NAFLD in the Primary Care and Diabetes Settings

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Disclosures:

- None

NAFLD: What is It?

- Non-alcoholic fatty liver disease
  - Presence of fatty infiltrates in the liver (>5% steatosis)
    - Imaging or biopsy
  - Exclude other causes of hepatic fat accumulation*

TABLE 1. Common Causes of Secondary HS

Macrovesicular steatosis

- Excessive alcohol consumption
- Hepatitis C (genotype 3)
- WD
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (e.g., mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, corticosteroids)

Microvesicular steatosis

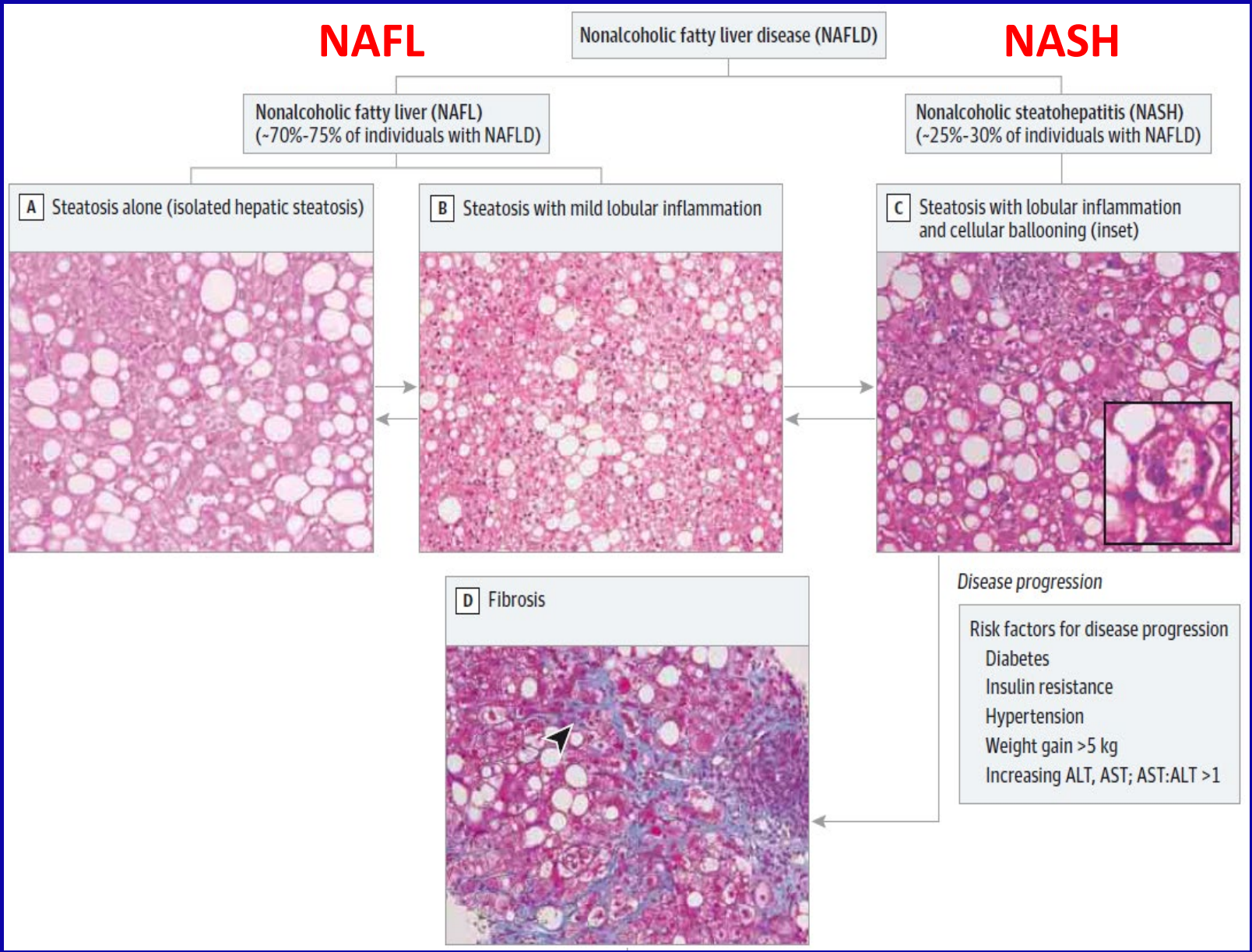
- Reye's syndrome
- Medications (valproate, antiretroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (e.g., lecithin-cholesterol acyltransferase deficiency, cholesterol ester storage disease, Wolman's disease)

More Definitions

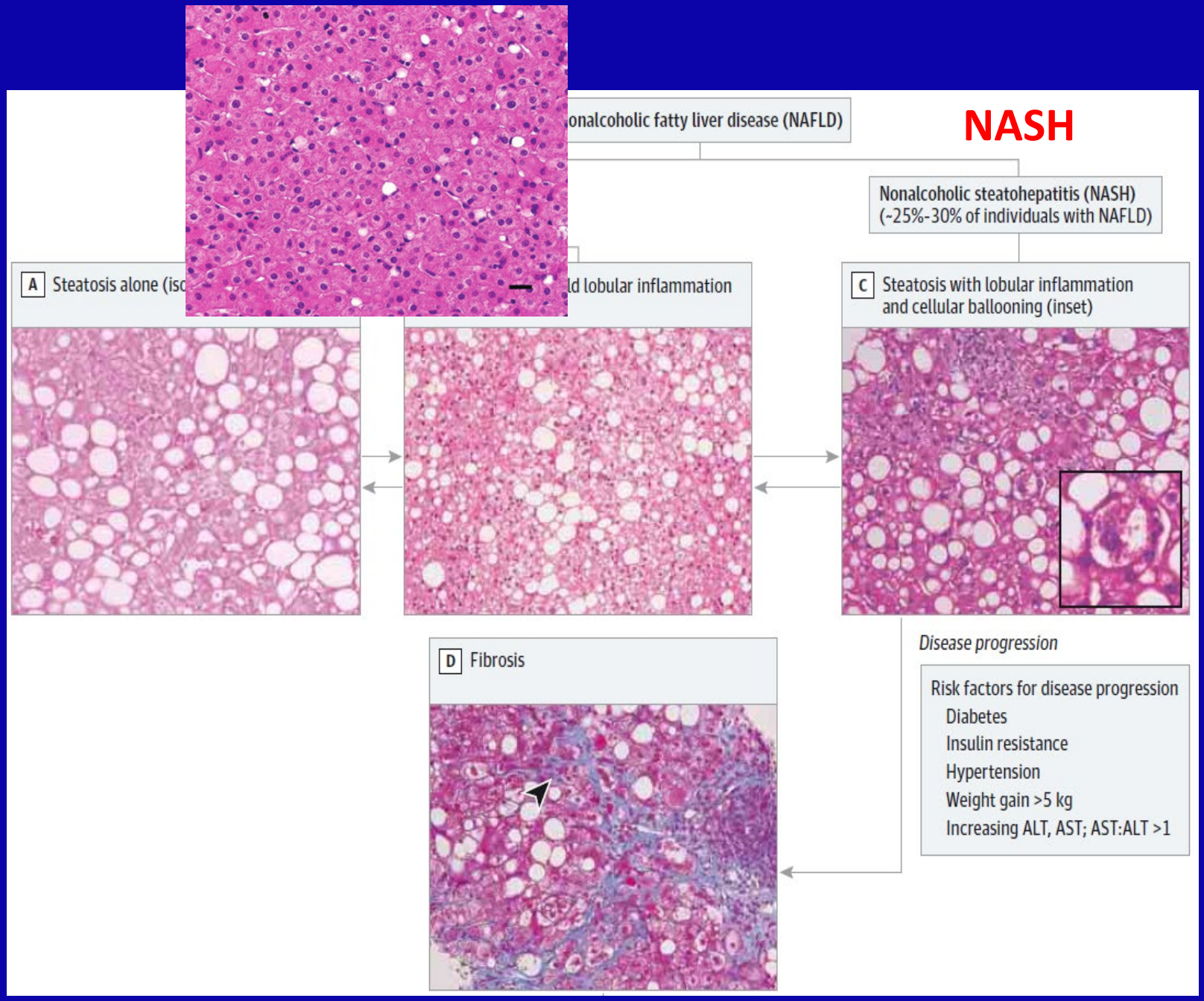
- NAFLD:
  - Includes entire spectrum of fatty liver disease

- NAFL vs NASH:
  - NAFL:
    - "Fatty liver"
    - No evidence of hepatocellular injury (hepatocyte ballooning, fibrosis)
  - NASH:
    - Non-alcoholic steatohepatitis
    - Presence of inflammation and hepatocyte injury (ballooning) +/-fibrosis

Younossi ZM, et al. Hepatology. 64(1). 73-84.


NAFL
Nonalcoholic fatty liver disease (NAFLD)
NASH
Nonalcoholic fatty liver (NAFL)
(~70%-75% of individuals with NAFLD)
Nonalcoholic steatohepatitis (NASH)
(~25%-30% of individuals with NAFLD)
A Steatosis alone (isolated hepatic steatosis)
B Steatosis with mild lobular inflammation
C Steatosis with lobular inflammation and cellular ballooning (inset)
Disease progression
D Fibrosis
Risk factors for disease progression
Diabetes
Insulin resistance
Hypertension
Weight gain >5 kg
Increasing ALT, AST; AST:ALT >1

NASH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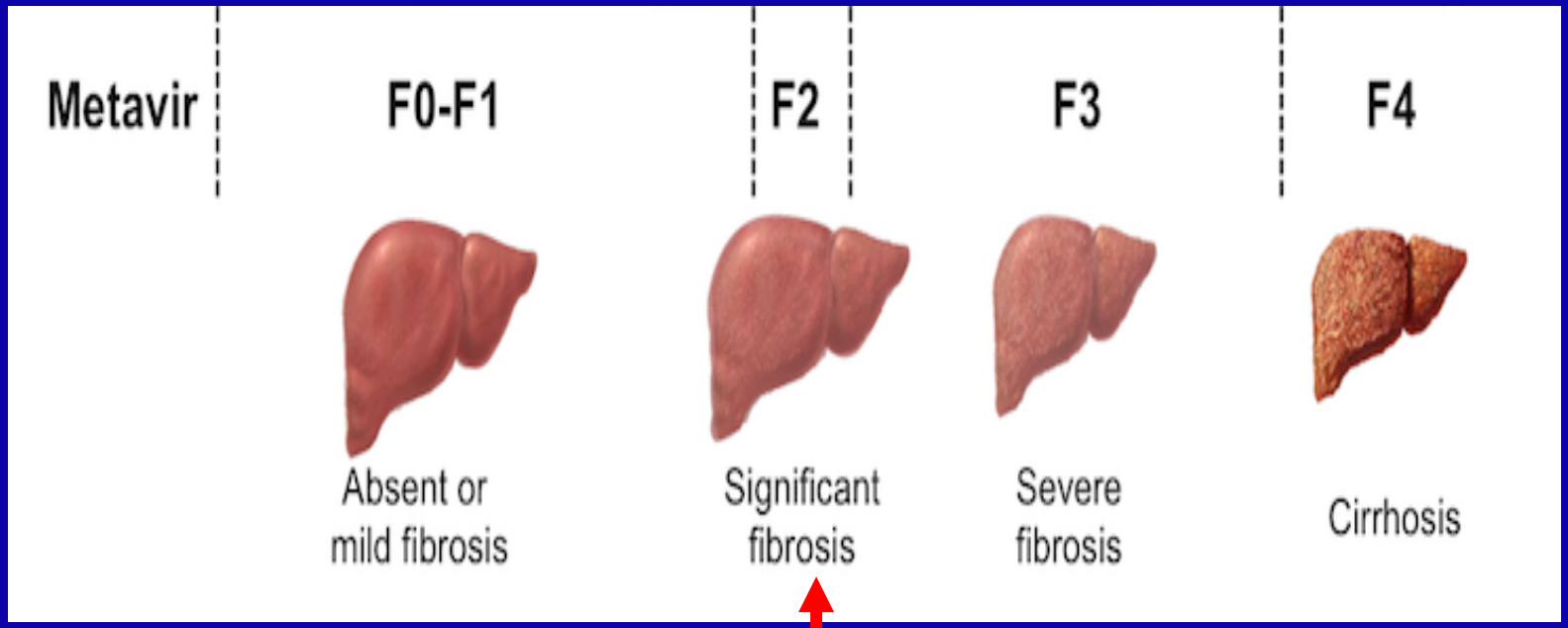
Stages of Fibrosis



NAFLD: Beyond definitions

"NAFLD is a disease of over-nutrition."

- NASH is <u>strongly</u> associated w/ obesity & the MetS.
  - >80% of NASH patients are overweight/obese
  - 72% of NASH patients have dyslipidemia
  - 44% of NASH patients have type-2 diabetes mellitus.
- NAFLD → independent predictor of insulin resistance in non-obese patients.

"Hepatic correlate of the metabolic syndrome"

Jeong SK, et al. J Kor Med Sci. 2008 Oct;23(5):789-95.
Younossi ZM, et al. Hepatology 2016; 64: 73-84.
Diehl AM, et al. N Engl J Med 2017;377:2063-72

Metabolic Syndrome

Table 1
Diagnosing criteria for metabolic syndrome

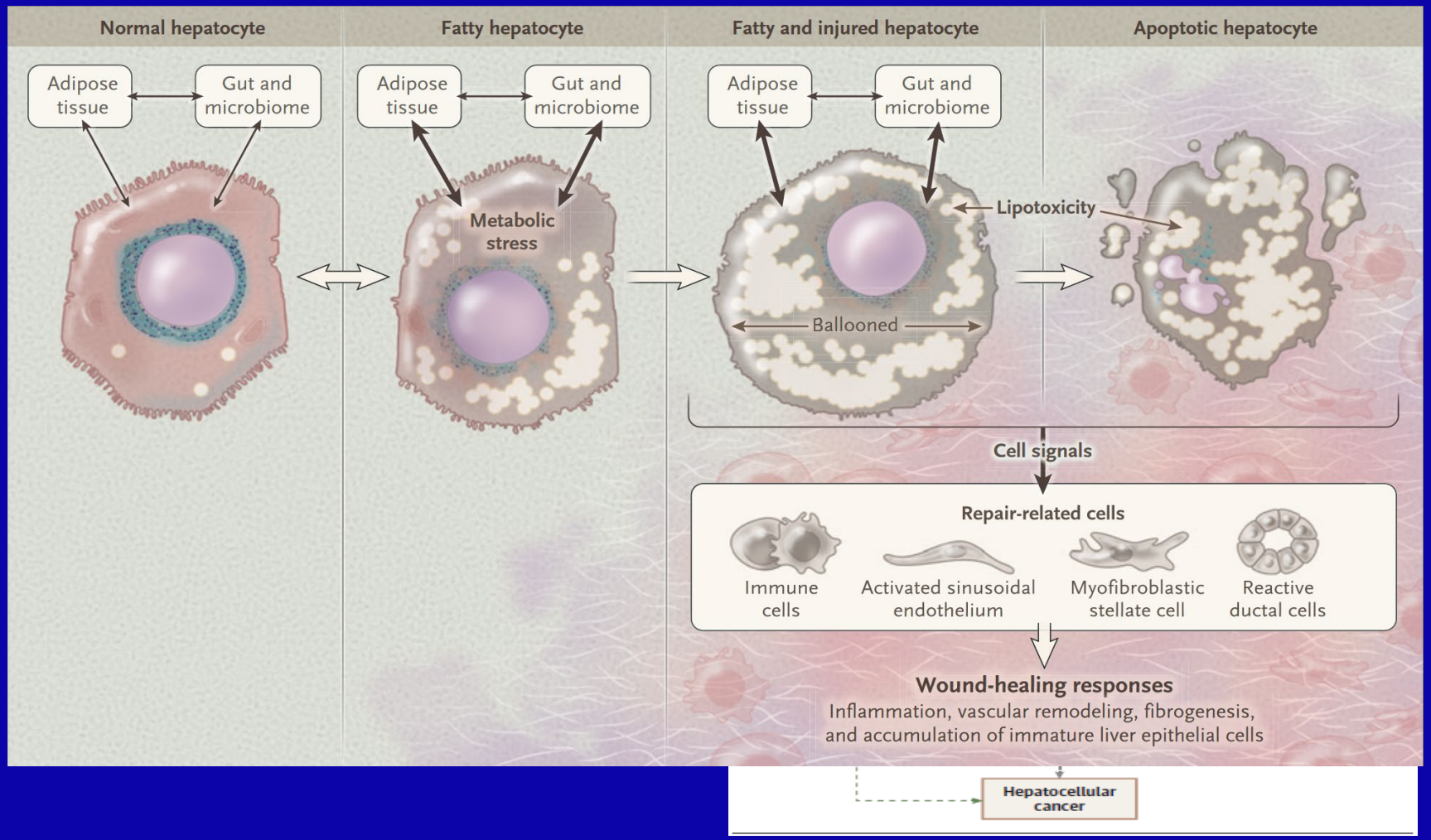
Criteria	Categorical Cut Points
Elevated waist circumference	Ethnicity-specific definitions
Elevated fasting glucose	≥100 mg/dL and/or drug treatment of elevated glucose
Elevated triglycerides	≥150 mg/dL and/or drug treatment for elevated triglycerides
Reduced HDL cholesterol	<40 mg/dL in men; <50 mg/dL in women
Elevated blood pressure	Systolic ≥130 and/or diastolic ≥85 mm Hg

Definition of MS: meeting at least 3 of the 5 criteria. Ethnicity specific definitions of elevated waist circumference: (1) Caucasian: 102 cm or greater in men and 88 cm or greater in women (2) Asian: 90 cm or greater in men and 80 cm or greater in women (3) Middle East, Mediterranean, African: 94 cm or greater in men and 80 cm or greater in women (4) Ethnic Central and South American: 90 cm or greater in men and 80 cm or greater in women.

