2019

LIVER SYMPOSIUM

Annenberg Center For Health Sciences at Eisenhower

Imparting knowledge. Improving patient care.

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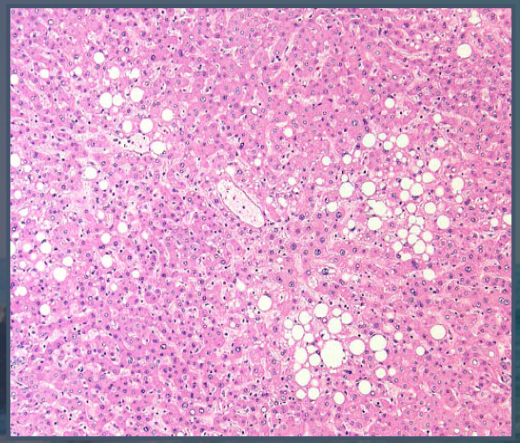
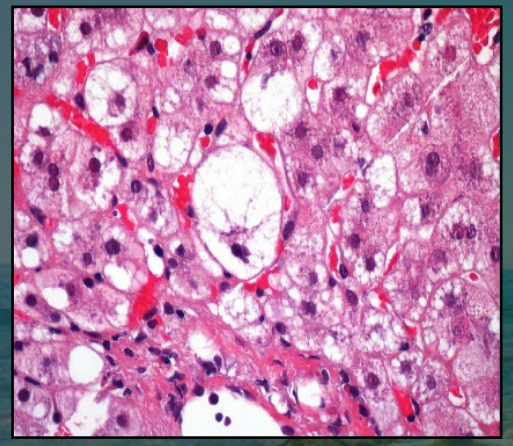
Southern California Society of Gastroenterology

NASH- The Next Frontier

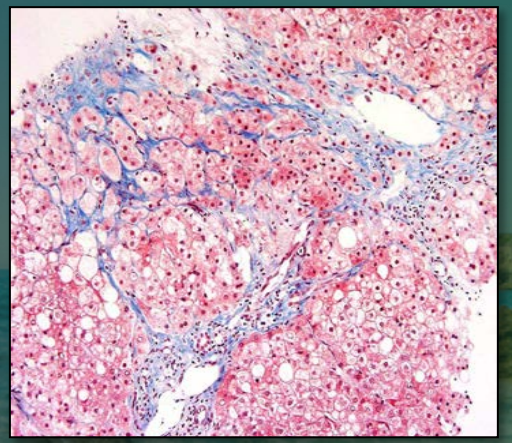
NAFL



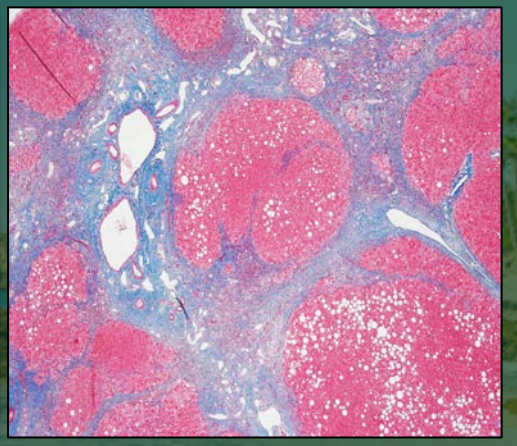
NASH



NASH with fibrosis



NASH Cirrhosis



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Conflicts of Interest

- *None*

Pre/Post Questions

1. NAFLD affects approximately 15% of the U.S. population: True or False

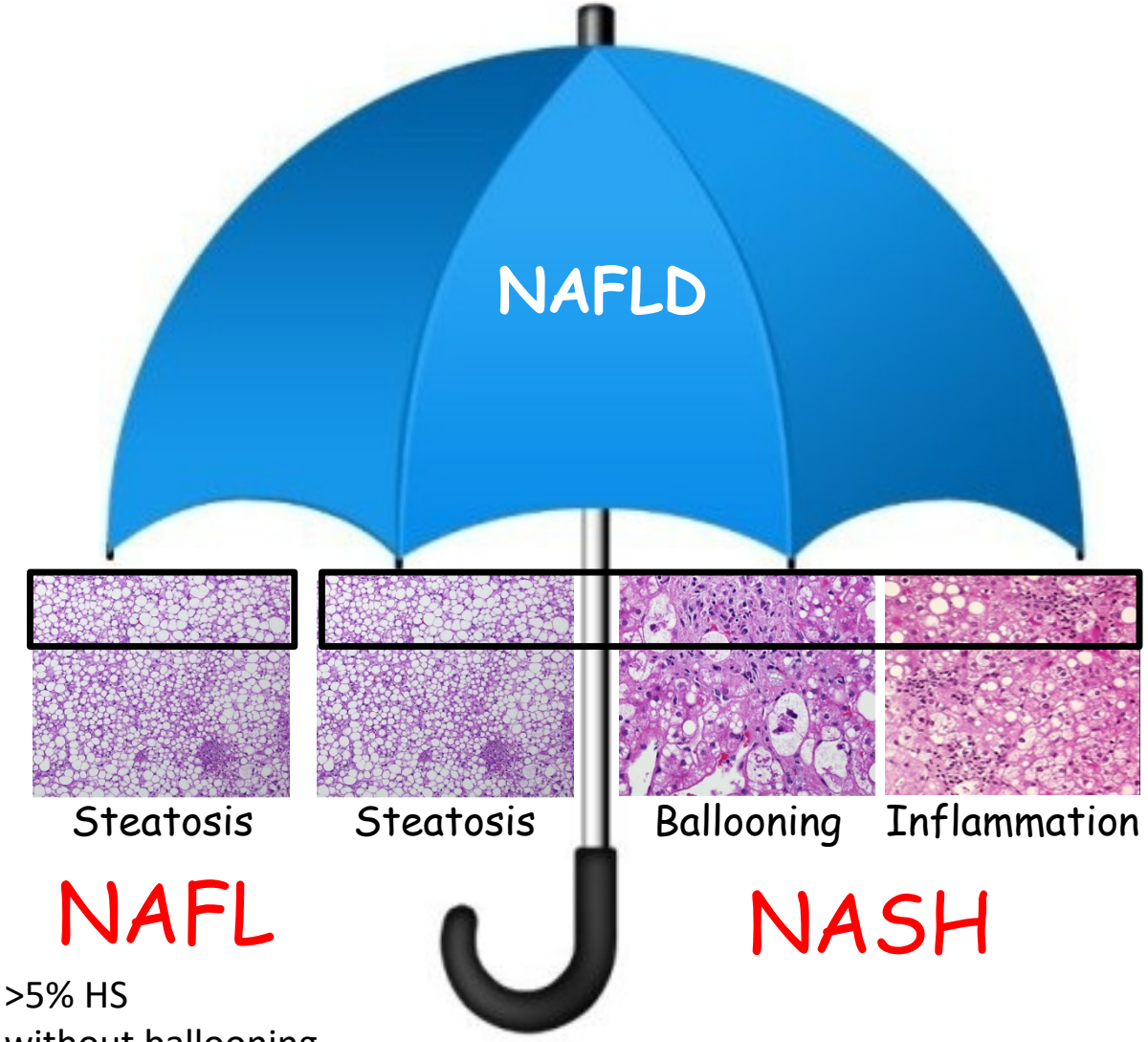
2. NAFLD is associated with which of the following:
   - Diabetes
   - Sleep apnea
   - PCOS
   - Development of hepatocellular carcinoma without cirrhosis
   - All of the above

3. A small fraction of NAFLD/NASH drugs in the pipeline target a specific aspect of the immune response: True or False

Outline

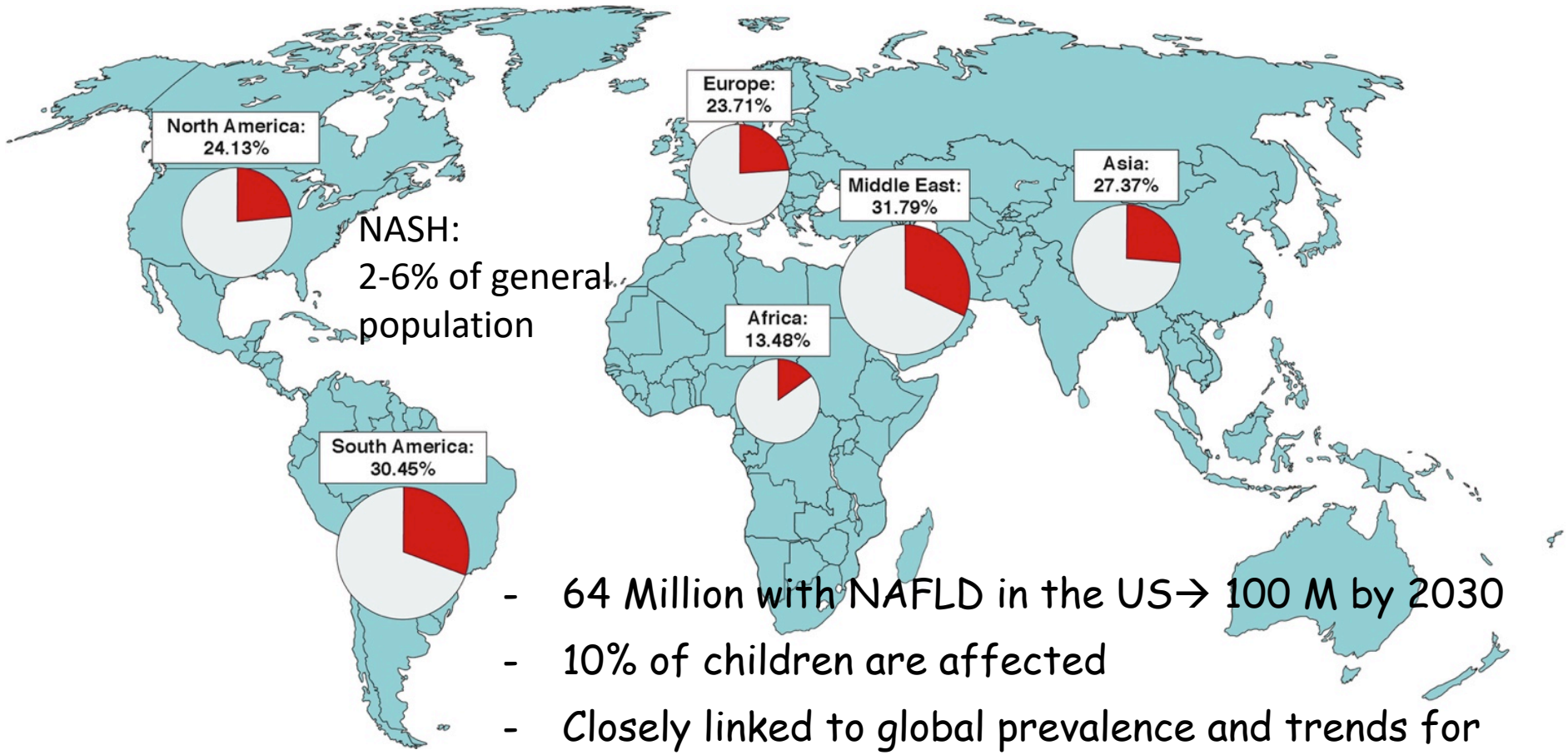
- Disease prevalence and comorbidities
  - Disease associations
  - Screening guidelines
  - CVD and malignancy risk
- Diagnosis
  - Imaging assessment
  - Indications for liver biopsy
- Natural history
- What do people with NASH die of?
- Treatment- diets; current and emerging pharmacologic agents

Nonalcoholic Fatty Liver Disease (NAFLD)



NAFLD is a global problem

Prevalence data using a radiologic NAFLD diagnosis

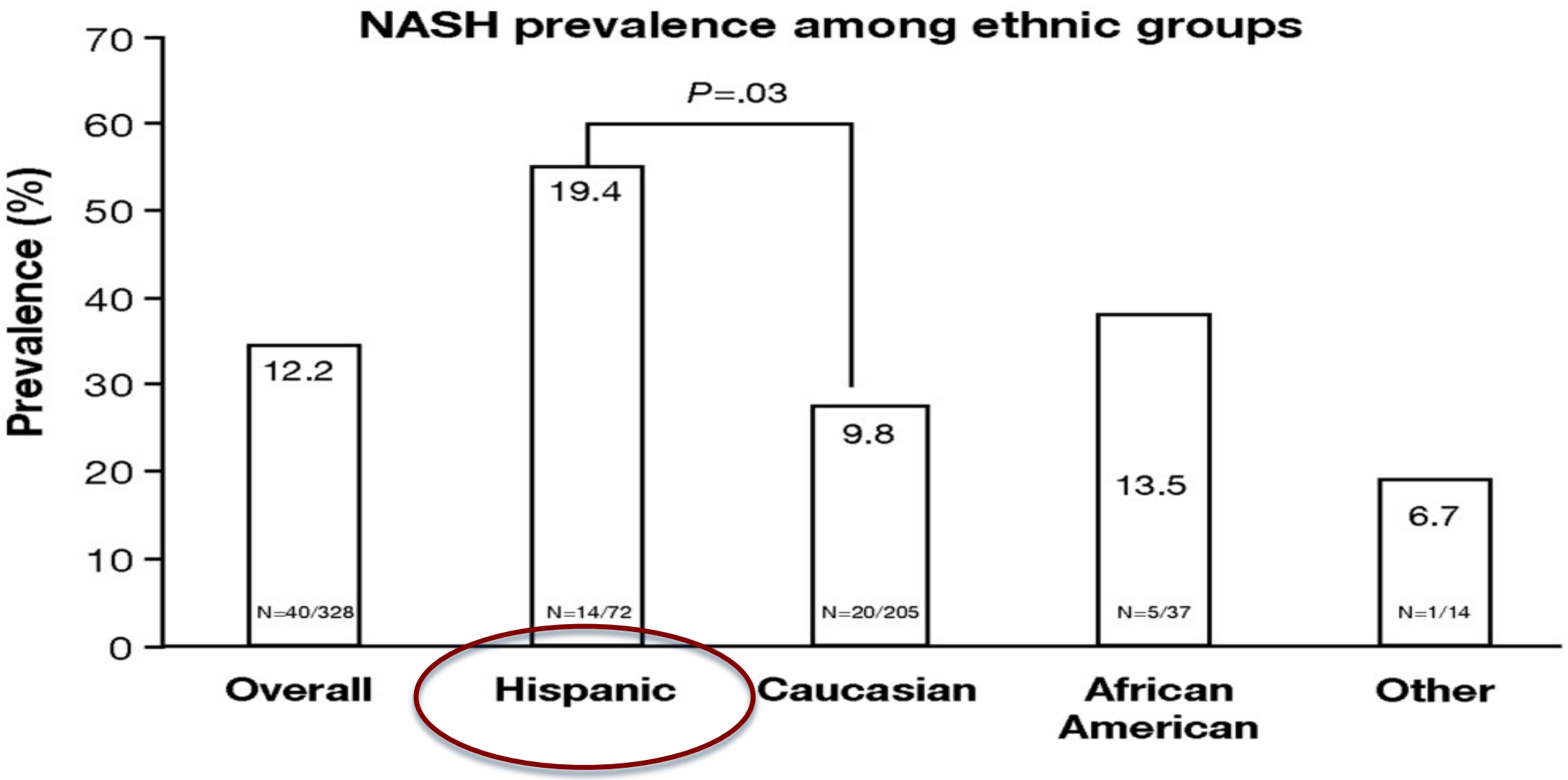


NASH:
2-6% of general population

- 64 Million with NAFLD in the US→ 100 M by 2030
- 10% of children are affected
- Closely linked to global prevalence and trends for T2DM and growing obesity epidemic

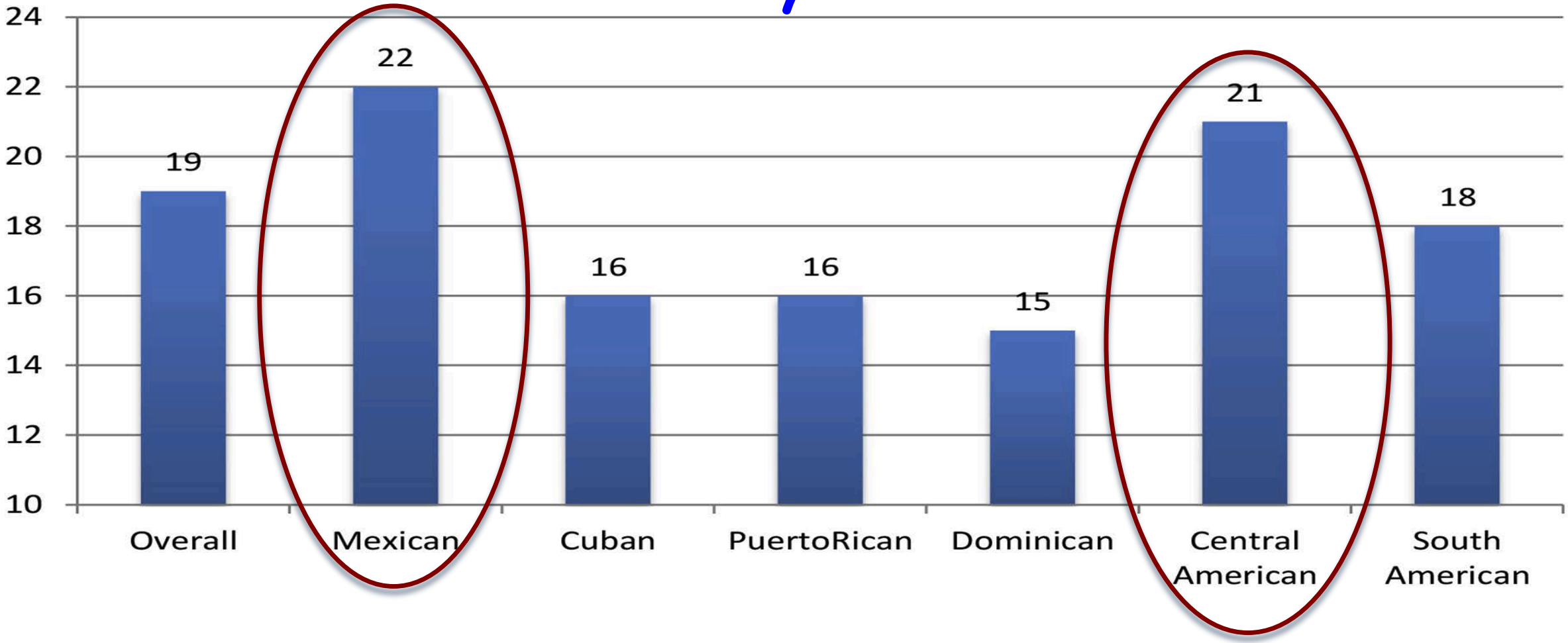
Younossi ZM, Gastroenterology 2016

Race / Ethnicity



Williams et al. *Gastroenterology*. 2011.

NAFLD Prevalence in Hispanics: Birth Country Matters



Kalia et al. *Clinics in Liver Disease*. 2015.
Kallwitz et al. *Clinc Gastroenterol Hepatol*. 2015.

