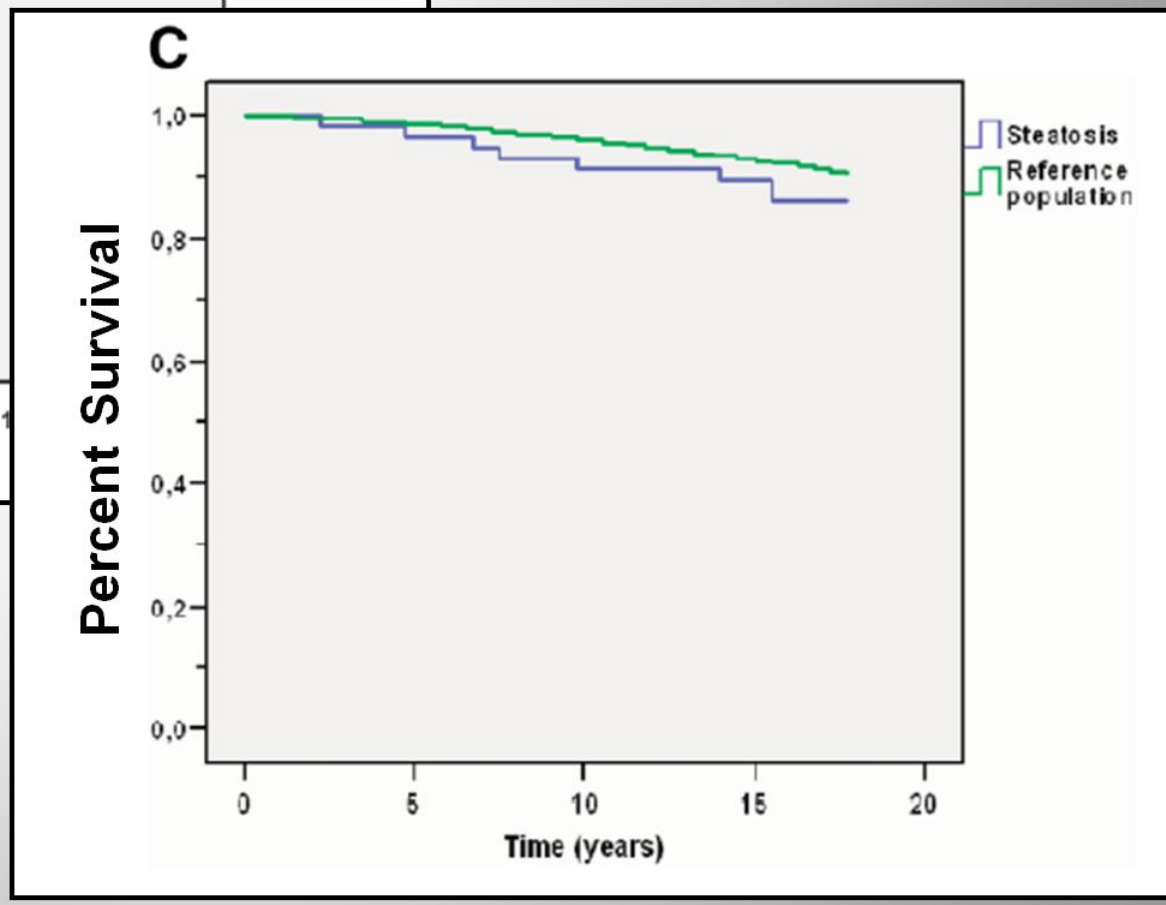