Data from Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–5.

Alberti KG, et al. Circulation.2009;120:1640-45.

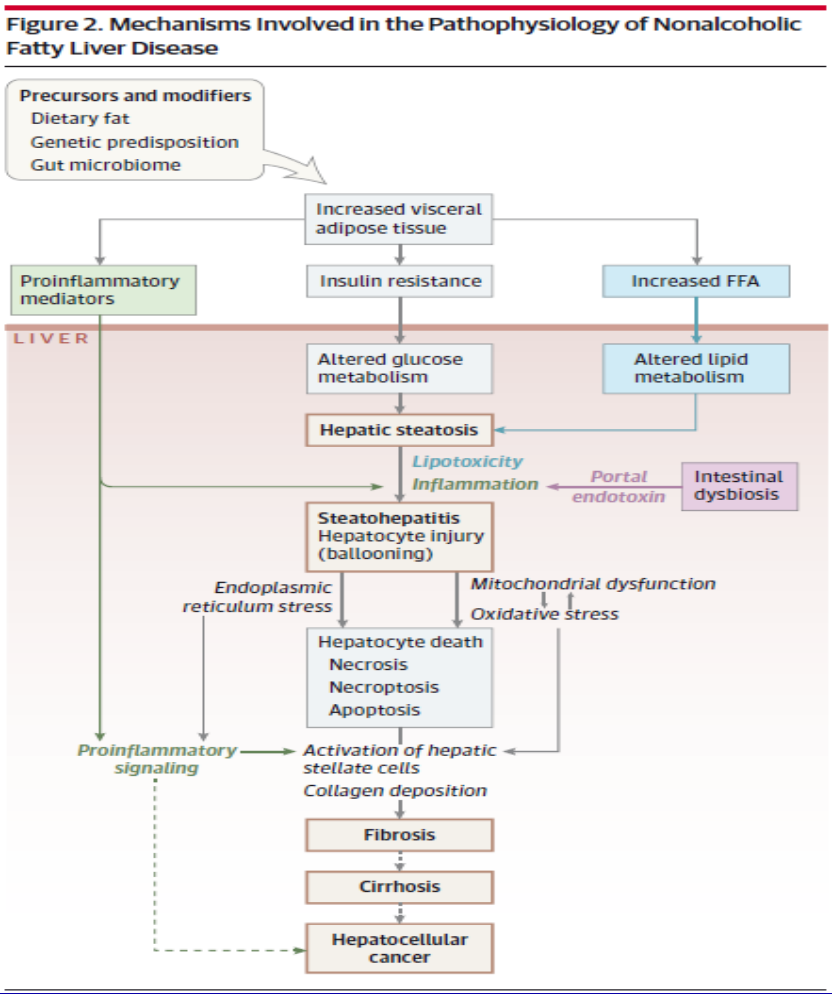
Pathophysiology of NAFLD



Furukawa S, et al. J Clin Invest. 2017;114(12):1752-1761.
Diehl AM, et al. N Engl J Med 2017;377:2063-72

Pathophysiology of NAFLD

- Starts with precursors to *visceral fat accumulation*
- Two-hit hypothesis
  1. Steatosis = “excess fat in liver”
  2. Lipotoxicity/oxidative stress = “triggers of liver inflammation”



Furukawa S, et al. J Clin Invest. 2017;114(12):1752-1761.
Diehl AM, et al. N Engl J Med 2017;377:2063-72

What about DM and NAFLD?

- Common mechanisms for NAFLD, DM and MetS
  - Visceral obesity → Common denominator

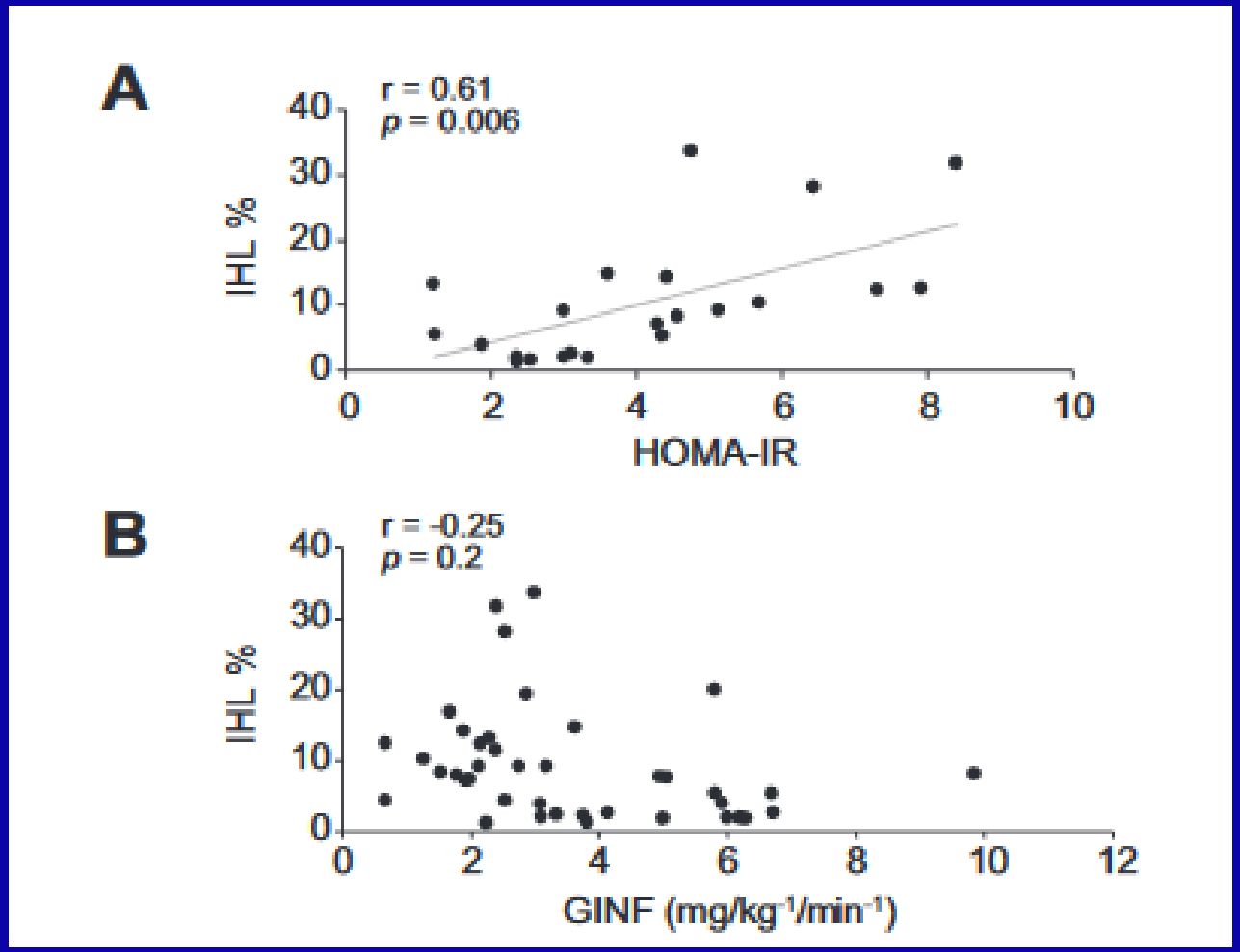
- Type-II diabetes prevalence in NAFLD:*
  - NAFL: 22.5% have DM-II
  - NASH: 43.6% have DM-II

~45% or more of DM-II have NAFLD

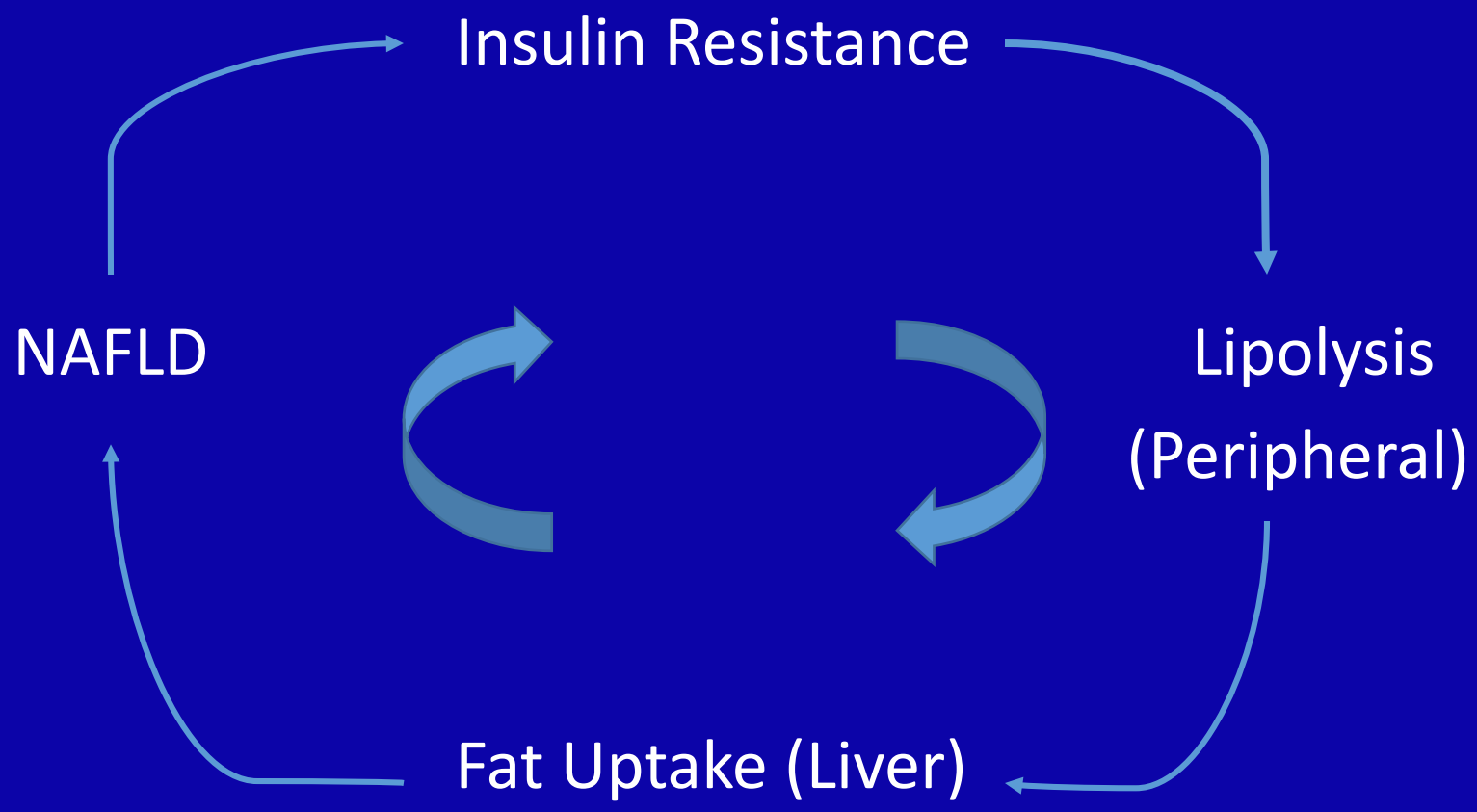
- Improvement in NAFLD is associated with reduced incidence in DM-II

Yamazaki H, et al. Diabetes Care 2015;38:1673-1679.

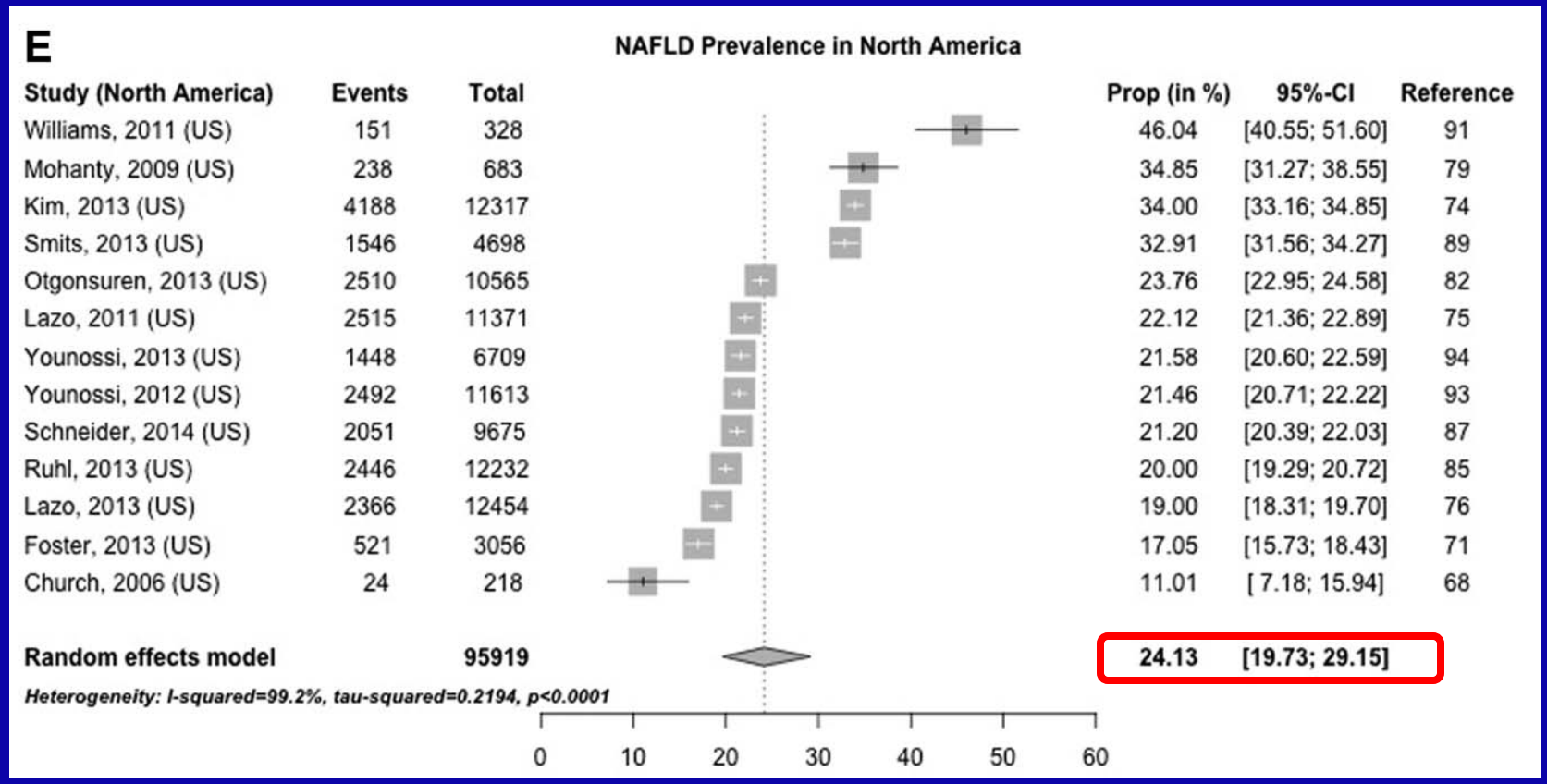
IR and hepatic fat have a linear relationship



Ryan MC, et al. Journal of hepatology. 2013 Jul 1;59(1):138-43.