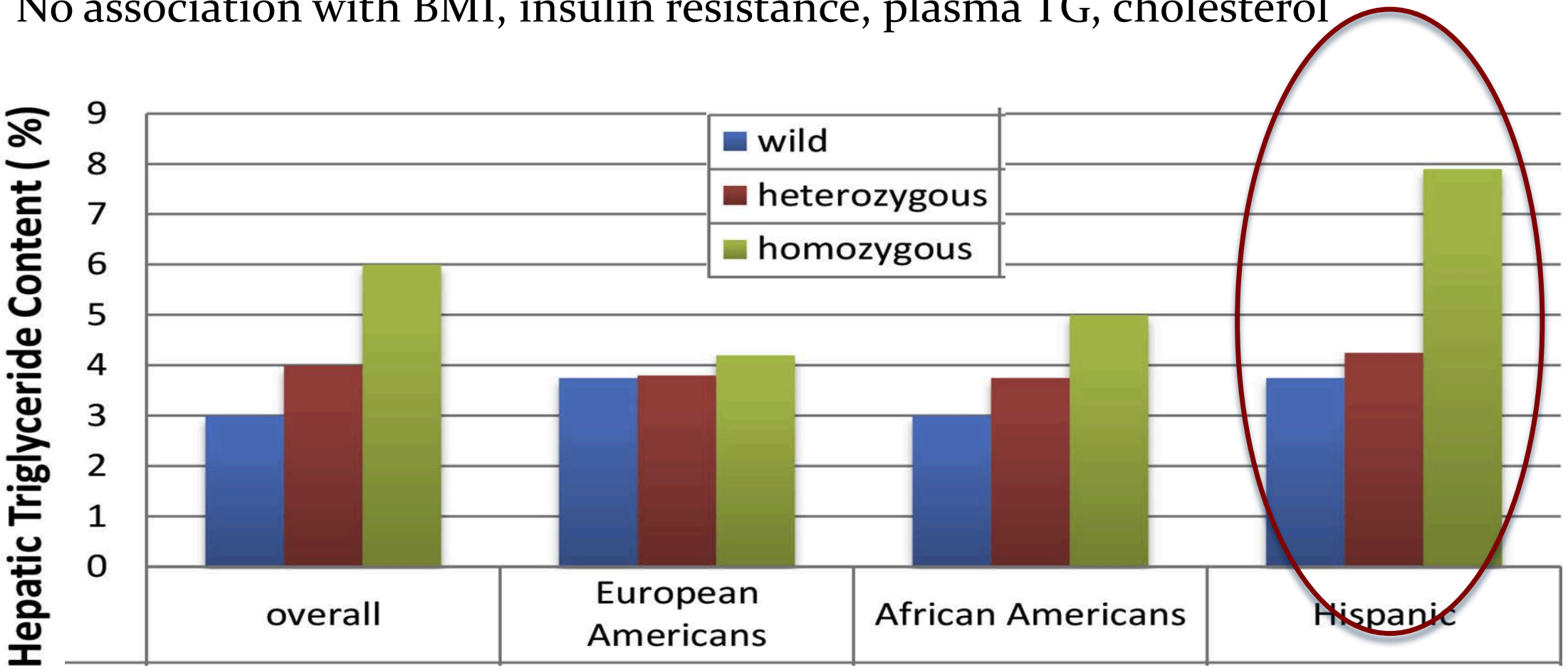
Role of PNPLA-3 (genetic variants)

- Role in lipid metabolism
- Risk factor for more advanced NAFLD, cirrhosis, and liver cancer

- ↑ rates of PNPLA-3 mutations in Hispanic populations compared to African Americans (40 vs 19%)
- Correlated with > NAFLD prevalence in Hispanics (24 vs 9%)

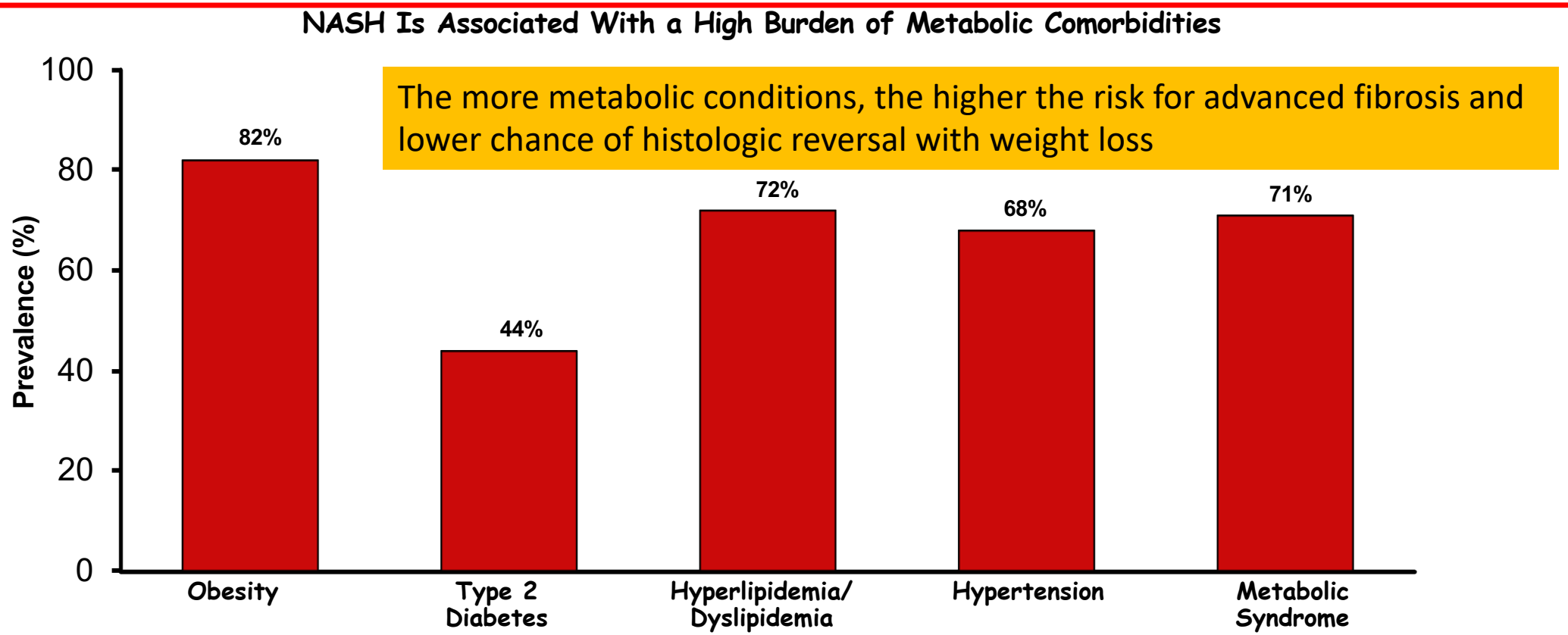
PNPLA3 - I148M Mutation

- Associated with ↑ **hepatic fat levels and ↑ ALT**
- No association with BMI, insulin resistance, plasma TG, cholesterol



Kalia et al. *Clinics in Liver Disease*. 2015.

Meta-Analytic Assessment: Global prevalence of comorbidities in NASH patients



Data from studies that diagnosed NAFLD by imaging (US, CT, MRI/SPECT) and NASH by histology in NAFLD patients. Number of studies reporting for NASH: obesity (n=4); type 2 diabetes (n=9); hyperlipidemia/dyslipidemia (n=4); hypertension (n=4); metabolic syndrome (n=2).

Younossi ZM, et al. Hepatology. 2016;64:73-84.

Is routine screening indicated for NAFLD?

- NAFLD increases the risk of premature cardiovascular disease and associated mortality.
- A case can be made for screening of NAFLD to facilitate early diagnosis and to prevent the hepatic and extra-hepatic complications in high risk sub-populations with morbid obesity, diabetes, and other metabolic risk factors.
- Recent Markov model, screening not cost-effective at present because of disutility of available treatment.

Koehler EM, Hepatology 2016; Kwok R, Gut 2016; Corey KE, Dig Dis Sci 2016

Current diagnostic tools for NASH & fibrosis

Work up of patients with NAFLD: Basics

- Imaging to establish the presence of steatosis
- Meticulous alcohol and medication history

  ~10-20g in women, 10-30g in men
- Exclusion of co-existing or competing etiologies
- Auto-antibodies and hyperferritenemia are common

  - Usually epiphenomena but ferritin > 1.5 ULN, fibrosis increased
- Fasting lipid profile and measures of insulin resistance
- Liver enzymes can be normal!!
- Liver biopsy to establish the presence of NASH in selected patients

Non-invasive diagnosis of NASH and NAFLD

Clinical/lab tests

- **NAFLD fibrosis score (NFS)**
- **FIB-4 index**
- BARD score
- AST:ALT ratio
- AST:platelet ratio index
- Fibrotest
- Hepascore
- Fatty liver index
- Index of NASH

Imaging

- Ultrasound
- Computer tomography
- Magnetic resonance imaging
- Magnetic resonance spectroscopy
- Transient elastography
- Acoustic radiation force impulse
- Magnetic resonance elastography

Biomarkers

- Hyaluronic acid
- CK-18
- Fucosylated haptoglobin (Fuc-Hpt)
- Macroglobulin-2 binding protein (Mac-2bp)
- Fuc-Hpt + Mac-2bp
- **ELF score**
- FIBROSpect®

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; MRI, magnetic resonance imaging.

Papagianni M et al. World J Hepatol. 2015;7:638–48; Golabi P et al. Expert Rev Gastroenterol Hepatol. 2016;10:63–71.

FIB-4

- Based on age, AST, ALT and Platelet Count
- Formula: (Age x AST)/(Platelets x (sqr[ALT])
- http://gihep.com/calculators/hepatology/fibrosis-4-score/
- Predicts advanced fibrosis with high specificity
- Reasonable correlation head-to-head with MRI and liver biopsy
- Its longitudinal changes predict changes in fibrosis
  - >3.25 → 1 in 5 patients will develop liver-related event

Sterling RK et al . Hepatology 43: 2006; 1317-1325; Imajo T, et al. Gastroenterology 2016

NAFLD Fibrosis Score (NFS)
http://nafldscore.com

- Risk score: -1.675 + 0.037 * age (years) + 0.094 * BMI (kg/m^2) + 1.13 * IFG/diabetes (yes=1, no=0) + 0.99 * AST/ALT ratio - 0.013 * platelet (x10^9/l) - 0.66 * albumin (g/dl)

- Based on six variables: Age, BMI, AST/ALT ratio, Hyperglycemia/diabetes, Platelet count and Albumin

- Independent predictor of advanced (bridging or cirrhosis) fibrosis.
- NAFLD Fibrosis Score predicts long term outcomes in individuals with NAFLD

Angulo P et al . Hepatology 45: 2007; 846-854; Kim D, et al. Hepatology 2013:57: 1357-1365; Angulo P et al: Gastroenterology 2013

Got normal LFTs? Can still have advanced fibrosis and cirrhosis

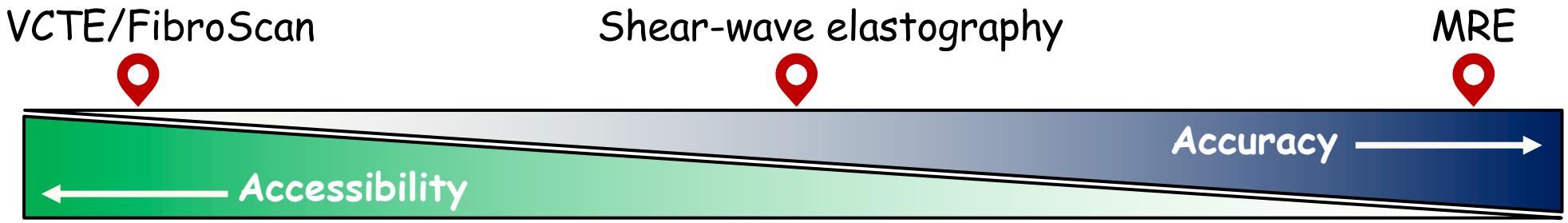
- N = 534 adults with NASH enrolled in the CRN with AST < 40 within 3 months of liver biopsy (43% of patients with NAFLD)
- 35% NASH, 20% (F2-F3), 7% (cirrhosis)
- Multiple logistic regression for F2-F3:
  - T2DM, LDL (per 10mg/dl decrement), White vs. non-white, AST/ALT, platelets, Triglycerides, history of hypertension

Am J Gastroenterology 2019; 114: 1626-1635

Caveats associated with available modalities

- Transient elastography, ARFI, and other ultrasound-based tests have limitations:
  - Obesity
  - Ascites
  - Acute inflammation
  - Cirrhosis

- MRE improves upon all except
  - Iron overload
  - Acute inflammation



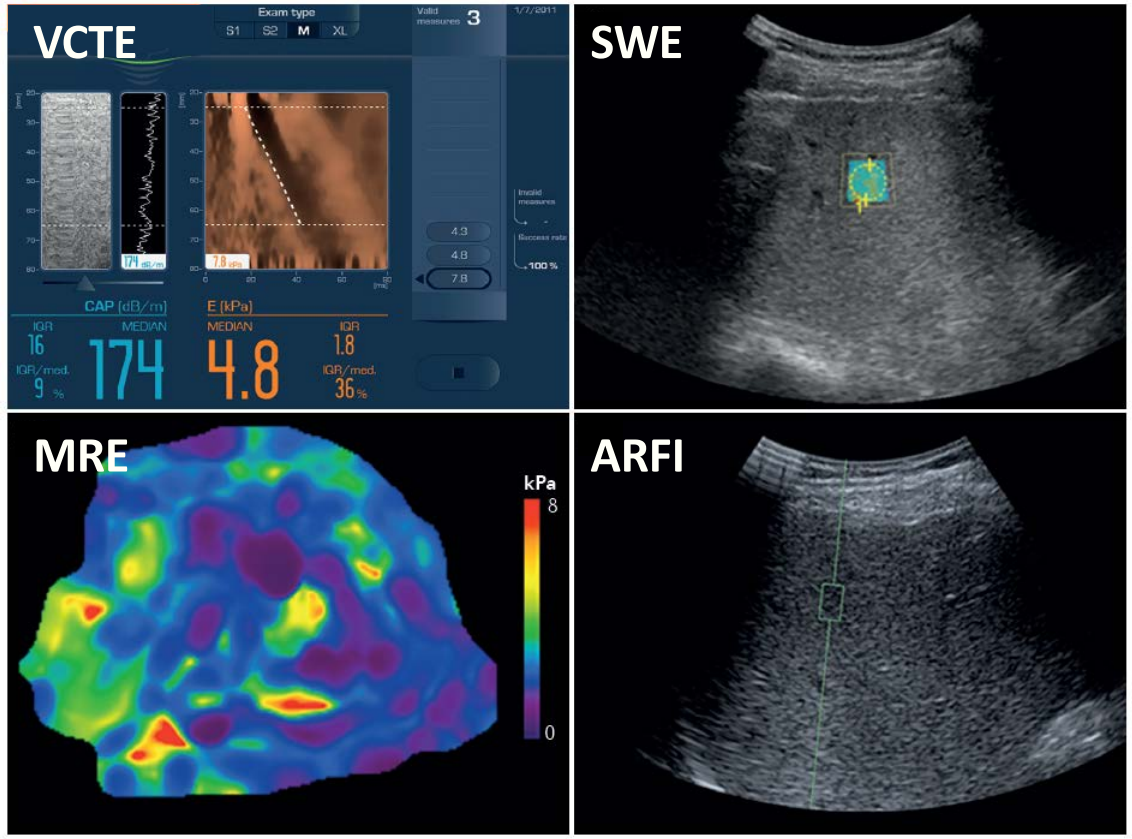
ARFI, acoustic radiation force impulse; MRE, magnetic resonance elastography; VCTE, vibration-controlled transient elastography.

Non-invasive assessment of liver fibrosis

Elastography-based methods to estimate liver stiffness

Tapper EB and Loomba R. Nat Rev Gastroenterol Hepatol 2018;15:274-282

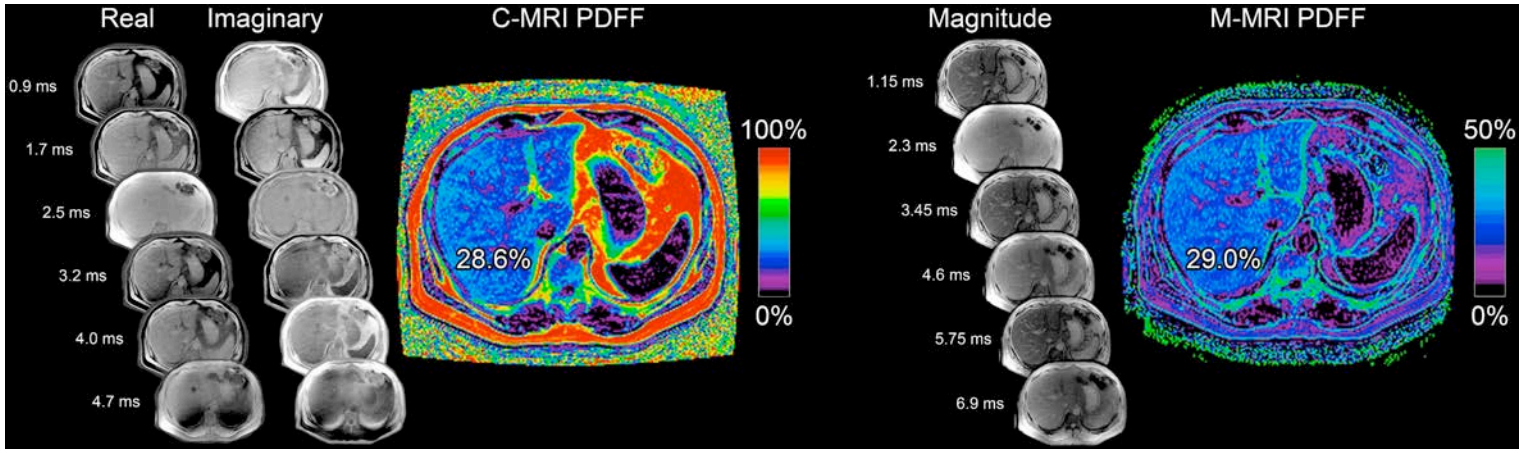
- VCTE (FibroScan) is most widely used
  - ≥10 images are required
  - Accurate for stages F3-4
  - Can estimate steatosis when used with CAP (controlled attenuation parameter)
- Shear Wave Elastography SWE/ARFI can be used to measure stiffness in a single region of interest (ROI)
- MRE measures stiffness across multiple ROIs



ARFI, acoustic radiation force impulse; CAP, controlled attenuation parameter; MRE, magnetic resonance elastography; ROI, region of interest; SWE, shear wave elastography; VCTE, vibration-controlled transient elastography.

