NASH vs. NAFLD (what about ASH?): Diagnostic and Treatment Implications

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Disclosures

Please see www.robertgish.com

Alcohol use in USA: highest increases in women, older adults and racial/ethnic minorities

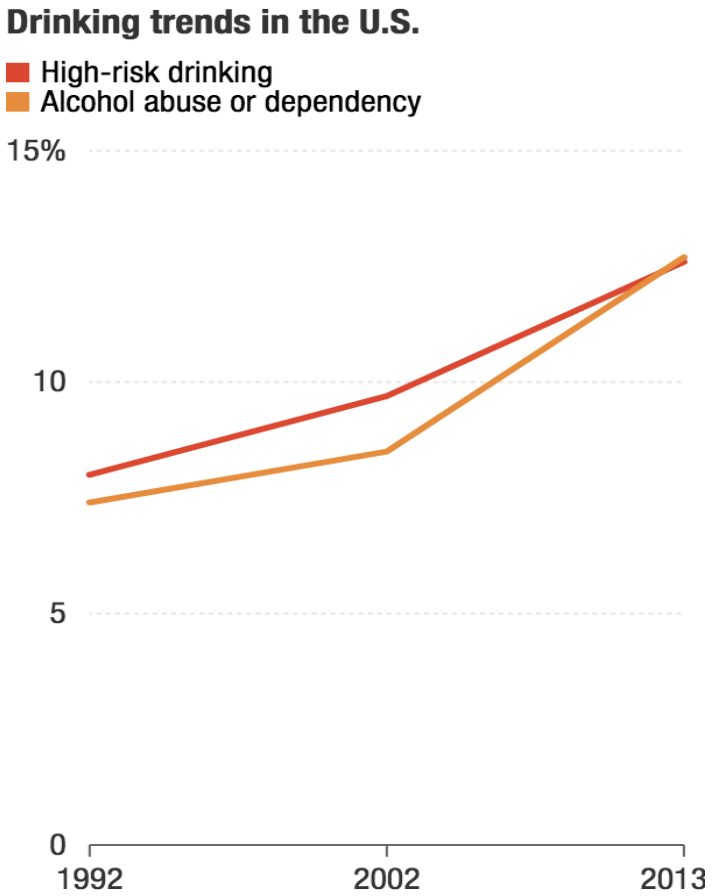
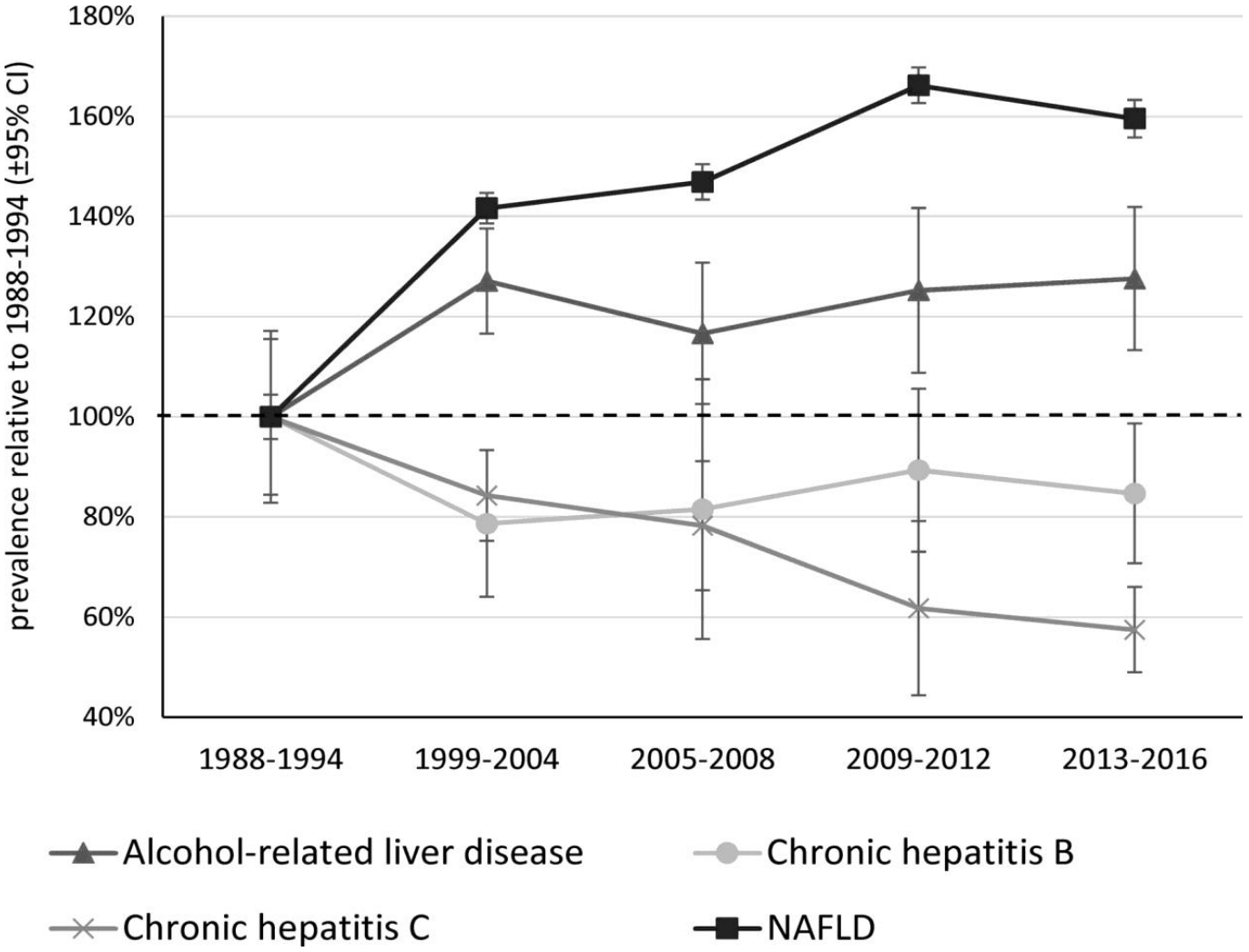


Table 1. Prevalence of and Percentage Change in 12-Month Alcohol Use by Sociodemographic Characteristics, 2001-2002 and 2012-2013

Sociodemographic Characteristic	% (95% CI) NESARC 2001-2002 (n = 43 093)	% (95% CI) NESARC-III 2012-2013 (n = 36 309)[a]	% Change
Total	65.4 (64.3-66.6)	72.7 (71.4-73.9)	11.2
Sex			
Men	71.8 (70.6-73.0)	76.7 (75.5-77.9)	6.8
Women	59.6 (58.0-61.1)	69.0 (67.5-70.5)	15.8
Race/ethnicity			
White	69.5 (68.2-70.8)	75.3 (73.7-76.9)	8.3
Black	53.2 (51.6-54.9)	66.1 (63.8-68.3)	24.2
Native American	58.2 (53.0-63.4)	73.9 (69.1-78.1)	27.0
Asian or Pacific Islander	48.4 (44.3-52.5)	62.5 (59.4-65.5)	29.1
Hispanic	59.9 (58.1-61.7)	70.2 (68.8-71.7)	17.2
Age, y			
18-29	73.1 (71.5-74.7)	80.1 (78.8-81.3)	9.6
30-44	71.9 (70.4-73.4)	79.5 (78.1-80.8)	10.6
45-64	64.3 (62.9-65.7)	71.9 (70.3-73.5)	11.8
≥65	45.1 (43.4-46.8)	55.2 (52.8-57.6)	22.4

ALD and NAFLD rates increasing compared to other risk factors for CLD



Excess Consumption of Alcohol:

- Is the third leading preventable cause of death in the US
- Cirrhosis, accidents, domestic violence, several cancers, pancreatitis
- Disproportionately affects younger persons
- Results in 2.3 million years of potential life lost every year
- ~30 years of life lost per alcohol-associated death
- Huge non-lethal toll: marital breakdown, drunk driving, work absences

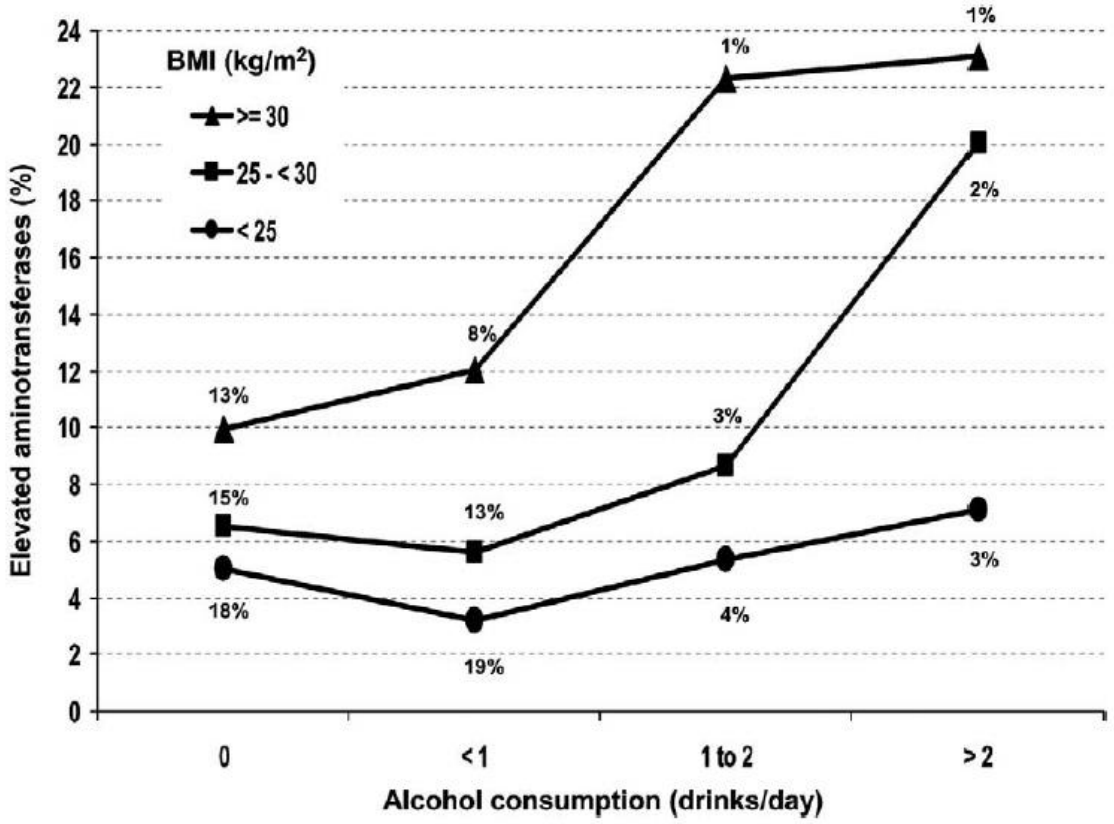
Alcoholic Liver Disease is a World Health Problem:

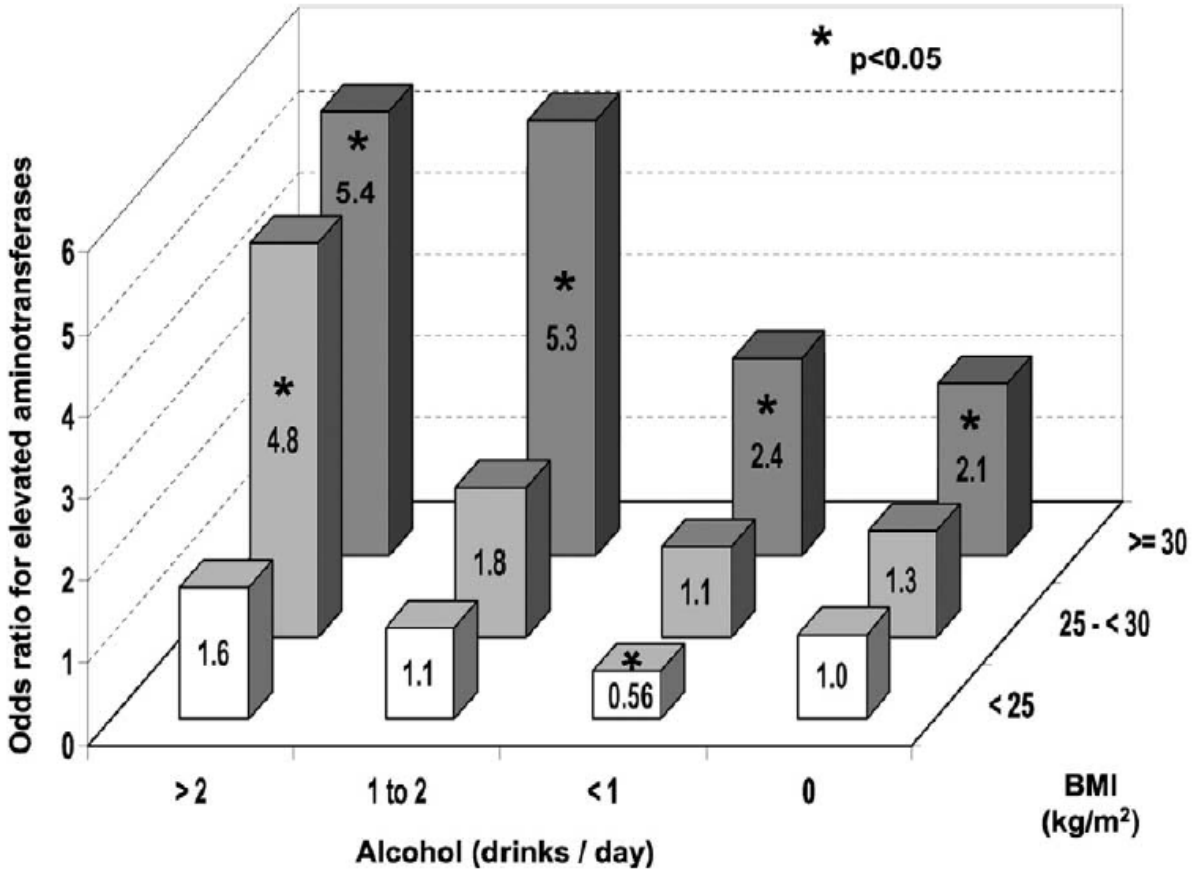
- 493,000 deaths in 2010
- 0.9% of all deaths
- 47.9% of all cirrhotic deaths
- ALD-associated liver cancer: 80,600 deaths

Rehm J et al. Global burden of alcoholic liver diseases.
J. Hepatol 2013; 59: 160-168

All treatment of alcoholic liver disease begins with abstaining from drinking

Joint Effects of Body Weight and Alcohol on Elevated Serum ALT





Ruhl and Everhart. Clin GastroHep 2005

Moderate Alcohol Use in Nonalcoholic Fatty Liver Disease

Beneficial effects of moderate alcohol use on cardiovascular mortality well recognised.
Cardiovascular mortality is the most common cause of death in NAFLD.