Insulin Resistance
NAFLD
Lipolysis
(Peripheral)
Fat Uptake (Liver)

Epidemiology of NAFLD in North America



Younossi ZM, et al. Hepatology. 2016. 64(1). 73-84.

Epidemiology of NAFLD in North America

TABLE 1. NAFLD Prevalence Stratified by Region

Region	N	Prevalence (%)	95% CI (%)	I^2 (%)
Africa	2	13.48	(5.69-28.69)	84.37
Asia	14	27.37	(23.29-31.88)	99.17
Europe	11	23.71	(16.12-33.45)	98.78
Middle East	3	31.79	(13.48-58.23)	99.14
North America	13	24.13	(19.73-29.15)	99.19
South America	2	30.45	(22.74-39.44)	69.10
Overall	45	25.24	(22.1-28.65)	99.07

Study sources in Supporting Table A (imaging as a diagnosis technique for all studies included).

0 10 20 30 40 50 60

Younossi ZM, et al. Hepatology. 2016. 64(1). 73-84.

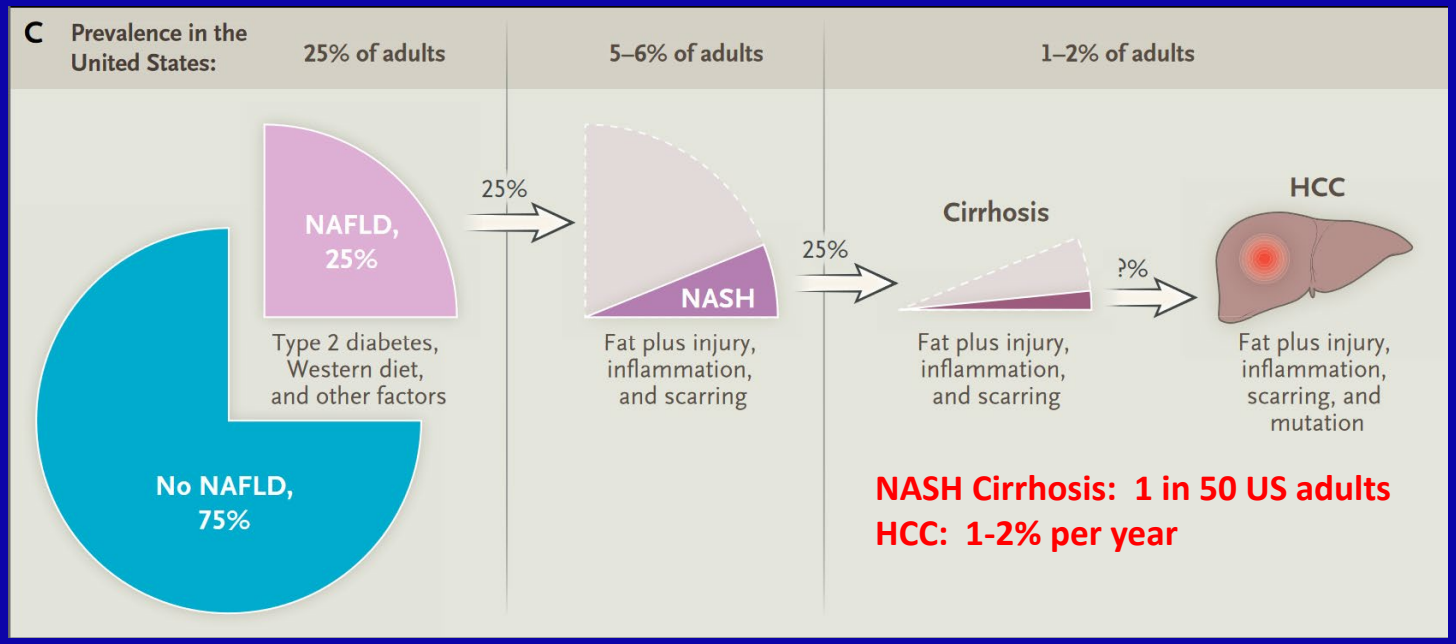
NAFLD Prevalence

- 24-30% of the US population
- 45-76% of diabetic and obese patients
- >90% of patients undergoing bariatric surgery

Younossi ZM, et al. Hepatology. 2016. 64(1). 73-84.
Portillo SP, et al. J Clin Endocrinol Metab. 2014Oct
Kasturiratne A, et al. J GastroenterolHepatol. 2013;28:142-147.

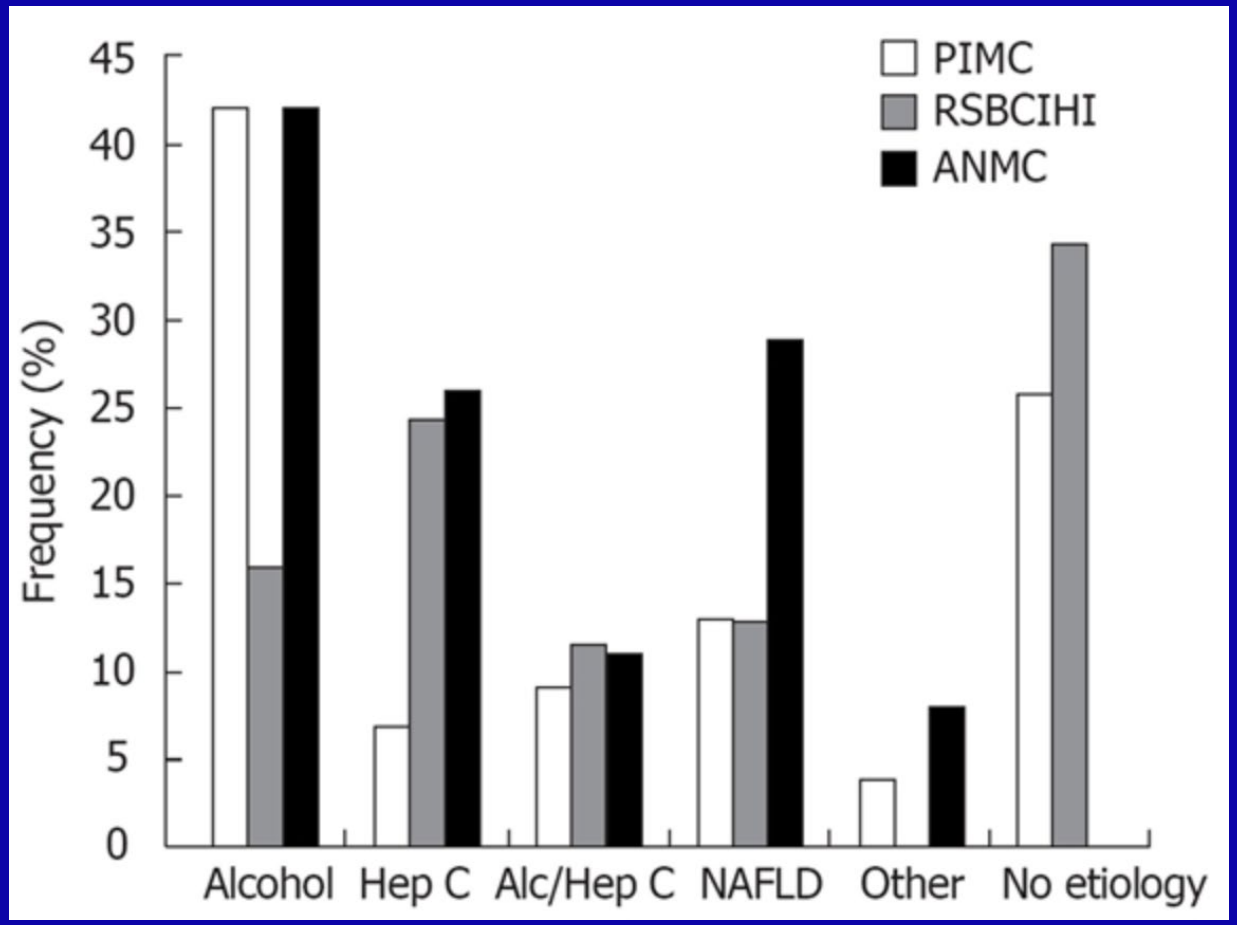
Prevalance of NASH (US)

- NASH estimates:
  - 5-6% of the US population
  - NASH-related cirrhosis→2nd indication for liver transplants in the US.



Diehl AM, et al. N Engl J Med 2017;377:2063-72

NAFLD in AI/ANs:



Scott, JD et al. World J Gastroenterol. 2008 Aug 7; 14(29): 4607–4615.

NAFLD in AI/ANs:

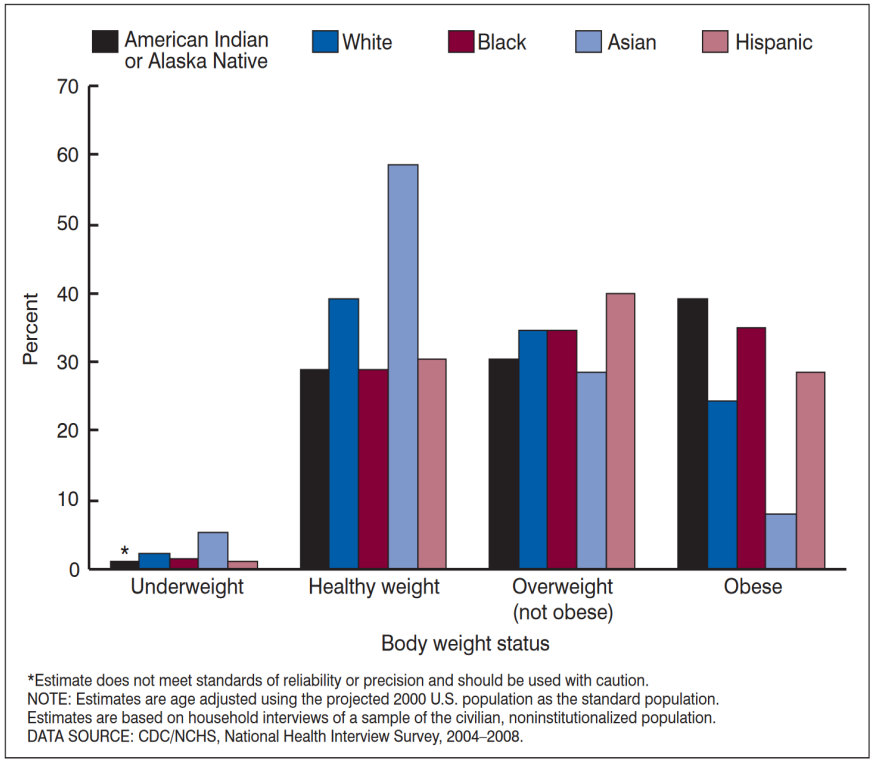


Figure 3. Percent distribution of body weight status for adults aged 18 years and over, by race and ethnicity: United States, 2004–2008

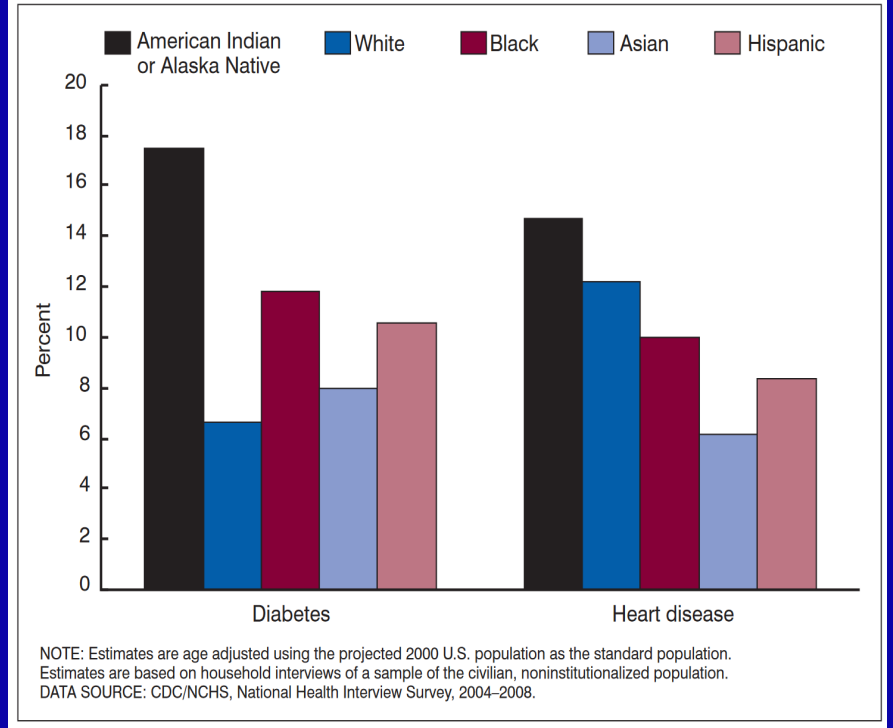


Figure 4. Percentage of adults aged 18 years and over who have ever been diagnosed with diabetes, and percentage of adults aged 18 years and over who have ever been diagnosed with heart disease, by race and ethnicity: United States, 2004–2008

Barnes Pm, et al. Natl Health Stat Report. 2010 Mar 9;(20):1-22.

NAFLD in AI/ANs:

- PNPLA3
  - Gene involved in regulation of TRG and retinol metabolism
  - *I148M polymorphism*
    - Most prevalent in Hispanic populations.
      - More prevalent in Asian and AI/AN pops**
    - Strong association w/ hepatic steatosis, steatohepatitis, fibrosis, and cancer.
    - Promotes liver damage caused by alcohol-induced fatty liver disease and chronic hepatitis C.

Diehl AM, et al. N Engl J Med 2017;377:2063-72

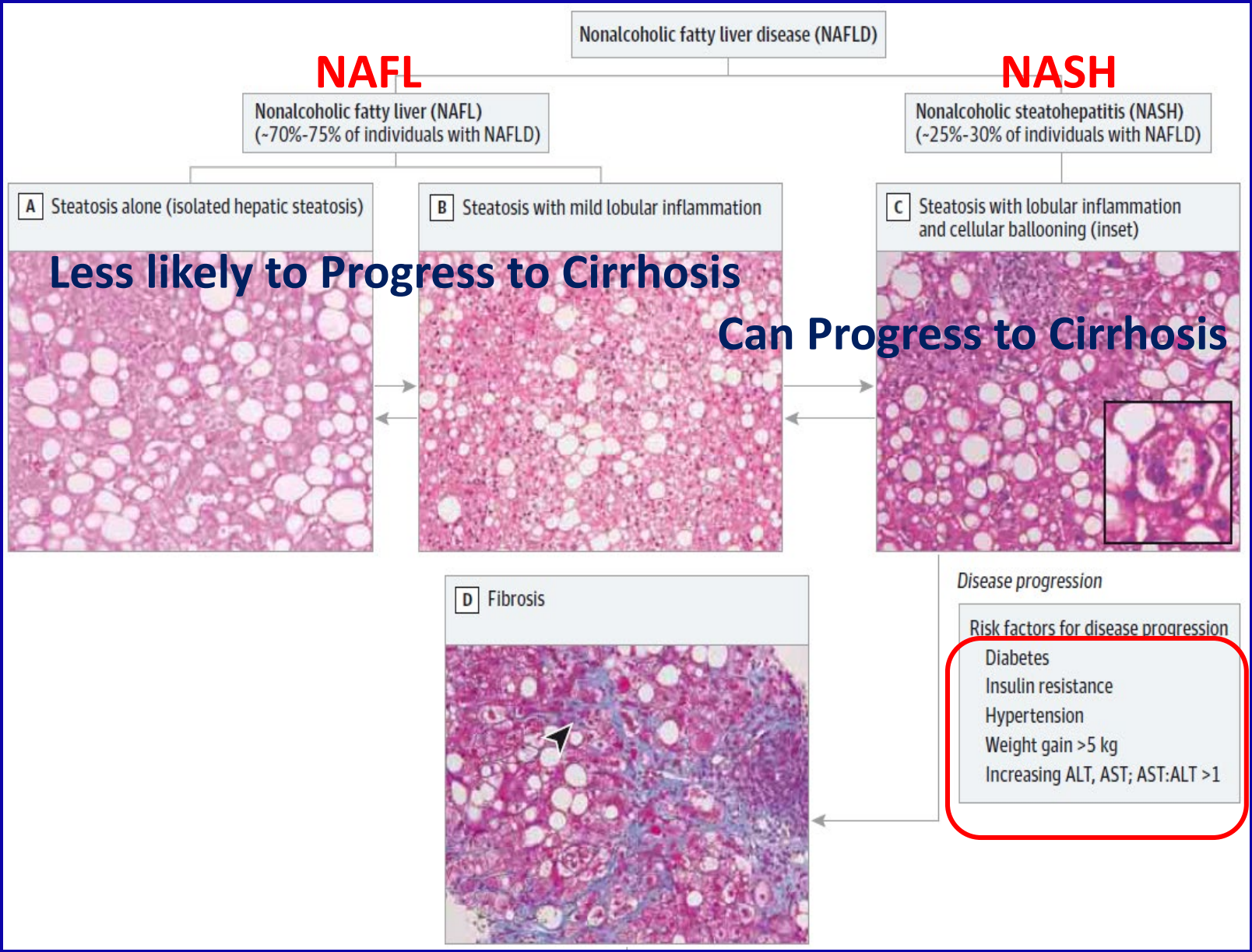
NAFLD: Implications

TABLE 3. Incidence and IRR for Progression of NAFLD and NASH

Population	Outcome	Incidence Rate Per 1,000 Person-Years*	Number of Studies	95% CI
NAFLD	CVD-specific mortality	4.79	6	(3.43-6.7)
NAFLD	HCC	0.44	3	(0.29-0.66)
NAFLD	Liver-specific mortality	0.77	7	(0.33-1.77)
NAFLD	Overall mortality	15.44	7	(11.73-20.34)
NASH	Advanced fibrosis	67.95	3	(46.84-98.56)
NASH	HCC	5.29	1	(0.75-37.56)
NASH	Liver-specific mortality	11.77	3	(7.1-19.53)
NASH	Overall mortality	25.56	2	(6.29-103.8)
		IRR*		
NAFLD	Liver-specific mortality	1.94	5	(1.28-2.92)
NAFLD	Overall mortality	1.05	5	(0.7-1.56)
NASH	Liver-specific mortality	64.6	3	(35.43-117.8)
NASH	Overall mortality	2.56	2	(0.63-10.39)

- NAFL → Typical morbidity & mortality (CVD, cancer)
- NASH → liver-related M&M, cirrhosis, HCC + CVD

Younossi ZM, et al. Hepatology. 2016. 64(1). 73-84.