Assessing liver steatosis by MRI-PDFF (proton-density fat fraction)

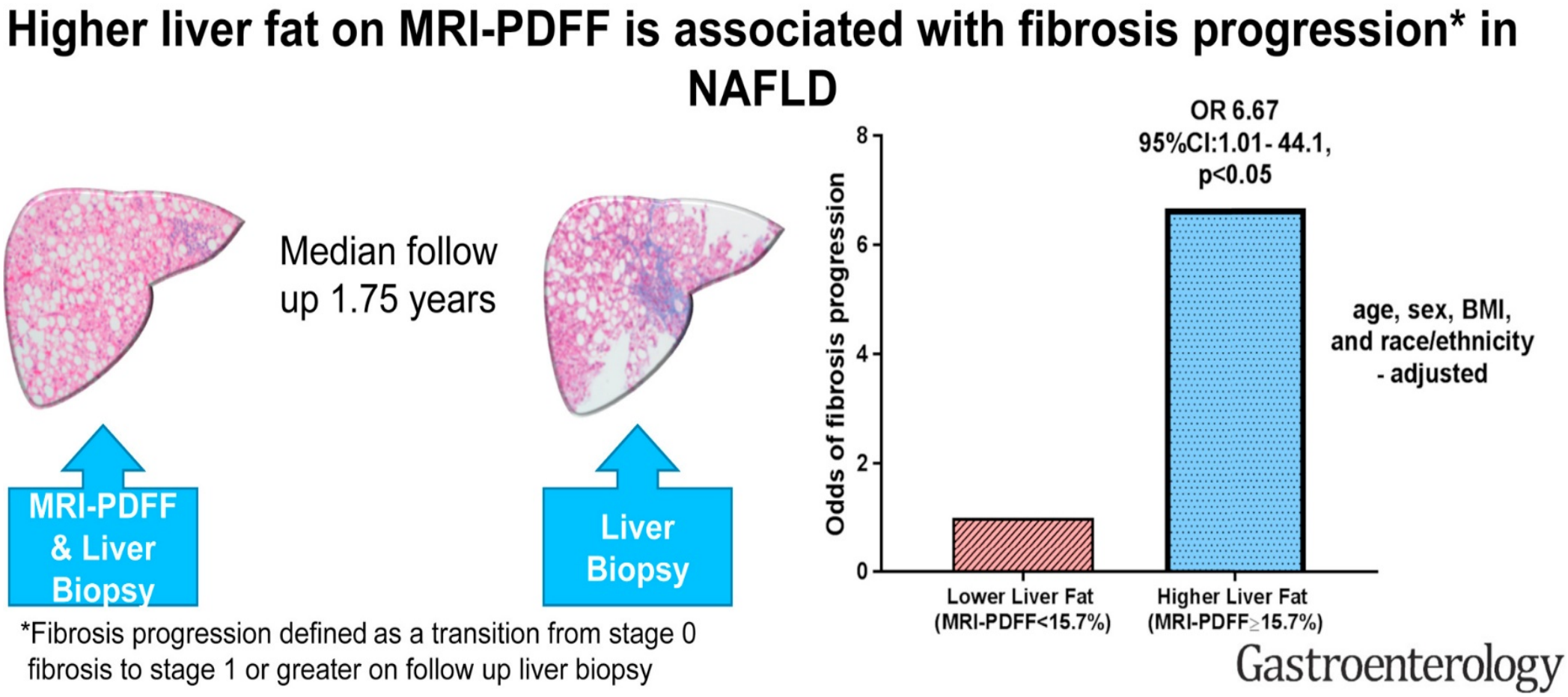
- Addresses confounding factors, unlike conventional in-phase and opposed-phase
- **Not** affected by
  - Scanner field strength
  - Patient factors: age, sex, BMI, etiology of liver disease
  - Concomitant liver abnormalities: iron overload, necroinflammation



BMI, body mass index; MRI, magnetic resonance imaging; PDFF, proton density fat fraction

Yu H et al. Magn Reson Med 2008;60:1122–34; Bydder M et al. Magn Reson Imaging 2008;26:347–59; Bydder M et al. Magn Reson Imaging 2010;28:767–76; Hansen MRI 2012; Kang BK et al. Invest Radiol 2012;47:368–75; Kühn JP et al. Radiology 2012;265:133–42; Tang A et al. Radiology 2013;267:422–31; Dulai PS, Sirlin CB, Loomba R. J Hepatol 2016;65:1006–16.

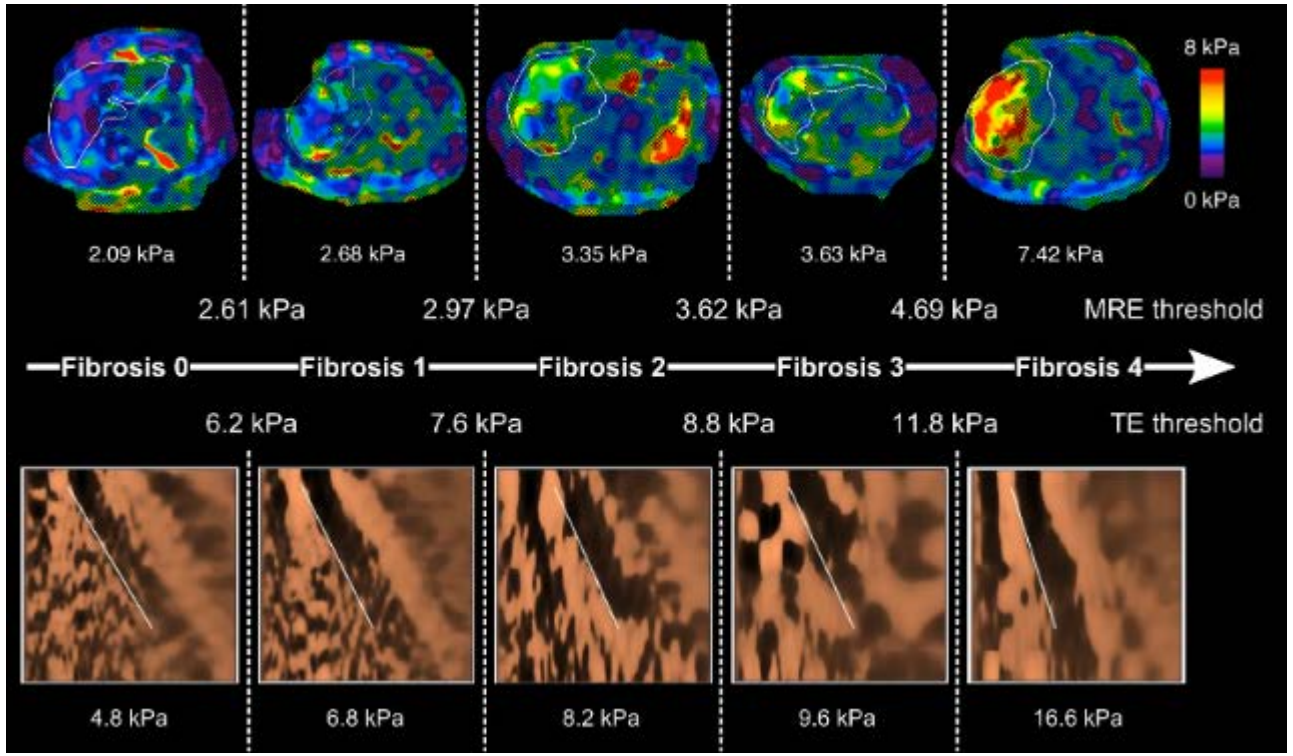
Higher liver fat may be prognostic



Ajmera, et al. Gastroenterology. 2018 Aug; 155(2): 307–310

Exploring noninvasive tests: Important Thresholds to Remember

Utility of MRE and VCTE in staging liver fibrosis in NAFLD



MRE <2.55	MRE >3.63
Low risk of fibrosis	Predicts fibrosis

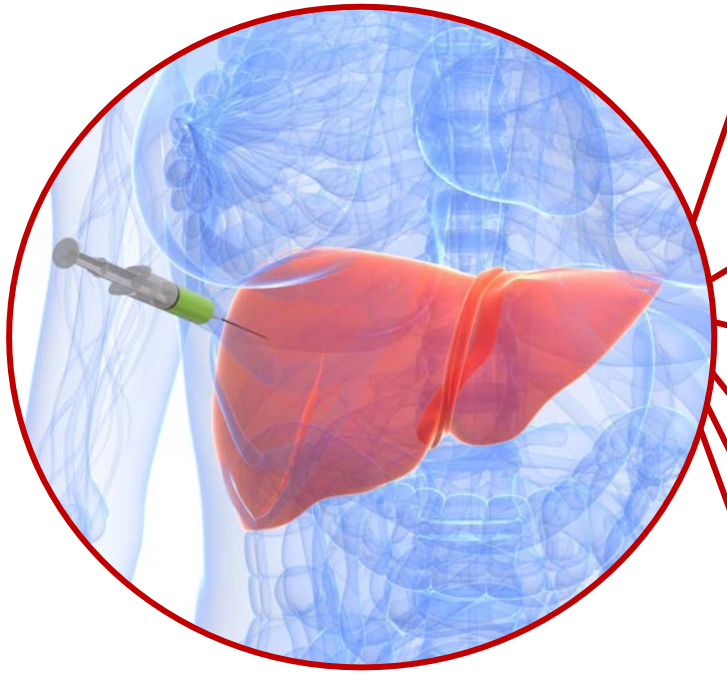
kPa: kilopascal; TE: transient elastography; VCTE: vibration controlled transient elastography

Is there a threshold for a clinically meaningful reduction in MRI-PDFF?

A relative decline of 30% from baseline is associated with a 2-point improvement in NAFLD activity score

Hsu C, et al. Clin Gastroenterol Hepatol 2019;17:630–7; Loomba R, et al. AASLD 2017 #2123

Indications for liver biopsy



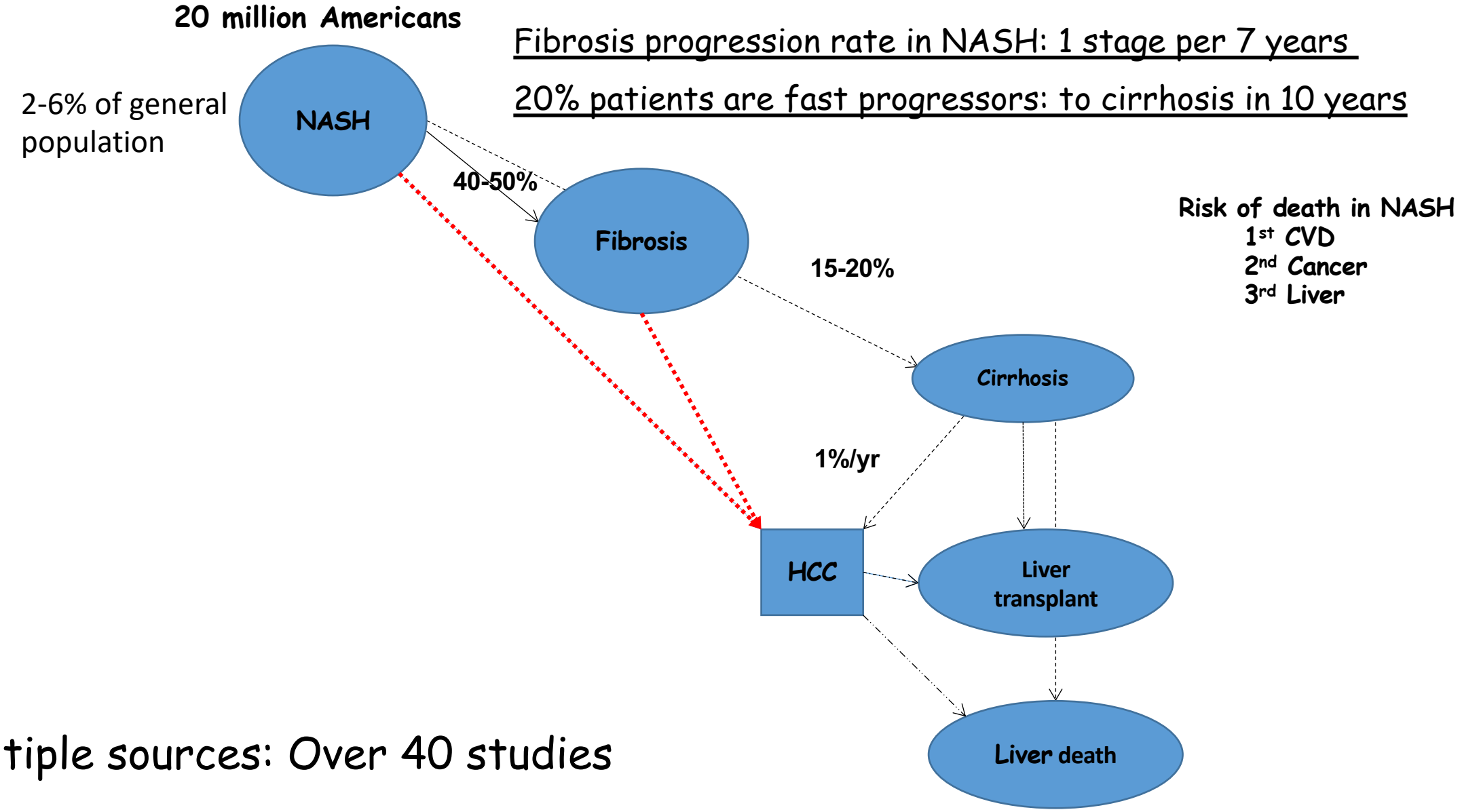
- Metabolic syndrome
  - Obesity
  - ↑ TG
  - Low HDL
  - Impaired glucose tolerance/DM
- FIB4 or NFS above threshold
- Family history?
- Cholecystectomy or bariatric surgery
- Old age
- Persistent inc LFTs despite weight loss

Disadvantages of biopsies

- Sampling variability
- Pain
- Infection
- Bleeding
- Perforation
- Impractical for population management
- Death

ALT, alanine aminotransferase; AST, asparatate aminotransferase; HDL, high-density lipoprotein; TG, triglycerides.

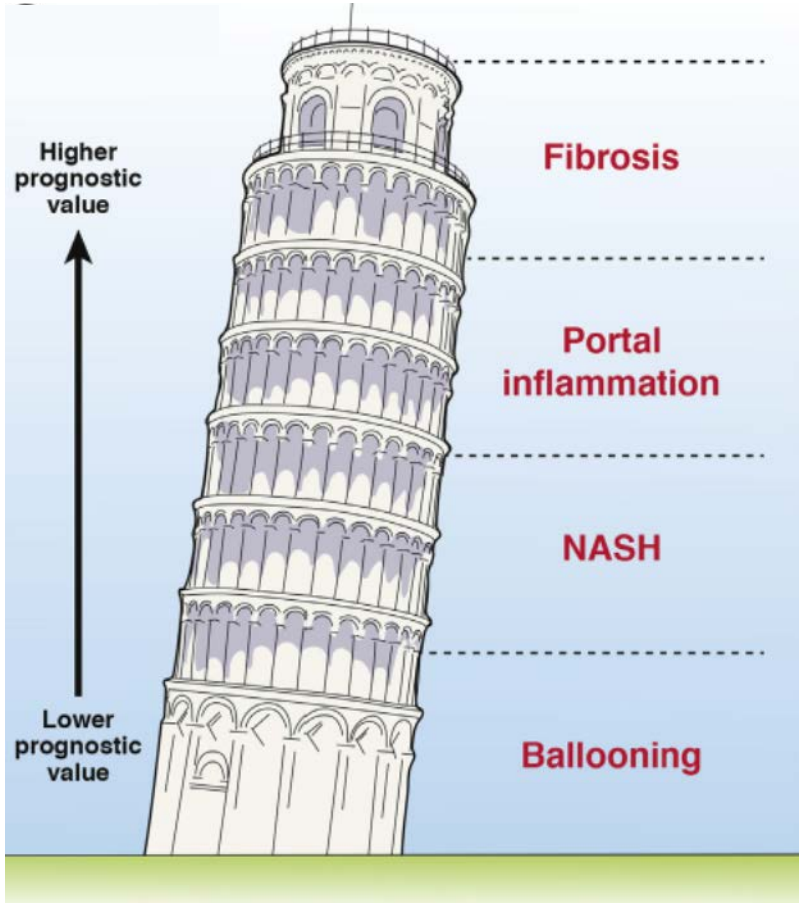
Natural history of NASH



Multiple sources: Over 40 studies

Fibrosis is the major determinant of mortality in NAFLD

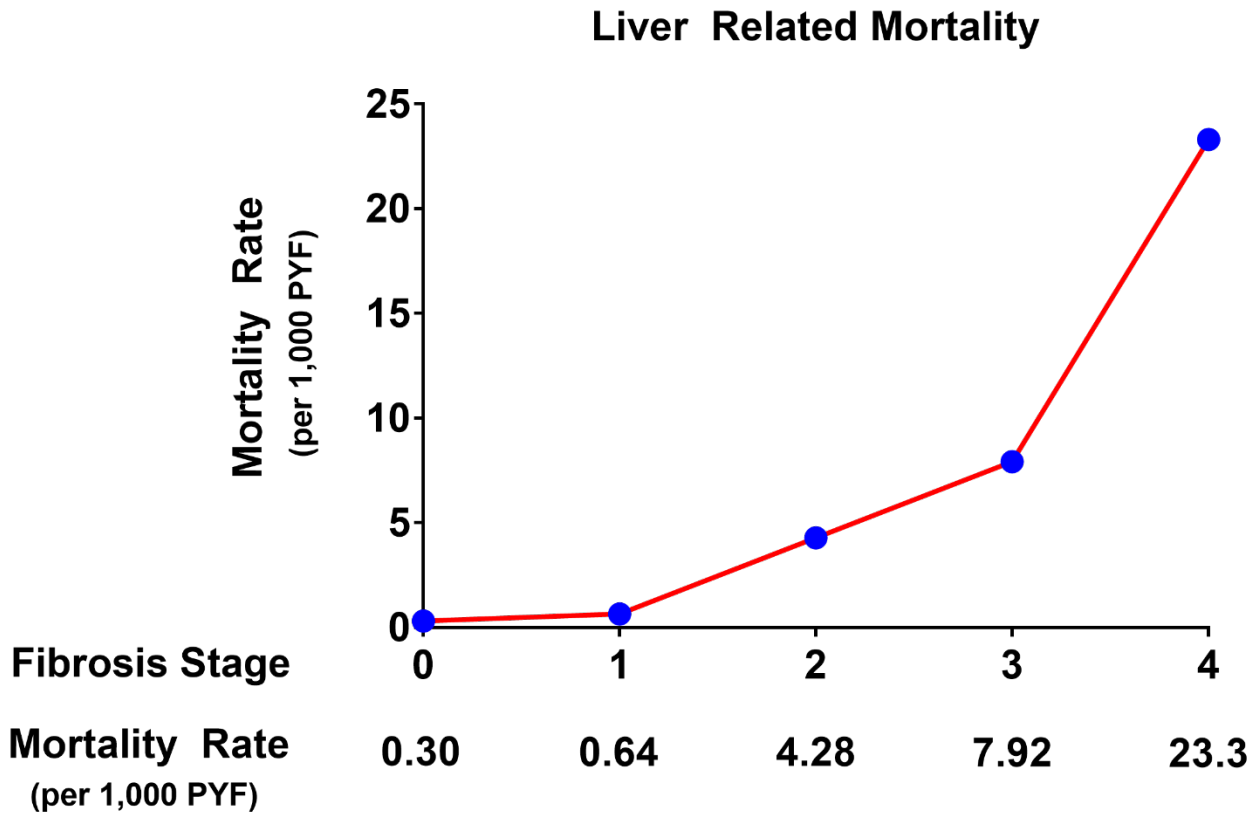
- Presence of advanced fibrosis
- Presence of fibrosis
- Presence of NASH