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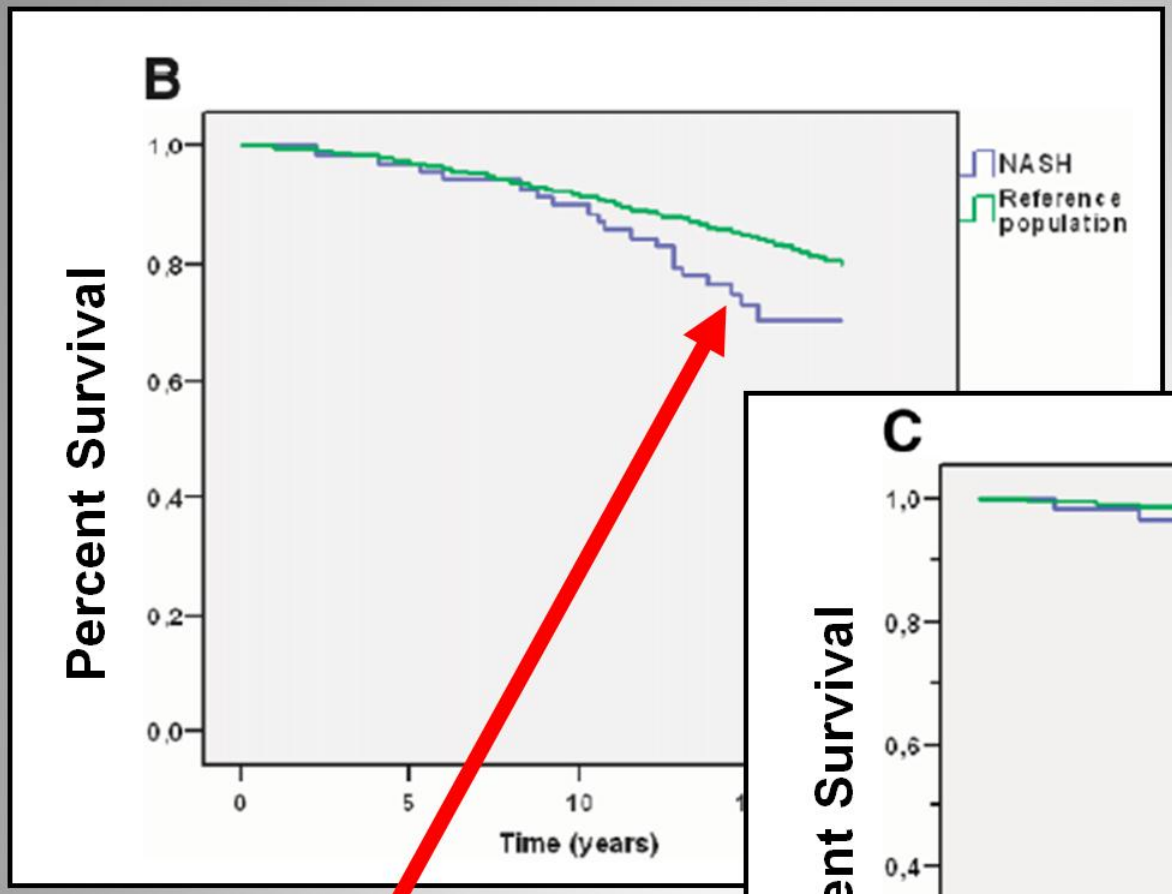