Do patients with NALFD benefit from moderate alcohol use?

Sinn	1797:2280	Korea	Reduced risk of carotoid plaque/stenosis
Dunn	331/582	USA	Reduced NASH and fibrosis
Kwon	52/77	USA	Reduced fibrosis
Dixon	57/108	Australia	Reduced NASH
Cotrim	75/132	Brazil	Increased NASH
Ekstedt	65/71	Scandinavia	Fibrosis with heavy episodic alcohol
Ascha	58/195	USA	Increased HCC if cirrhosis

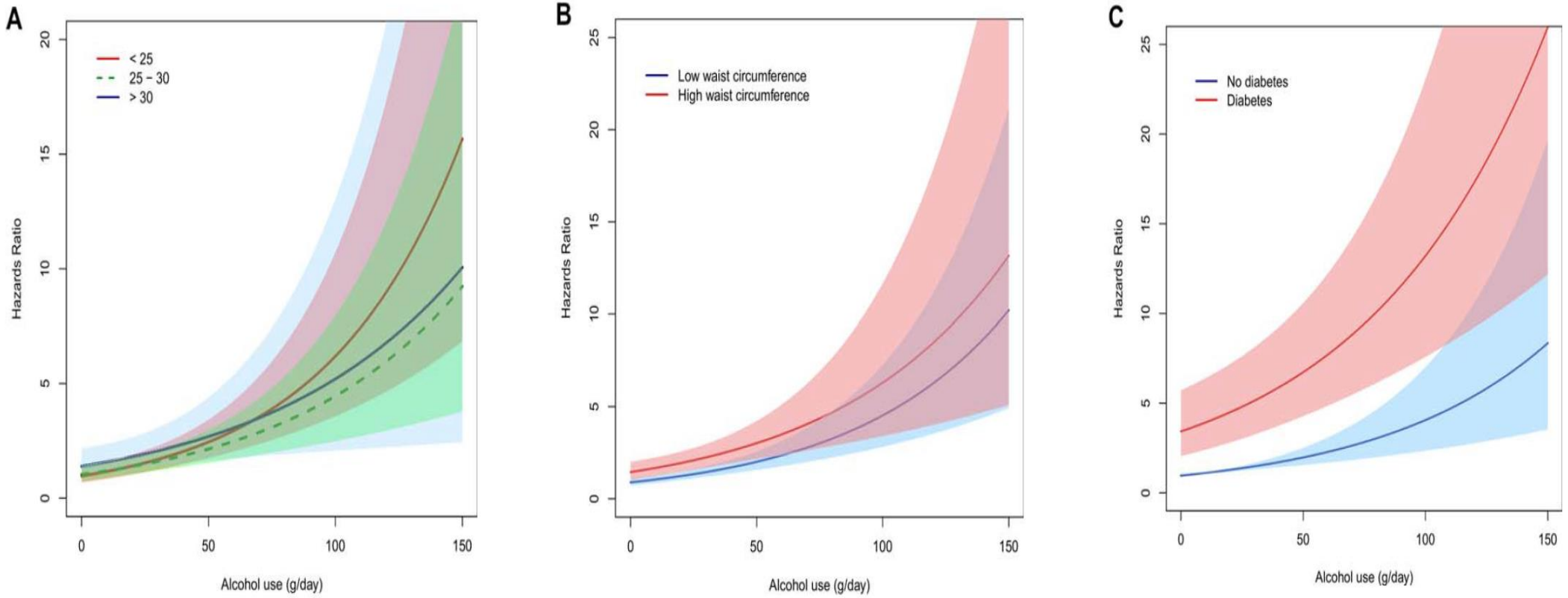
Ajmera et al. Hepatology 2017

Metabolic Factors Predictive of Severe Liver Events in 6732 Finnish Patients

	HR	95% CI	P
Age (years)	1.02	1.00 - 1.04	0.04
Alcohol (g/wk)	1.002	1.001 – 1.002	<0.001
Diabetes	2.75	1.56-4.84	<0.001
HOMA-IR	1.01	1.01-1.02	<0.001
Total/LDL Chol	2.64	1.67-4.16	<0.001
Waist/BMI	3.7	1.74-7.89	0.001

Alcohol was also significant even when average alcohol intake was within limits regarded as normally defining nonalcoholic fatty liver disease.

Relationship between Alcohol use and Risk of Severe Liver Disease Stratified According to BMI, Waist circumference, Diabetes



Effect of Alcohol on Mortality in Non-Alcoholic Fatty Liver Disease

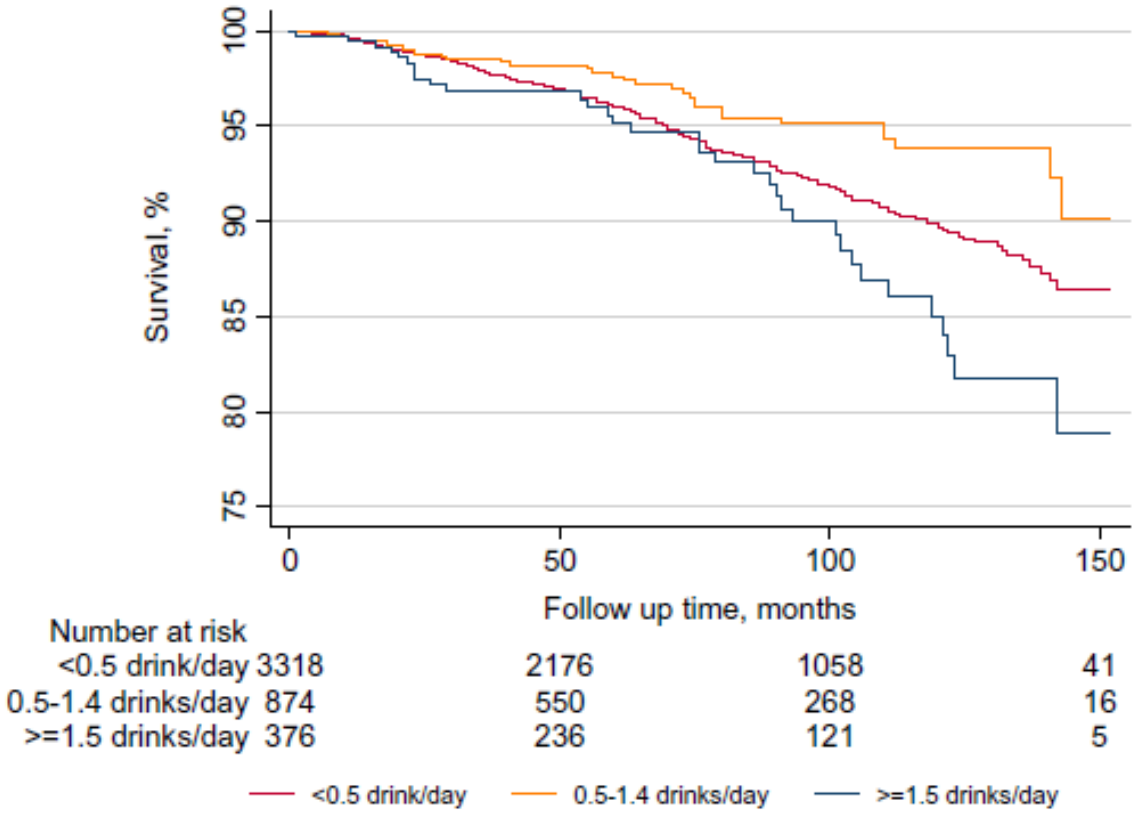
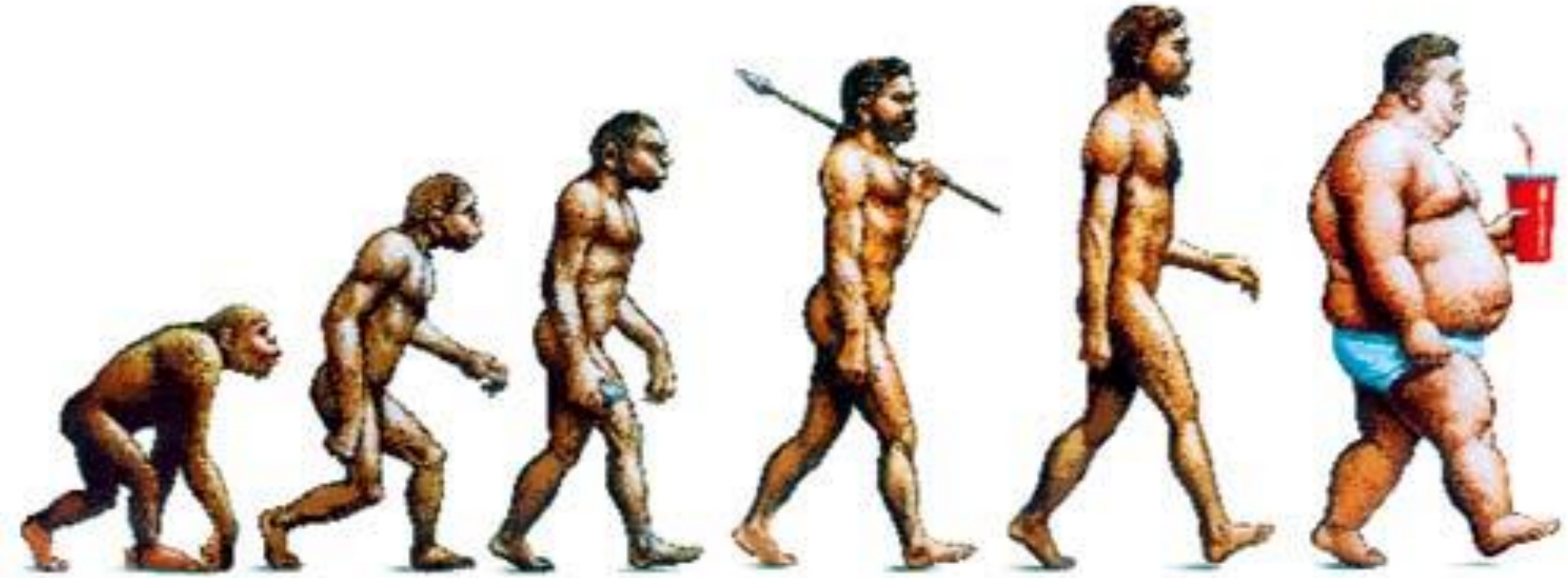


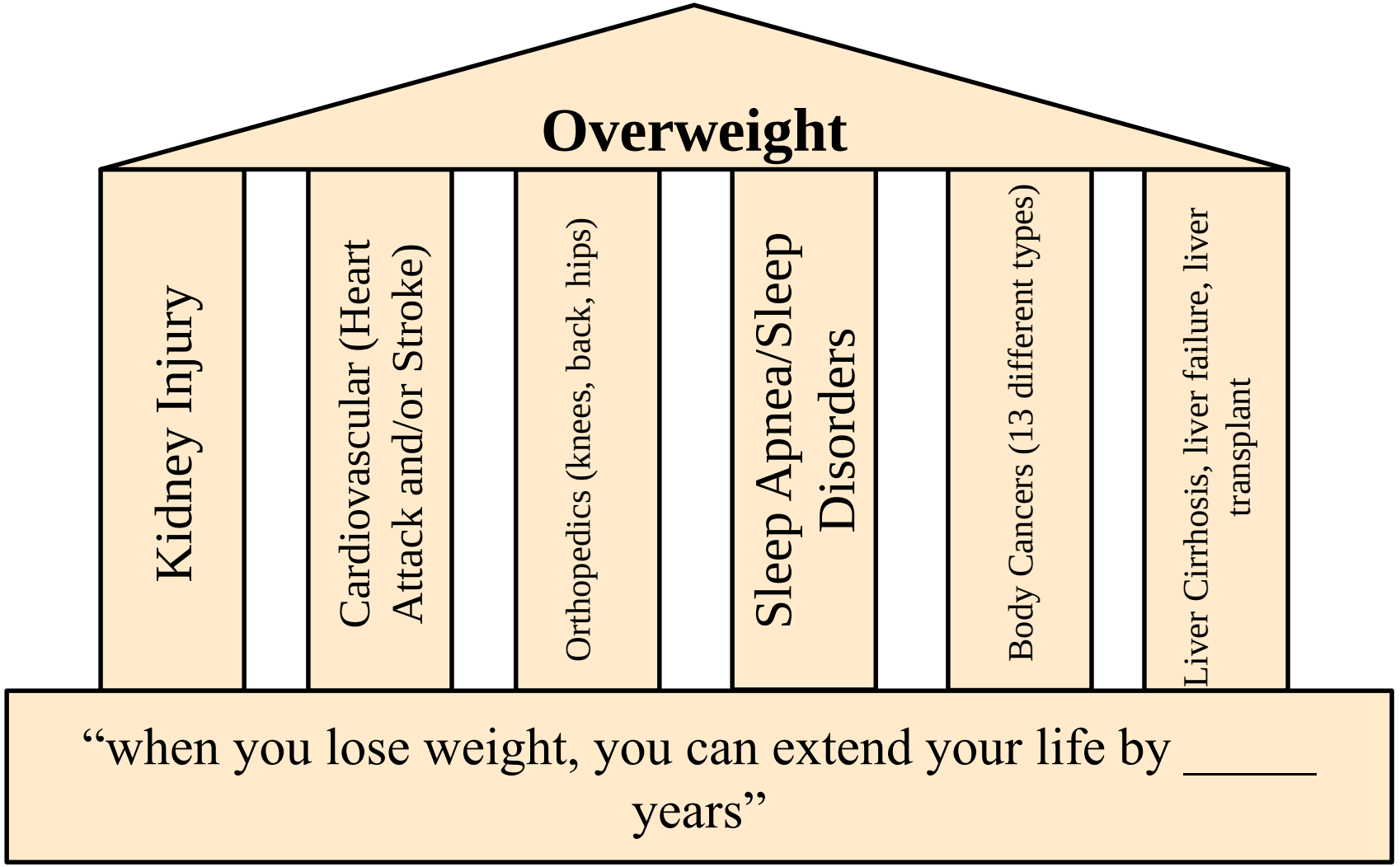
FIG. 2. Unadjusted Kaplan-Meier survival curves for effect of alcohol consumption on all-cause mortality in patients with nonalcoholic fatty liver disease.