NASH fibrosis: Progresses one stage every decade

NAFLD and Children

- NASH in children is strongly associated with obesity.
- Childhood obesity → increased risk of HCC in adulthood (Denmark)

Berentzen TL, et al. J Hepatol 2014;60:325-30.

Diagnosing NAFLD:

- The goal is to not only identify NAFLD but also identify who may be at high risk for complications related to NAFLD

Typical situation:

- Transaminases are drawn as part of an “LFT Panel”
- AST, ALT are mildly elevated
- RUQ Ultrasound is done → steatosis.
- Other causes to elevated AST/ALT are ruled out
  - Viral hepatitis
  - Autoimmune
  - Alcohol
  - Etc

Now what?

Think NAFLD in everybody

- 25% of adults in the US have it
- Think NASH if there are risk factors for it

Think NAFLD in persons with DM-II

- Persons with NAFLD:
  - 45-50% of persons with DM-II had NAFLD
  - NAFLD increases the incident risk of developing DM

Table 2 Baseline prevalence and 3-year incidence of diabetes mellitus in subjects with and without non-alcoholic fatty liver disease (NAFLD)

Subject description	Number of prevalent cases	Number disease-free	Prevalence per 1000 population (95% CI)		OR (95% CI)
NAFLD ($n = 926$)	308	618	332.6 (302.3–364.0)		2.15 (1.80–2.57)
Non NAFLD ($n = 1954$)	368	1586	188.3 (171.2–206.4)		
	Number of incident cases	Number disease-free	Person-time of follow-up (years)	Incidence per 1000 PY of follow-up (95% CI)	HR (95% CI)
NAFLD ($n = 543$)	106	437	1666.4	63.6 (52.1–76.9)	1.92 (1.49–2.47)
Non-NAFLD ($n = 1314$)	138	1176	4060.6	34.0 (28.6–40.2)	
NAFLD† ($n = 528$)	104	424	1620.2	64.2 (52.5–77.8)	1.95 (1.51–2.52)
Non-NAFLD ($n = 1314$)	138	1176	4060.6	34.0 (28.6–40.2)	

†After exclusion of subjects who started alcohol consumption above the safe-limit.
CI, confidence interval; HR, hazards ratio; OR, odds ratio; PY, person years.

Kasturiratne A, et al. J Gastroenterol Hepatol. 2013;28:142-147.

But also think about NASH:

Table 2. Variables Associated with Presence of Advanced Fibrosis (Stage 3-4) in the Estimation Group (n = 480)

	Unadjusted (Univariate)			Adjusted (Multivariate)		
Variable	Odds Ratio	95% CI (low, high)	*P* Value	Odds Ratio	95% CI (low, high)	*P* Value
Age (per year)	1.07	1.05, 1.09	<0.0001	1.04	1.01, 1.07	0.007
Gender (M)	0.42	0.28, 0.64	<0.0001			
Race (Caucasian)	0.71	0.34, 1.40	0.3			
BMI (continuous)	1.10	1.06, 1.14	<0.0001	1.10	1.04, 1.16	<0.001
Obesity	2.69	1.74, 4.25	<0.0001			
BMI (categories)						
normal (reference)	1					
overweight	2.35	0.78, 10.2	0.3			
obese	5.70	1.96, 23.95	<0.001			
Waist circumference(continuous)	1.01	0.99, 1.02	0.3			
Central obesity	1.22	0.80, 1.87	0.4			
Waist-to-hip ratio	0.21	0.002, 20.5	0.5			
AST/ALT ratio	6.89	4.00, 12.31	<0.0001	2.70	1.33, 5.62	0.007
Albumin (g/dl)	0.15	0.09, 0.25	<0.0001	0.51	0.25, 1.05	0.073
Bilirubin (mg/dl)	1.68	1.21, 2.40	0.002			
Platelet count ($\times 10^9$/l)	0.98	0.98, 0.99	<0.0001	0.987	0.98, 0.99	<0.001
AST/platelet	2.23	1.72, 3.00	<0.0001			
Hyperglycemia	5.86	3.79, 9.19	<0.0001	3.12	1.77, 5.51	<0.001
Diabetes mellitus	4.19	2.71, 6.50	<0.0001			
Hypertriglyceridemia	0.65	0.43, 0.99	0.03			
Low HDL cholesterol	2.10	1.35, 3.25	0.0003			
Hypertension	2.61	1.70, 4.04	<0.0001			
HOMA-IR (continuous)	1.11	1.05, 1.18	0.0001			
Biopsy length (mm)	1.003	0.97, 1.04	0.9			
Portal areas (n)	1.03	0.92, 1.14	0.6			

Angulo P, et al. Hepatology. 2007 Apr;45(4):846-54.

Think NASH in persons with MetS

- Consists of cluster of inter-related factors
  - Truncal obesity
  - Dysglycemia
  - Dyslipidemia
  - Hypertension

Risk Factors for NASH fibrosis!

- NHANES: MetS prevalence of 34.7% in 2011
  - Women > Men
  - Hispanics have highest prevalence in N America

Marchesini G, et al. Hepatology 2003;37:917–23.

Again…think NAFLD in everybody

- Four phenotypes of patients with NAFLD have been defined:
  I. Obese
  II. Type 2 diabetes
  III. Metabolic syndrome
  IV. Lean patients (smokers, older age, Hispanic & Asian, ? AI/AN)
- *Excess caloric consumption* leading to obesity and related comorbidities is a leading risk factor for NAFLD.
  - Even a modest 3–5 kg weight gain may predicts the development of NAFLD, regardless of baseline BMI.

Younossi ZM, et al. Hepatology 2016;64:73–84.
Zelber-Sagi S, et al. J Hepatol 2012;56:1145–1151.

Pearl:

- "Overweight or obese persons with the metabolic syndrome, elevated serum aminotransferase levels, and a negative noninvasive workup for other causes of liver disease are likely to have NASH."

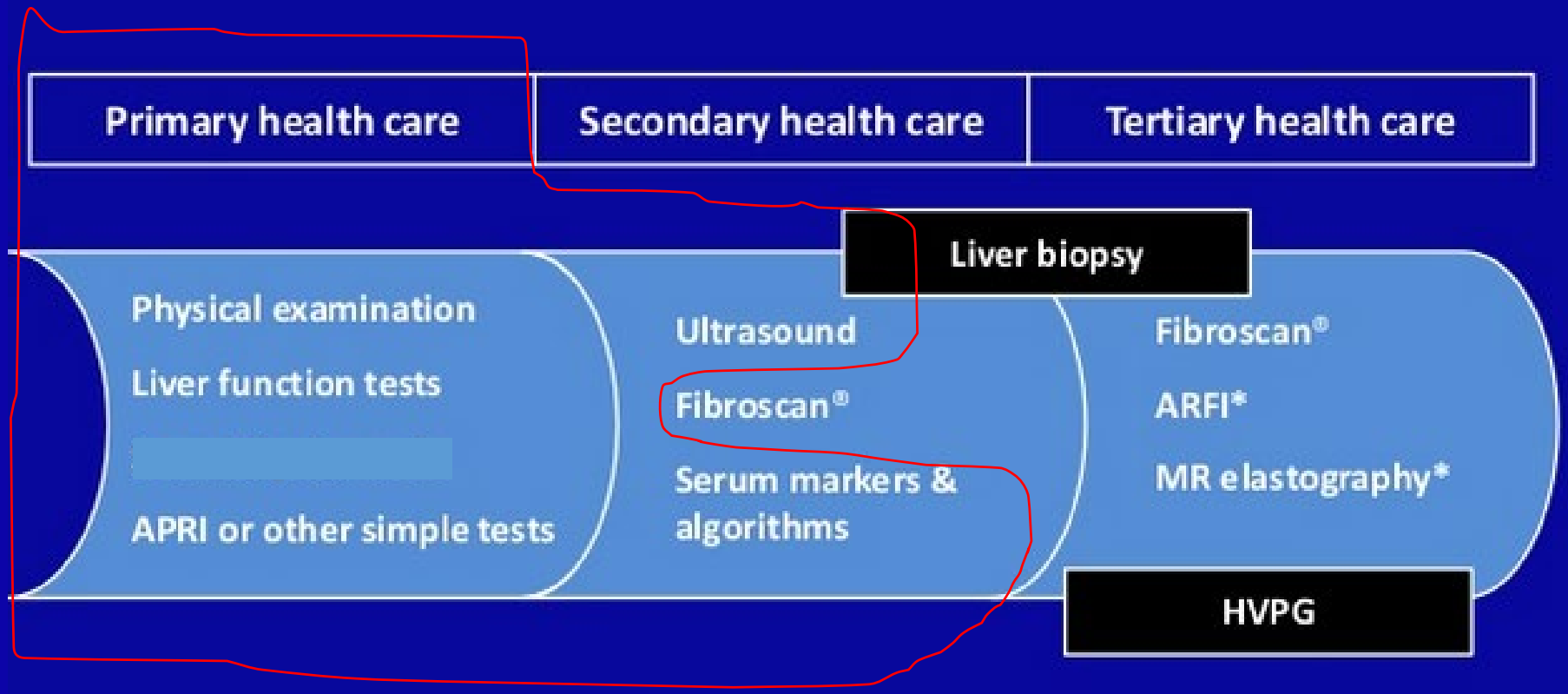
*Assumes LFTS and/or ultrasound/CT showing steatosis

Diehl AM, et al. N Engl J Med 2017;377:2063-72

Next steps:

- Patient felt to be at risk for NAFLD:
  - Assess for confounding risk factors for disease progression
  - Assess for NASH-related liver damage
  - Grade the severity of this injury & stage fibrosis
  - Formulate a disease management plan.

Evaluation of chronic liver injury according to health care level



* Promising but currently under investigation
ARFI: Acoustic Radiation Force Impulse Imaging
HVPG: Hepatic Venous Pressure Gradient
Castéra L et al. Gut 2010 ; 59 : 861 – 866.

Further assessment after NAFLD diagnosis

- Patient history and exam
  - Associated conditions (Hypopituitarism*, etc)
  - Confounding medications
    - Corticosteroids, tamoxifen, amiodarone, methotrexate
  - Alcohol use
    - AUDIT > CAGE
  - Exam:
    - Truncal obesity, acanthosis nigricans, etc.
    - Stigmata of portal hypertension
  - DM-II, MetS

Chalasani, et al. Hepatology. 2018;67:328-357

Order Serum ("wet") Biomarkers

- Albumin
- Prothrombin time
- Platelets
- Transaminases:
  - NAFLD is an ALT driven process
  - AST:ALT ratio is typically <1 in absence of fibrosis
  - Ratio tends to increase to > 1as the degree of fibrosis progresses
- Ferritin
  - Independent predictor of advanced fibrosis

Castera, L. et al. Nat. Rev. Gastroenterol. Hepatol. 10, 666–675 (2013);

Biomarkers for NAFLD

Score	Factors Included in Scoring		Cutoff Values for Advanced Fibrosis
NAFLD Fibrosis Score	• Age • Hyperglycemia • BMI	• Platelet count • Albumin • AST/ALT ratio	≤ -1.455 = F0-F2 -1.455 to 0.675 = indeterminate **> 0.675 = F3-F4**
FIB-4	• Age • AST	• ALT • Platelets	< 1.30: F0-F1 **> 2.67: ≥ F3**
BARD	• BMI • AST/ALT ratio	• T2D	**> 2: advanced fibrosis**
BAAT	• BMI • Age	• ALT • Triglycerides	**> 2.86: ≥ F3**

AST: Platelet Ratio (APRI score)

Table I. Sensitivity, specificity, positive and negative predictive value of APRI v. NFS

	Value	Sensitivity	Specificity	ppv	npv
APRI	0.98	75%	86%	54%	94%
NFS	-1.31	76%	69%	34%	93%

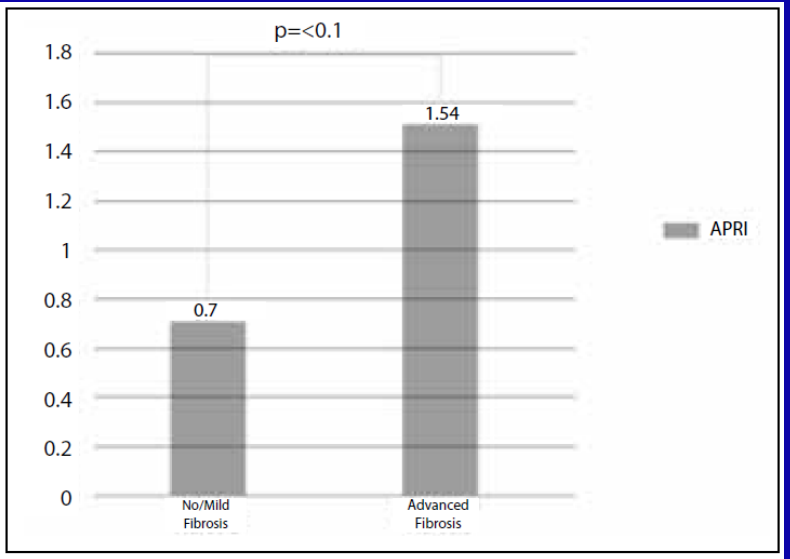


Fig. 3b. APRI and association with grading of NAFLD.

Who should be referred to a biopsy or VCTE (Fibroscan®)?