Loomba Gastroenterology 2015

Quantitative risk of liver mortality by fibrosis stage

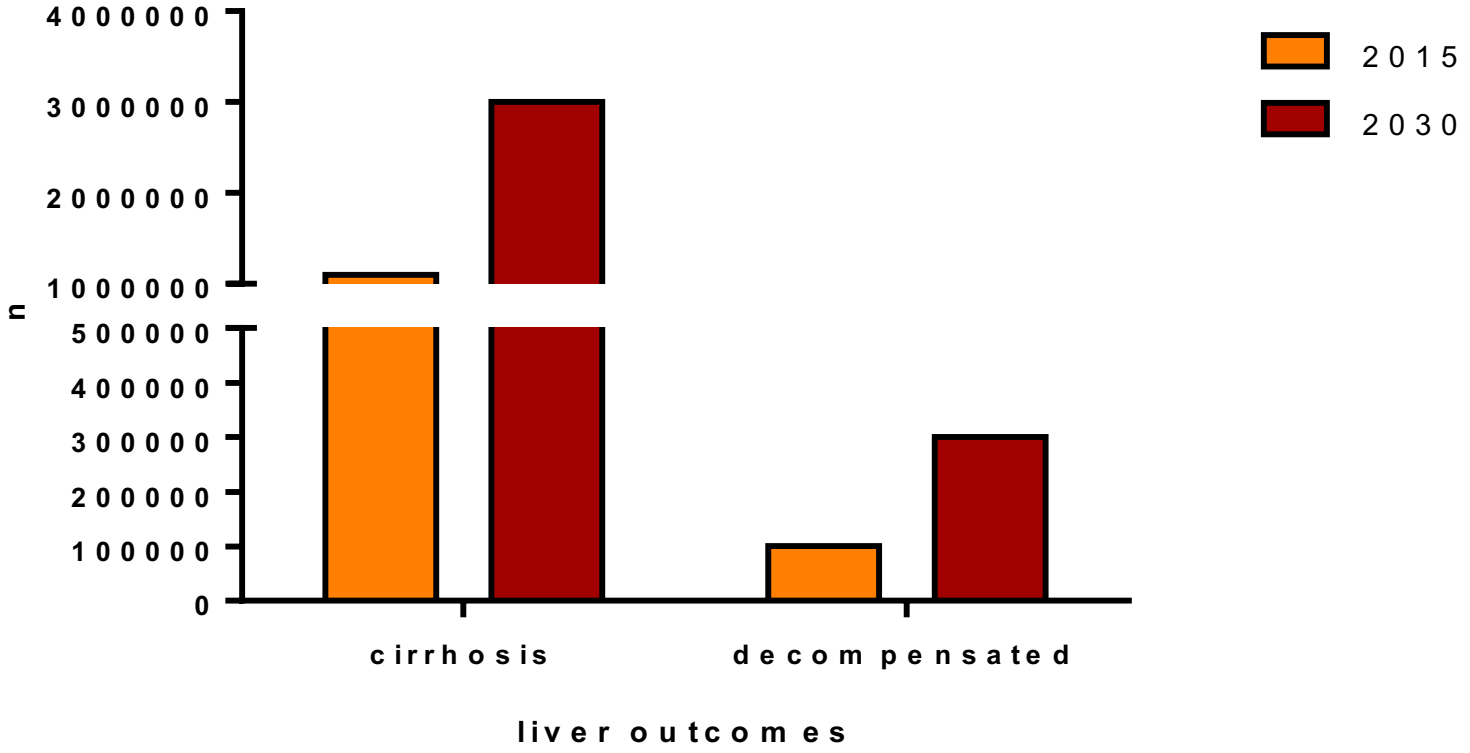
Fibrosis stage is the most important predictor of liver mortality in NAFLD



Dulai et al. Hepatology 2017

The consequences of inaction will be serious:

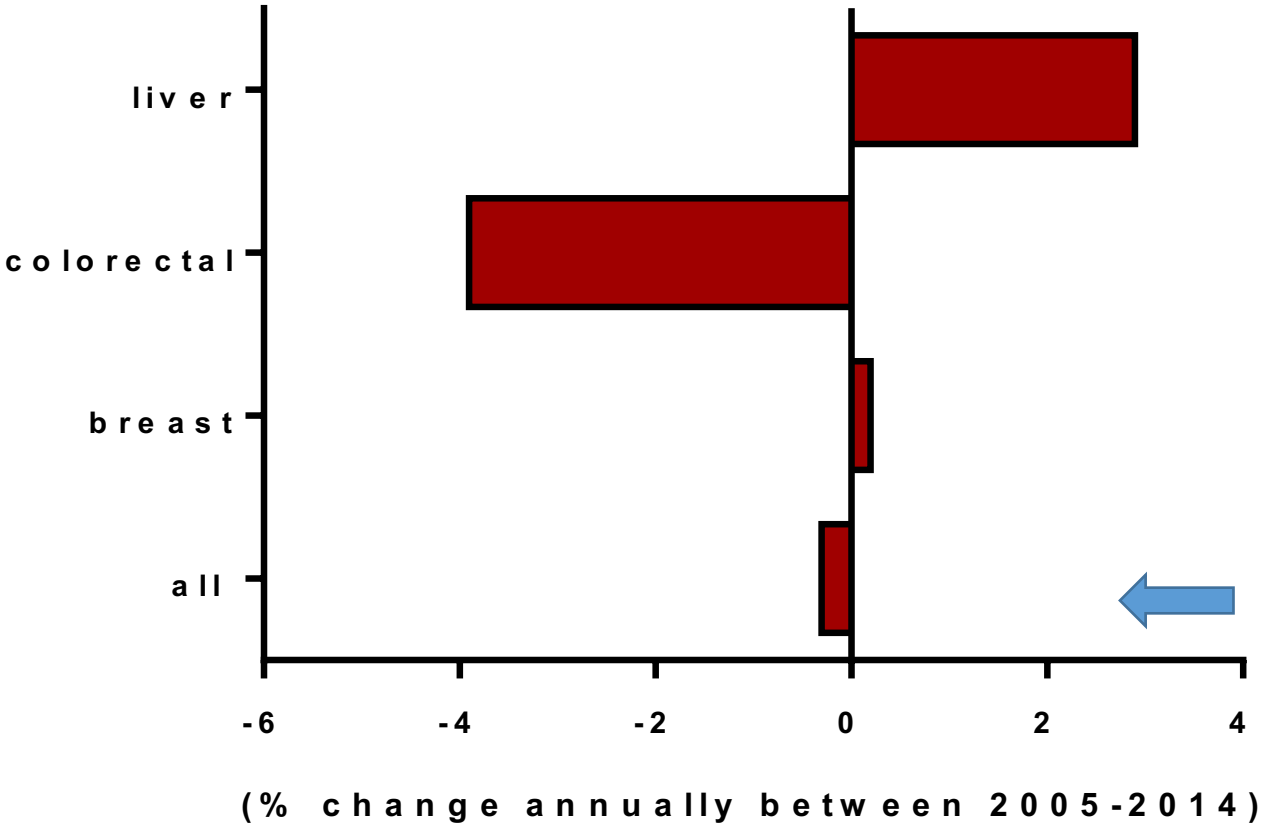
- *Number of those with cirrhosis will triple*
- *Over 300,000 people will have end-stage liver disease*
- *Many of these will be "today's" children*



Estes et al, Hepatology, 2018

NAFLD is driving the national increase in liver cancer

liver cancer rate related to obesity is increasing at 3% annually



Steele et al, MMWR, October 2017

HCC in NAFLD

- Patients with NAFLD-related HCC are:
  - older
  - have a shorter survival time
  - more often have heart disease
  - more likely to die from their primary liver cancer than other HCC patients
- Around 13% of HCC reported from a study of Veteran patients did not have cirrhosis.
  - Among other factors, having NAFLD was independently associated with HCC in the absence of cirrhosis.

Nurses Heath Study and Professional Health Follow-up Study Data

- **Presence of diabetes increased the risk of incident HCC**
  - 5 times in women
  - 3.5 times in men
- **Duration of diabetes increased the risk of incident HCC**
  - > 7 times for duration >= 10 years

Is NAFLD associated with development of non-liver cancers?

HICDA
05710421 Fatty liver
05710431 Steatohepatitis, nonalcoholic

ICD-9-CM
571.5 Cirrhosis of the liver without mention of alcohol
571.8 Other chronic nonalcoholic liver disease
571.9 Unspecified chronic liver disease without mention of alcohol

ICD-10-CM
K75.81 Nonalcoholic steatohepatitis
K76.0 Fatty liver, NOS

N= 7,412

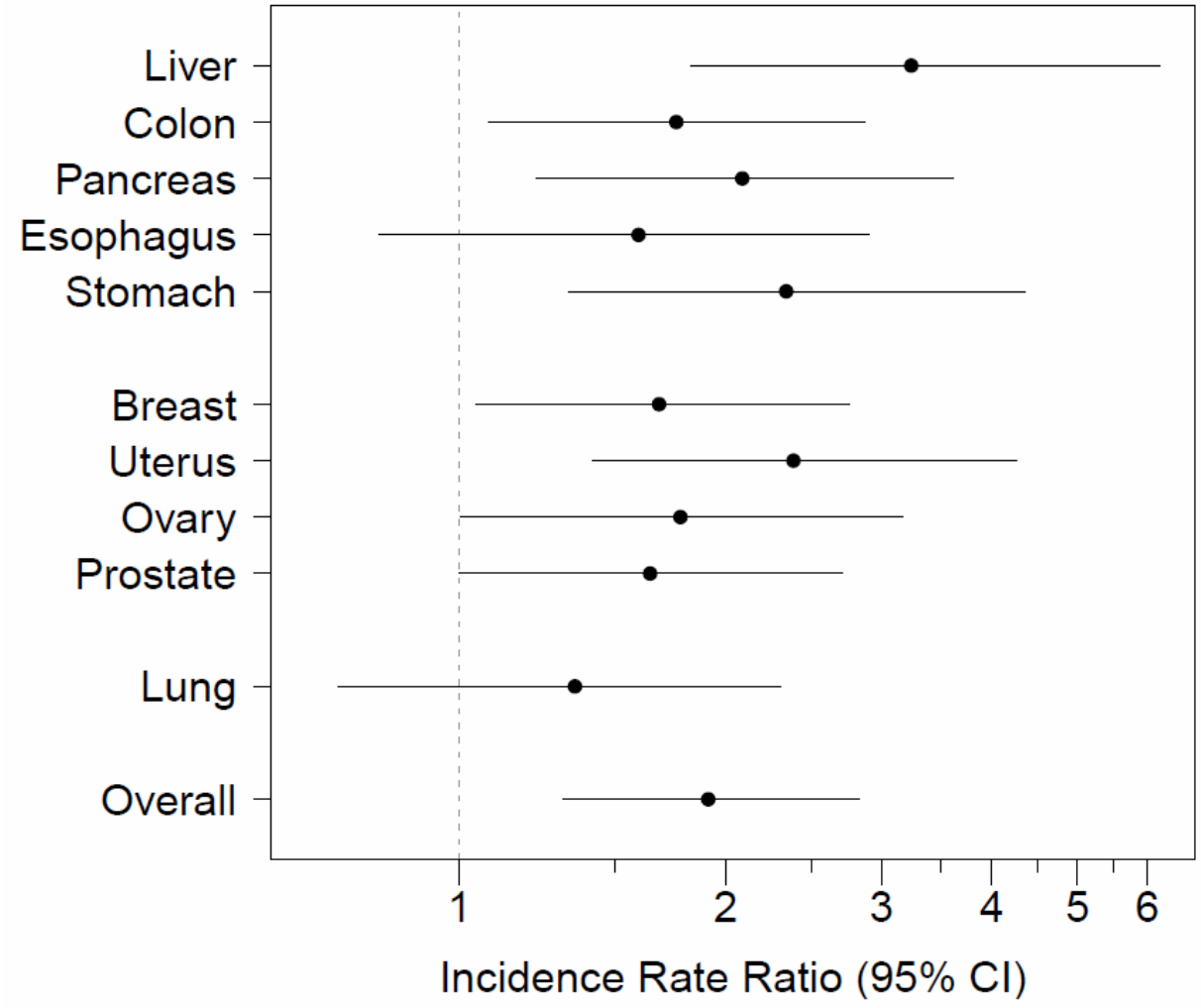
EXCLUDED
N= 2,631

- Hepatitis, viral and autoimmune N= 747
- Alcoholic liver disease N=1,253
- Other liver diseases N=124
- No research authorization N=8
- Inconclusive Olmsted County residency N=340
- Follow-up time <1 year N=159

NAFLD
N= 4,781

Alina Allen, Mayo Clinic

Incidence rate ratios in NAFLD *vs* controls



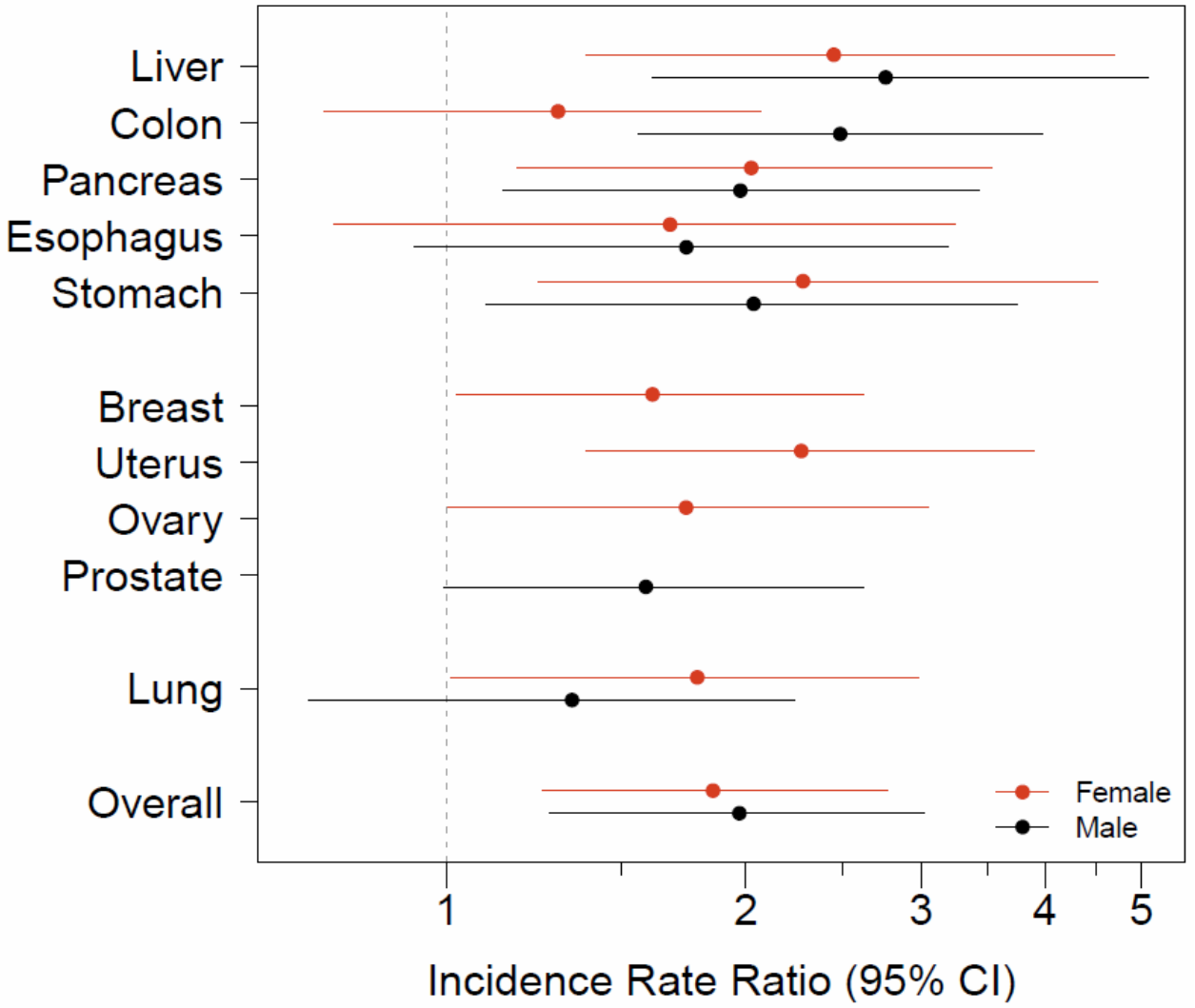
Highest increase in risk:

	RR
Liver	3.24
Uterus	2.39
Stomach	2.34
Pancreas	2.09
Colon	1.76
Overall	1.91

Alina Allen, unpublished, Mayo Clinic

Malignancy risk in men *vs* women with NAFLD

Women	IRR
Liver	2.45
Stomach	2.28
Uterus	2.27
Pancreas	2.02



Men	IRR
Liver	2.76
Colon	2.49
Stomach	2.04
Pancreas	1.97

What do patients with NAFLD die of?

- Patients with NAFLD have increased overall mortality compared to matched control populations without NAFLD.
- The most common cause of death in patients with NAFLD is cardiovascular disease (CVD), independent of other metabolic comorbidities.
- Although liver-related mortality is the 12th leading cause of death in the general population, it is the second cause of death among patients with NAFLD.
- Cancer-related mortality is among the top three causes of death in subjects with NAFLD.

Chalasani, AASLD Practice Guidelines 2018

The confluence of multiple factors in the development of metabolic syndrome and NAFLD

Relatives of patients with NASH cirrhosis have 12-fold increased risk of having advanced NASH fibrosis

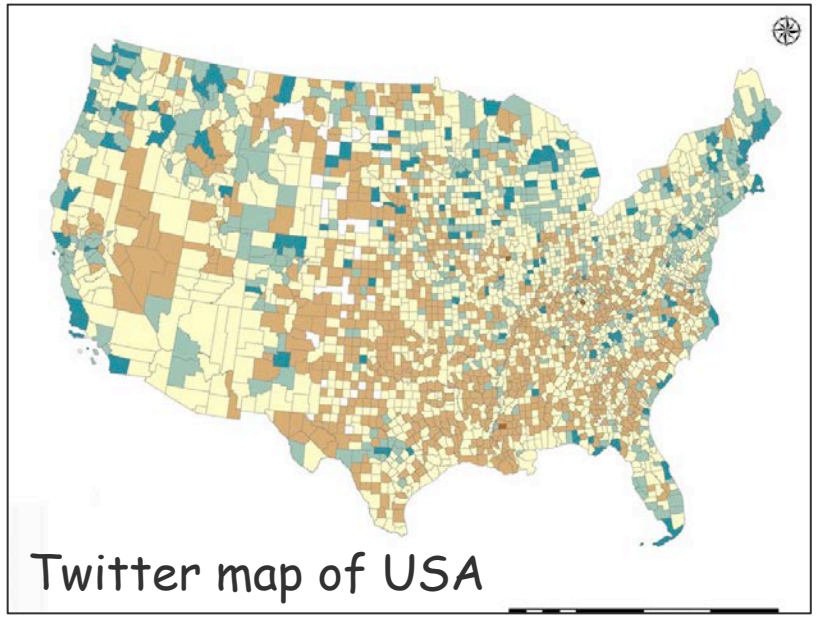
-Caussy et al., JCI 2017

Lifestyle and liver disease

Premature mortality (8025 +/- 2409/100000

Mortality	# of counties	Mean
% obesity	2989	30.7
% diabetes	3220	9.7
% leisure time inactivity	3140	25
% heavy drinking	3140	16

Positive sentiments toward Healthy foods and physical activity→ lower obesity and Mortality