Hajifathalian et al. Hepatology.2018

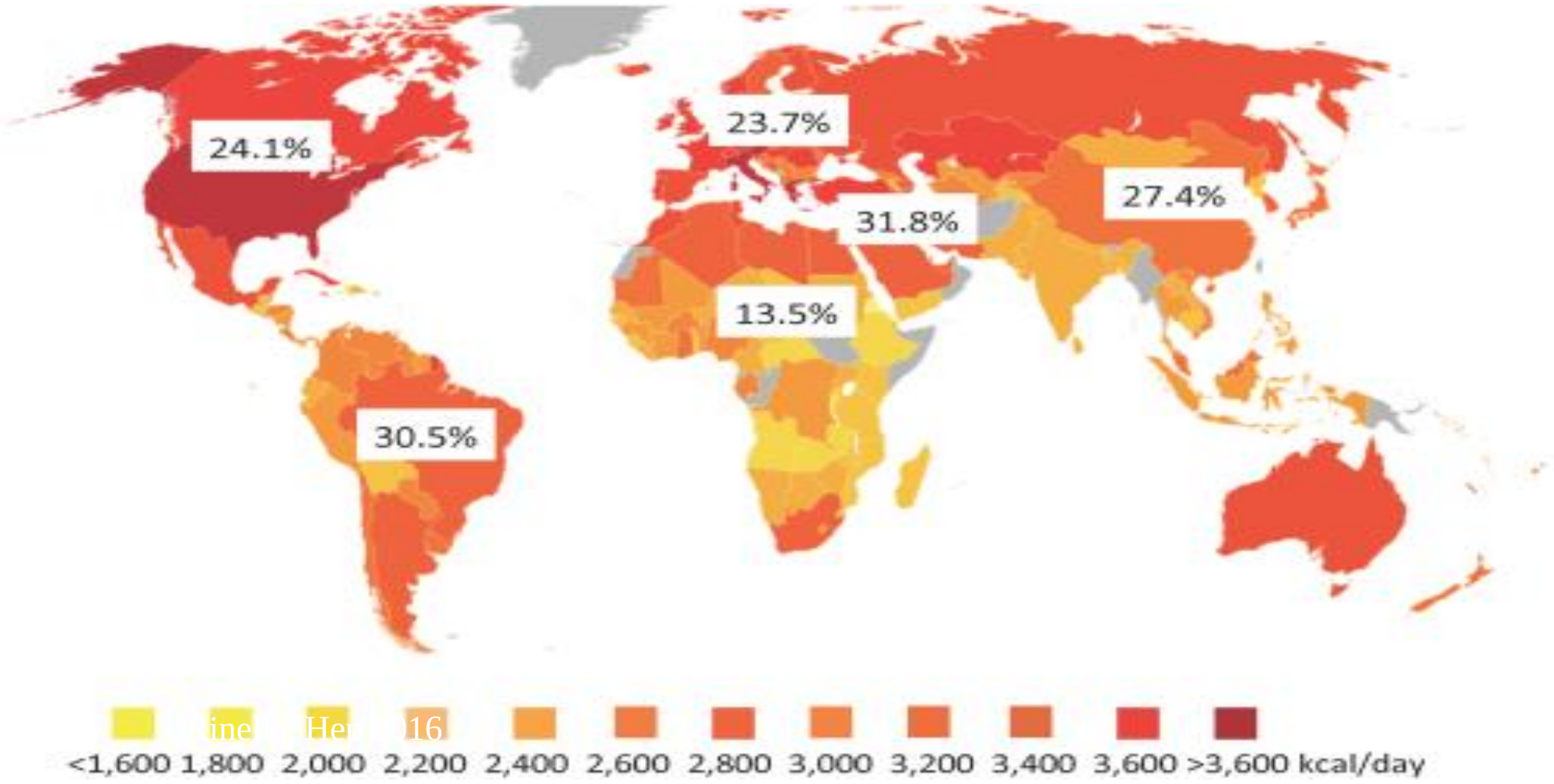
A Disturbing Evolutionary Development



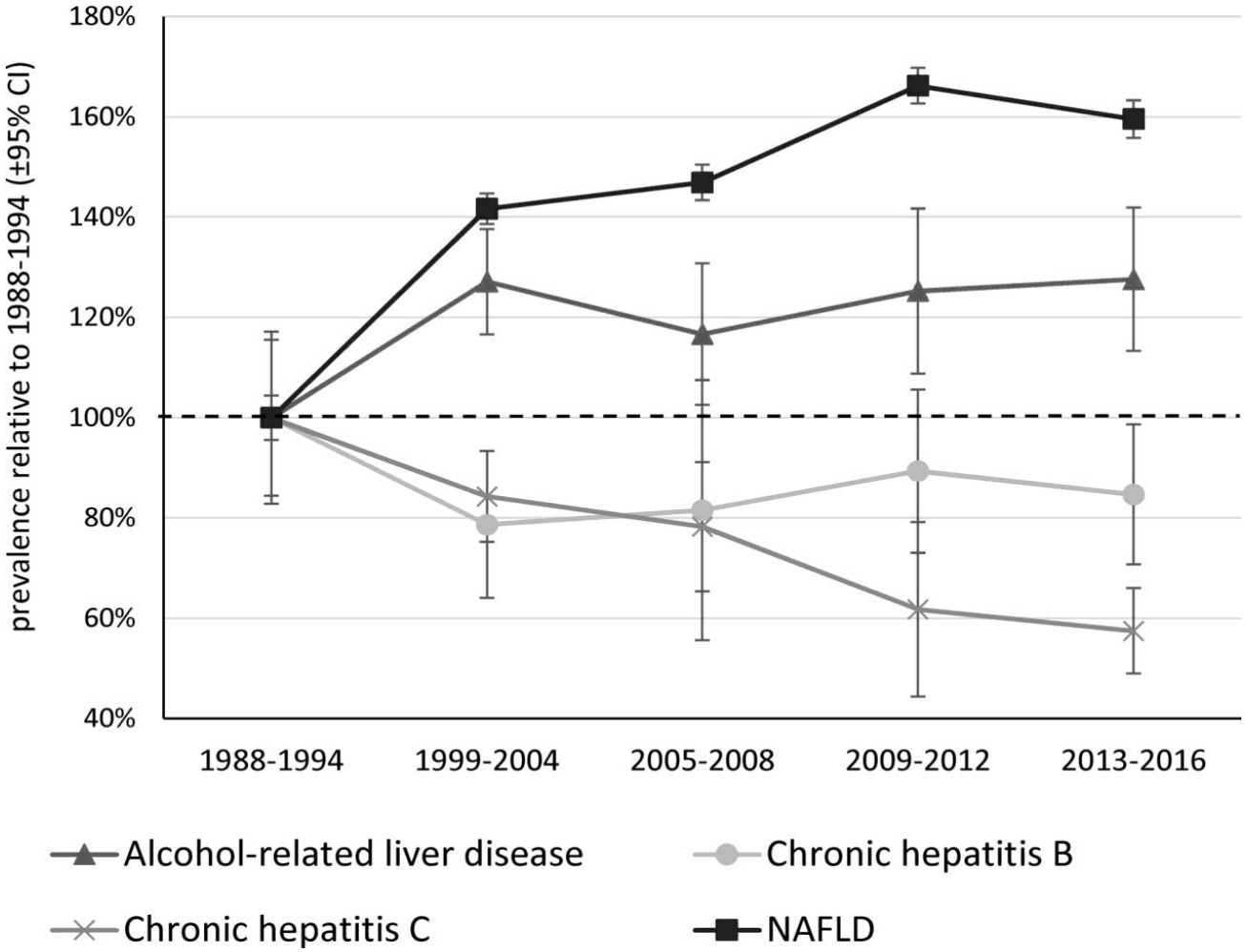
Short life span and low quality of life



NAFLD is Seen Globally



NAFLD rates increasing compared to other risk factors for CLD

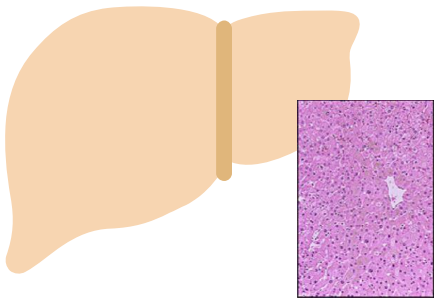


Younossi ZM et al, Gut 2019

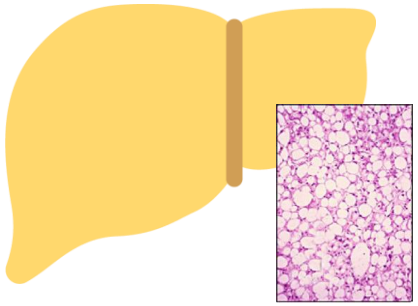
The NAFLD Continuum

NAFLD

Normal Liver

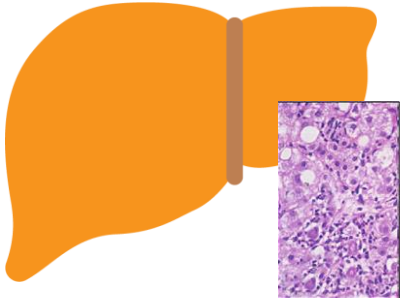


Steatosis "NAFL"



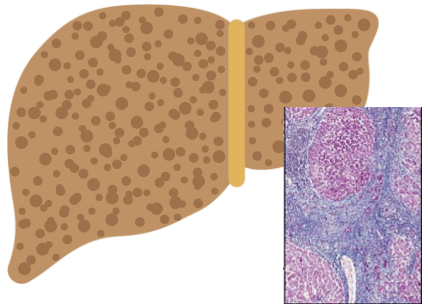
Fatty liver without inflammation or hepatocyte ballooning

Steatohepatitis "NASH"



Fatty liver with inflammation and hepatocyte ballooning

Cirrhosis



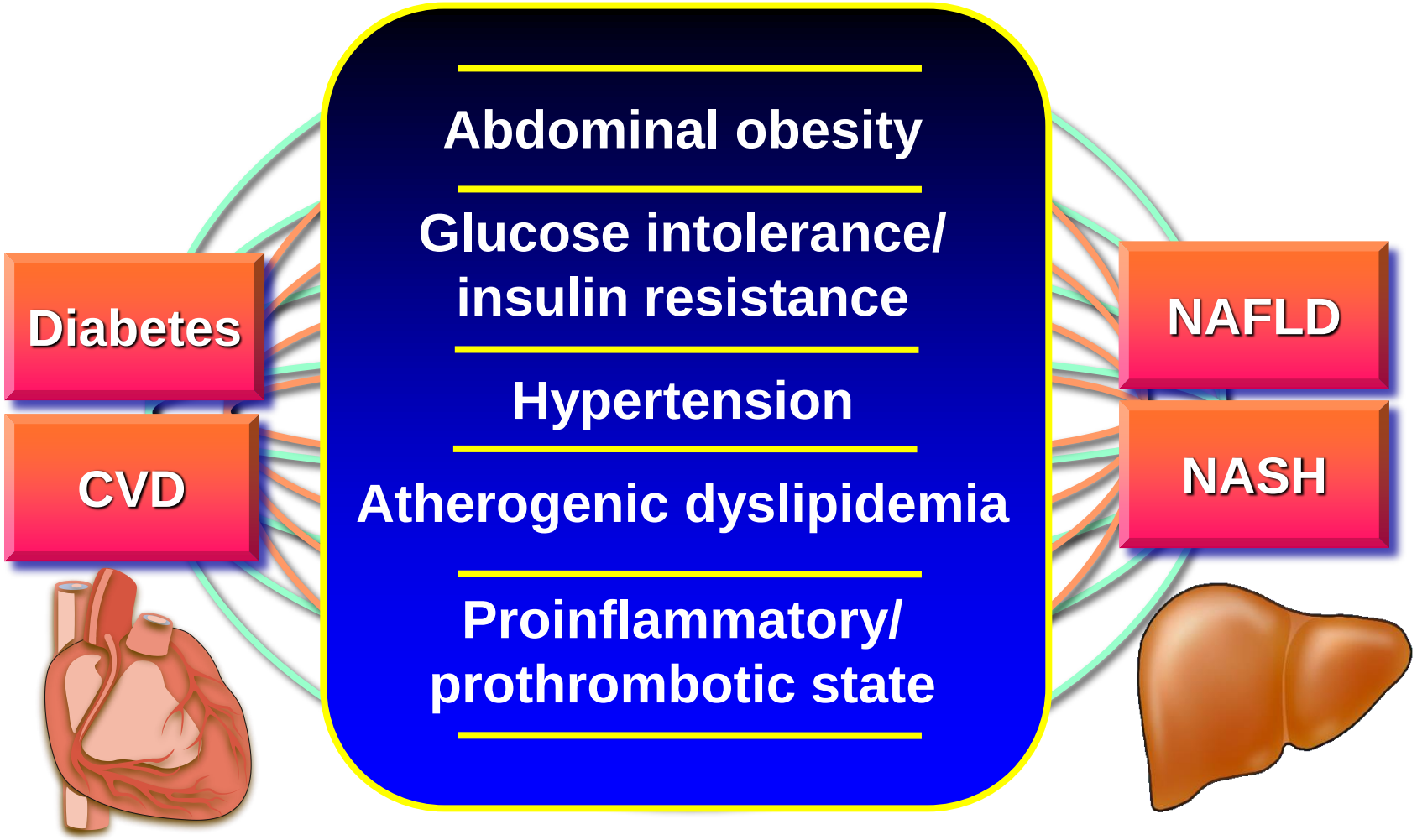
Increasing fibrosis leading to cirrhosis, hepatocellular carcinoma

Worldwide prevalence:	~ 25%	1.50% to 6.45%

Chalasani. Hepatology. 2018;67:328.