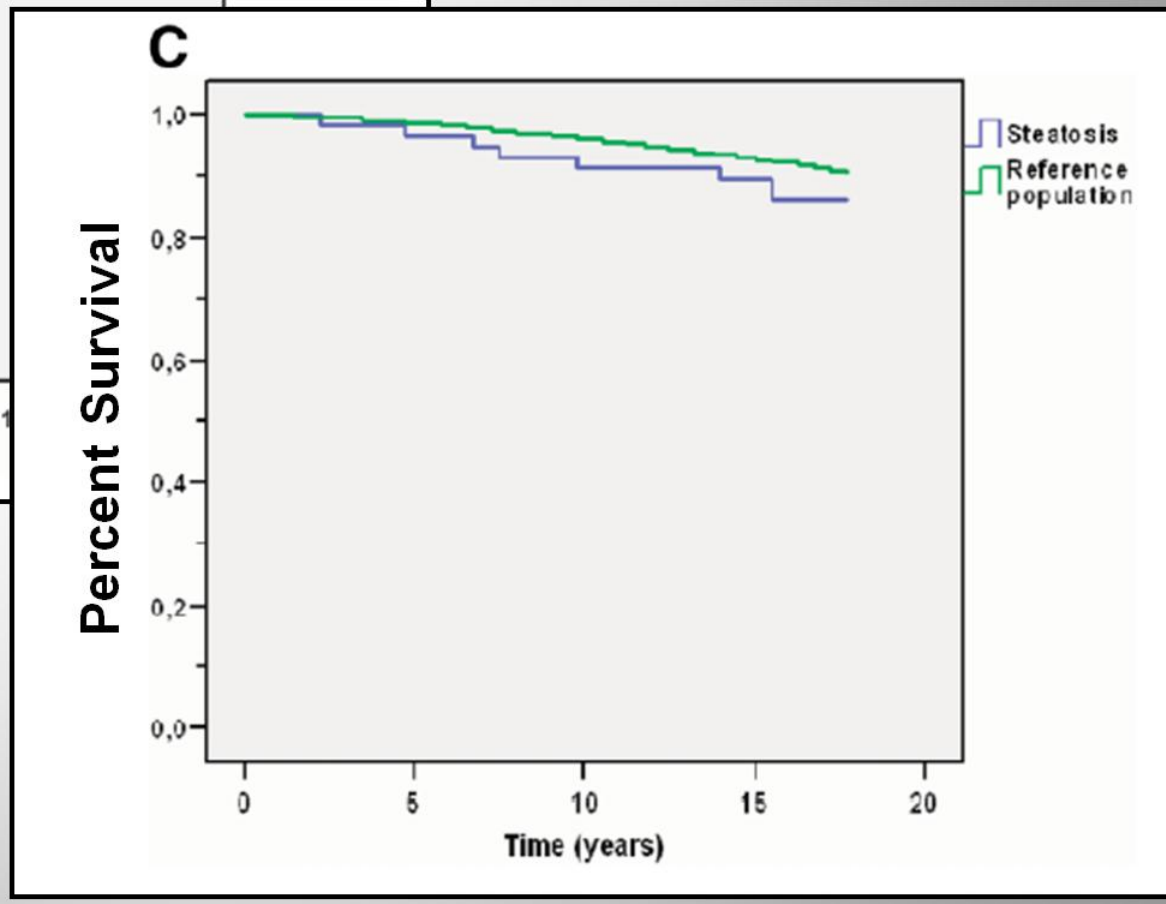

NASH produces a significant increase in mortality

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Clinical Vignette

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Pediatric Clinical Vignette: Progression of Fibrosis

	Patient A		Patient B	
	Biopsy #1	Biopsy#2	Biopsy #1	Biopsy#2
Age	11	16	10	13
Weight (kg)	67.7	122.2	75.1	103.6
BMI	28.2	38.6	31.8	36.05
AST	59	114	112	256
ALT	134	172	240	390
GGT	73	105	97	89
Platelet count	355	252	262	239
NAFLD Activity Score	4/8	4/8	4/8	6/8
Fibrosis Stage	1c/4	3/4	1c/4	3/4