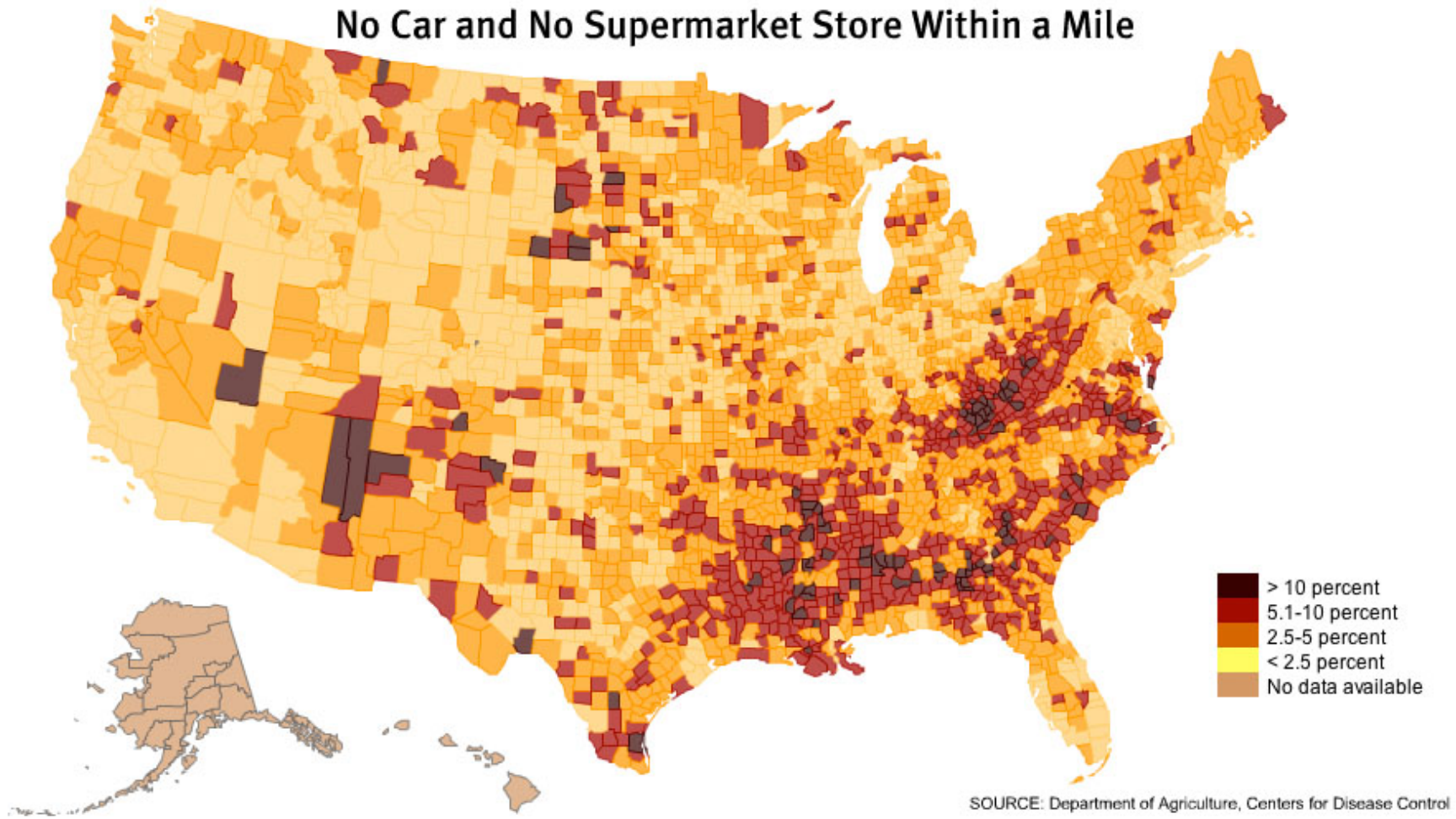
Twitter map of USA

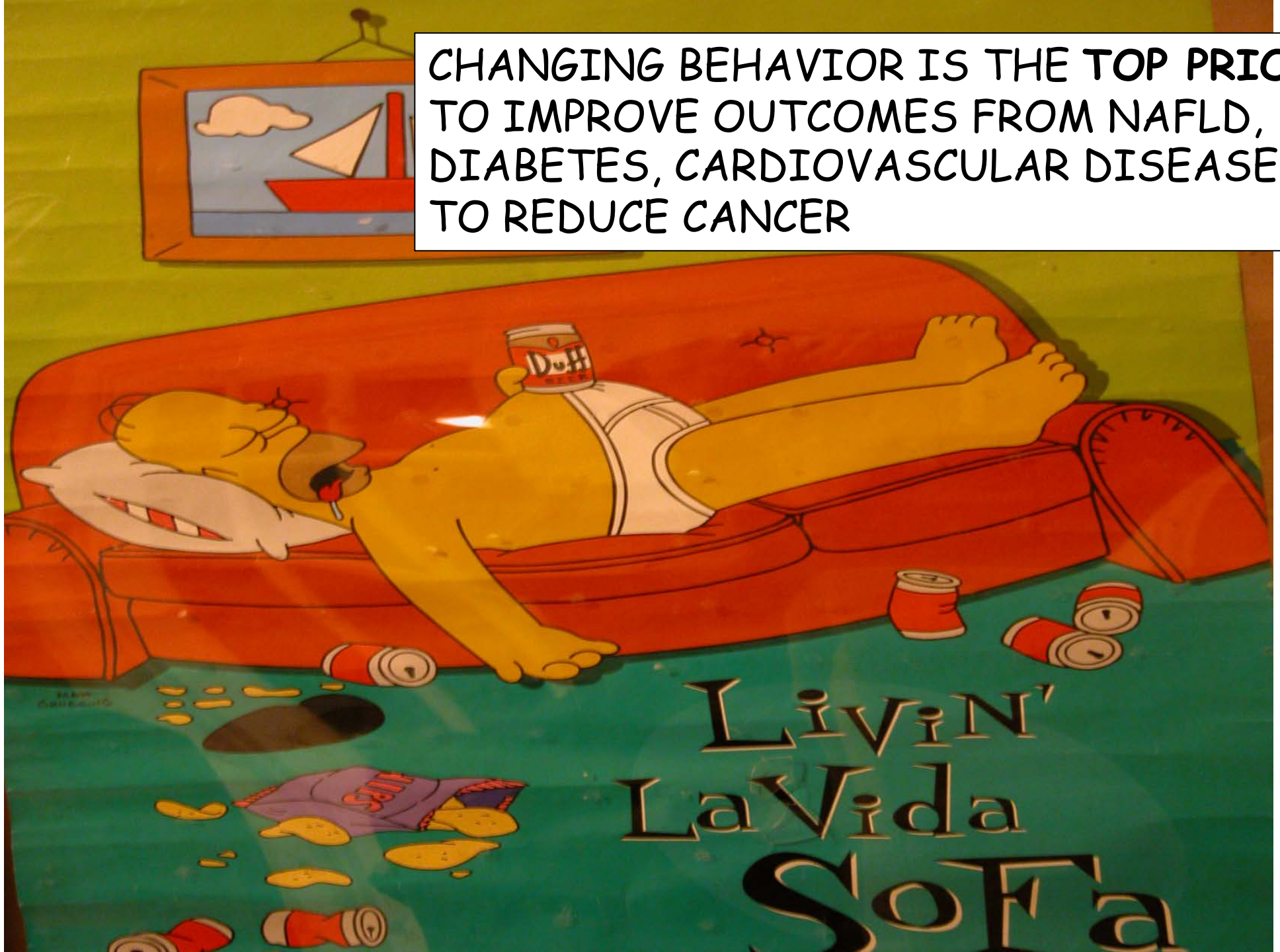
N= 80 million geo-tagged tweets
3140 counties

Physical inactivity and fast foods
Linked to obesity rates per county

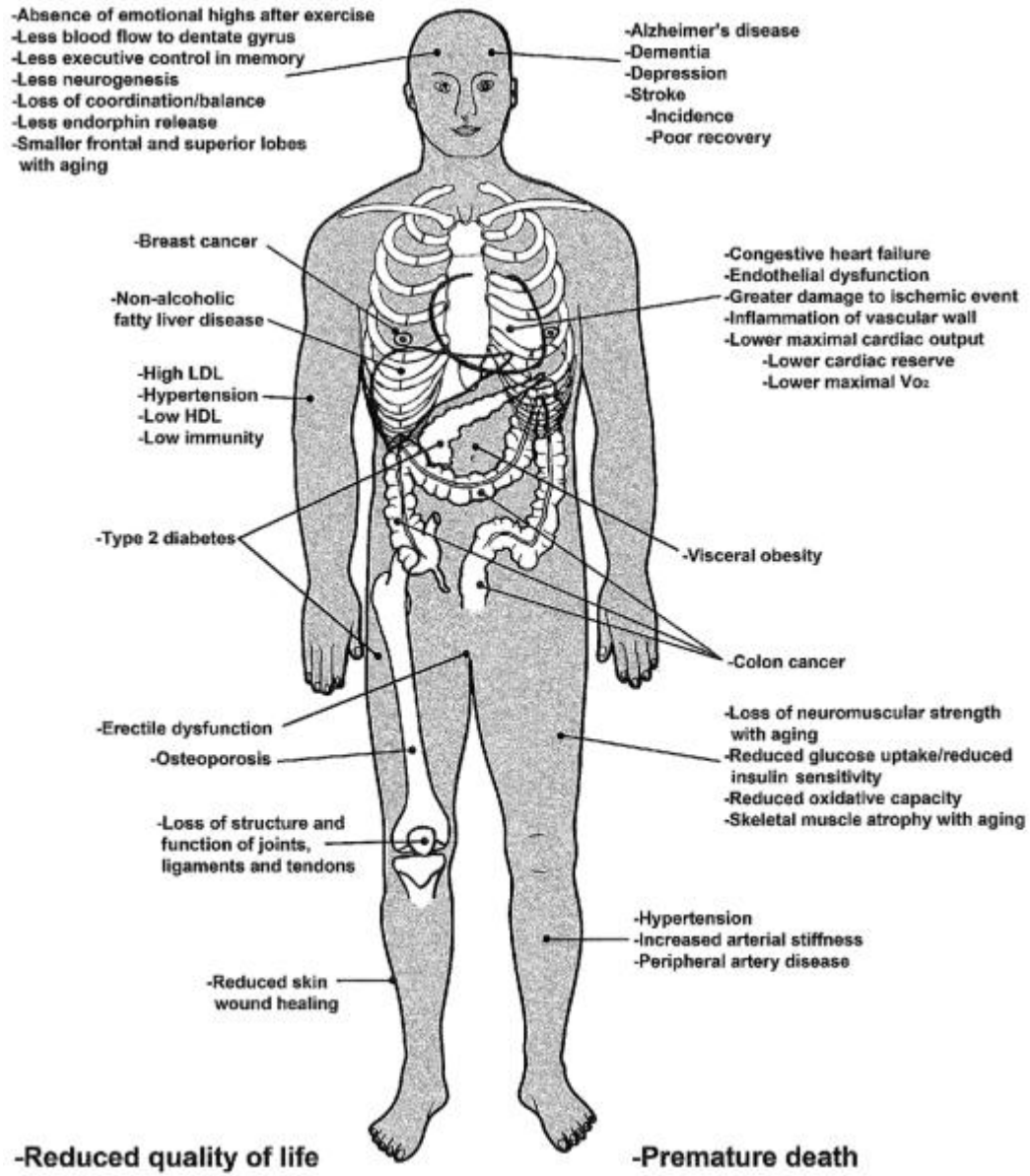
Nguyen et al, Am J Public Health. 2017 Sep 21:e1-e7. doi: 10.2105/AJPH.2017.303993. [Epub ahead of print]

Access to healthy foods is limited in areas of greatest obesity




CHANGING BEHAVIOR IS THE **TOP PRIORITY** TO IMPROVE OUTCOMES FROM NAFLD, DIABETES, CARDIOVASCULAR DISEASE AND TO REDUCE CANCER
Duff
LiviN'
LaVida
SoFa

Physical inactivity is a major cause of chronic disease and ill health



Booth et al, Compr Physiol. 2012

Disordered sleep is common and a driver of outcomes and must be managed

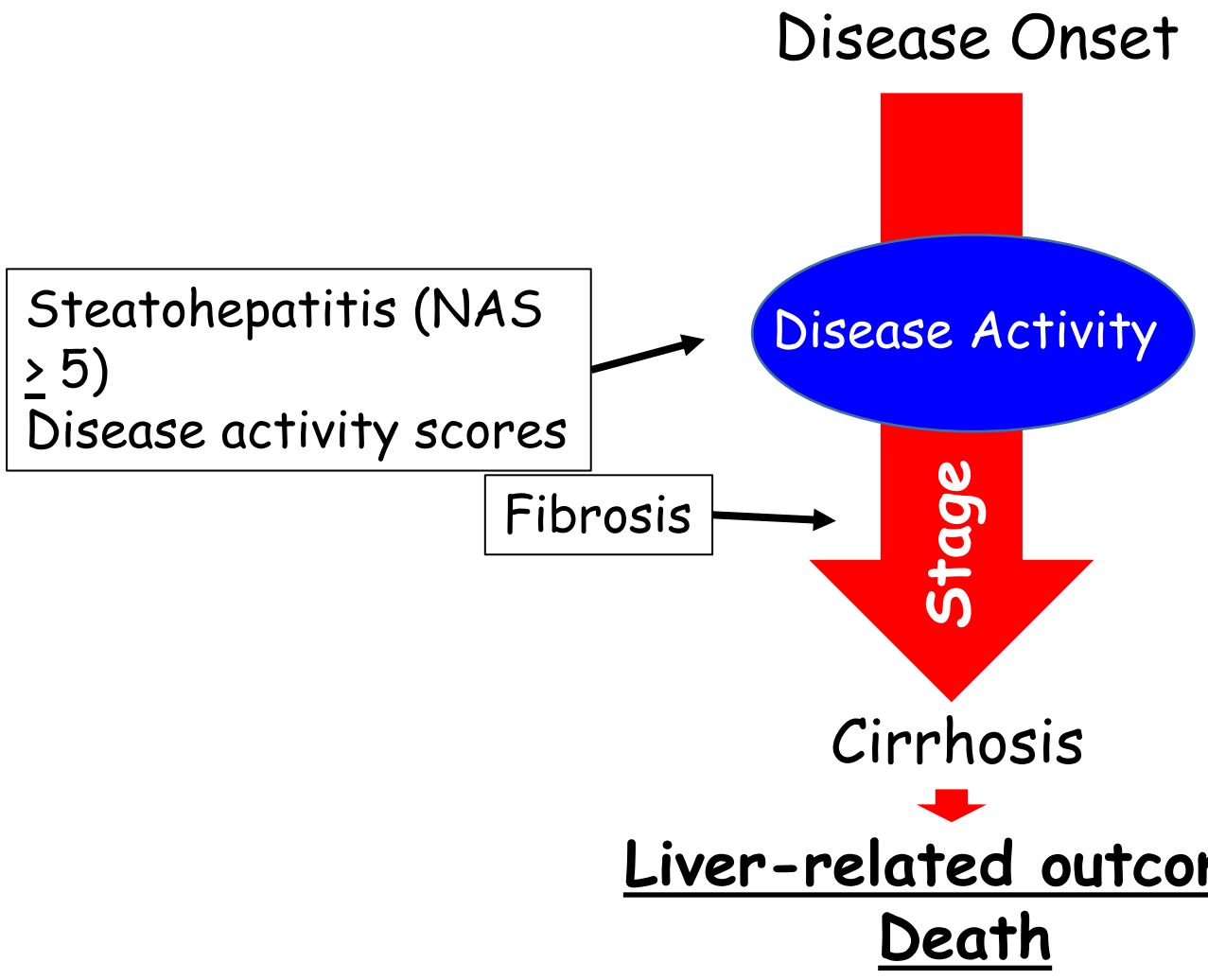
Courtesy- Elizabeth Hickman

Prevalence and severity of NAFLD among caregivers of patients with NAFLD

- 57 caregivers: NAFLD present in 79% (nearly 3-fold higher prevalence than general population).
  - Disproportionately higher obesity, DM, and dyslipidemia.
  - Greater total daily energy intake and consumption of sat FAs and carbohydrates
- Only 12% were aware of their diagnosis of underlying NAFLD.
- Shared environment (dietary intake and physical activity) of cohabitants may have a profound impact on NAFLD.

Siddiqui M, Clin Gastro Hep 2019

Key concepts in approach to treatment of NASH



***In the short term**: improve disease activity and/or fibrosis (surrogate outcome)*

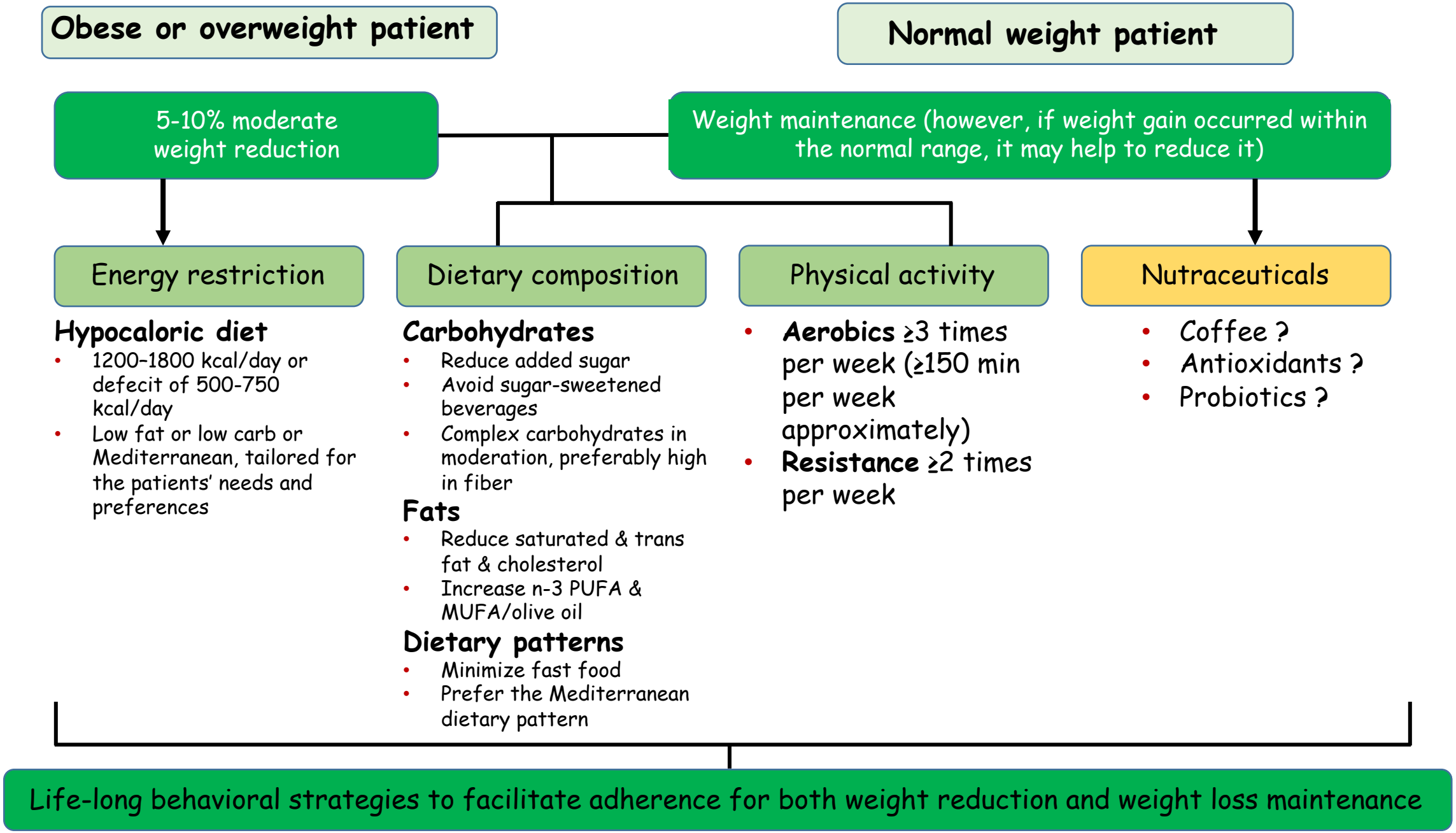
***In the long term**: reduce progression to cirrhosis and clinical outcomes*

May require lifelong Rx like diabetes

Sanyal et al, Hepatology, 2015; 61: 1392-1405

Non-pharmacologic/non-surgical treatments

- Weight loss and increased physical activity are pillars of treatment.
- Modifiable risk factors- soft drinks/fast food:
  - Physicians and dietitians should routinely include questions regarding soft drink consumption as part of the patient's history and advise patients to minimize its consumption.
  - Reducing the consumption of fast food which combines several potential hepatotoxic nutrients, i.e., saturated fat, refined carbohydrates, fructose, industrially produced trans fatty acids, and is low in fiber.
- Recommend weight loss of 5-10%.
  - *A reduction in body weight of 3–5% may improve hepatic steatosis, but more significant weight loss (5–10% body weight) is needed to reduce hepatic inflammation.*
- Very low-calorie diets are inappropriate in liver disease patients who are likely to also be sarcopenic (low muscle mass, low strength).
  - Sarcopenia associated with 2X greater risk of F3-F4 fibrosis.
- The diet of choice should be the one which individuals are able to adhere for years rather than weeks.