Defer	Consider Fibroscan if available

- ≤ 2 features of the MetS
- Absence of DM-II and normal LFTs
- Motivated patient (lifestyle changes, etc)
- NFS ≤ -1.455

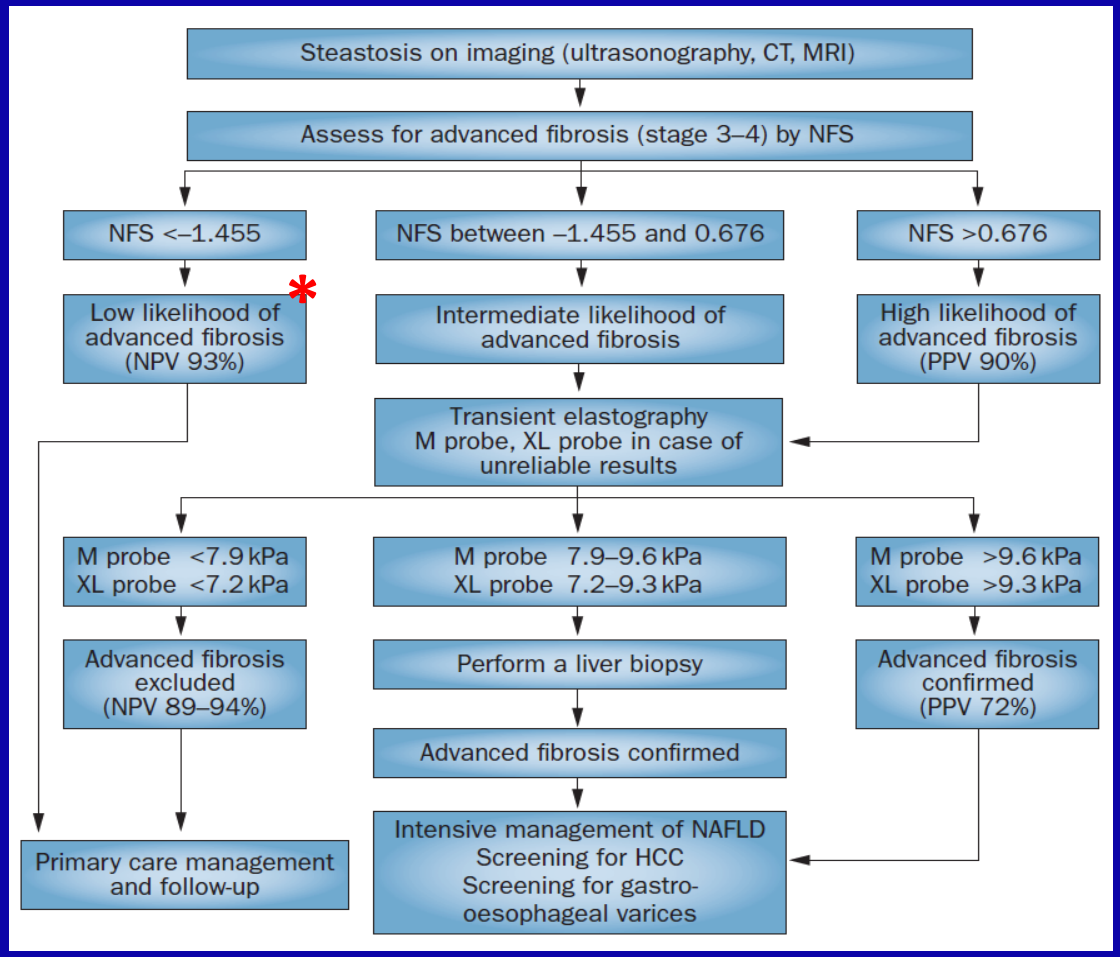
Refer	Recommend Fibroscan if available

- Features of MetS and obesity
- DM-II and elevated LFTs
- Patient who is not motivated to make lifestyle
- changes
- NFS > -1.455

No algorithm for guiding NASH referrals.

- Need to consider risk factors for worse outcomes
  - MetS
  - Obesity
  - DM-II (especially with other risks)
  - Smoking
  - Hypertension
  - Age
  - Increasing AST over time, AST:ALT >1
  - NFS, FIB-4 scores

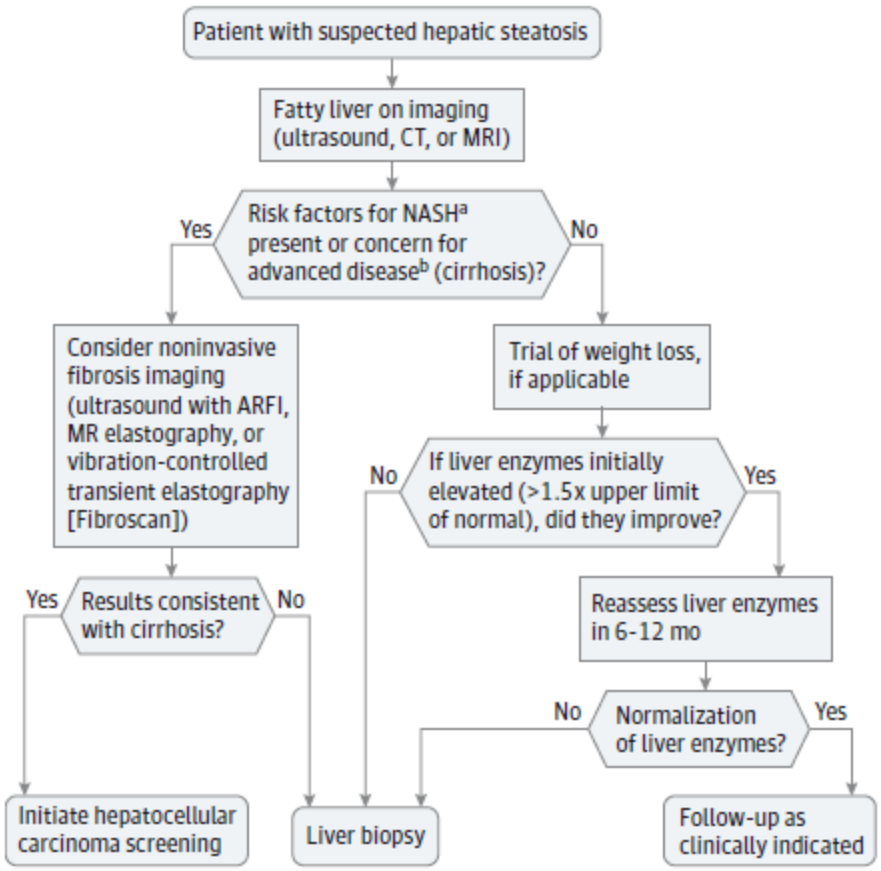
But here is an algorithm for consideration…



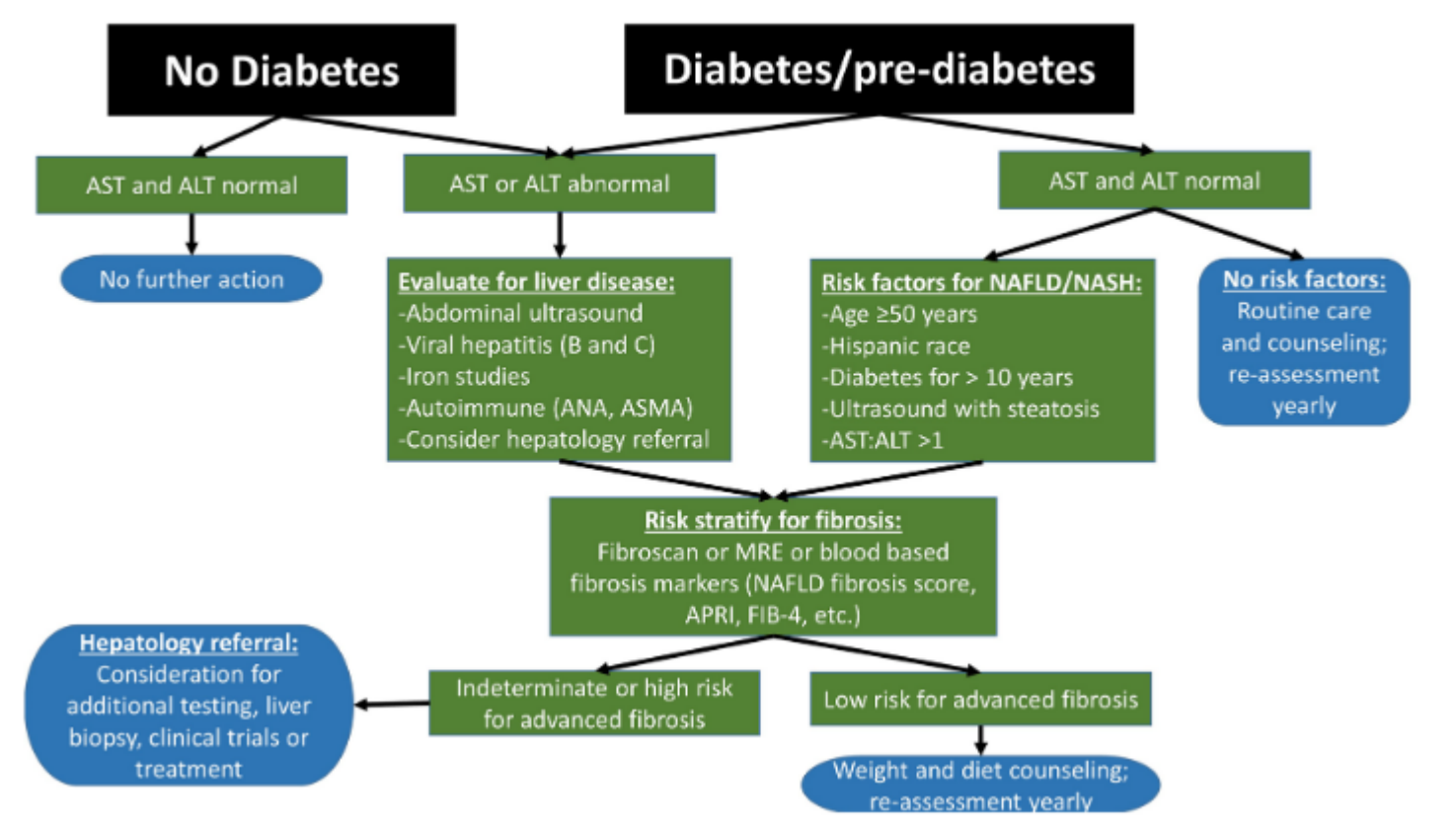
Castera, L. et al. Nat. Rev. Gastroenterol. Hepatol. 10, 666–675 (2013)

…And another one…

Figure 3. Algorithm for the Decision to Perform Liver Biopsy in Patients With Presumed Nonalcoholic Fatty Liver Disease After Negative Serological Evaluation and Exclusion of Alcohol as a Contributing Factor



…And one for the diabetes practitioner (combine with first)



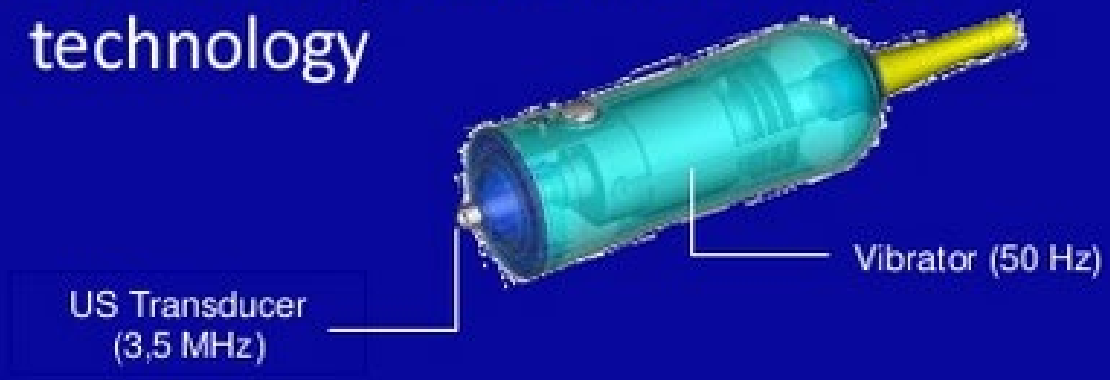
For indeterminate or high-risk patients for advanced fibrosis

- Three options:
  1. Liver biopsy:
     - Remains the gold standard!
     - But some considerations
       - Severe complication rate of 1.1% and mortality rate of 0.3%.
       - Sampling error as high 25-30%.
  2. Transient Elastography (VCTE)
     - Noninvasive, quick, highly accurate, low cost
  3. Magnetic Elastography (ME)

Seeff LB, et al. Clin Gastroenterol Hepatol 2010; 8: 877-883
Maharaj B, et al. Postgrad Med J 1992;68:964-967.
Talwalkar JA. Gastroenterology 2008;135:299-302.

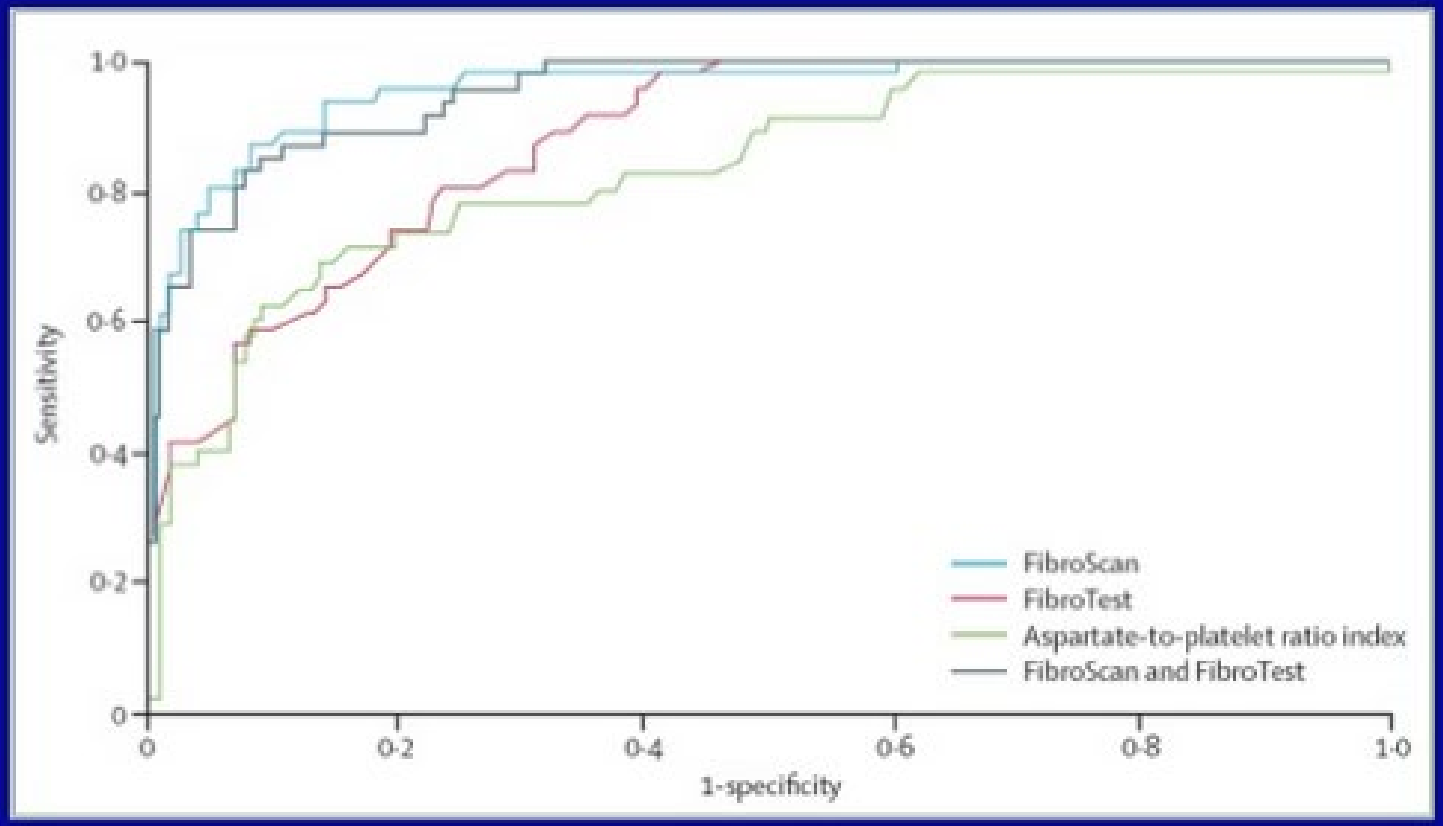
Fibroscan® device

- Electronic platform
  - Ultrasonic signals acquisition
  - Numerical signal processing
- Integrated computer
  - Stiffness measurement
  - Examinations database
- Dedicated probes with unique technology



Fibroscan® (Echosens, Paris, France)

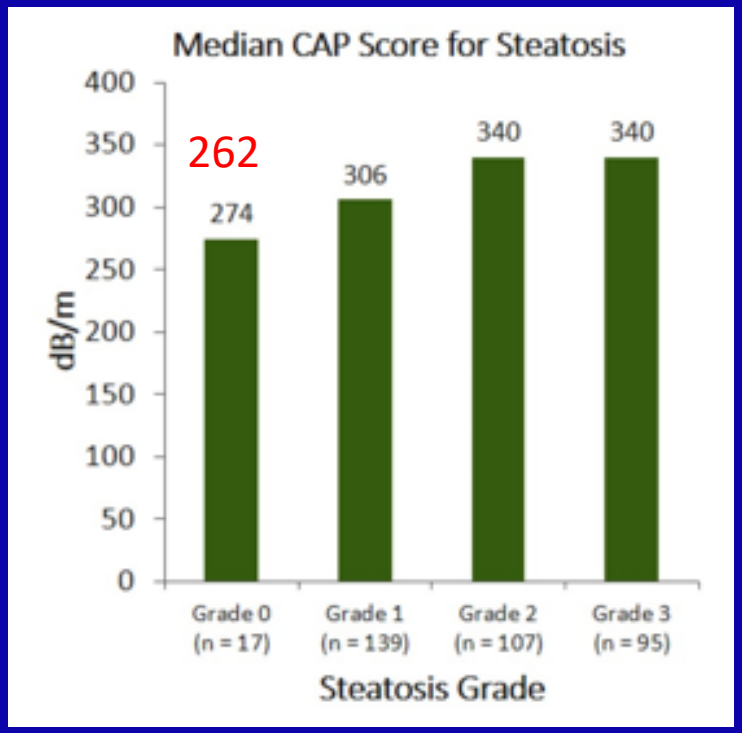
R0C curves for FibroScan, FibroTest, & APRI for cirrhosis (F0 – F3 vs F4)



Castera L et al. Gastroenterology 2005 ;128 : 343 – 50.