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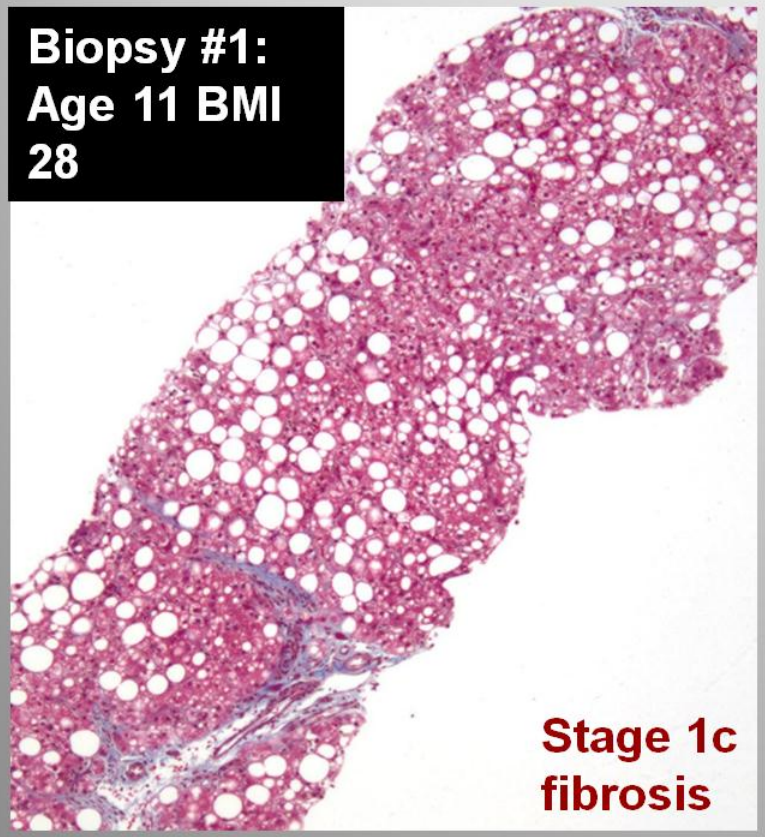
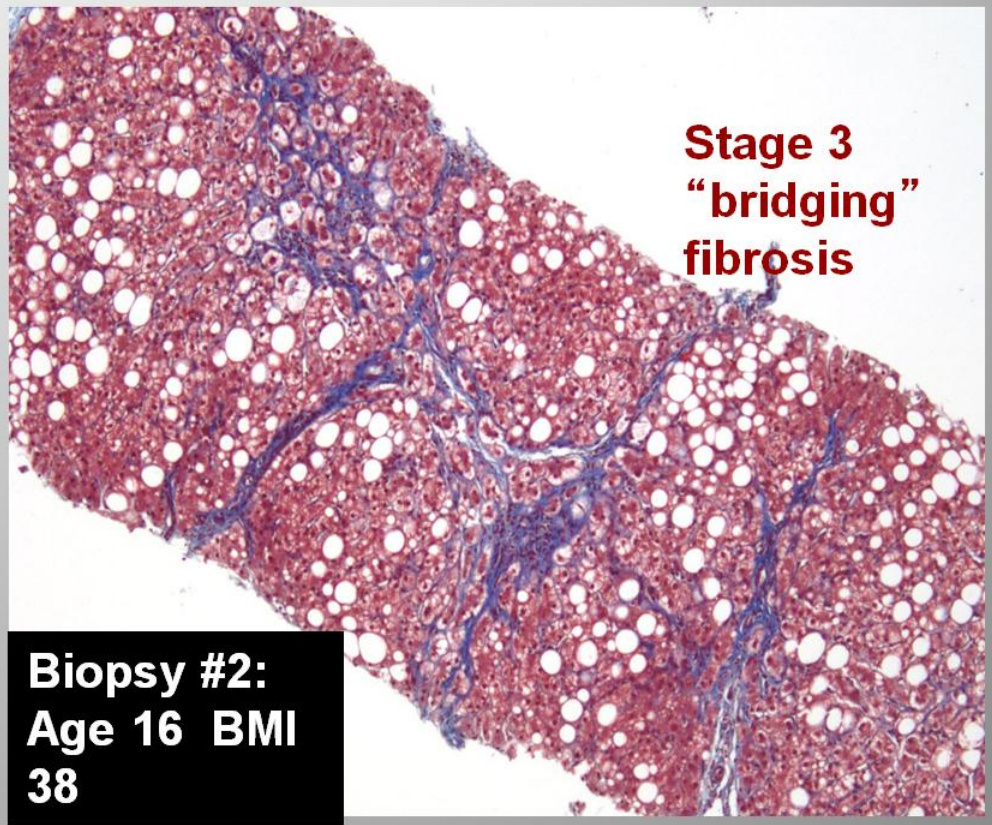
Kohli R et al. *JPGN* . 2010; 50(4):453-6.