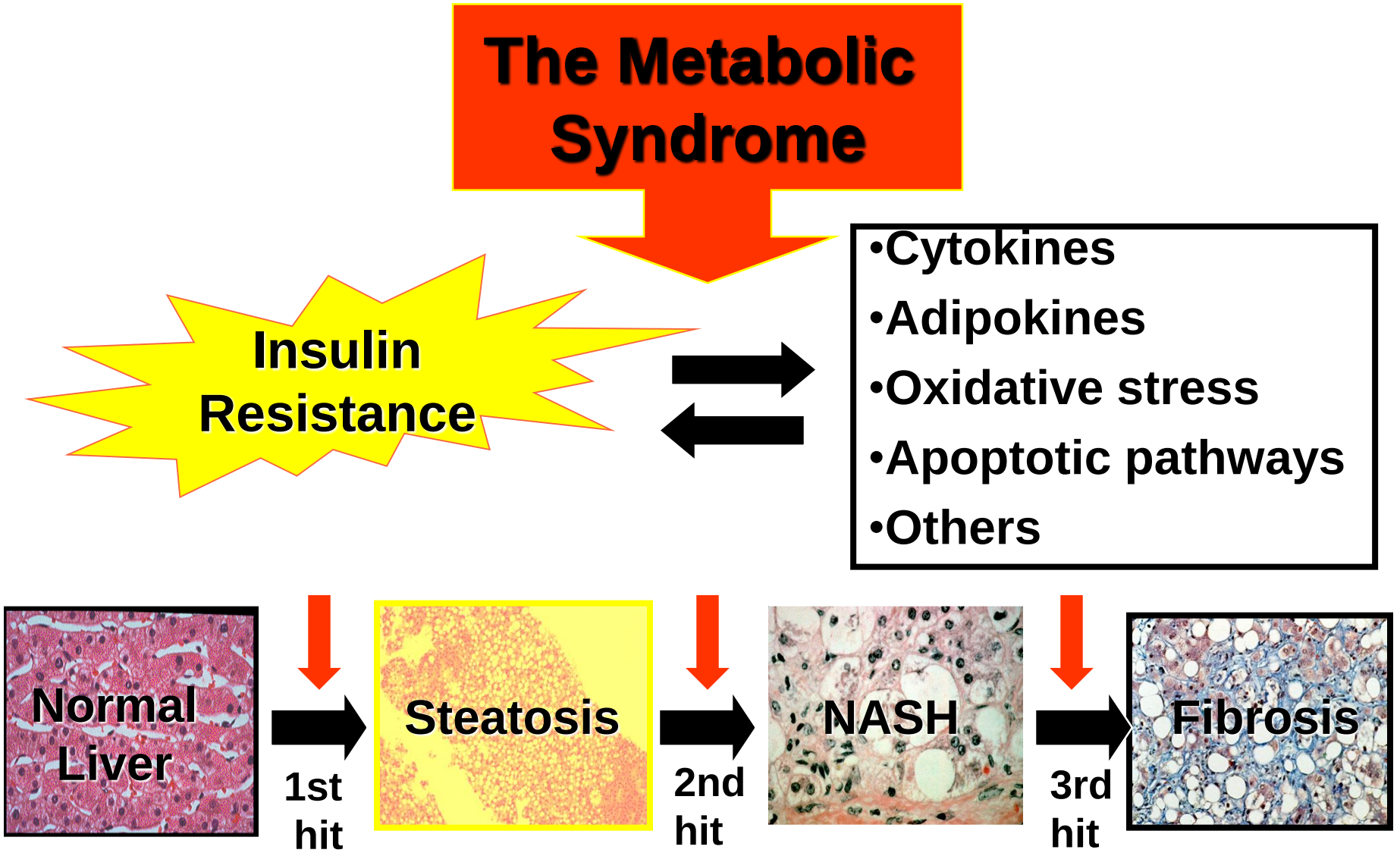
Slide credit: clinicaloptions.com

Metabolic Syndrome and Its Hepatic Manifestation



National Cholesterol Educational Program (NCEP), Adult Treatment Panel (ATP) III; 2001.

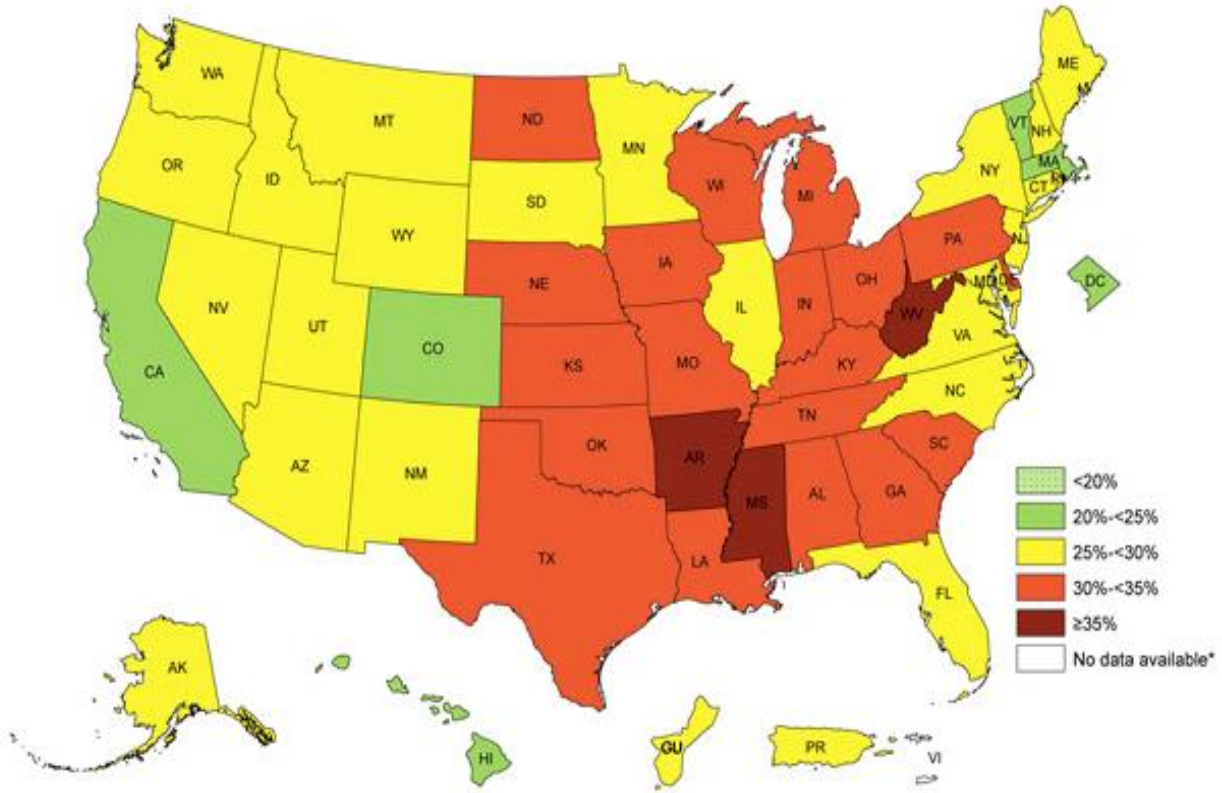
Pathogenesis of NASH : The Multi-hit Hypothesis



The Latest Epidemic

Prevalence¶ of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2014

¶Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



Source: Behavorial Risk Factor Surveillance System, CDC.

*

Risk Factors for NAFLD

Major Co-morbidities

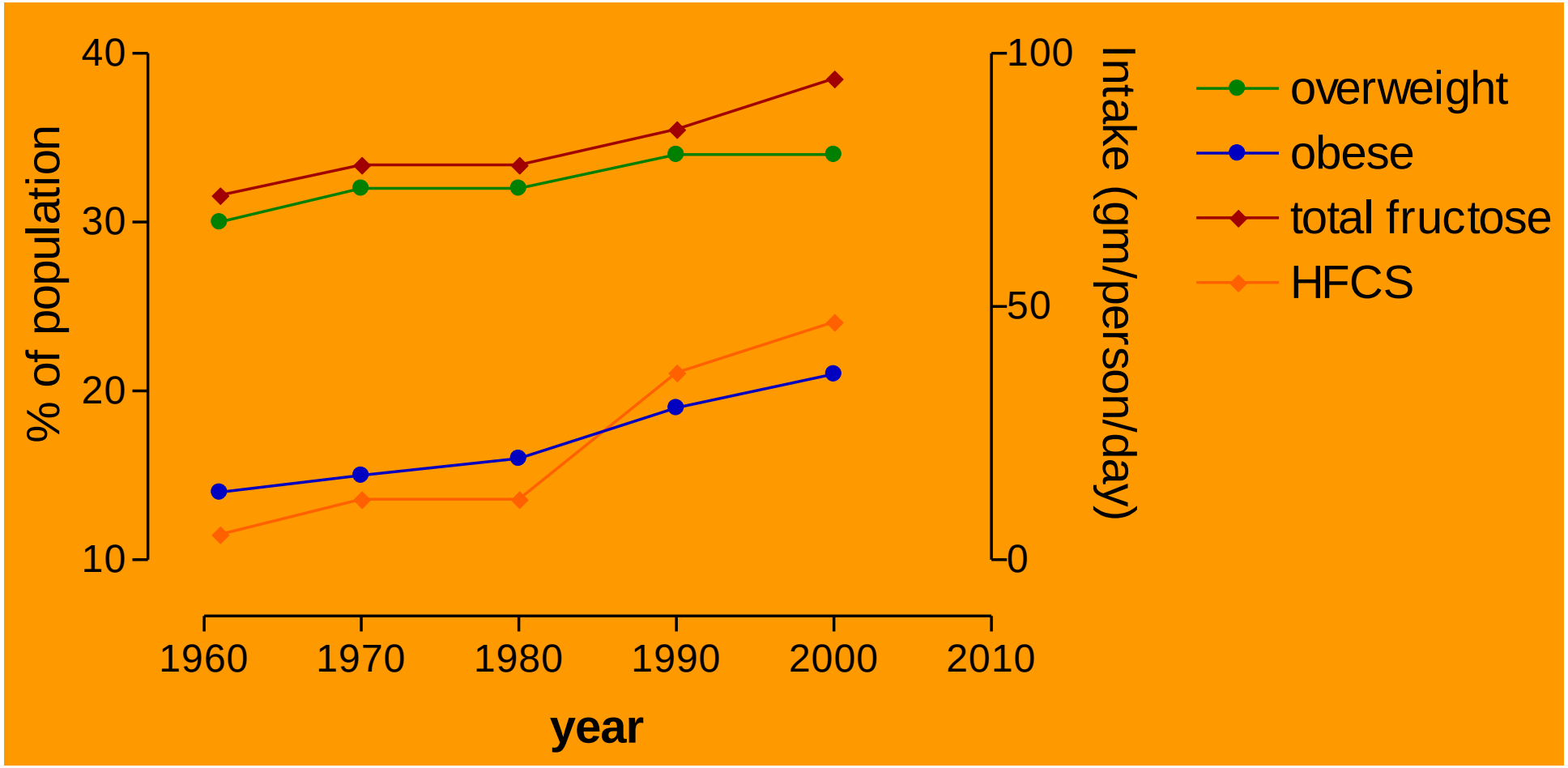
- Type 2 Diabetes
- Dyslipidemia
- Obesity
- Metabolic Syndrome
- HTN

Emerging Associations

- Hypothyroidism
- Sleep Apnea
- Hypopituitarism
- Polycystic Ovary Syndrome
- Increased waist circumference in Lean Nash

Lonardo A, et al. J Hepatol 2006; 44: 1196-1207
McCullough A et al. J Clin Gastroenterol 2002;34:255-262

Estimated fructose intake and weight trends in the U.S.



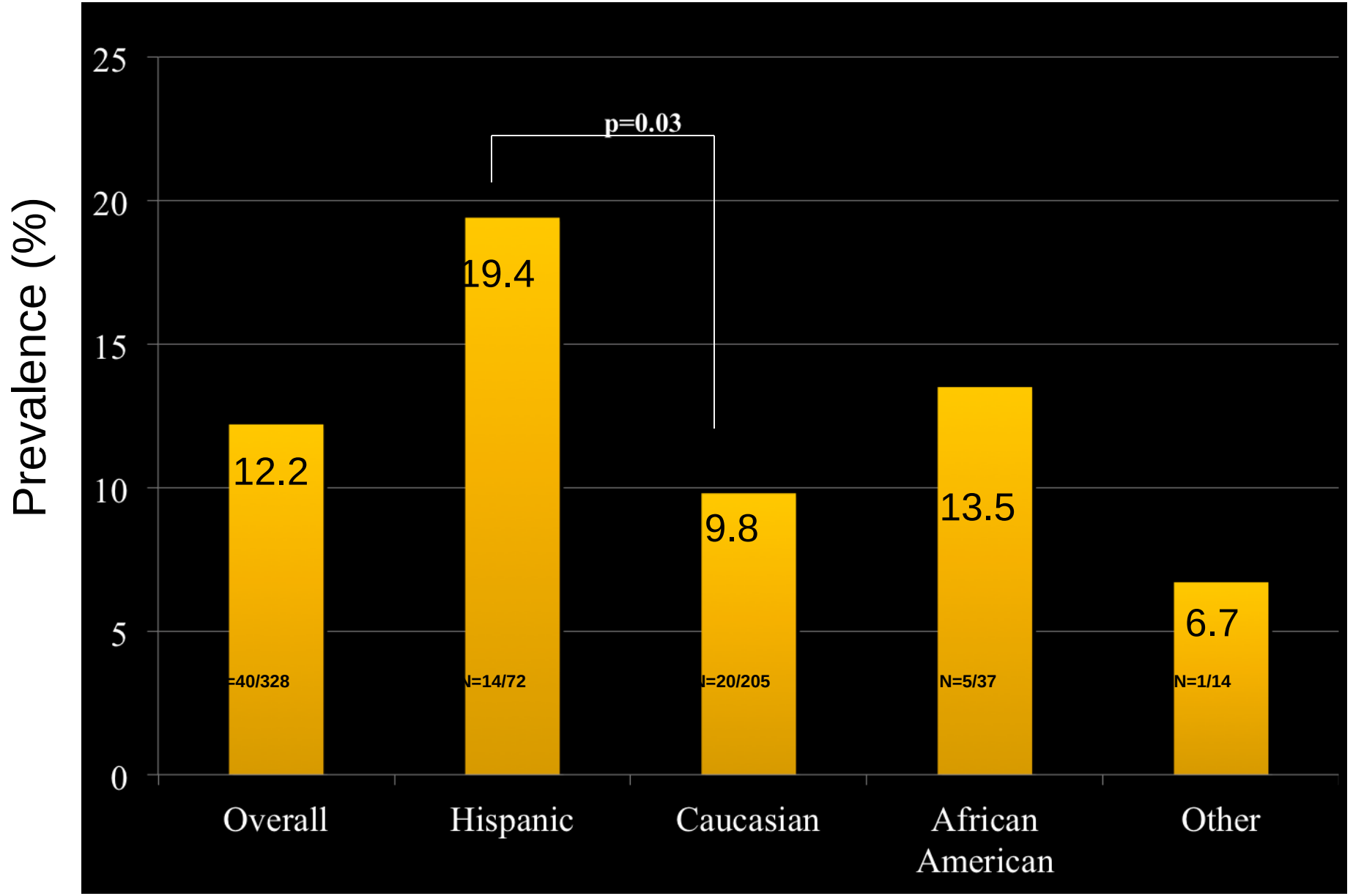
Bray et al, Am J Clin Nutr, 2004, 79:537-43