Castera L et al. Lancet 2010 ; 375 : 1419 – 20.

VCTE:
CAP (262) and kPa (6.5-7 range)



	F0 to F1	F2	F3	F4
Hepatitis B	2 to 7 kPa	8 to 9 kPa	8 to 11kPa	18 kPa or higher
Hepatitis C	2 to 7 kPa	8 to 9 kPa	9 to 14 kPa	14 kPa or higher
HIV/HCV Coinfection	2 to 7 kPa	7 to 11 kPa	11 to 14 kPa	14 kPa or higher
Cholestatic Disease	2 to 7 kPa	7 to 9 kPa	9 to 17 kPa	17 kPa or higher
Non-alcoholic Fatty Liver Disease (NAFLD or NASH)	2 to 7 kPa	7.5 to 10 kPa	10 to 14 kPa	14 kPa or higher
Alcohol Related Disease	2 to 7 kPa	7 to 11 kPa	11 to 19 kPa	19 kPa or higher

Dulai PS, et al. J Hepatol. 2016;65:1006-16.
SOURCE: https://www.mskcc.org/

VCTE and Obesity

- New XL probe has overcome many of the limitations for patients who are overweight/obese.

Table 5. Optimal Liver Stiffness Cutoffs Using the M and XL Probes According to Liver Disease Etiology*

	M Probe					XL Probe				
	Cutoff (kPa)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Cutoff (kPa)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
F2-4 vs. F0-1 fibrosis										
Overall	≥**7.8**	82 (72-90)	78 (67-87)	80 (70-88)	80 (70-89)	≥**6.4**	83 (64-89)	68 (59-77)	72 (63-79)	80 (71-88)
Viral hepatitis	≥**6.5**	96 (85-99)	72 (51-88)	86 (74-94)	90 (68-99)	≥**6.8**	79 (66-88)	77 (60-90)	85 (72-93)	69 (52-83)
NAFLD	≥**7.8**	84 (67-95)	79 (64-90)	75 (58-88)	87 (73-96)	≥**6.4**	81 (67-92)	66 (53-77)	61 (48-74)	84 (71-93)
F4 vs. F0-3 fibrosis										
Overall	≥**21.5**	84 (60-97)	91 (85-95)	55 (36-74)	98 (94-100)	≥**14.0**	92 (73-99)	86 (80-90)	44 (30-59)	99 (96-100)
Viral hepatitis	≥**14.0**	92 (62-100)	83 (71-92)	52 (30-74)	98 (89-100)	≥**10.1**	93 (68-100)	83 (73-91)	52 (32-71)	98 (92-100)
NAFLD	≥**22.3**	80 (28-99)	91 (82-97)	40 (12-74)	98 (92-100)	≥**16.0**	100 (54-100)	91 (84-96)	40 (16-68)	100 (96-100)

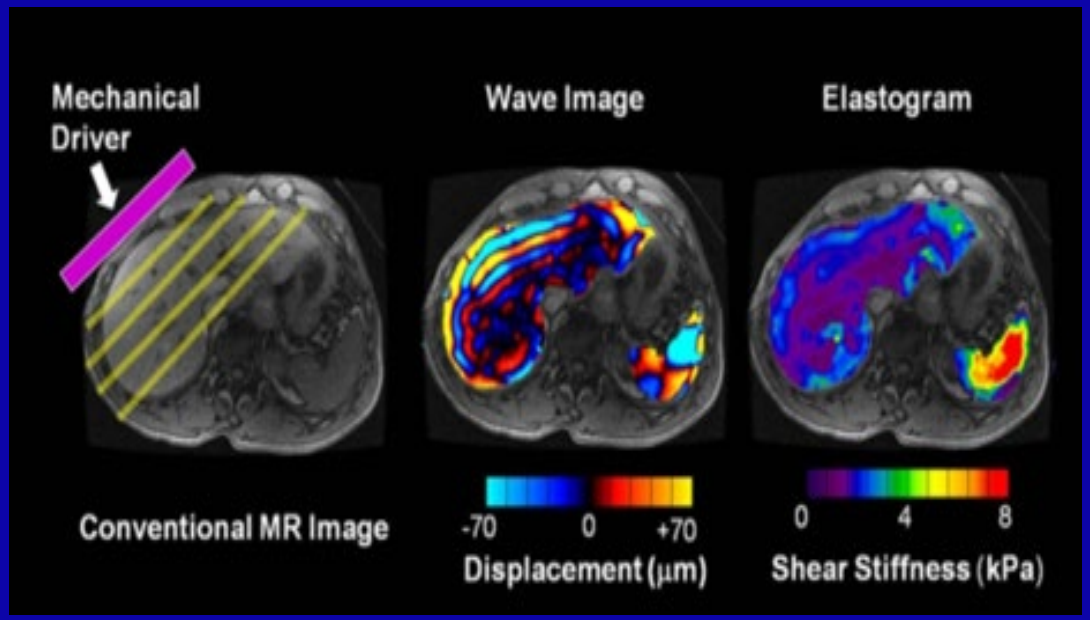
*Subgroup analyses restricted to patients with ≥10 valid measurements with the respective probes and interpretable liver biopsies. See Supplementary Table 1 for the numbers of patients within each analysis. Optimal liver stiffness cutoffs defined by the maximal sum of sensitivity and specificity.

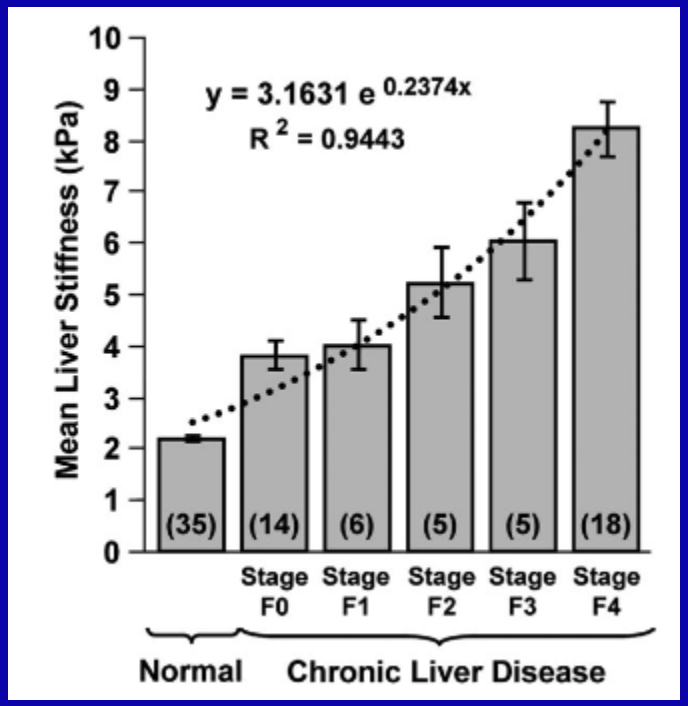
Myers, et al.Hepatology 55, 199–208 (2012).

MR Elastography: Future in Dx & Prognostication

Use for patients at high risk in absence of cirrhosis by PE, Fibroscan, & biomarkers.

- NFS > 0.675
- VCTE > 7-8 kPa
- If MRE > 3kPa → biopsy





Venkatesh SK, et al. J. Magn. Reson. Imaging 2013;37:544–555.

Who should be referred for liver biopsy?

It's easier to say who may be reasonable deferred with close monitoring of LFTs over time.

Defer Liver Biopsy
• ≤ 2 features of the MetS • Absence of DM-II and normal LFTs • Motivated patient (lifestyle changes, etc) • NFS ≤ -1.455 • ***VCTE < 6.5 kPa***

Who should be referred for liver biopsy?

- NFS > -1.455 AND
- VCTE > 6.5-8.0 kPa +/- MRE > 3 kPA
- Risk factors for NASH with advanced fibrosis
  - DM-II
  - MetS
  - Age & smoking status
- Findings suggesting cirrhosis
  - Thrombocytopenia, AST > ALT, low albumin

When in doubt, refer to a GI or hepatologist

Treating NAFLD

Management of NAFLD

- Treatment should address
  - Liver disease*
  - Underlying metabolic comorbidities
    - Obesity
    - Hyperlipidemia
    - Insulin resistance
    - Type 2 diabetes mellitus
  - Immunization

NAFLD Subtype	Treatment Focus
NAFL	Address metabolic comorbidities
NASH w/o advanced fibrosis	Address metabolic comorbidities
NASH with advanced fibrosis	Address metabolic comorbidities +/- Pharmacotherapy
Cirrhosis	List for Liver Transplant

Lifestyle Interventions

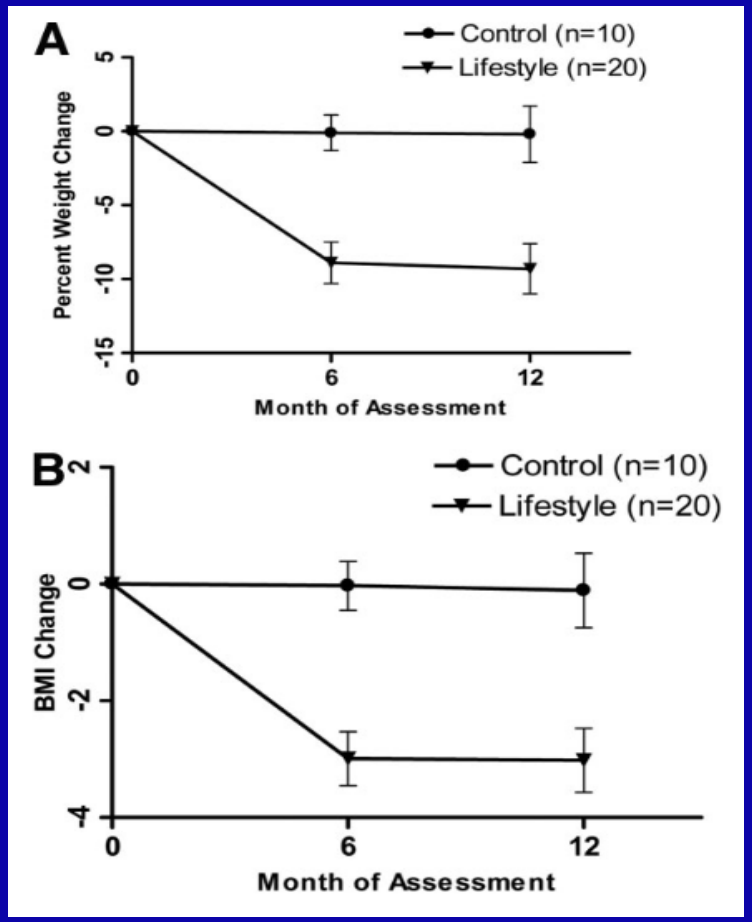
- **<u>Weight loss</u>**→ Cornerstone of treatment of NAFLD.
- Entails:
  - Exclusion of processed food and *fructose*
  - Calorie restrictions to achieve 5%-10% weight loss
    - Improves clinical biochemistry, histologic steatohepatitis, and fibrosis.
- Consider: Mediterranean diet
  - Easier to follow
  - Reduces steatosis & improve insulin sensitivity/glucose tolerance*

Bach-Faig A, et al. Public health nutrition. 2011 Dec;14(12A):2274-84.
Ryan MC, et al. Journal of hepatology. 2013 Jul 1;59(1):138-43.

*independent of weight loss.

Weight loss

- Weekly-biweekly group meetings.
- Calorie goal based on their starting weight)
- Daily fat gram goal designed to produce a 25% fat diet (28 –33 g for 1000-1200 kcal diet).
- Meal plans provided x 8 weeks (including commercial plans)
- Focus on moderate intensity activities (walking).
- Given pedometers and encouraged to self-monitor their eating and exercise
- Self-monitoring records were reviewed weekly by the therapist



Promrat K, et al. Hepatology. 2010 Jan;51(1):121-9.

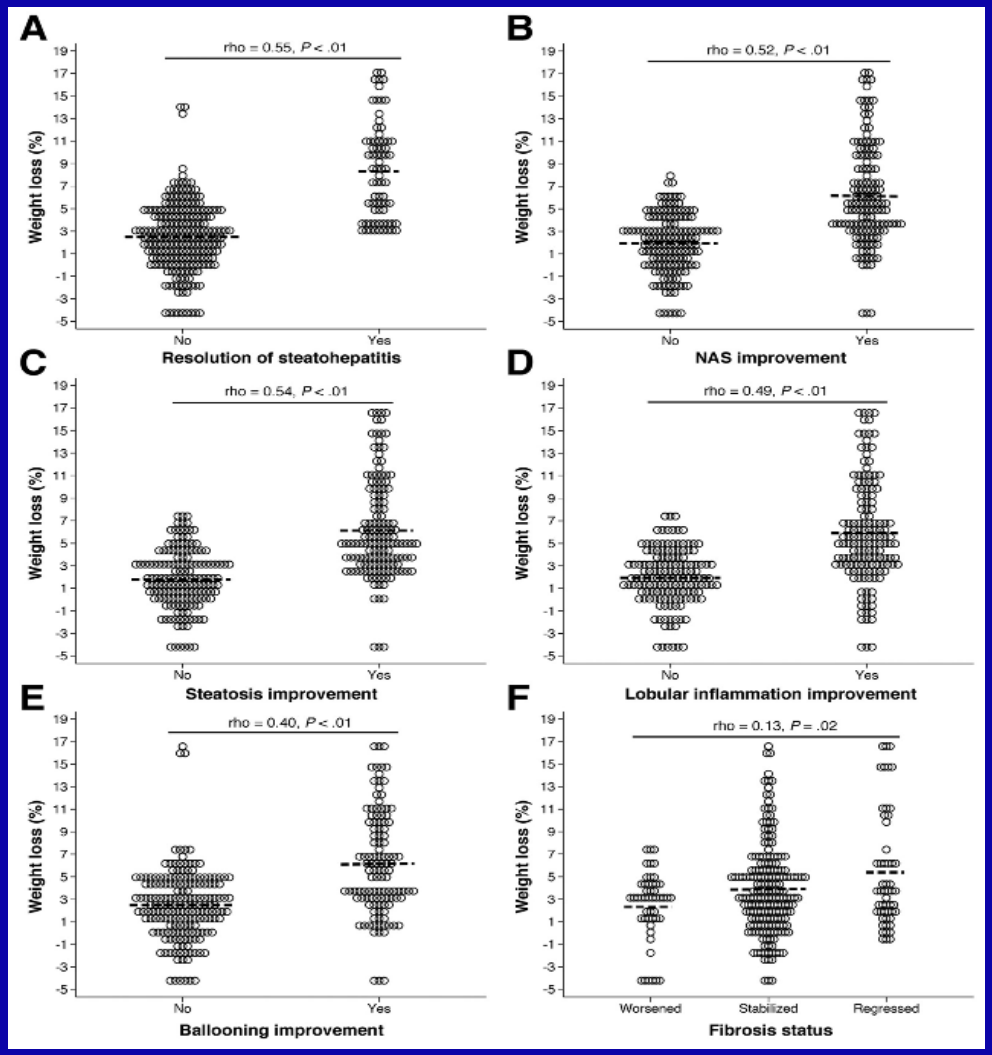
Weight Loss > 7% may be the best therapy

Table 4. Baseline Characteristics and Change (mean [SD]) in Histological Parameters According to Study Goal Weight Reduction (≥7%)

Variable	Weight Loss < 7% (n = 17)	Weight Loss ≥ 7% (n = 11)	*P* Values
Baseline characteristics			
BMI category, N (%)			
overweight (25-29.9 kg/m^2)	5 (26.3)	3 (27.3)	0.21
obesity class I (30-34.9 kg/m^2)	5 (26.3)	6 (54.5)	
obesity class II (35-40 kg/m^2)	9 (47.4)	2 (18.2)	
Diabetes, N (%)	10 (52.6)	4 (36.4)	0.39
On metformin, N (%)	7 (36.8)	2 (18.2)	0.28
Histological parameters			
Fat (0-3)	-0.41 (0.80)	-1.36 (0.67)	<0.001
Lobular inflammation (0-3)	-0.24 (0.75)	-0.82 (0.75)	0.03
Ballooning injury (0-2)	-0.53 (0.80)	-1.27 (0.47)	0.03
Fibrosis (0-4)	+ 0.06 (0.83)	-0.45 (0.93)	0.10
NAS (0-8)	-1.18 (1.59)	-3.45 (1.21)	<0.001
Participants with ≥3 points' improvement in NAS from baseline, N (%)	4 (23.5)	9 (81.8)	0.003
Participants with NAS ≤2 at follow-up, N (%)	4 (23.5)	10 (90.9)	<0.001

Promrat K, et al. Hepatology. 2010 January ; 51(1): 121–129.