Progression of Fibrosis





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NAFLD: Diagnosis

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Limitations of AST and ALT

Poor correlation with histology

Broad differential diagnosis

- Viral hepatitis
- Autoimmune hepatitis
- Wilson's disease
- Alpha-1 antitrypsin
- Hemochromatosis
- Celiac disease
- Medication toxicity
- Genetic and metabolic disorders

NAFLD and ALT

The median upper limit of ALT at children's hospitals was 53 U/L while 95th percentile levels for ALT in healthy weight, metabolically normal, liver disease-free, NHANES pediatric participants were 25.8 U/L (boys) and 22.1 U/L (girls).

Serum alanine aminotransferase levels may decrease on placebo and is not a reliable measure of treatment response in NAFLD.

Schiwmmer et al. *Gastro.* 2010;138(4):1357-64.
Loomba et al. *Clinical Gastro Hep.* 2008;6(11):1243-8.

NAFLD and ALT

The median upper limit of ALT at … hospitals was 53 U/L while … levels for ALT in … metabolically … NHANES … 22.1 U/L (girls).

NAFLD may be missed if we use ALT alone to diagnose it!

… aminotransferase levels may … on placebo and is not a reliable measure of treatment response in NAFLD.

Schiwmmer et al. *Gastro.* 2010;138(4):1357-64.
Loomba et al. *Clinical Gastro Hep.* 2008;6(11):1243-8.

Ultrasound

Non-invasive

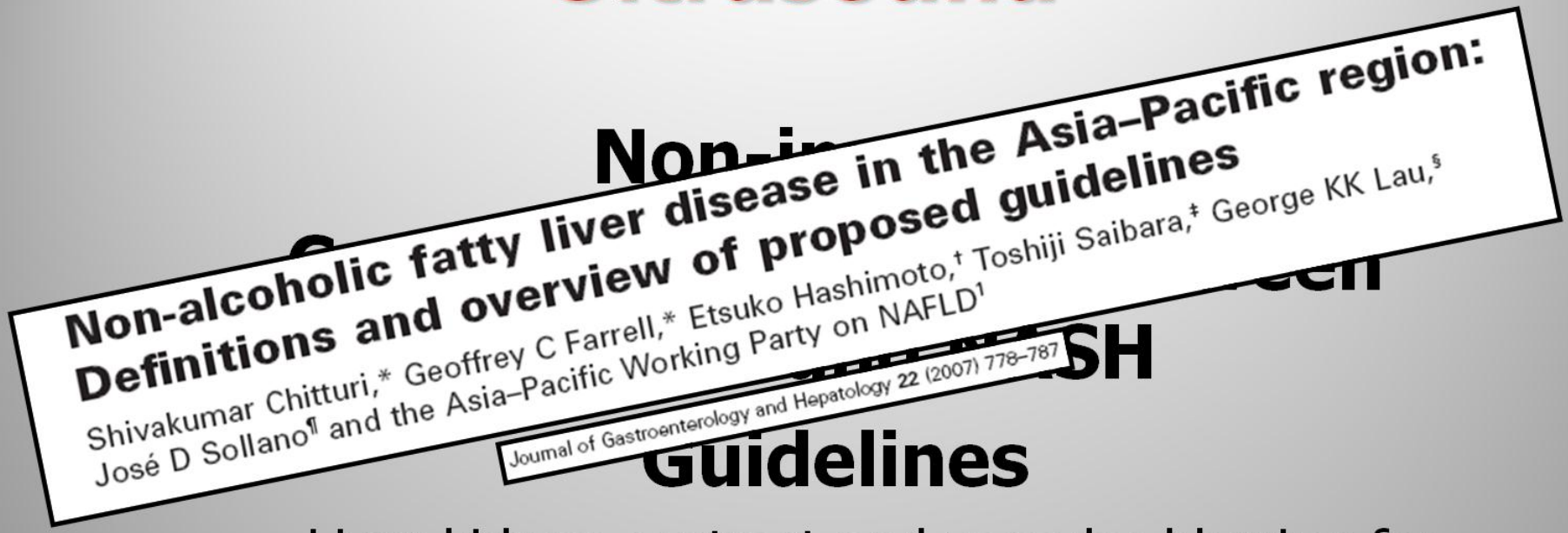
Cannot differentiate between NAFLD and NASH

Guidelines

- Liver-kidney contrast and vascular blurring for fatty liver
- Sensitivity 83%, Specificity 100%, Accuracy of 96%

Yajima et al. *The Tohoku Journal of Experimental Medicine*.139, 1 (43-50) .