Fructose

- Dietary Carbohydrates can be converted to fat in the liver
- Fructose (alone or as part of sucrose) drives lipogenesis and promotes NAFLD
- Epidemiologic studies, clinical trials, and animal studies show that excess carbohydrate consumption contributes to NAFLD
- High fructose consumption depletes hepatic ATP and impairs recovery from ATP depletion mitochondrial toxin

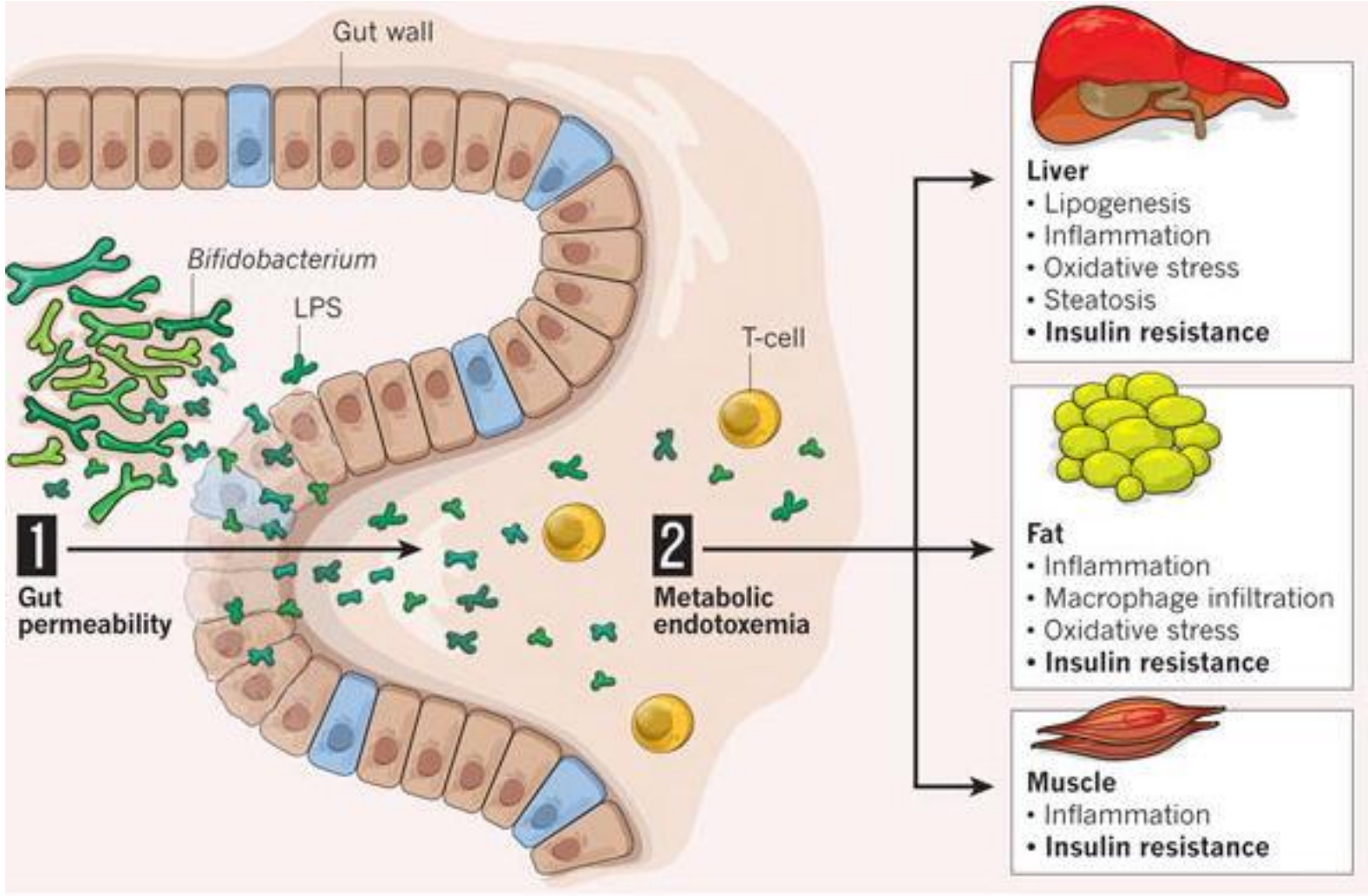
Abdelmalek M, Hepatology 2012

NASH Prevalence Among Ethnic Groups

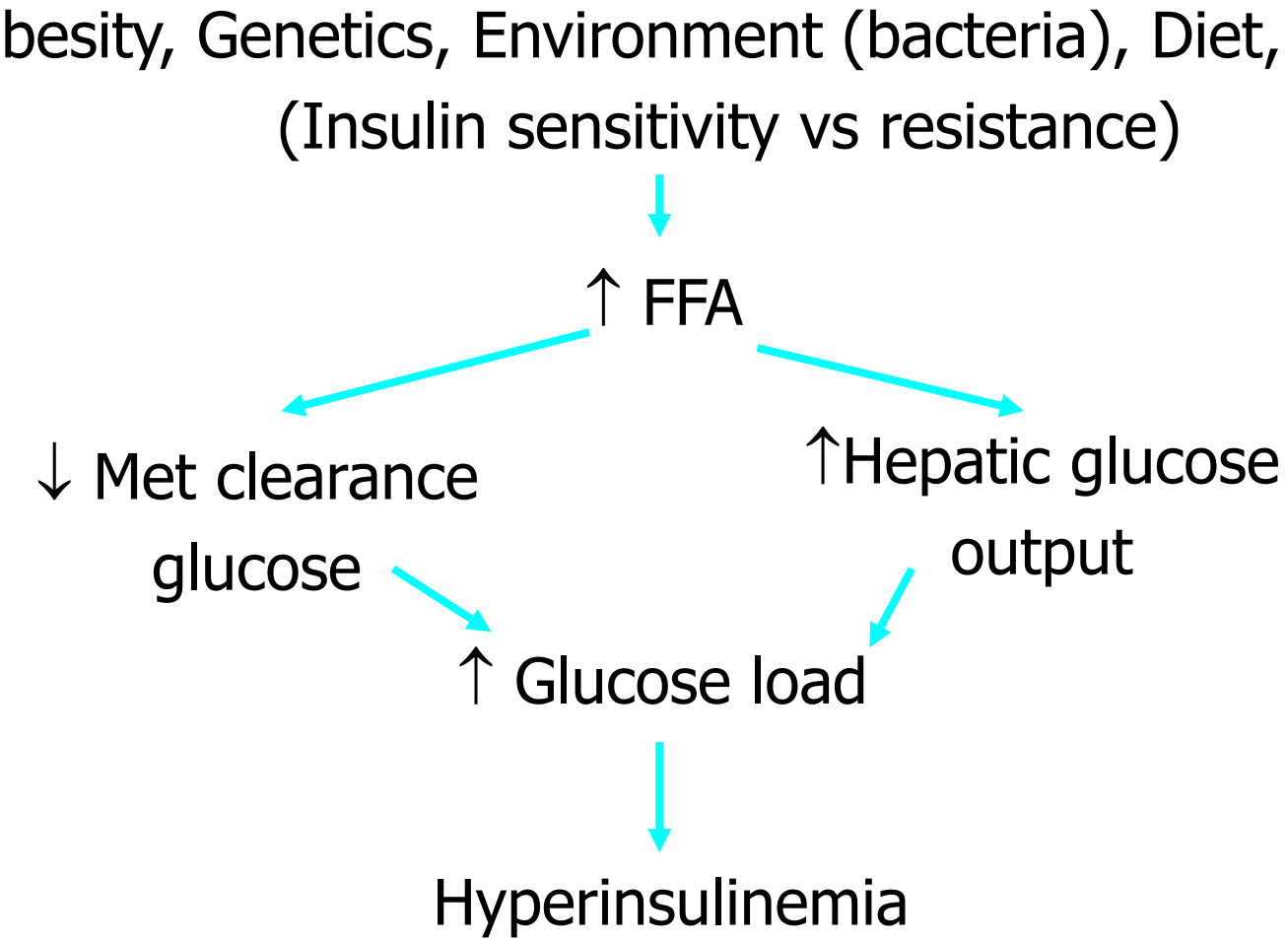


Williams, Gastroenterology 2011

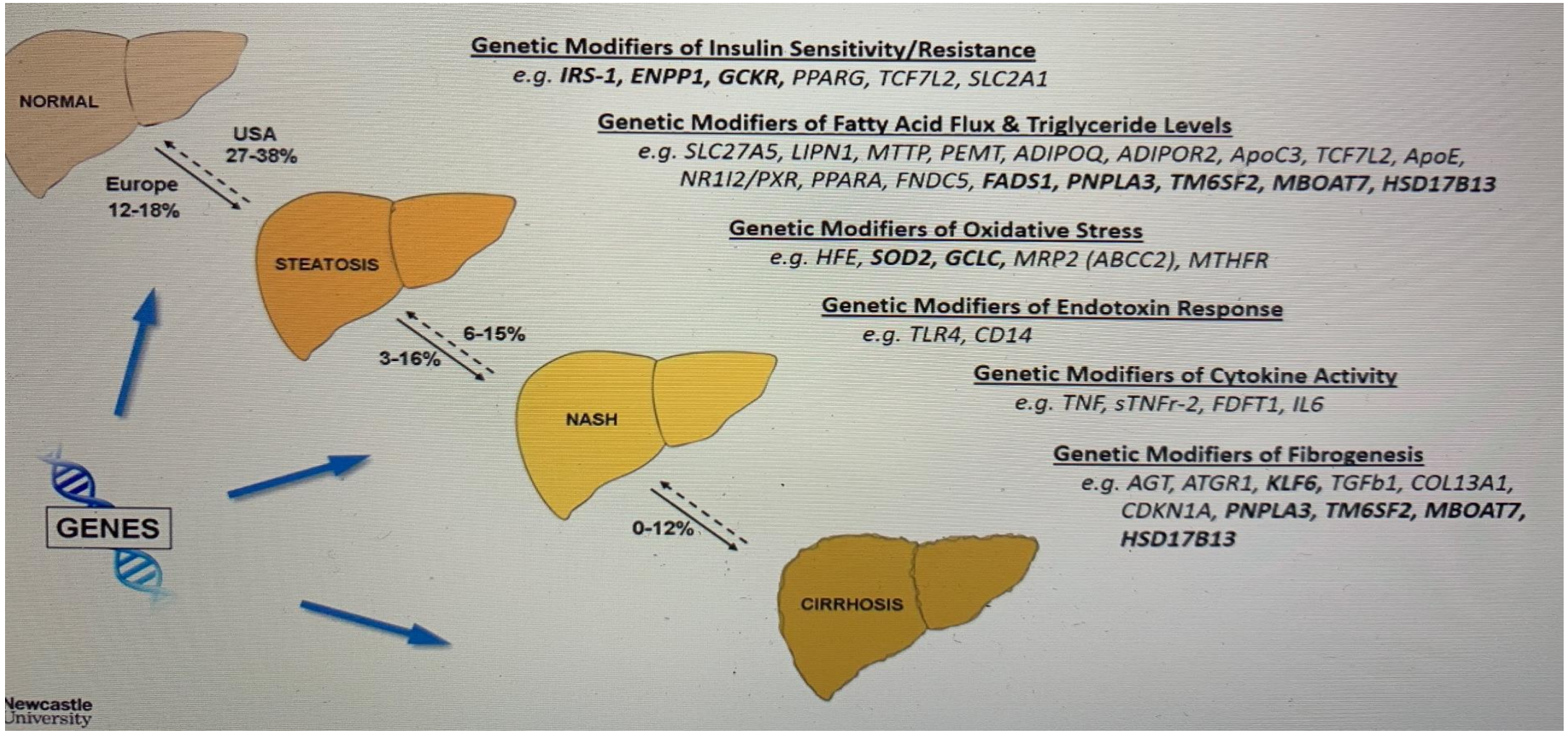
The intestinal microbiome modulates insulin resistance and metabolism