Again, weight Loss > 7% may be the best therapy



Vilar-Gomez E, et al. Gastroenterology 2015; 149:367–378.

Mediterranean Diet

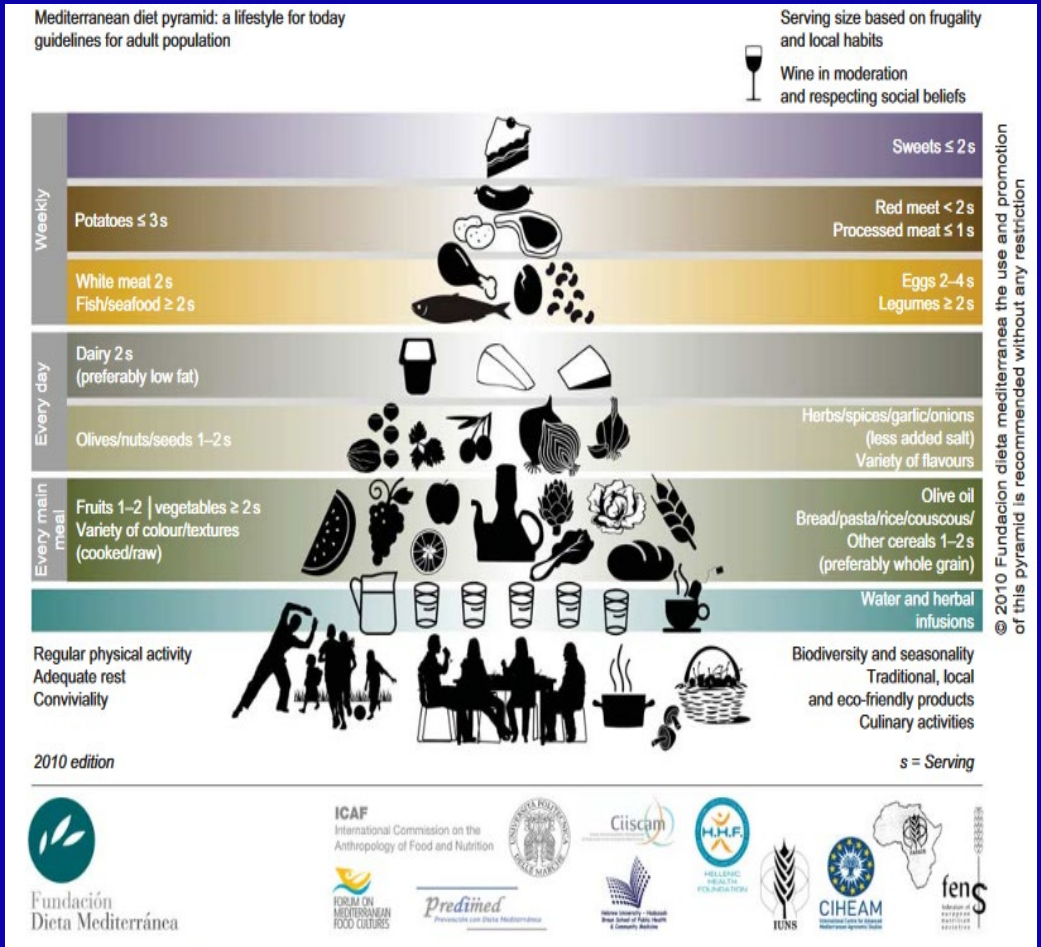
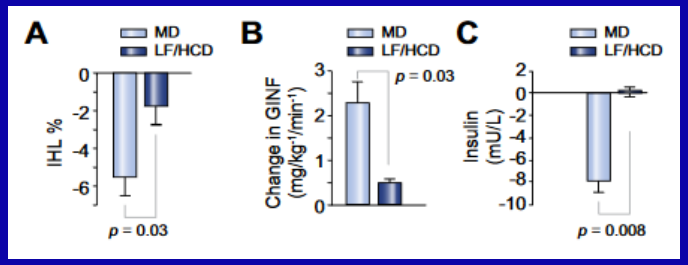


Fig. 2 (colour online) Mediterranean diet pyramid: a lifestyle for today



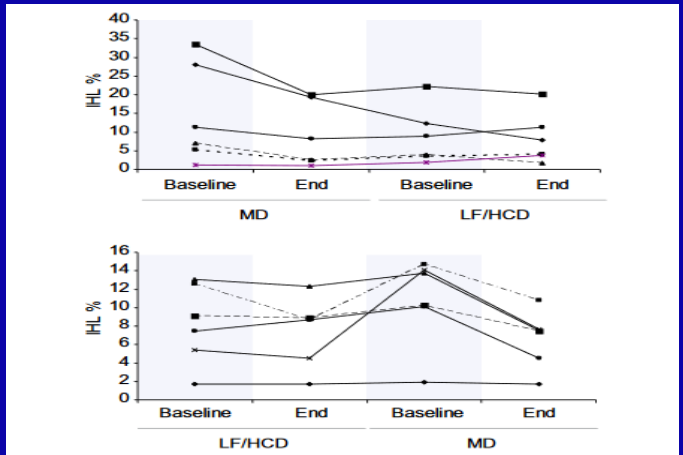
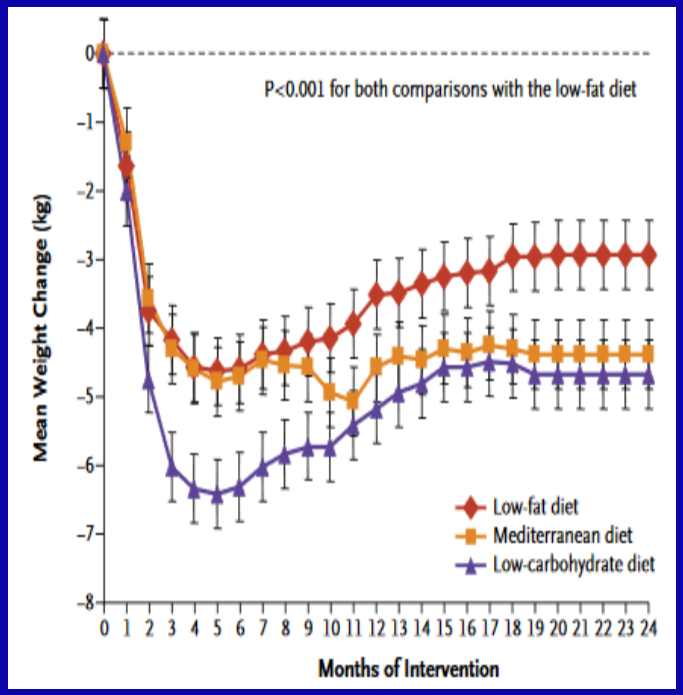
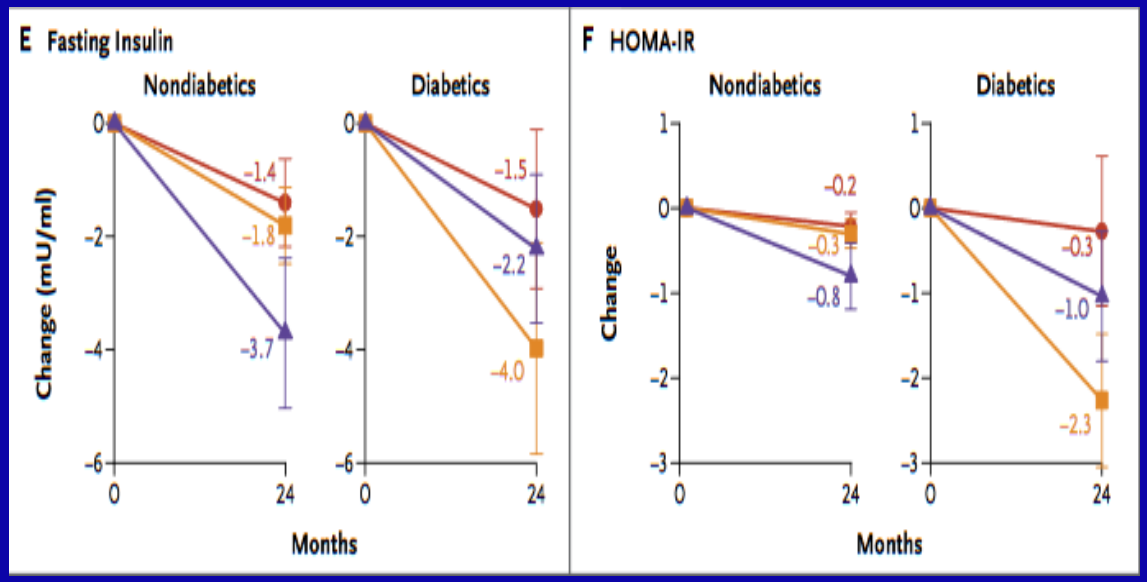


Fig. 3. Change in intrahepatic lipid for individual subjects across the two diet periods and wash-out period.

Bach-Faig A, et al. Public health nutrition. 2011 Dec;14(12A):2274-84.
Ryan MC, et al. Journal of hepatology. 2013 Jul 1;59(1):138-43.

Mediterranean Diet

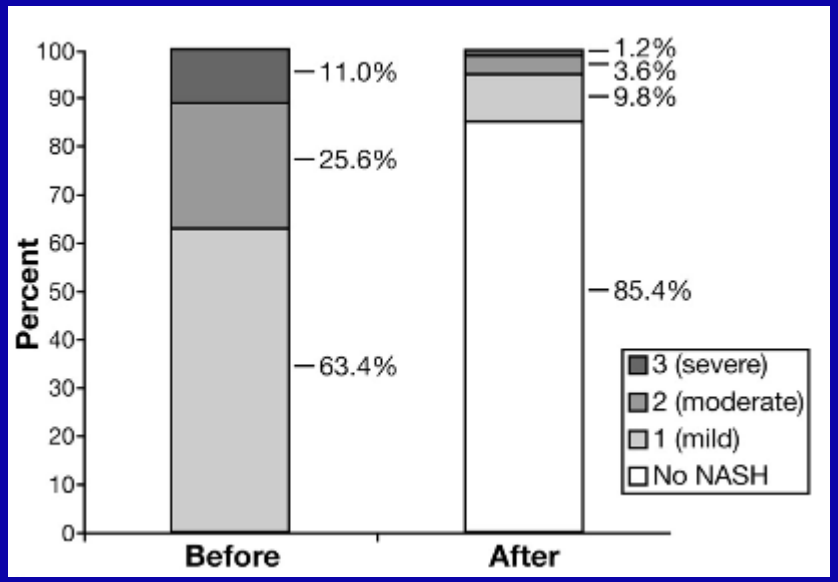




Shai I, et al. N Engl J Med 2008;3:229–241

NAFLD and Bariatric Surgery

- Decrease in NASH noted in several observational studies.



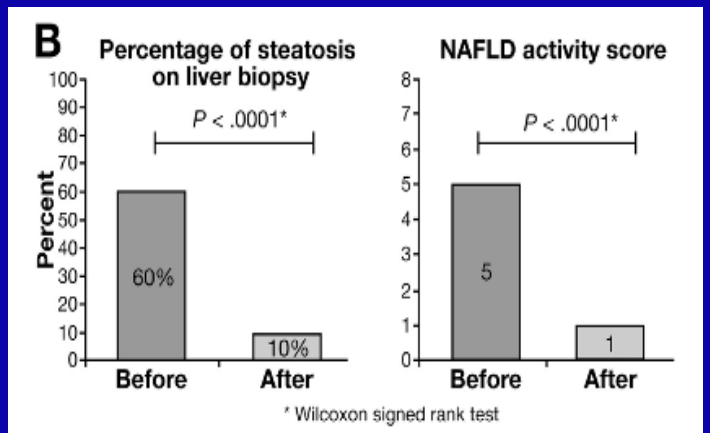
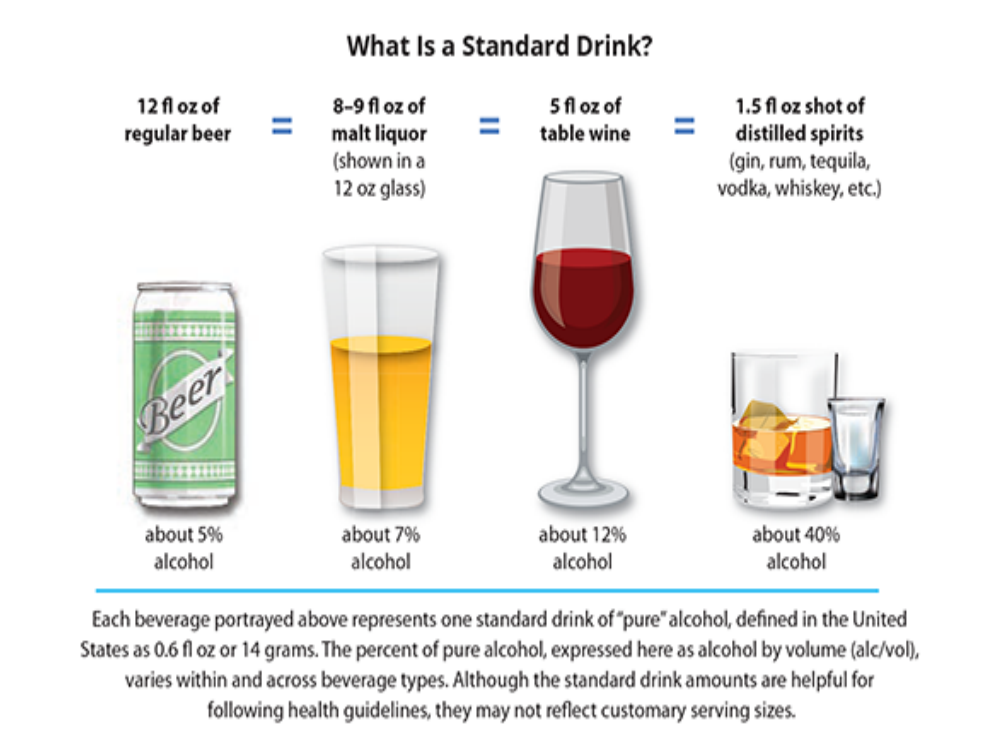


Figure 3. Change of histologic features 1 year after bariatric surgery. (*A*) Percentage of improvement in hepatocellular ballooning and in lobular inflammation 1 year after bariatric surgery. (*B*) Median of NAS and steatosis at baseline and at 1 year after surgery. *Wilcoxon signed rank test.

Lassailly G, et al. Gastroenterology 2015;149:379–388

Alcohol and NAFLD

- Heavy alcohol use should be avoided.
  - Men: more than 14 drinks per week or 4 drinks on any day
  - Women: more than 7-10 drinks per week or 3 drinks on any day



SOURCE: https://www.drugabuse.gov/sites/default/files/files/AUDIT.pdf

AUDIT to identify at-risk drinkers

The Alcohol Use Disorders Identification Test: Self-Report Version

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest. Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	
					Total	

SOURCE: https://www.drugabuse.gov/sites/default/files/files/AUDIT.pdf

Other lifestyle recommendations:

- Moderate physical activity
- Smoking cessation
- Coffee?