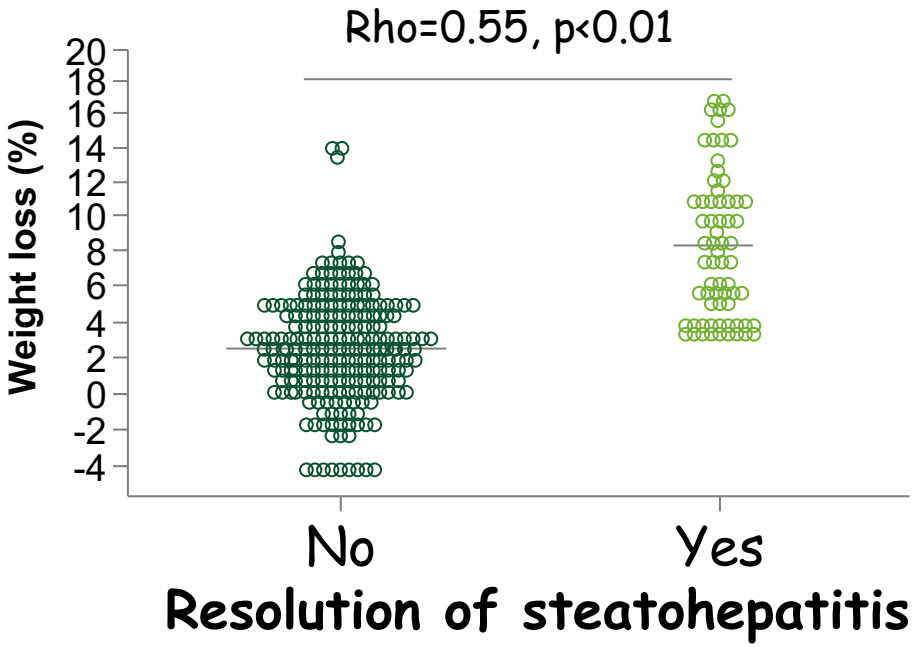
Zelber-Sagi S, Ther Ad Gastroenterol. 2016; 9: 392-407

Diet options and factoids

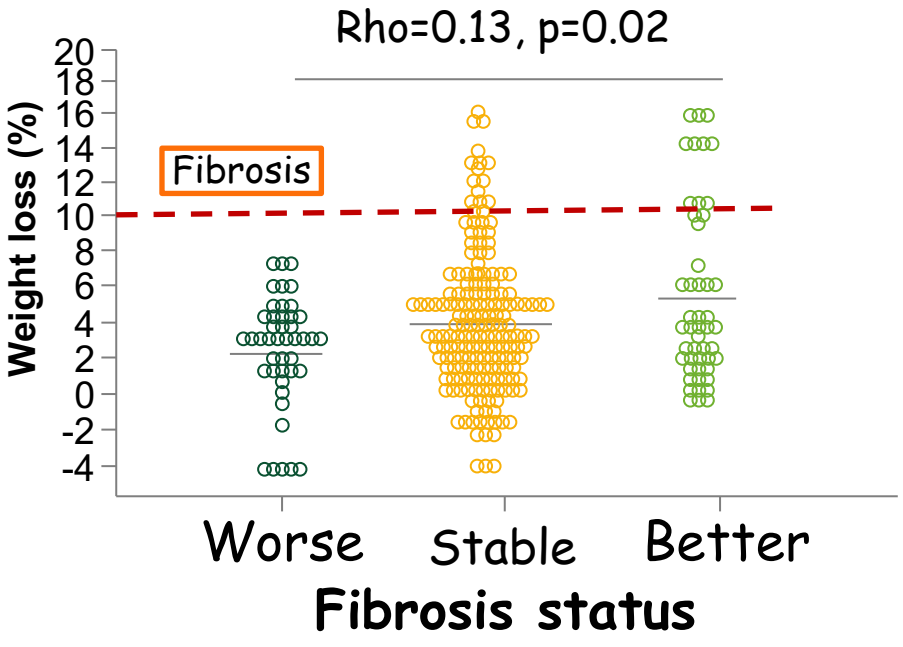
- ***Mediterranean diet, which is high in antioxidants and is anti-inflammatory***. Benefits with increased consumption of high-fiber foods and reduced consumption of refined and/or processed foods.
- ***Paleo Diet.*** Foods that humans ate during the Paleolithic era, which extends from a few million years ago, up to the year 11,000 BC.
- stop eating refined and processed foods, including sugar, but also cereals, dairy and legumes.
  - you can have fruits and vegetables, fish and seafood, any type of food that you could hunt back in the days (but also including grass-fed lean meat), eggs, nuts, seeds,refined oils, and all sorts of fruits and vegetables
  - *Shown to have a significant and persistent effect on liver fat and differed significantly from a conventional LFD at 6 months. This difference may be due to food quality, for example, a higher content of mono- and polyunsaturated fatty acids in Paleo.*
- ***Ketogenic diet*** (fat intake for a 2,000 calories per day diet with a balanced meal plan is between 44 to 78 grams per day ~3X recommended).
  - In humans, KD have been associated with significant reductions in total cholesterol, increases in HDL cholesterol levels, decreases in triglycerides levels and reductions in LDL cholesterol levels. In rodents, ketogenic diet induces hepatic inflammation and NAFLD, but these findings have not been reported in humans.

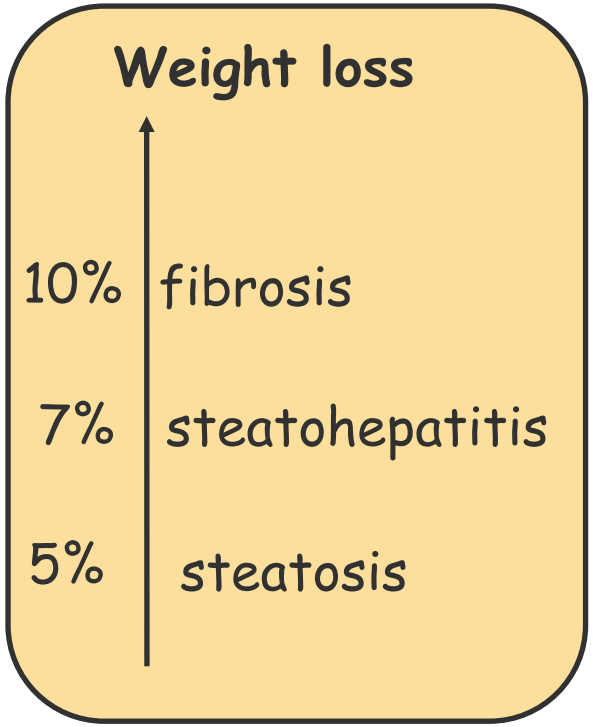
Weight loss (WL) can improve histology (12 month lifestyle intervention)

Correlations between WL and steatohepatitis resolution



Correlations between WL and fibrosis status at the end of intervention





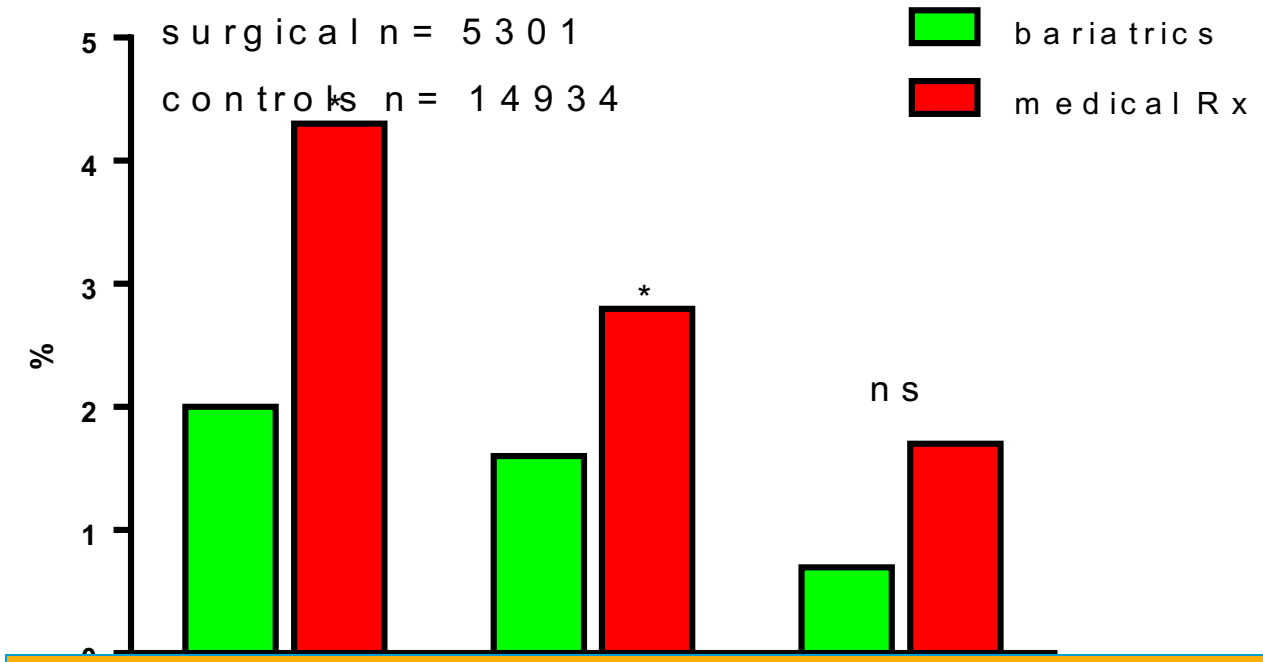
- Weight loss does not guarantee NASH resolution (esp if MetS)
- Fibrosis improvement can occur with less than 10% weight loss

Vilar-Gomez et al, Gastroenterology. 2015 Aug;149(2):367-78

Bariatric Surgery: AASLD Practice Guidance Statements

- Foregut bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH.
- It is premature to consider foregut bariatric surgery as an established option to specifically treat NASH.
- The type, safety, and efficacy of foregut bariatric surgery in otherwise eligible obese individuals with established cirrhosis due to NAFLD are not established.

Bariatrics: a viable option for some patients



Histological resolution:

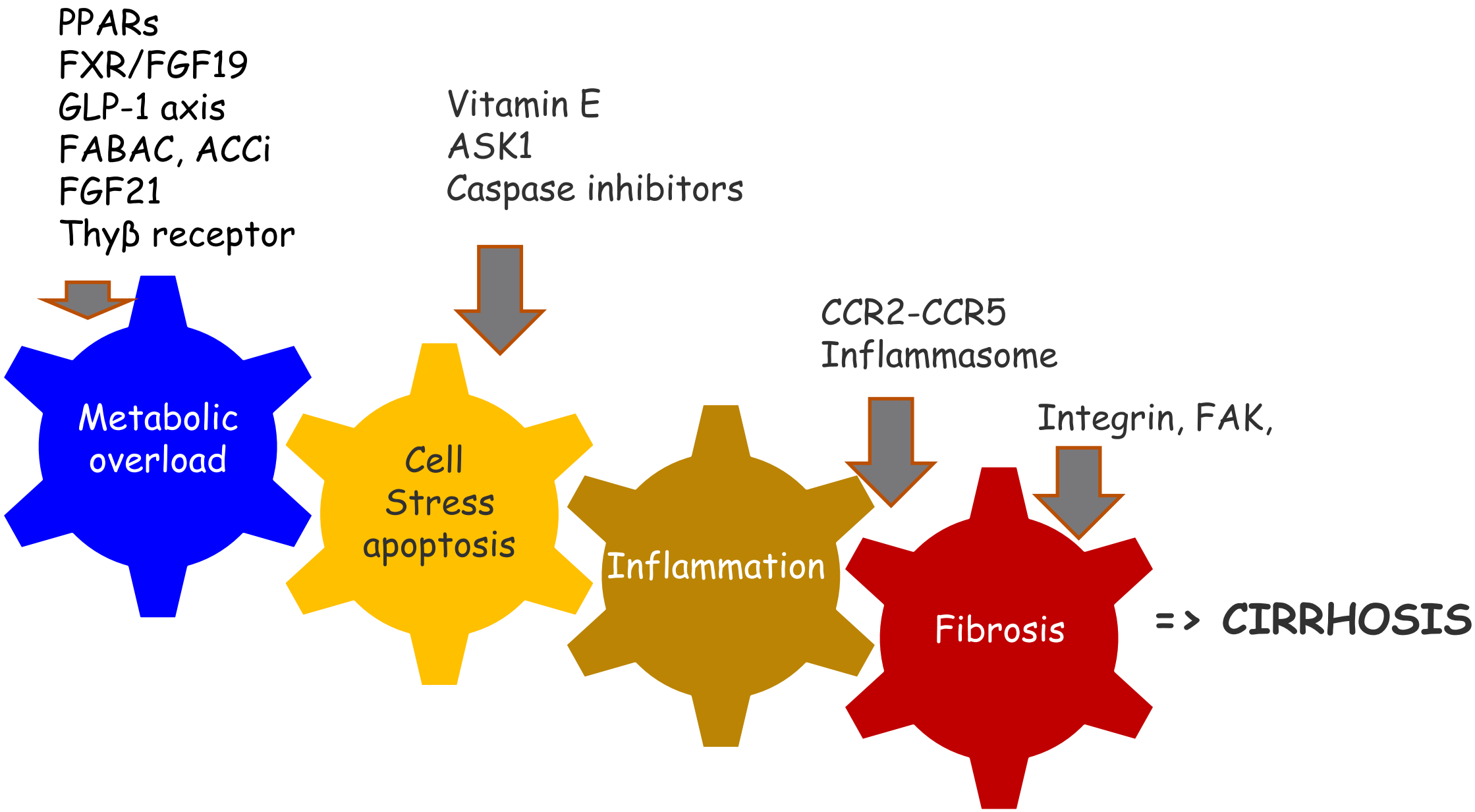
- Steatosis resolution: 66%
- Lob Inflammation: 50%
- Ballooning: 76%
- Fibrosis: 40%
- 12% had worsening fibrosis

Roux-en-Y Gastric Bypass (RYGB) is better than gastric sleeve in reversing advanced hepatic fibrosis, the latter has 45% chance fixed fibrosis despite weight loss/metabolic improvement; findings underscore importance of staging prior to surgical choice. AASLD Oral Presentation 2019

Statins can be used safely in patients with NAFLD

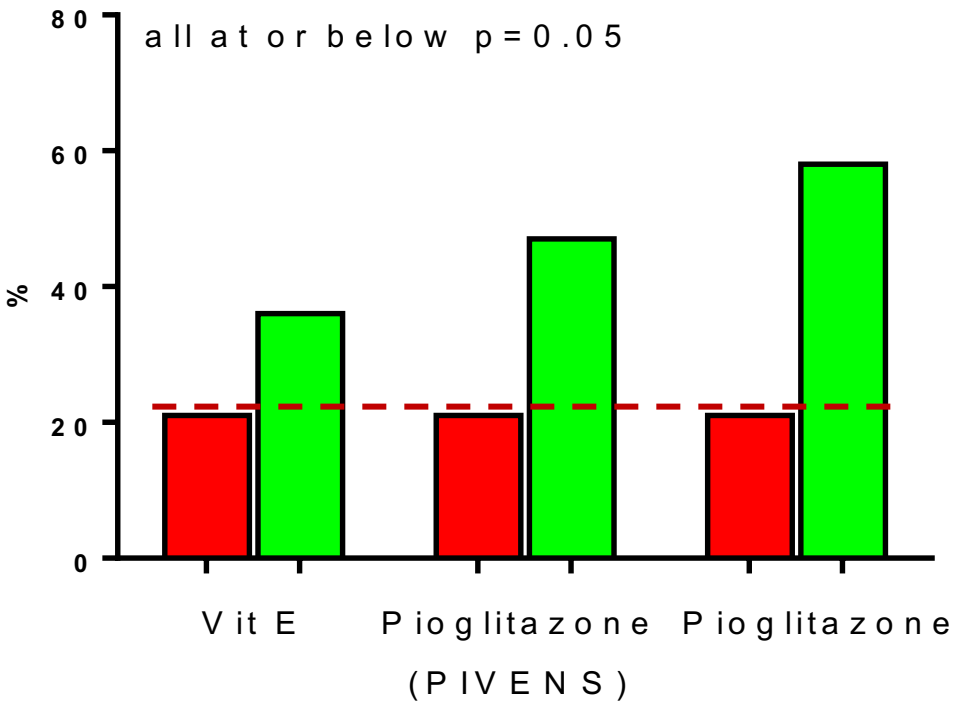
- Patients with NAFLD are important targets for statins
- Risk of serious hepatotoxicity from statins is very rare
- Patients with underlying liver disease are not at higher risk for statin hepatotoxicity
- Case series have shown histological improvement in NASH
- Fish oil is probably the first choice to treat hypertriglyceridemia