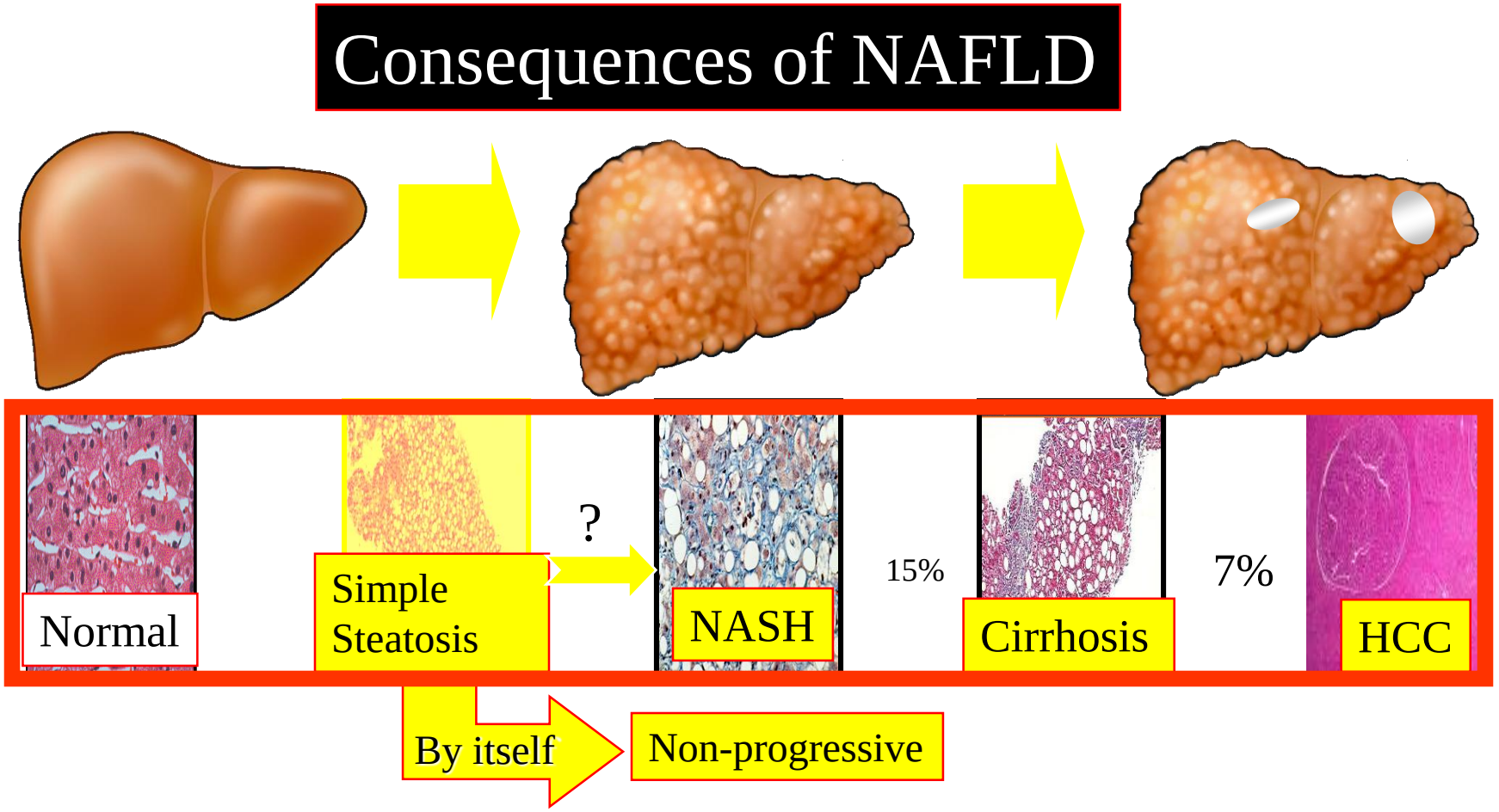
Risk Factors for NAFL-Disease (NAFLD)



Genetic Modifiers of NAFLD Risk & Progression



Is NAFLD Progressive?

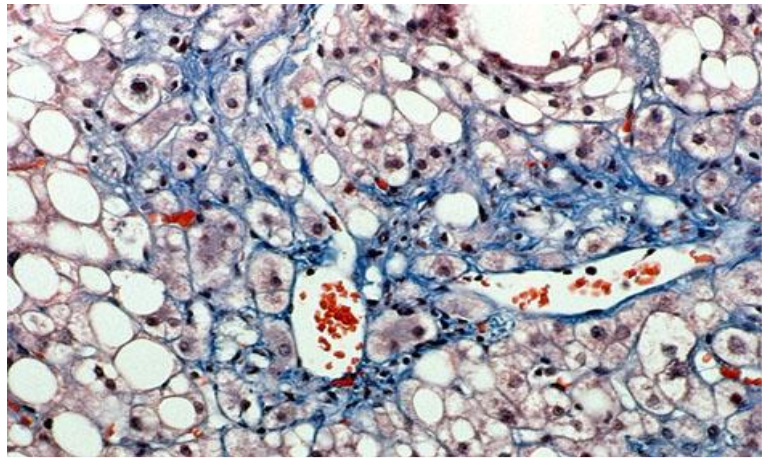


Ludwig 1980 , Diehl 1988, Lee 1989, Powell 1990, Bacon 1994, Matteoni 1999, Angulo 1999, Caldwell 1999, Ponawala 2000, Contos 2001, Ong 2001,, Bugianesi 2002, Ratziu 2002, Harrisson 2003, Marchesini 2003, Younossi 2004, Fassio 2004Sanyal 2004, Ong 2005, Adams 2005, Ong 2006, Rafiq 2008

Types of Fatty Liver Disease

Over 10 years

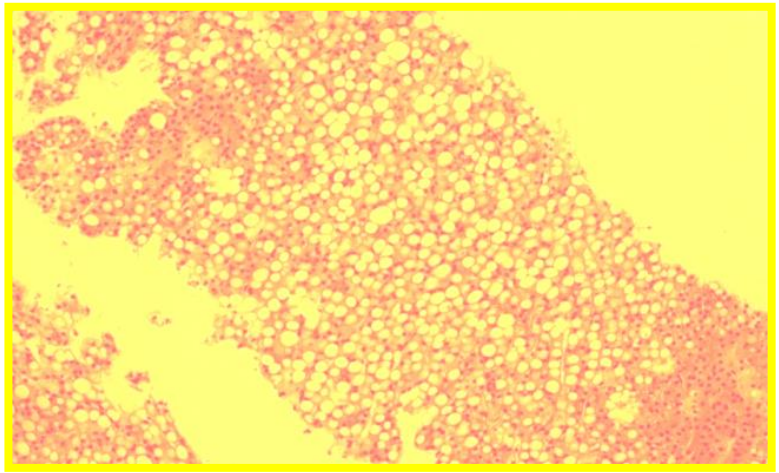
NASH



10%-20%

Cirrhosis

Steatosis alone (NAFL)



By itself

Benign

Outcomes in NAFL-D

	Surrogates	# Studies	OR [95% CI]
Overall Mortality	•NAFLD vs. General Population	8 studies	1.57 [1.18-2.10]
Incident CVD	•ALT as a surrogate •GGT as a surrogate •Imaging as a surrogate	6 studies 10 studies 7 studies	1.10 [0.85-1.41] 1.57 [1.42-1.74] 2.05 [1.81-2.31]
Incident type2 DM	•ALT as a surrogate •GGT as a surrogate •Imaging as a surrogate	17 studies 12 studies 3 studies	1.97 [1.77-2.20] 2.74 [2.39 – 3.14] 3.51 [2.28-5.41]

Williams Annals of Internal Medicine 2011

Liver-Related & Overall Mortality in Patients with NAFLD

	Author	n	Follow-up (mean, yrs)	Liver-related mortality	Overall mortality	Increased Mortality¶
Simple Steatosis	Matteoni et al (1999)	49	9	2.0%	33.0%	No
	Ekstedt et al (2006)	58	14	0.0%	12.1%	No
	Rafiq et al (2009)	74	19*	2.7%	56.8%	No
	Soderberg et al (2010)	67	21	3.0%	34.3%	No
	Dam-Larsen et al (2009)	170	21	0.6%	28.2%	No
	Total/mean	**418**	**17**	**1.7%**	**32.9%**	
NASH	Matteoni et al (1999)	29	8	10.0%	30.0%	Yes
	Ekstedt et al (2006)	71	14	2.8%	26.8%	Yes
	Rafiq et al (2009)	57	19*	17.5%	63.2%	Yes
	Soderberg et al (2010)	51	21	5.9%	47.1%	Yes
	Evans et al (2002)	26	9	-	15.0%	Yes
	Adams et al (2005)	49	8	8.1%	35.0%	Yes
	Younossi et al (2011)	131	10*	15.7%	21.3%	NR
	Total/mean	**349**	**11**	**8.6%**	**34.1%**	
NAFLD-related cirrhosis	Hui et al (2003)	23	7	21.0%	26.0%	NR
	Sanyal et al (2006)	152	10	14.5%	19.1%	NR
	Yatsuji et al (2009)	68	5	7.3%	27.9%	NR
	Bhala et al (2011)	247	7	5.7%	13.4%	Yes
	Total/mean	**490**	**7**	**12.1%**	**24.3%**	

Lomonaco & Cusi, 2012

Clinical Features of NAFL/NASH

Symptoms:

Variable
Vague (fatigue, malaise, RUQ discomfort)
Mostly absent

Signs:

Hepatomegaly common
Splenomegaly in some
Portal hypertension unusual

Labs:

Increased AST, ALT typical
± increased Alk. Phos., GGT
Increased cholesterol, triglycerides common
Increased glucose common
Viral markers (-)
Autoantibodies (-)
Iron studies abnormal sometimes

Imaging:

Fatty liver

Work up of patients with NAFLD

- Imaging to establish the presence of steatosis
- Meticulous alcohol and medication history
- Exclusion of co-existing or competing etiologies
- Auto-antibodies and hyperferritenemia are common
- Fasting lipid profile and measures of insulin resistance
- Liver biopsy to establish the presence of NASH

Imaging Techniques for Evaluating Hepatic Steatosis

- Ultrasound, liver, full abdomen
- Elastography
  VCTE (Fibroscan), 2D, Point, MRE
- Computed tomography
- Magnetic resonance imaging
  - Percent fat calculations
  - Estimated protein-density fat-fraction
  - Magnetic resonance elastography
- Controlled attenuation parameter
  - For fat using FibroScan

How to establish diagnosis of NAFLD and identify patients with NASH ?

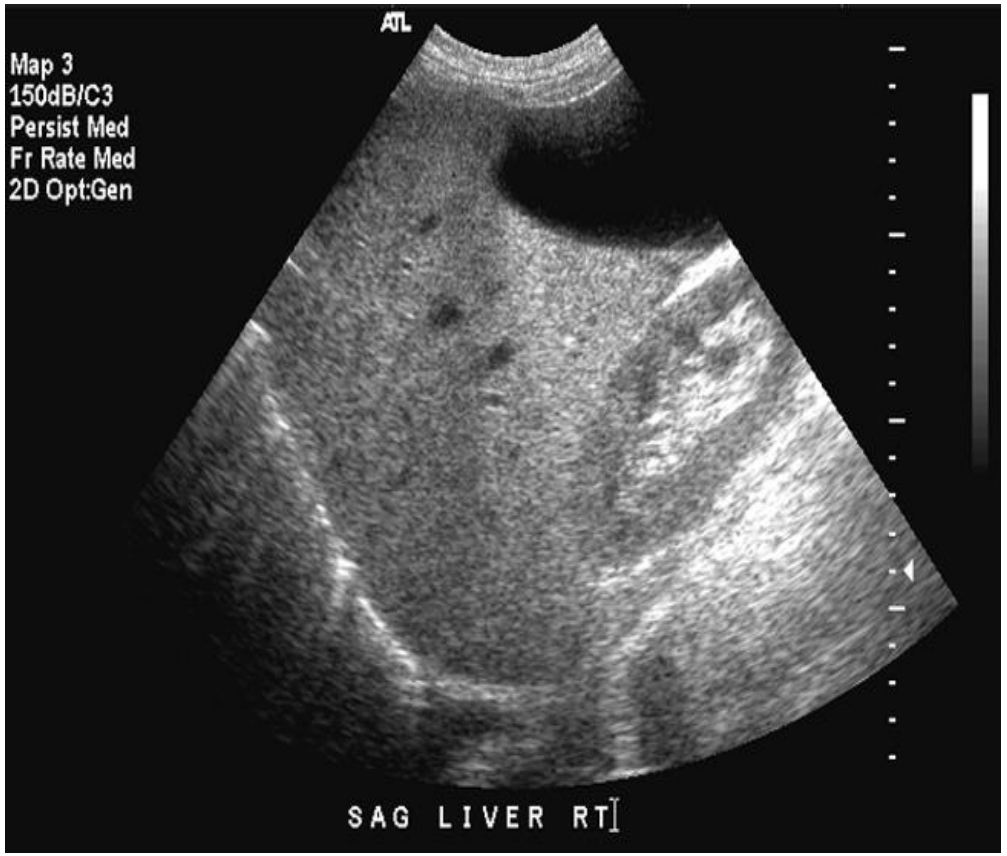
- Patients with NAFLD or NASH are generally asymptomatic
- Clinical presentations cannot distinguish NASH
- Current radiologic modalities are unable to distinguish NASH or accurately detect fibrosis
- Non-invasive biomarkers are not established (getting closer)
- Therefore, in 2017, liver biopsy remains “the imperfect gold standard” to diagnosis and stage NASH

Clinical Factors that are different between Isolated Fatty Liver and NASH

Clinical Variable	Not NASH (n=89)	NASH (n=40)	P Value
BMI	31.7 (5.3)	34.4 (5.4)	0.01
Fasting Insulin	14 (8.4)	23.2 (13)	<0.0005
ALT (U/L)	36.2 (15.7)	50.9 (19.6)	<0.0005
AST (U/L)	25.6 (7.4)	36.3 (13.1)	<0.0005
HDL (mg/dL)	49.2 (15.7)	44.3 (9)	0.03
Adiponectin (ng/mL)	11028 (13078)	7815 (4811)	0.02
hsCRP (ng/mL)	5355 (5537)	7351 (6397)	0.04
CK-18 (U/L)	210.3 (118)	307.1 (233.1)	0.02