Pharmacotherapy and NAFLD

- Not used for most cases of NAFLD
- Reserved for those with NASH w/ advanced fibrosis on biopsy (F2+)
- Could be considered in those not meeting lifestyle modification goals
  - Need to discuss risks, benefits, alternatives.

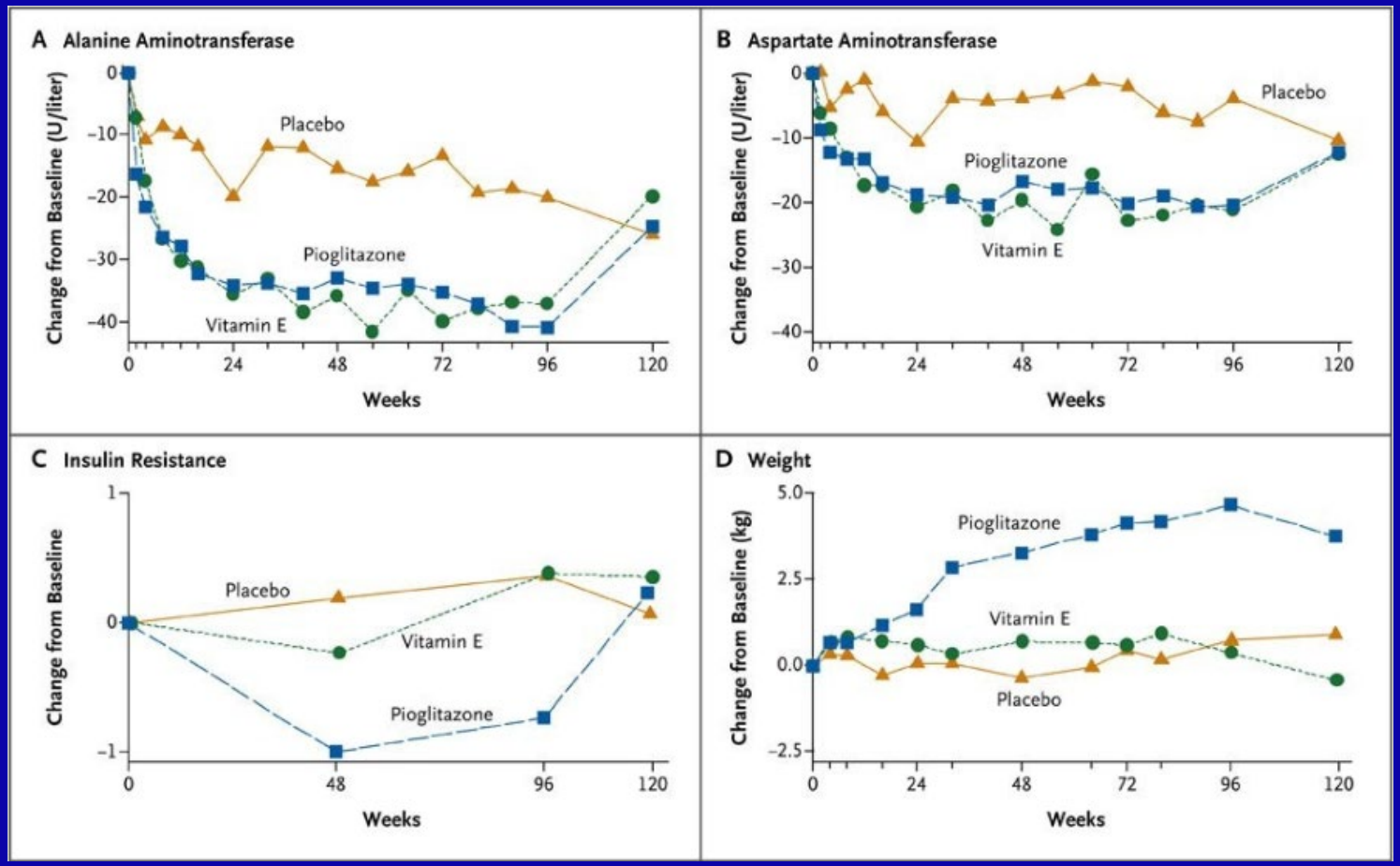
TREAT THE CVD RISK FACTORS!

Pharmacologic Therapy

Medication	Effect on liver histology
Metformin	No improvement
Thiazolidinediones Rosiglitazone Pioglitazone*	 Improvement in HS but not necro-inflammation and fibrosis Improved NAS & steatosis in diabetics with NASH. Less clear benefit for NAS in non-diabetics with NAFLD but resolution of NASH has been demonstrated (PIVENS 47% versus 23% NASH resolution).
Glucagon-like peptide-1 agonists	Possible improvement in SH
Vitamin E*	Improvement in steatosis, inflammation, ballooning, NAS scores in non-diabetics. (PIVENS 43% vs 19%, TONIC 58% vs 28%) Resolution of NASH compared to placebo (PIVENS 52% v 23%) Unclear effect on fibrosis.
UDCA ("Ursodiol")	No histologic benefit
Omega-3 fatty acids	No clear benefit in limited POC studies. Can be considered in NAFLD patients with hypertriglyceridemia.

Chalasani N, et al. Hepatology. 2018 Jan 1;67(1):328-57

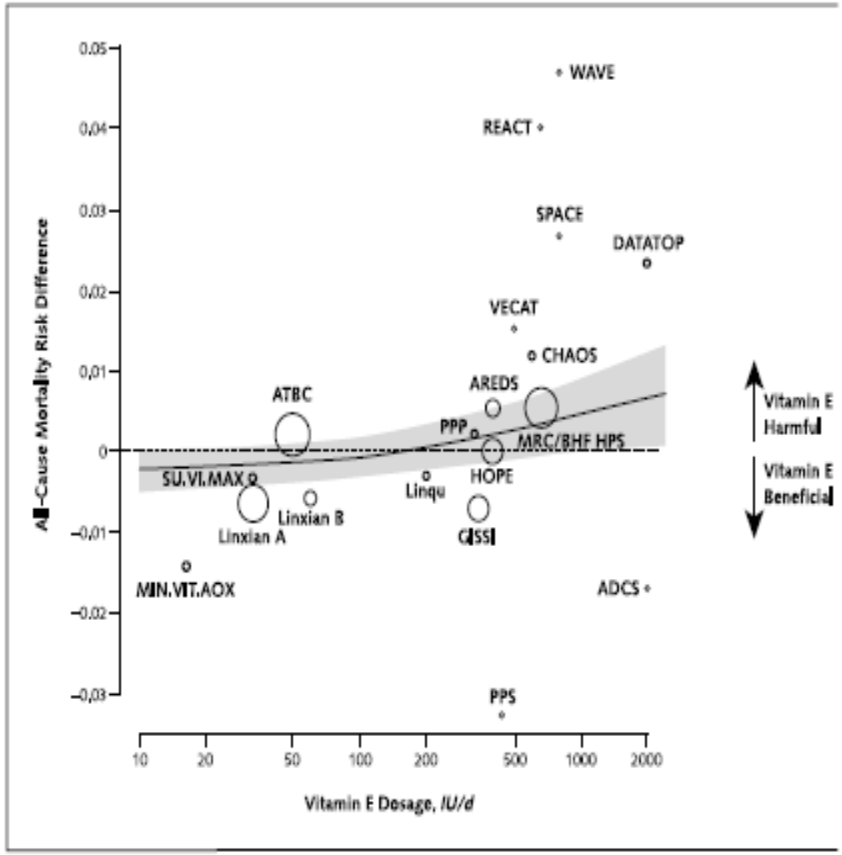
Vitamin E & Pioglitazone (PIVENS)



Sanyal AJ, et al. N Engl J Med 2010; 362:1675-1685.

Vitamin E & mortality risk

Figure 3. Dose–response relationship between vitamin E supplementation and all-cause mortality in randomized, controlled trials.



Pearl:

- Address CVD risk factors!!

NAFLD: Address CVD Risk & Dyslipidemia

- NAFLD → "risk marker" for CVD
  - Possible mechanistic links
- CVD risk factor modification should be approached aggressively
  - Treating dyslipidemia in patients with DM & MetS reduces CVD and improves mortality
- GREACE Study:
  - Statins improve transaminases presumed attributed to NAFLD
- Studies have demonstrated statin safety in patients with liver disease regardless of transaminases

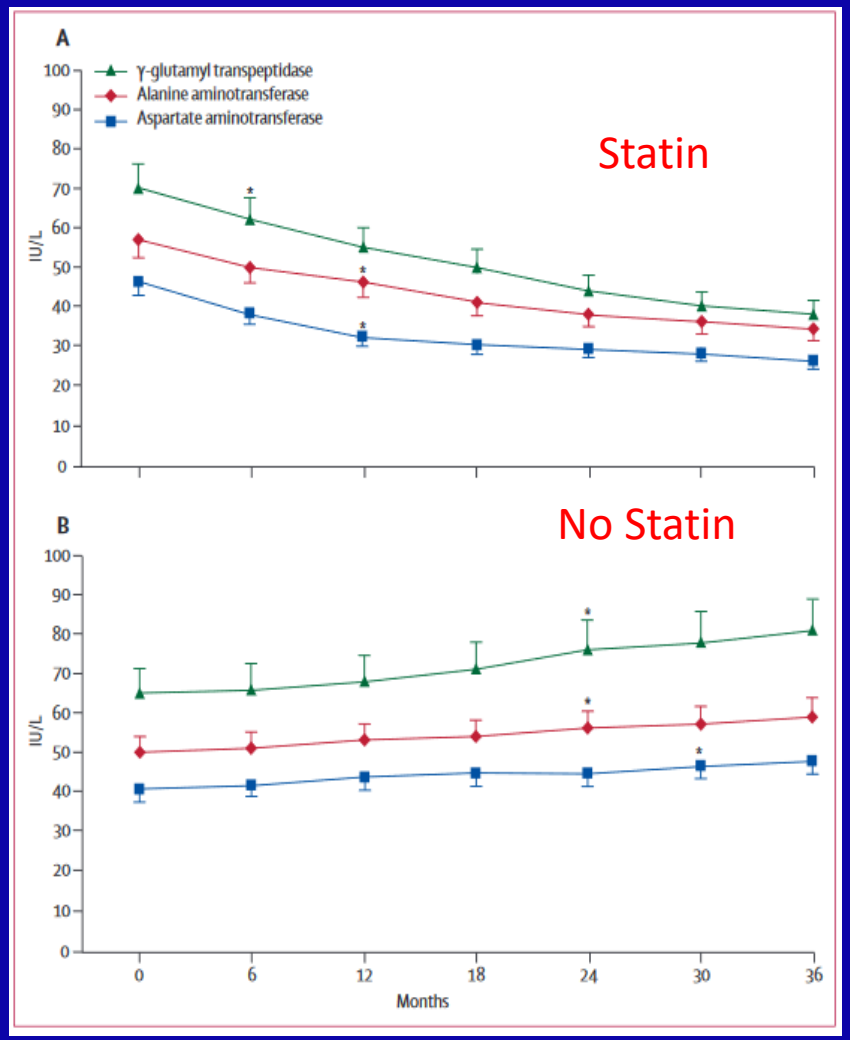
- AASLD (2018):

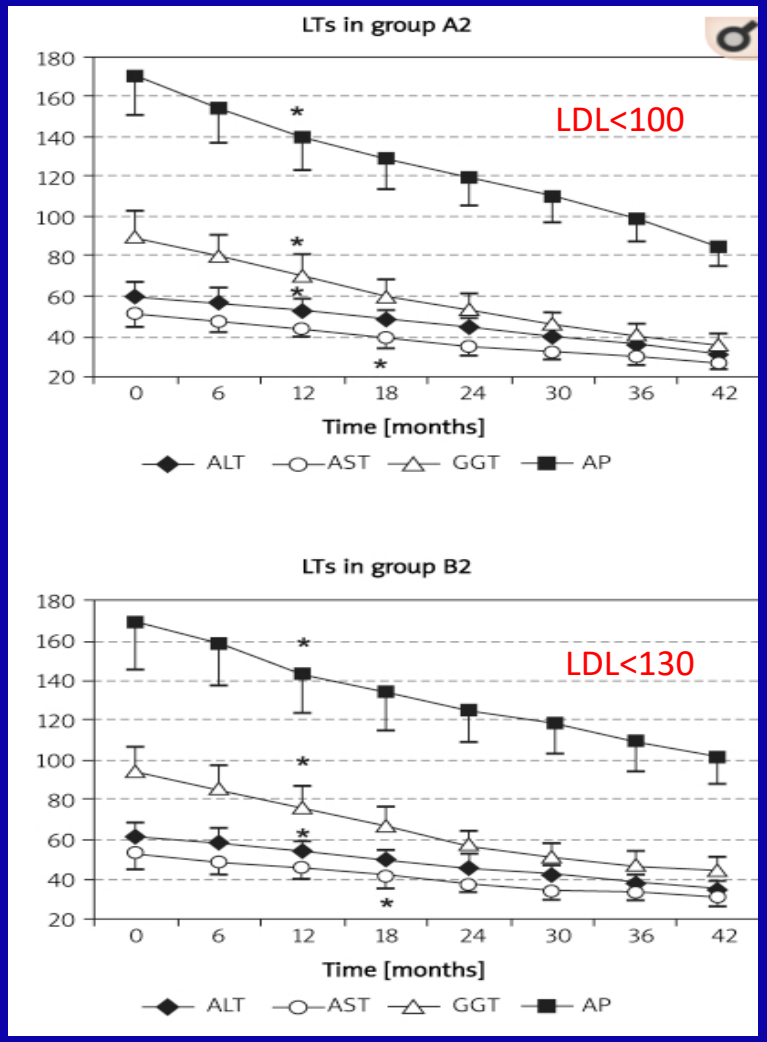
  "Several studies have established the safety of statins in patients with liver disease regardless of baseline elevation in liver chemistries."

Chalasani N, et al. Hepatology. 2018 Jan 1;67(1):328-57

AASLD (2018):

"Several studies have established the safety of statins in patients with liver disease regardless of baseline elevation in liver chemistries."





Lancet. 2010 Dec 4;376(9756):1916-22
Arch Med Sci. 2011 Oct;7(5):796-805.

Pearls

- Weight loss and diet modification remain the mainstays of NAFLD therapy
- Addressing dyslipidemia and CVD risk should be priorities in all patients with elevated risk profiles (ASCVD)
- Vitamin E (rrr α-tocopherol) can be considered in NASH patients with advanced fibrosis or in NAFLD patients at higher risk unable to meet lifestyle goals
- Pioglitazone can be considered in patients +/- DM-II with NASH and biopsy-proven advanced fibrosis
- Cirrhotic patients need HCC & varices screening, OLT referrals.

NASH and Liver Transplantation

- NASH will become the most common indication for OLT in forthcoming years.
- Good Practice: Refer cirrhotic patients early!
  - MELD ≥ 10 or HCC.
- Higher BMI → increased risk of mortality and allograft failure
  - Sleeve gastrectomy as adjunct at time of OLT.

Other Considerations:

- HCC Screening in patients with NASH cirrhosis
  - RUQ US +/- AFP every 6 months
- Varices Screening in NASH cirrhosis
- Other considerations:
  - Encephalopathy
  - Renal Function
  - Ascites
- Immunizations
- Concomitant liver disease

Monitoring NAFLD/NASH

- NAFL or NASH without advanced fibrosis:
  - Obtain serum aminotransferases q 3-6 months as patients try to meet their weight goals
    - If the aminotransferases do not return to normal levels with weight loss or if they increase → liver biopsy (if not done) and consider other causes.
  - Unable to meet goals or felt at risk, refer to GI-hepatology
- NASH with fibrosis on biopsy (but not cirrhosis)
  - Non-invasive assessment q 3 years (biomarkers, VCTE)
  - More aggressive if unable to meet their goals or LFTs are not improving.
  - If fibrosis is worsening on monitoring, consider repeat liver biopsy

Note: guidance is less clear on this. If in doubt refer to hepatologist.

Pearls:

- Referral to a hepatologist
  - Aminotransferases that remain elevated despite loss of ≥5-7% of body weight (to evaluate for other etiologies of liver disease)
  - Clinical features of advanced liver disease (eg, ascites, splenomegaly, jaundice)
  - Steatohepatitis on liver biopsy
  - Advanced fibrosis (fibrosis stage ≥F3) on a noninvasive liver assessment
  - Refer cirrhotic patient with MELD >10 to a transplant center.

Thank You

- Questions?