Ultrasound


Non-alcoholic fatty liver disease in the Asia–Pacific region: Definitions and overview of proposed guidelines

Shivakumar Chitturi,* Geoffrey C Farrell,* Etsuko Hashimoto,† Toshiji Saibara,‡ George KK Lau,§ José D Sollano¶ and the Asia–Pacific Working Party on NAFLD¹

Journal of Gastroenterology and Hepatology 22 (2007) 778–787

Non-i… Guidelines

- Liver-kidney contrast and vascular blurring for fatty liver
- Sensitivity 83%, Specificity 100%, Accuracy of 96%

Yajima et al. *The Tohoku Journal of Experimental Medicine*.139, 1 (43-50) .

When to Refer to GI?

- BMI > 95% for age
  - Ultrasound to check for steatosis
  - Check liver enzymes

- Steatosis and elevated AST/ALT
  - If persistently elevated > 2ULN for 3 months
  - Refer to Pediatric Gastroenterologist for further work up

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MR/CT

- Pros:
  - Can identify fatty liver accurately
  - Can provide quantitative estimate of fat in liver
- Cons
  - Expensive
  - Cannot differentiate between NAFLD and NASH

Diagnostic Panels

A Combination of the Pediatric NAFLD Fibrosis Index and Enhanced Liver Fibrosis Test Identifies Children With Fibrosis

- **Pediatric NAFLD Fibrosis Index was based on**
  - age,
  - waist circumference,
  - and levels of triglycerides
- **The Enhanced Liver Fibrosis test was based on**
  - hyaluronic acid,
  - aminoterminal propeptide of type III collagen,
  - and tissue inhibitor of metalloproteinase-1

Combining PNFI and ELF gave a better ROC-AUC

Alkhouri et al. *Clin Gastro Hepatol.* 2011;9:150.