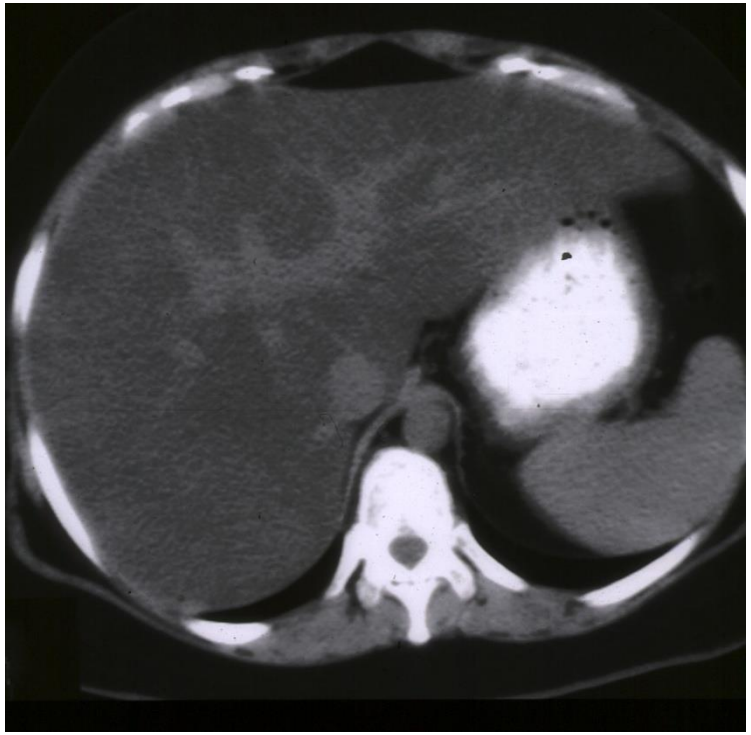
Williams CD, Gastroenterology 2011

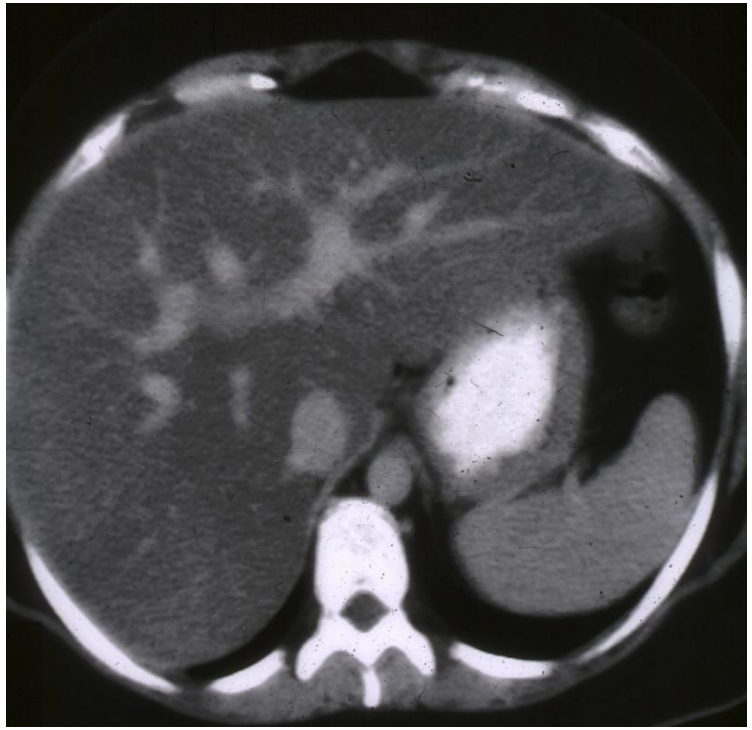
NAFLD: sonographic evidence



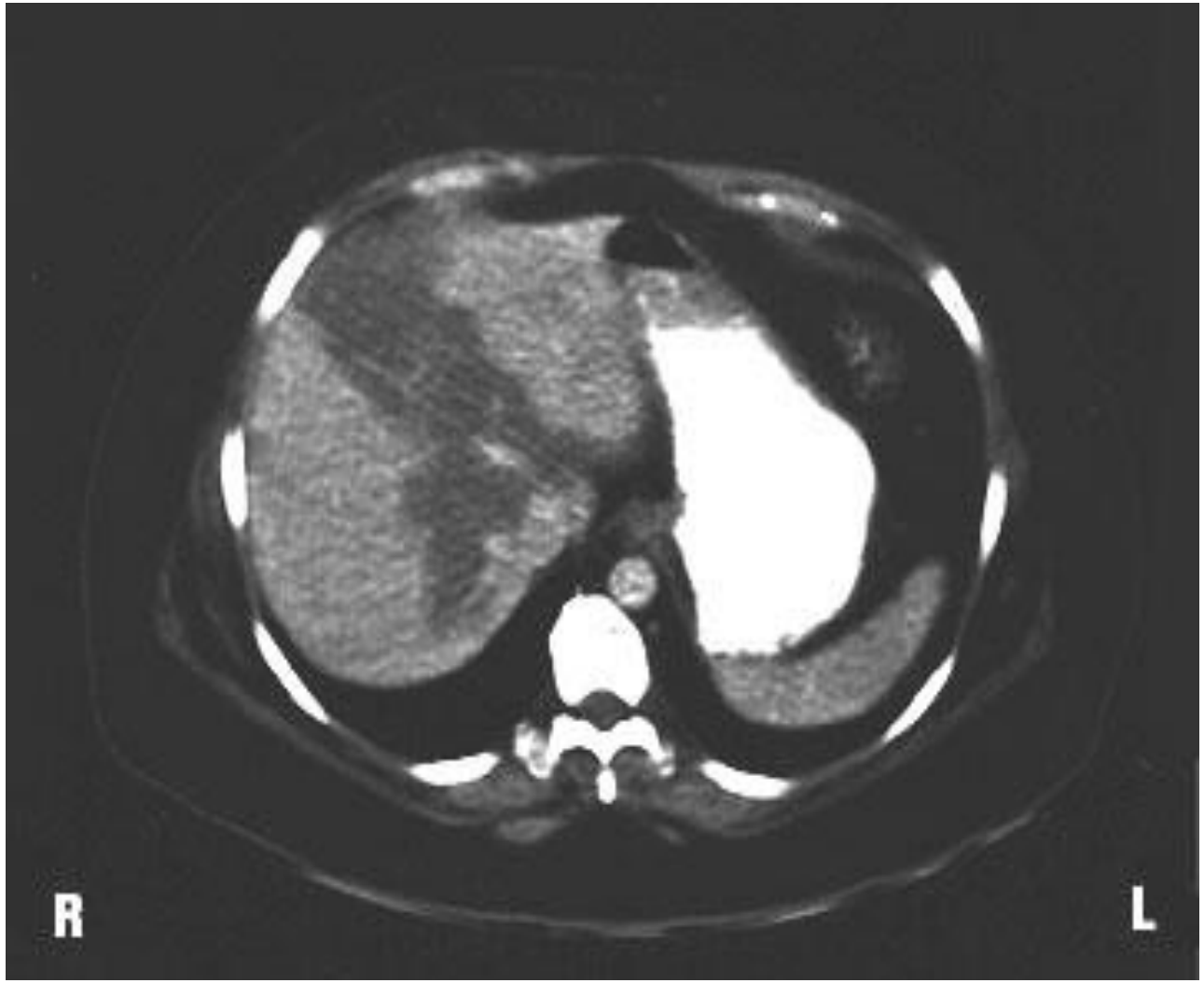
- Bright liver
- Echotexture increased compared to kidney
- Vascular blurring

CT scan: fatty liver





Fat in the liver may be focal



Treatment of NASH

The Metabolic Syndrome

Farnesoid-X Receptor Agonist

Weight Loss

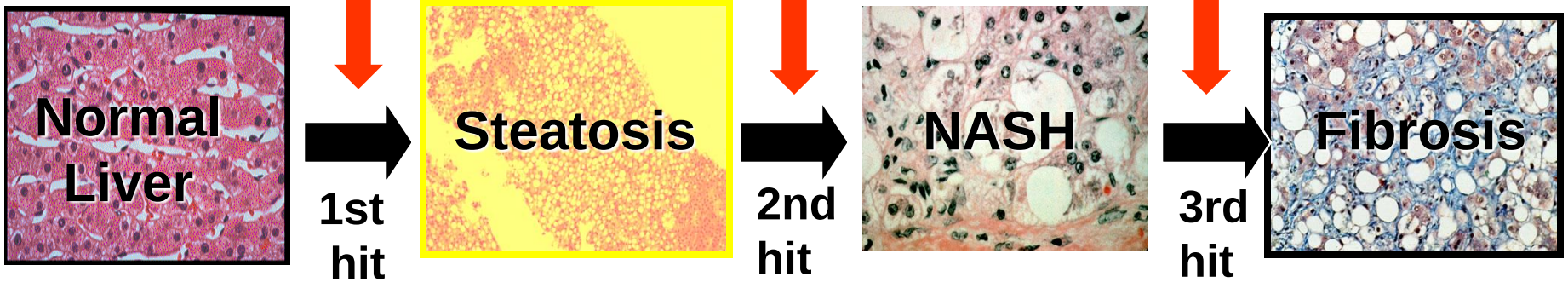
Antioxidants

Insulin Sensitizing Agents

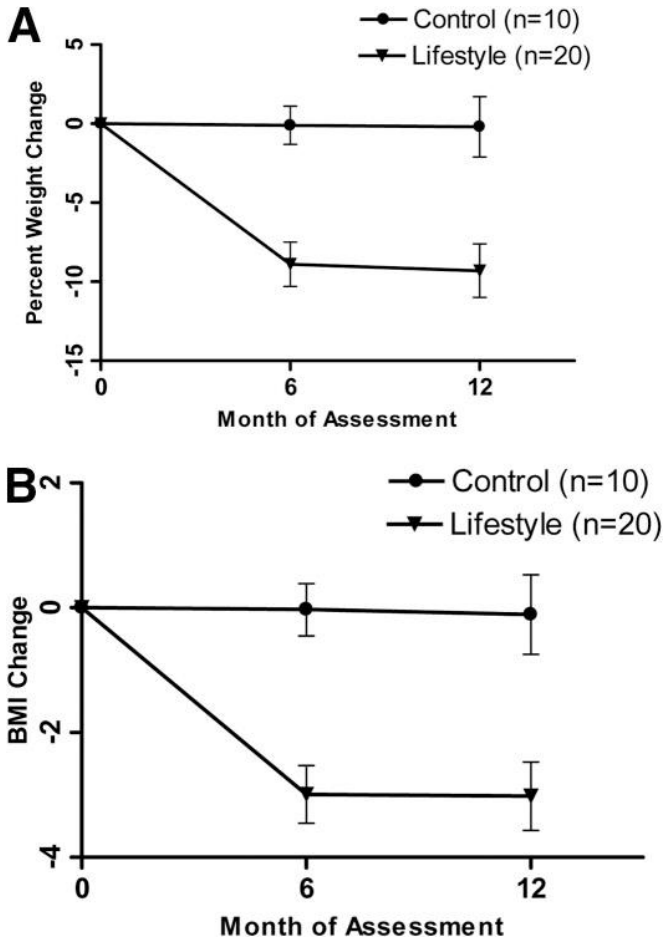
Insulin Resistance

Lipid Lowering Agents

- Cytokines
- Adipokines
- Oxidative stress
- Others



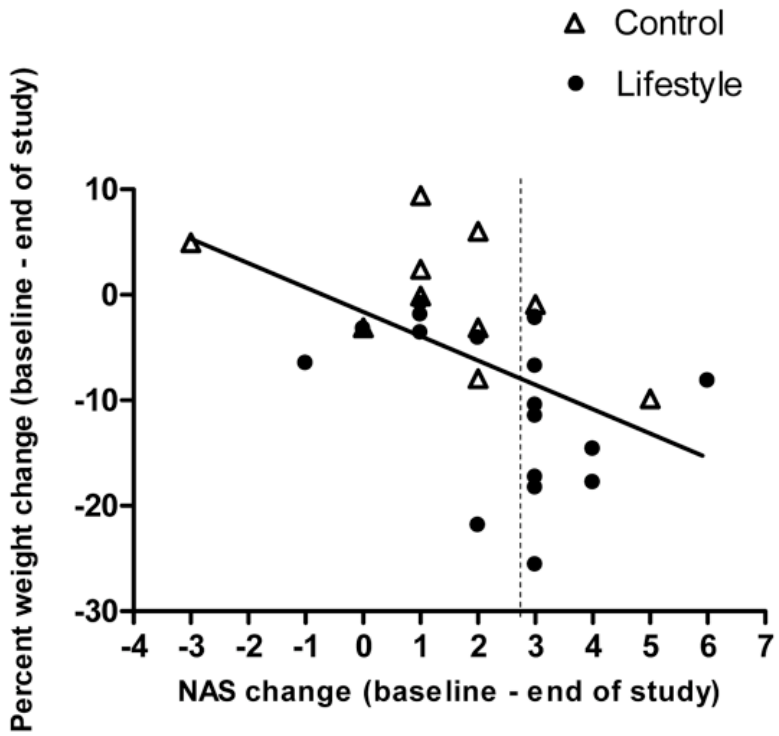
Weight Loss Works



31 Patients Randomized, controlled trial

40% in intervention group lost 10% body weight vs 0% in control group

72% vs 30% achieved study endpoint



Weight loss of ≥ 7% associated with improvement in all parameters of NASH except fibrosis (need 10% for fibrosis)