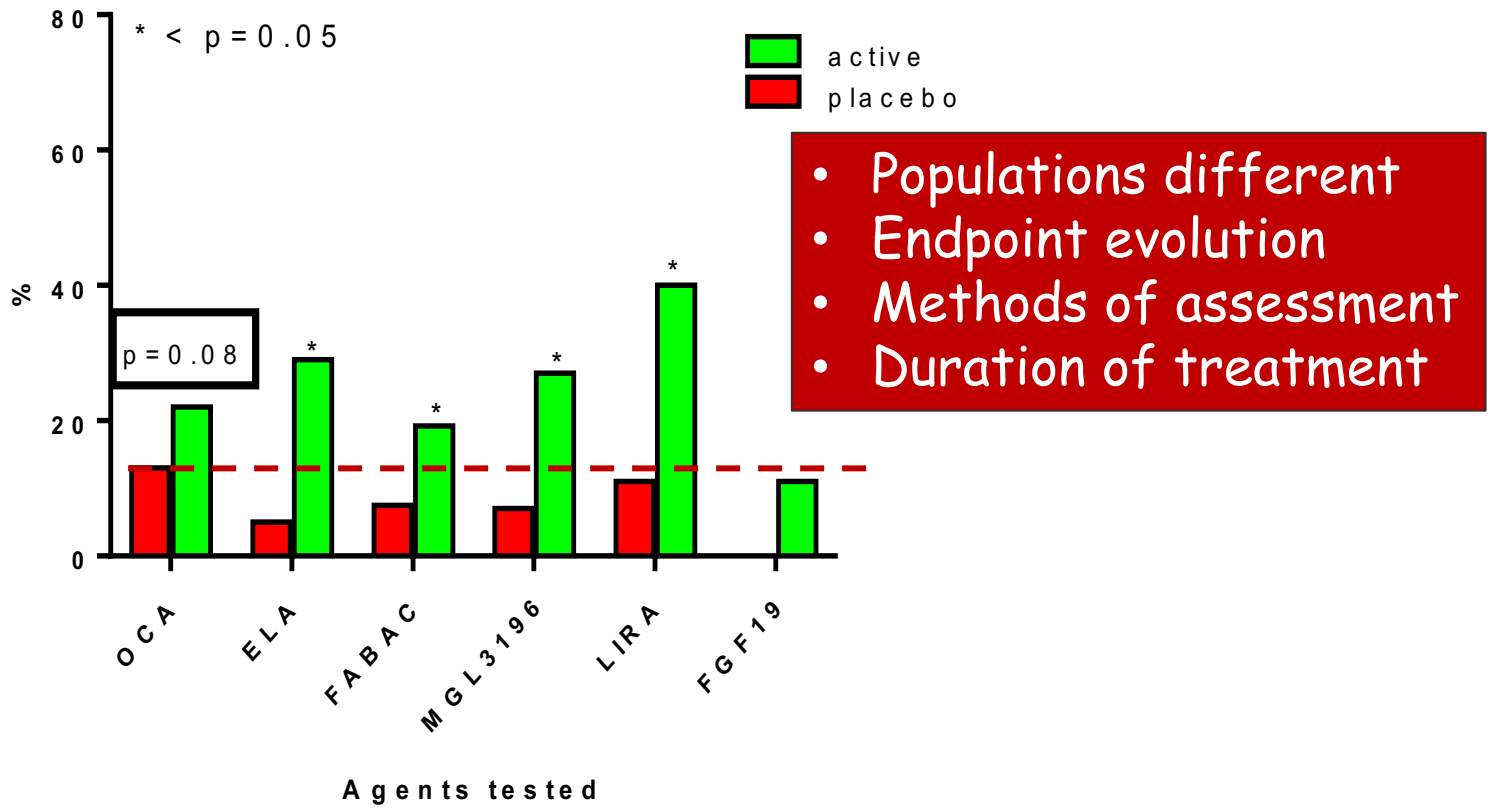
Chalasani N. Hepatology 2005; 41:690-695; Hepatology. 2007;46:1453-63



Adapted from Friedman et al, Nature Med 2018

Current status of drug treatment: Impact on NASH resolution





- Populations different
- Endpoint evolution
- Methods of assessment
- Duration of treatment

Sanyal et al, NEJM 2010; Cusi et al, Ann Intern Med 2016; Tetri et al, Lancet 2015; Ratziu et al, Gastro 2016, Armstrong et al, Lancet 2016; AASLD late breakers LB 5, LB22,

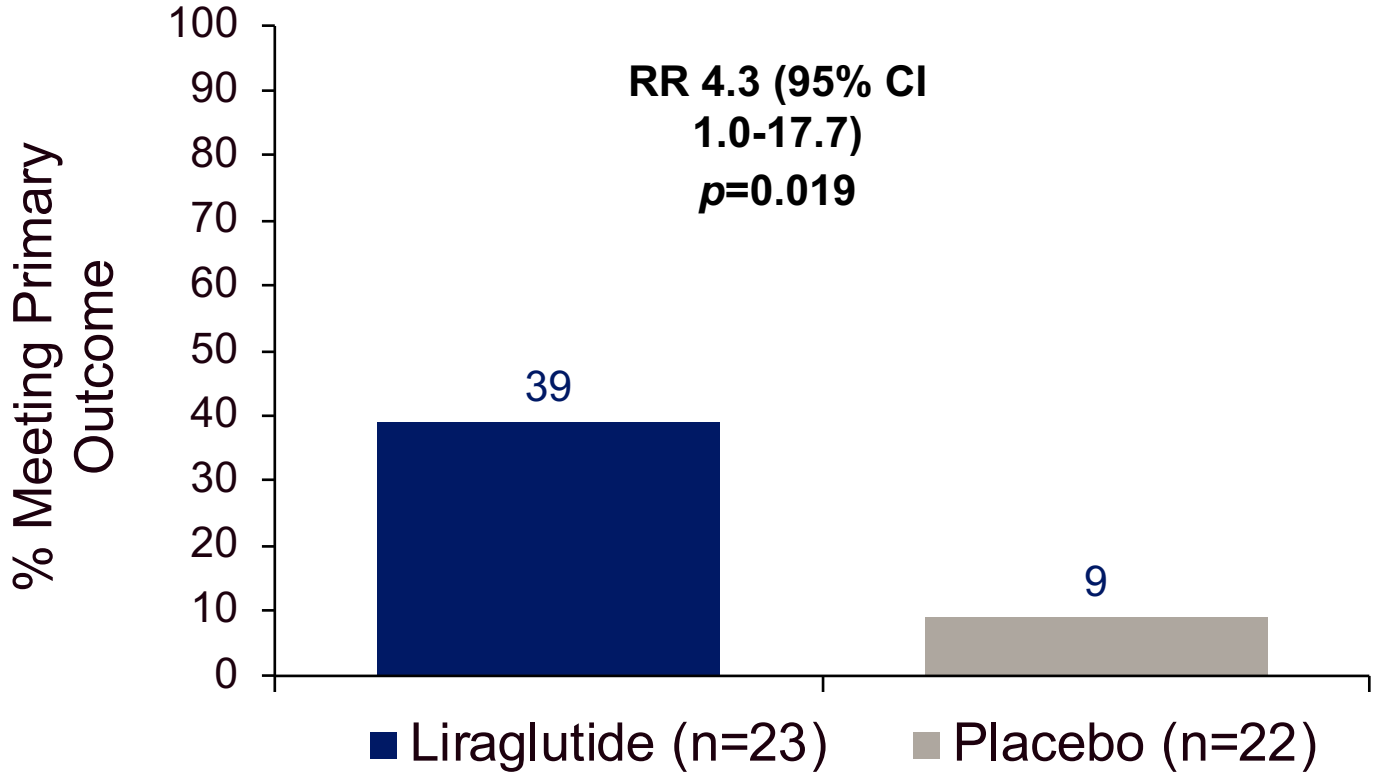
Primary Outcome: Resolution of NASH with no worsening in fibrosis

Glucagon like peptide (GLP-1)

- Liraglutide SQ injections

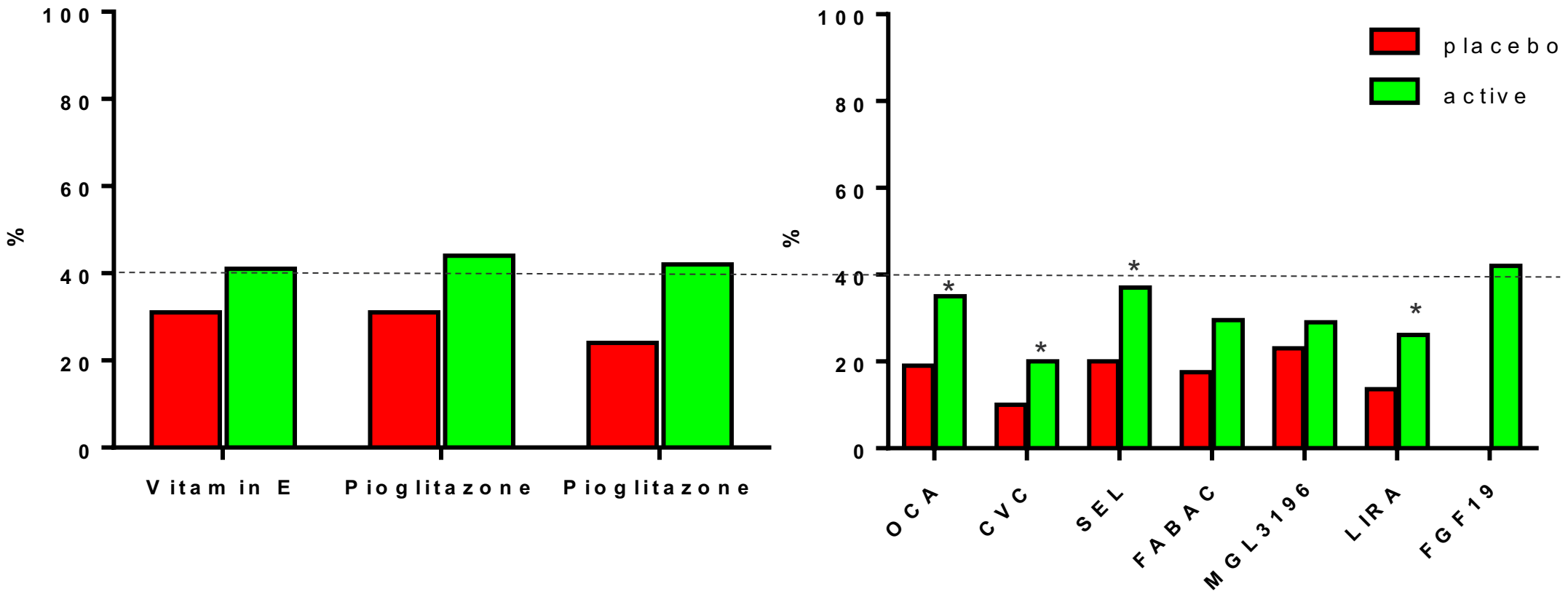
Inc weight loss
Decrease HbA1c
No change in overall NAFLD score

Semaglutide in phase III

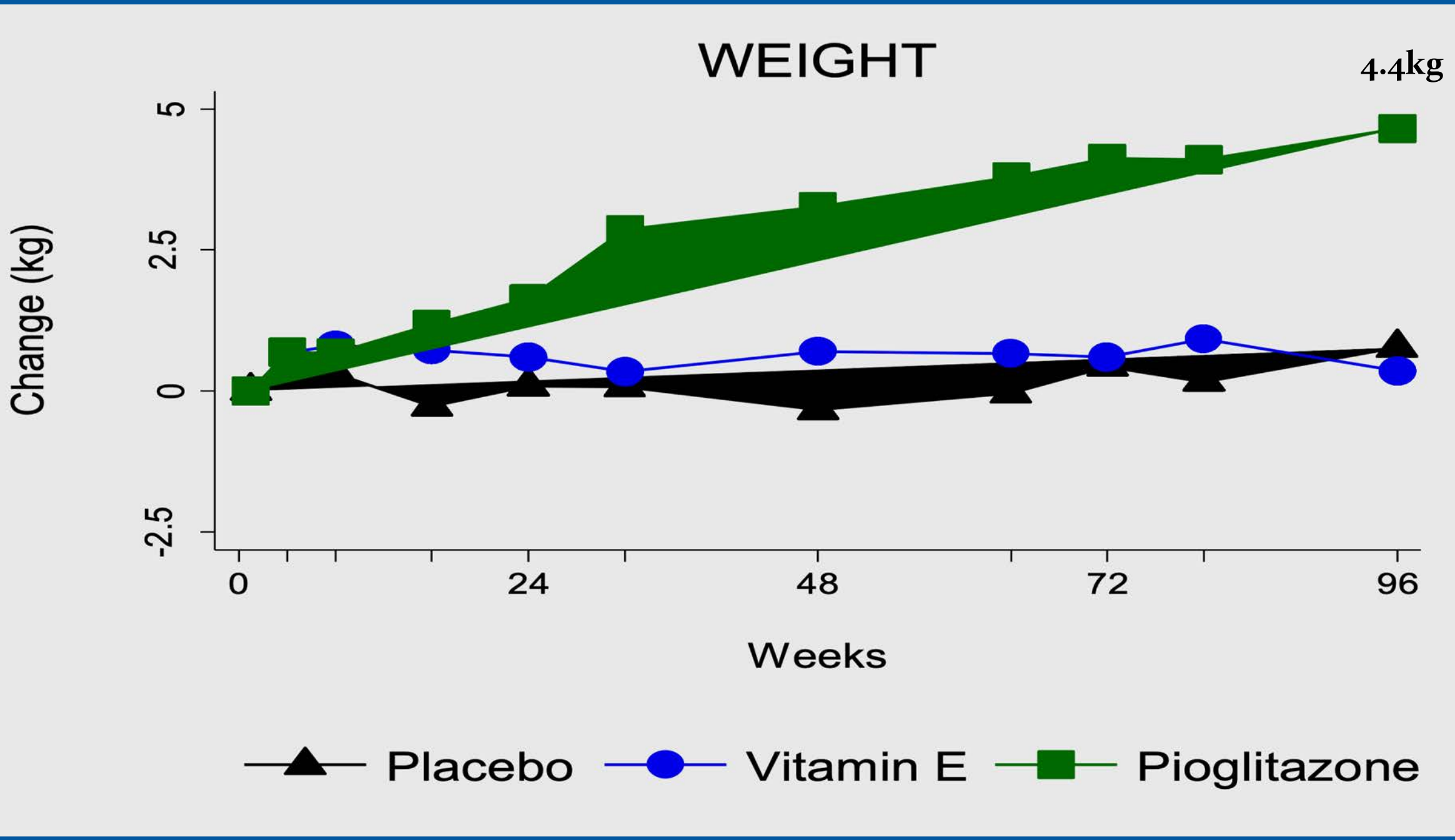


Response similar in patients with or without T2DM

Fibrosis improvement with current agents

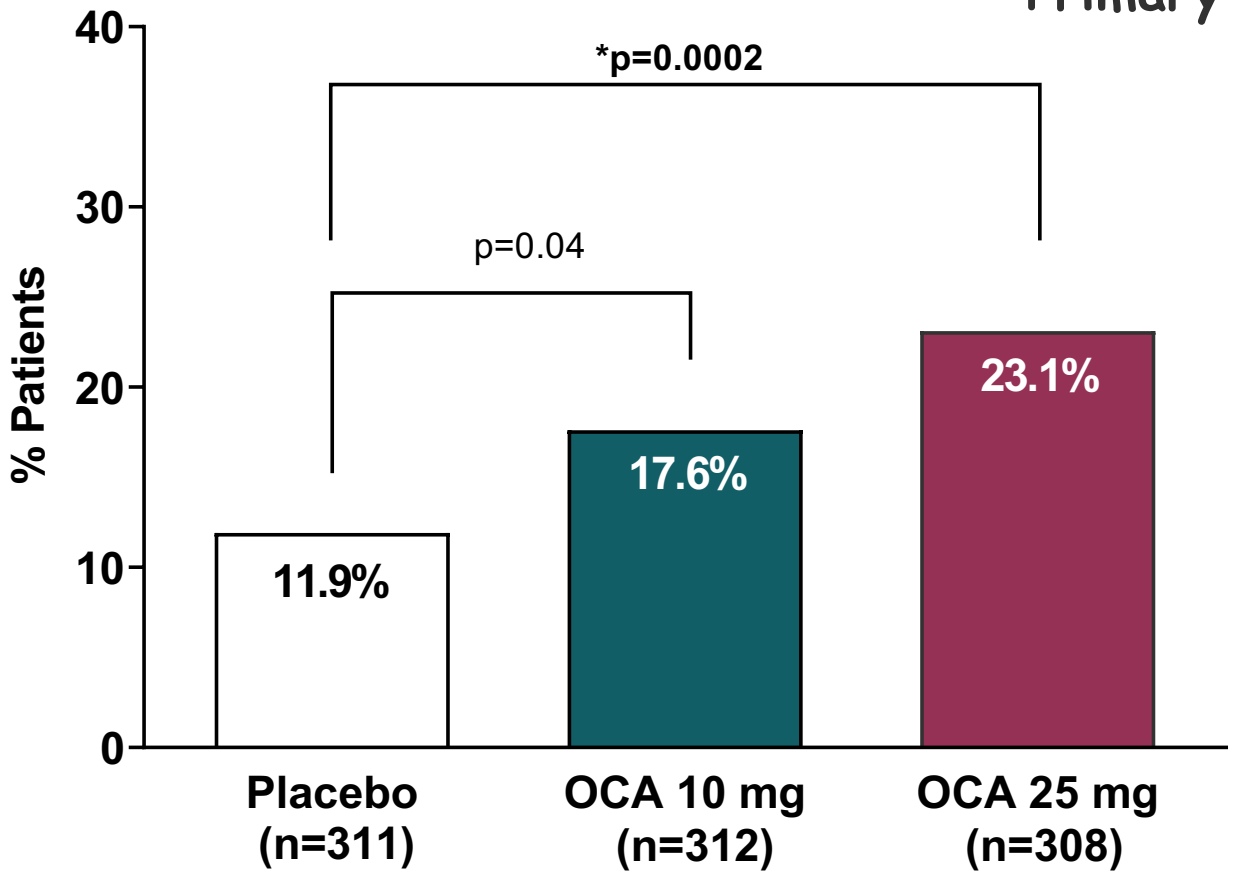


Sanyal et al, NEJM 2010; Cusi et al, Ann Intern Med 2016; Tetri et al, Lancet 2015; Ratziu et al, Gastro 2016, Armstrong et al, Lancet 2016; AASLD late breakers LB 5, LB22,


WEIGHT
4.4kg
Change (kg)
5
2.5
0
-2.5
0
24
48
72
96
Weeks
Placebo
Vitamin E
Pioglitazone

Fibrosis improvement by ≥1 stage with no worsening of NASH

Primary Endpoint: ITT Population, N=931



Obeticholic acid, synthetic derivative of Primary human bile acid, chenodeoxycholic Acid (72 wks)

Primary endpoint definition: fibrosis improvement by ≥1 stage (NASH CRN) with no worsening of NASH (defined as no worsening of hepatocellular ballooning, lobular inflammation or steatosis).
Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 interim analysis.
*Statistically significant in accordance with the statistical analysis plan as agreed with the FDA. All other p values are nominal.