Liver Biopsy

Current Gold Standard

Persistent elevated enzymes >2 ULN

Limitations

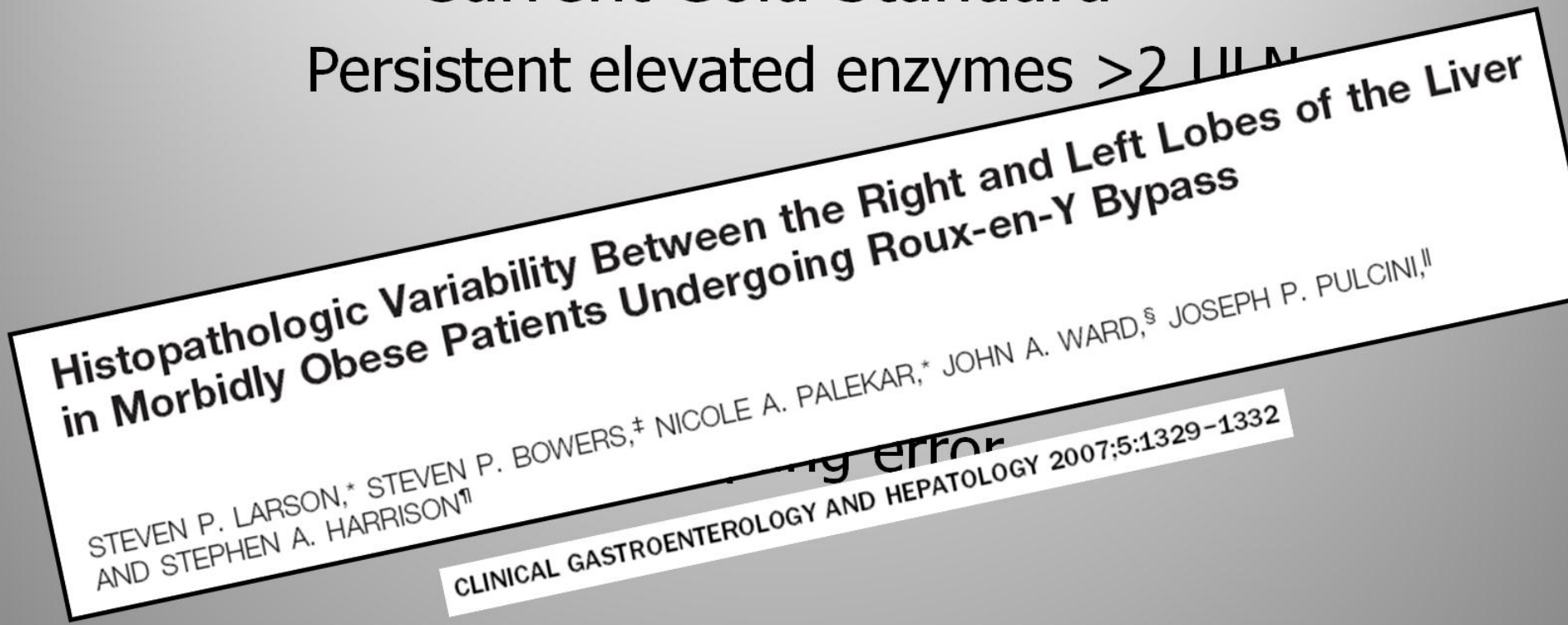
Invasive

Sampling error

Liver Biopsy

Current Gold Standard

Persistent elevated enzymes >2 ULN



Histopathologic Variability Between the Right and Left Lobes of the Liver in Morbidly Obese Patients Undergoing Roux-en-Y Bypass