REGENERATE
NASH FIBROSIS STUDY

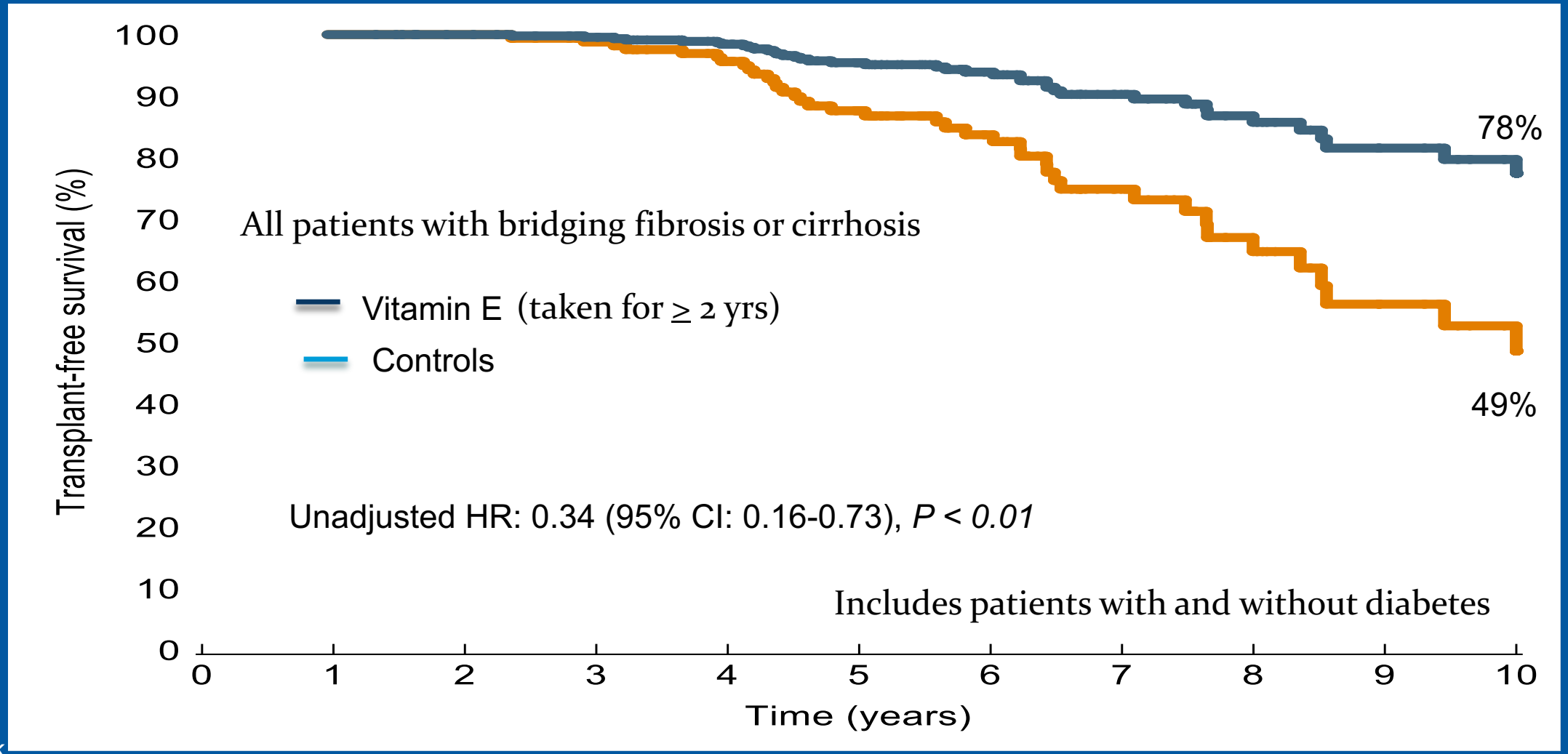
Vitamin E in NASH

- In non-diabetic, non-cirrhotic adults with NASH: Vitamin E 800 IU/day (96 wks) leads to greater resolution of NASH and significant decrease in the NAFLD activity score.
  - No improvement in fibrosis.

- In children with NASH: Vitamin E 800 IU/day led to greater resolution of NASH (25% vs 11% placebo, p=0.006) and significant decrease in the NAFLD activity score (p=0.02).
  - No improvement in fibrosis.

Sanyal, et al. N Engl J Med 2010; 362:1675-1685
Lavine J, et al, JAMA 2011: 305:1659-1668

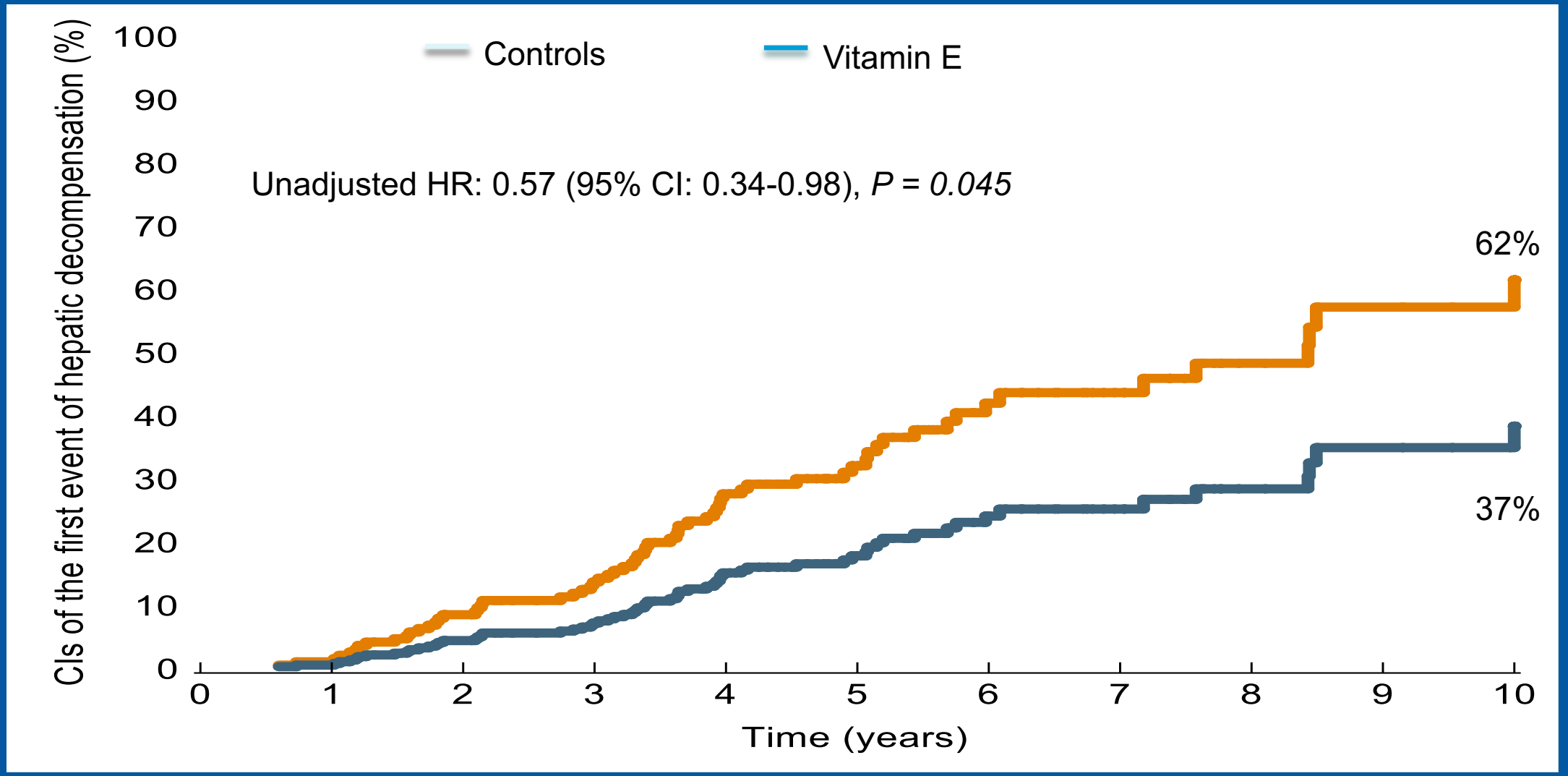
Long-term vitamin E effect on transplant-free survival



No. at risk										
Vitamin E	90	89	84	77	67	55	38	21	13	10	8
Controls	90	90	89	85	76	55	41	29	19	12	8

Vilar-Gomez E, Chalasani N, et al. Hepatology 2019 (Epub)

Long-term vitamin E effect on hepatic decompensation



No. at risk											
Vitamin E	90	88	75	68	55	43	26	19	12	9	6
Controls	90	90	83	74	54	34	20	15	8	5	5

Vilar-Gomez E, Chalasani N, et al. Hepatology 2018 (*in press*)

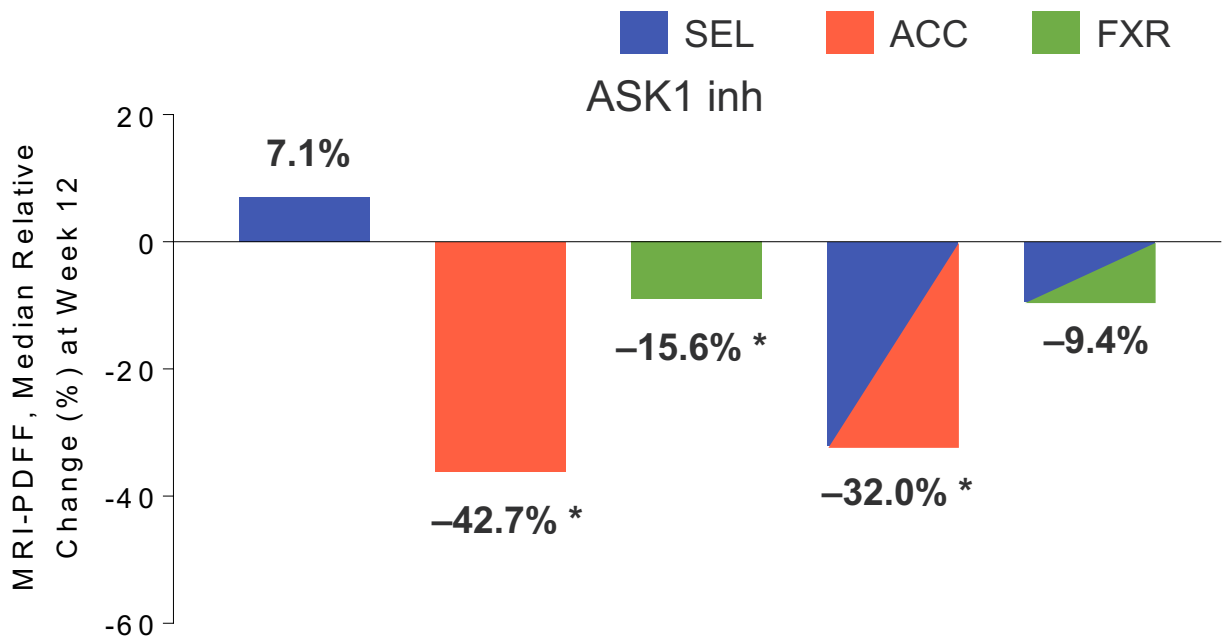
Many other agents appear promising

PHARMACOTHERAPY FOR NAFLD						
		% ≥ 30% RR Liver Fat (highest dose)	**Weight**	**HbA1C**	**Lipids**	**Adverse Events**
Cotadutide	GLp-1/glucagon R dual agonist, 26W	↓ALT/AST ↓NIT score	↓	↓	↓	GI AEs and HA
Licofliflozin	SGLT 1/2 inhibitor, 12W	67%	↓	↓	NA	Diarrhea
Tropifexor	FXR agonist, 12W	65%	↓	↓ IR	↑ LDL	Pruritus
Saroglitazar	PPARa/y agonist, 16W	41%	—	↓	↓	NO SAEs reported
PF-05221304	Liver-targeted ACCI, 16W	90%	NA	↓ in DM	↑TG, ApoB, ? SDLDL	transient ↑ ALT, AST

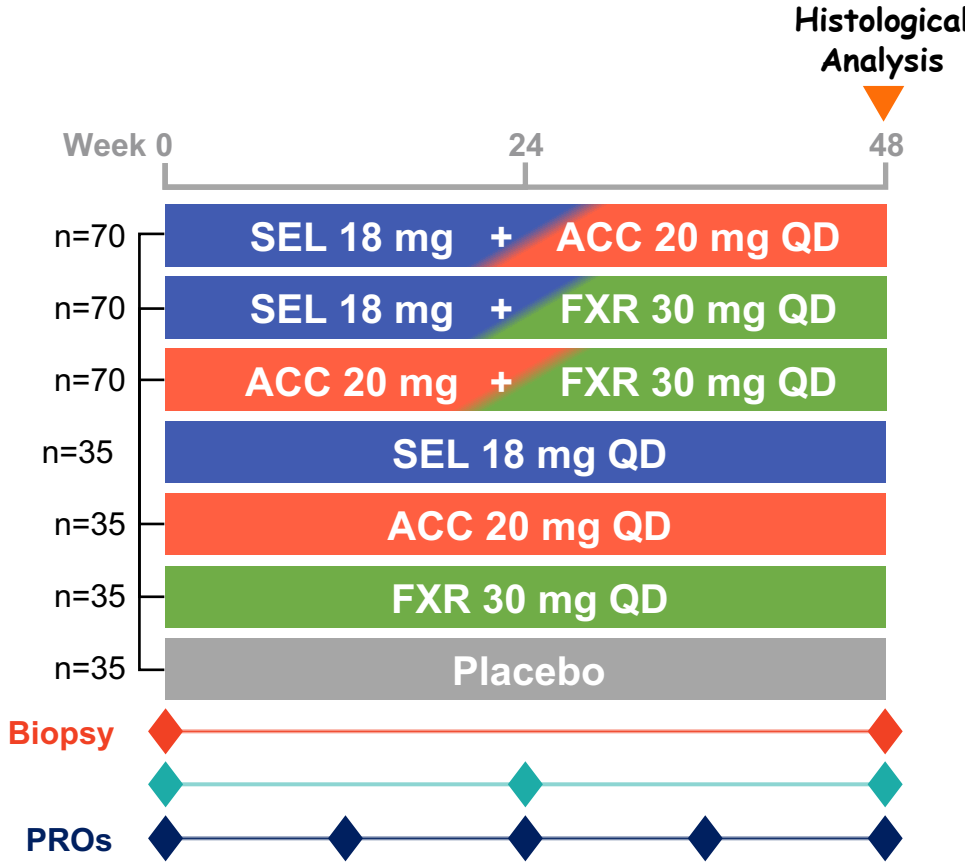
AASLD, November 2019

Leveraging varying mechanisms to build synergy

* p<0.05 for comparison of week 12 vs. baseline by Wilcoxon signed-rank test.



A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Selonsertib, Firsocostat, Cilofexor, and Combinations in Subjects With Bridging (F3) Fibrosis or Compensated Cirrhosis (F4) Due to NASH



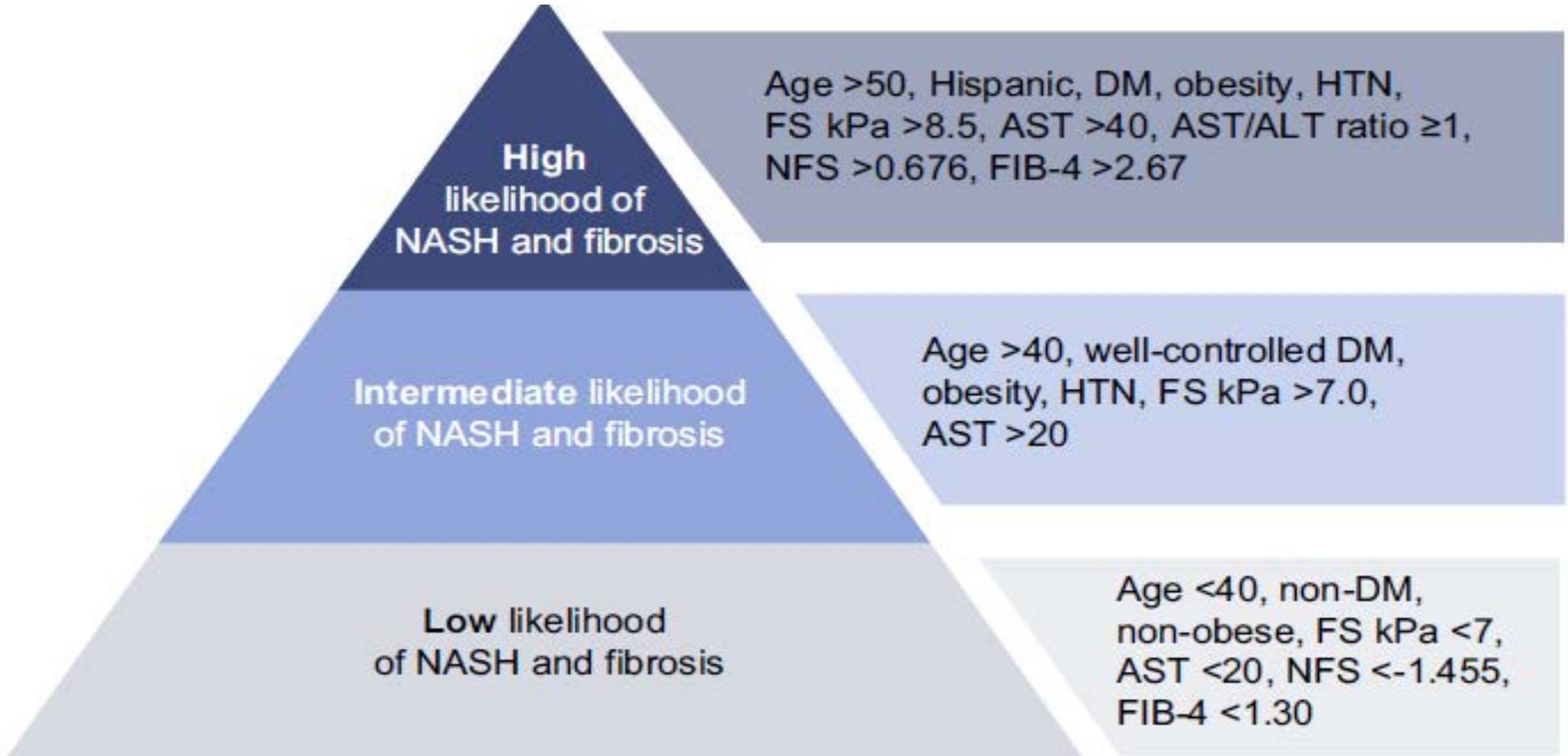
ATLAS trial- NASH F3/4

Lawitz et al, EASL 2018, courtesy Rob Myers

Summary

- NAFLD is the most common cause of liver disease in the Western hemisphere.
- Screening recommendations are likely to change as new therapies are developed.
  - First line therapies: Weight loss, vitamin E and insulin sensitizers
  - Noninvasive biomarkers and approaches needed to monitor disease progression and response to therapy.
    - Sampling of stool microbiome and peripheral adipose tissue in lieu of liver biopsy are emerging
- Cancer and cardiovascular disease are the most common causes of death in NAFLD.
  - Death from liver disease affects 1-2% of those with NAFLD.
- Many exciting drugs in the pipeline.
  - Phase III: OCA, elafibrinor (*PPAR*), cenicriviroc (*CCR2/5 antagonist*), selonsertib (*ASK1 inh*)
  - Leveraging multiple mechanisms and targets may lead to greatest synergistic effect.

Pre-screening criteria for clinical trials



Konerman, M, J. Hepatology 2017

STRENGTHS	WEAKNESSES
• NASH resolution up to 40-50% • Promising repurposed drugs • General consensus on endpoints and case-definitions	• Majority do not resolve NASH • No drug shown to prevent OR reverse cirrhosis
OPPORTUNITIES	**THREATS**
• Many targets • Drugs available for repurposing • Liver forum allows industry-FDA-academic cross talk to innovate	• Challenges in histological assessment • Variable placebo response • Seesaw effect in natural course • No pathway to a cure//duration of Rx

Courtesy, Arun Sanyal

Take Home Messages

- Exclude competing etiologies and look for co-existing liver diseases
- Steatosis is hepatically benign but NASH is progressive and can lead to cirrhosis
- Patients with NAFLD are at higher risk for incident type 2 diabetes and cardiovascular disease
- Management of NAFLD include managing underlying metabolic and cardiovascular risks as well as managing the liver disease. Weight loss, vitamin E (even in diabetics) and insulin sensitizers are the first line therapies.

Acknowledgments (slides and discussion)

- Arun Sanyal (VCU)
- Rohit Loomba (UCSD)
- Naga Chalasani (Indiana)
- Alina Allen (Mayo)

Questions?

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Xtra slides

- A recent study (Hepatology 2019; 69: 64-75) indicates that among about 59,000 patients, moderate alcohol consumption (10 to < 20 g/day) for women and 10 to < 30g/day for men is associated with worsening fibrosis. These findings suggest that moderate alcohol consumption may be a modifiable risk factor for progression of fibrosis in NAFLD patients and clinicians should consider alcohol counseling for all patients with NAFLD.