STEVEN P. LARSON,* STEVEN P. BOWERS,‡ NICOLE A. PALEKAR,* JOHN A. WARD,§ JOSEPH P. PULCINI,‖ AND STEPHEN A. HARRISON¶

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:1329–1332

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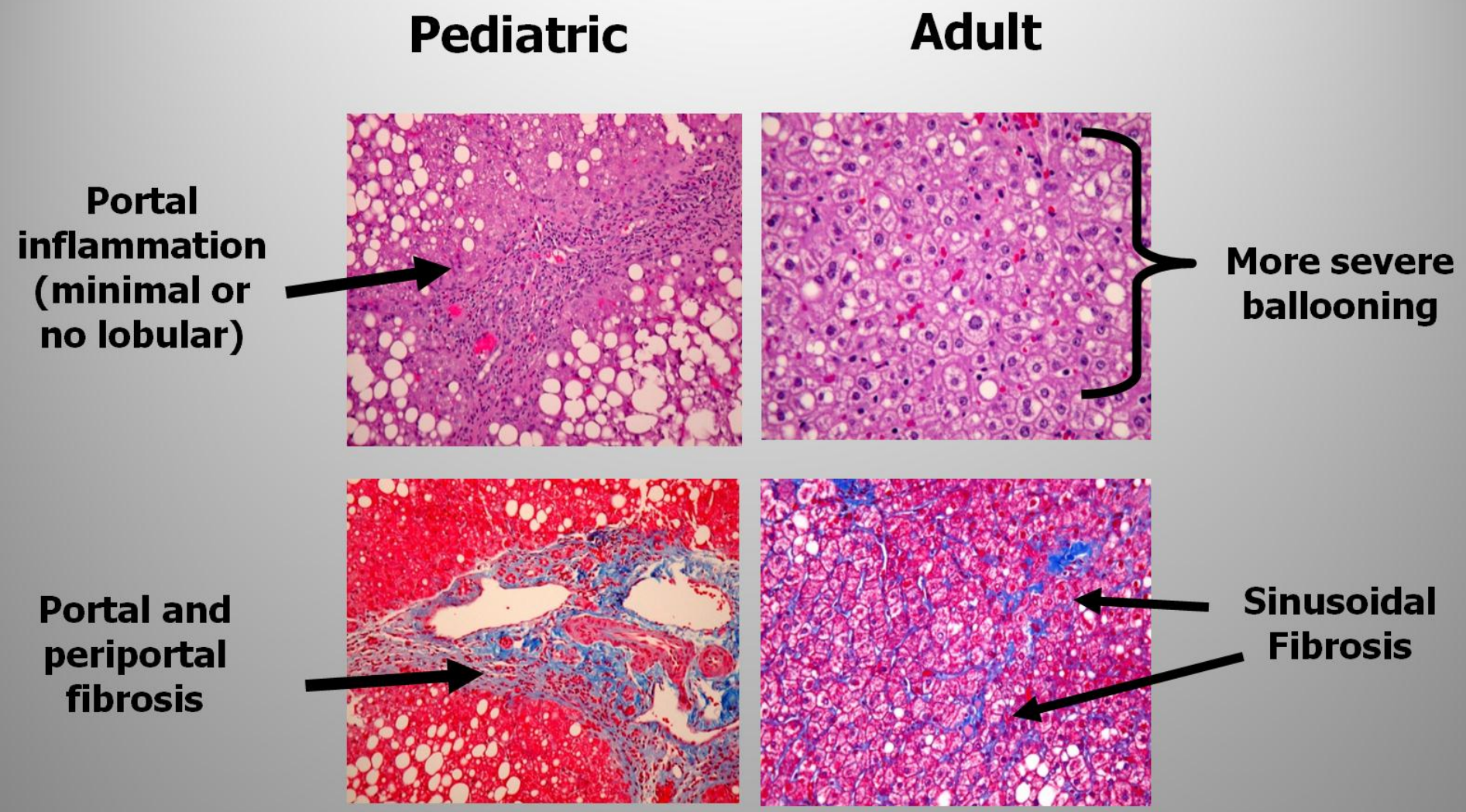
Features of Pediatric NASH



Brunt et al. *Hepatology* 2009 Mar;49(3):809-20.

NAFLD: Management

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Management: Lifestyle Modification

Lifestyle intervention for non-alcoholic fatty liver disease: prospective cohort study of its efficacy and factors related to improvement

- Recommended changes:
  - Increased physical activity
  - Limit screen time
  - Behavioral Counseling
  - Increase family time and interaction

Koot et al. *Arch Dis Child.* 2011;96:669.

Management: Dietary Changes

- Recommended changes:
  - Increase fruit and vegetable intake
  - Decrease sugar sweetened beverage intake
  - Reduce take out and fast food meals
  - Avoid hepatotoxins (Especially alcohol in teens)

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Management: Medications

- Treatment of Nonalcoholic Fatty Liver Disease in Children (TONIC)
  - Randomized 180 children to Metformin vs. Vitamin E vs. placebo
  - Results:
    - Significant improvement in resolution of NASH and improvement in NAFLD activity scores as seen with Vitamin E relative to placebo.
    - No effect of metformin.
    - Vitamin E as effective in resolving NASH in children as it is in resolving NASH in adults

Lavine et al. *JAMA.* 2011;305:16 (1659-68).

Management: Bariatric Surgery

Stringent Criteria:

- 6 months prior non-surgical weight management
- Extremely obese (BMI 40 or greater)
- When adult height reached

Take Home Points (1/2)

- Pediatric NAFLD is a global epidemic
- NASH has a worse prognosis than steatosis alone
- ALT does not correlate well with disease
- The gold standard for diagnosis is liver biopsy

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Take Home Points (2/2)

- Weight loss is the only long-term solution
- Protect your liver
  - Hepatitis A and B Vaccination
  - Avoid alcohol and other hepatotoxins
- Vitamin E is appropriate for biopsy-proven NASH in those who have had a biopsy