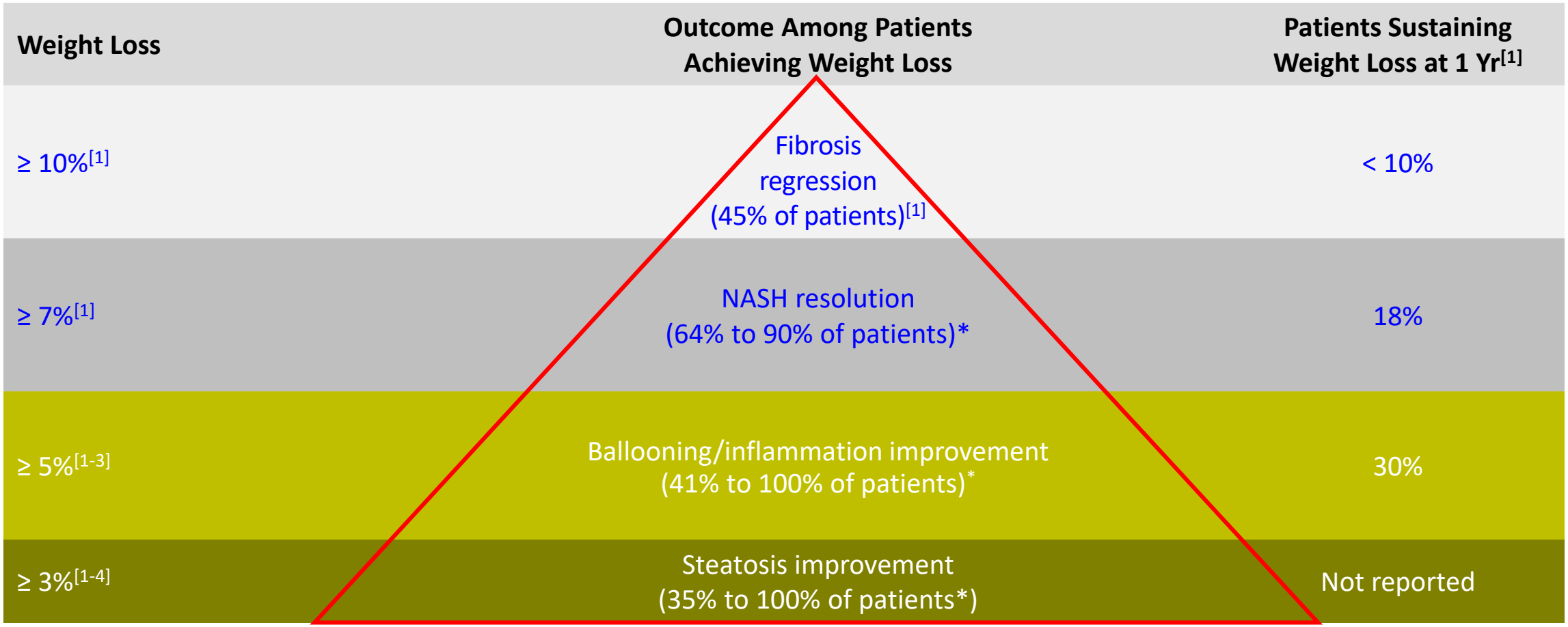
Promrat K, Hepatology 2010;51:121-129

Non-alcoholic fatty liver disease
Weight loss works

- 36 patients with obesity underwent paired liver biopsies at time of laparoscopic gastric banding and 24 months later
- Mean weight loss 34 kg
- Histologic improvements in steatosis, inflammation, and fibrosis
  - Only 4 fulfilled criteria for NASH at second biopsy (24 at entry)
  - 18 had improvement in fibrosis by 2 stages

Dixon et al. Hepatology.2004:39(6):1647

Percentage of Weight Loss Associated With Histologic Improvement in NAFLD

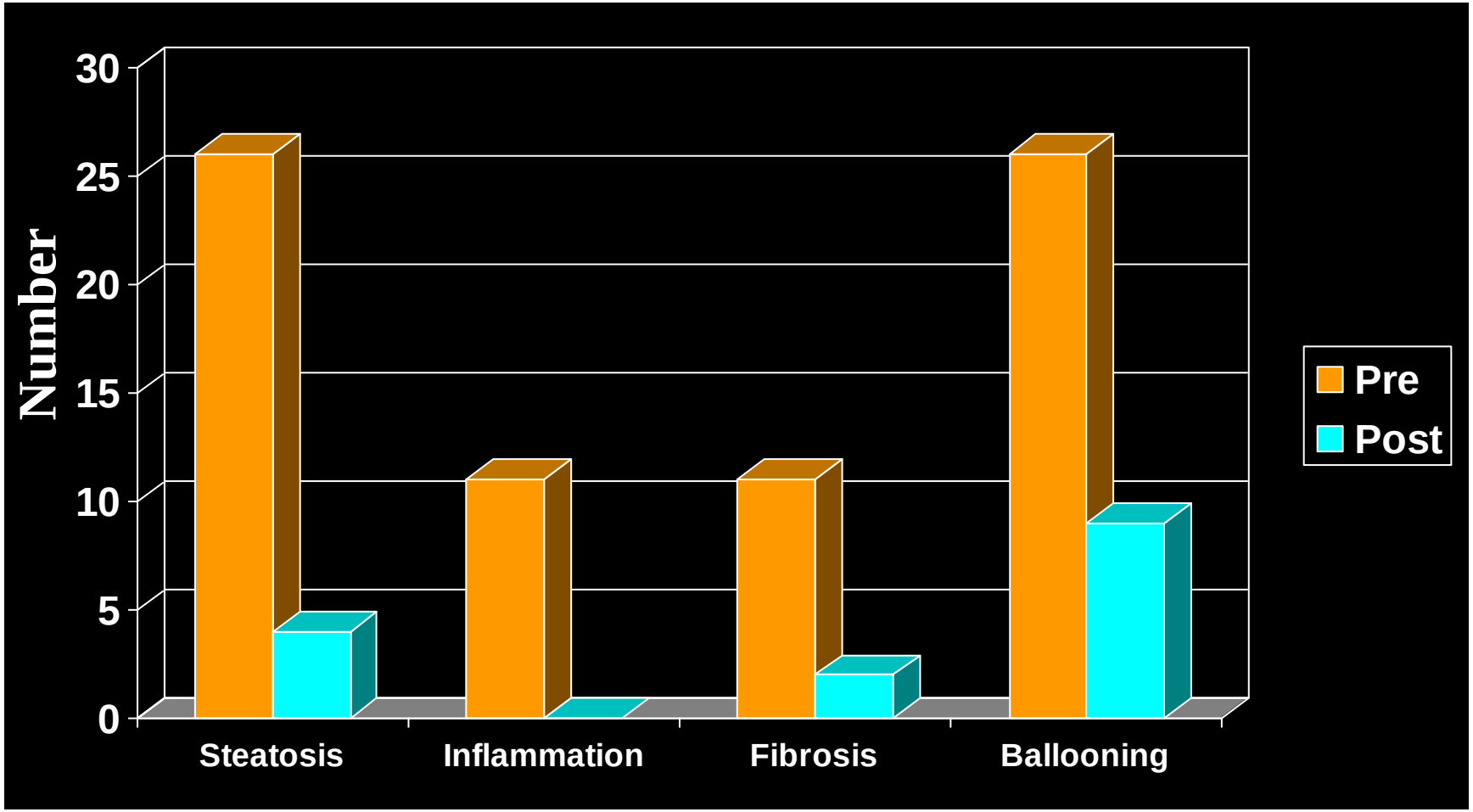


*Depending on degree of weight loss.

1. Vilar-Gomez. Gastroenterology. 2015;149:367. 2. Promrat. Hepatology. 2010;51:121.
3. Harrison. Hepatology. 2009;49:80. 4. Wong. J Hepatol. 2013;59:536.

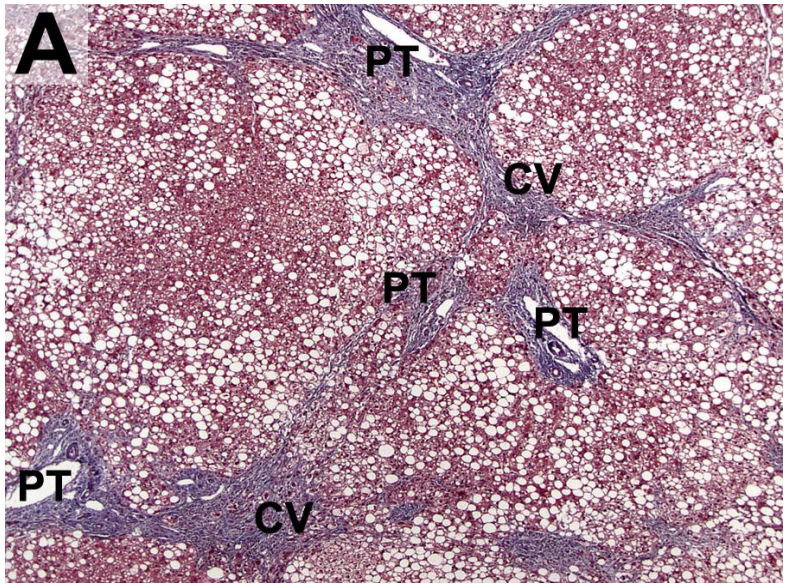
Slide credit: clinicaloptions.com

Liver Histology After Gastric Bypass

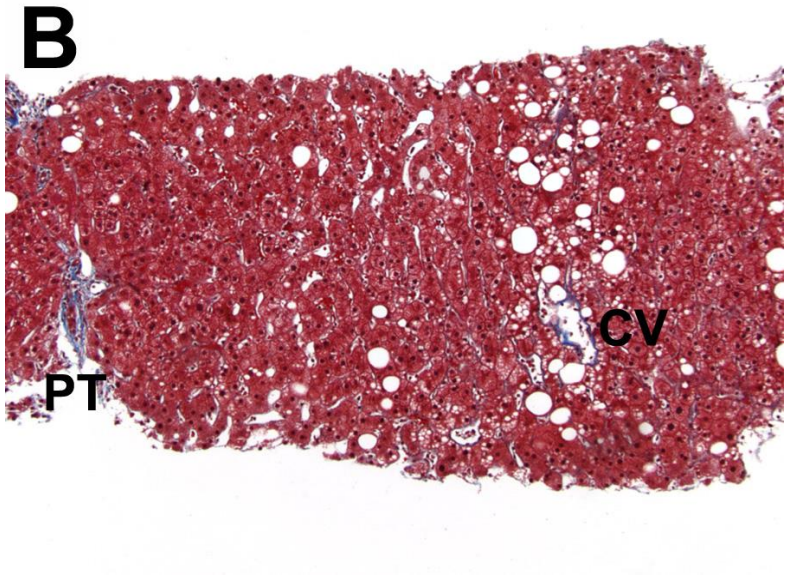


Hepatology 2004;39:1647-54

Significant Improvement in histology following bariatric surgery



1st biopsy



2nd biopsy at 8.5 months

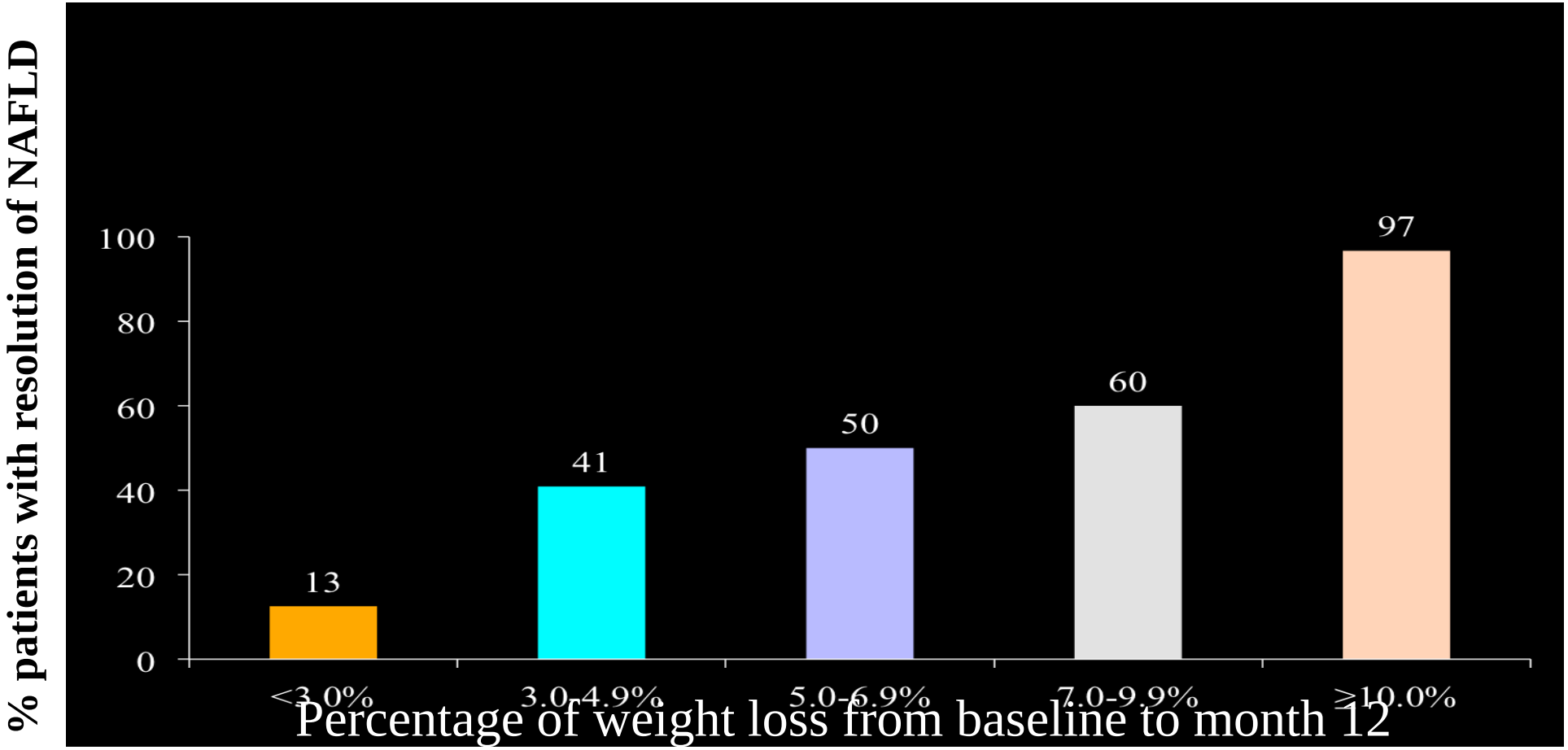
Mattar SG et al. Annals of Surgery 2005; 242: 610-620

Lifestyle Modification Program

- Assessed benefits of dietician led lifestyle modification for 12 months
  - Weekly meetings x 4 month, then monthly x 8
  - Moderate carbohydrate, low fat, low glycemic index
    - Emphasis on fruits and vegetables
  - Exercise: moderate intensity for 30 minutes 3-5 days/week
    - Increased to daily
- 154 Patients Enrolled
- Primary Endpoint
  - Remission of NAFLD: IHTG of < 5% by MRS
- 64% in intervention group resolved NAFLD
- 20% in control group resolved NAFLD

Wong VW, J Hepatol 2013

Degree of weight loss and resolution of NAFLD by hepatic TG content

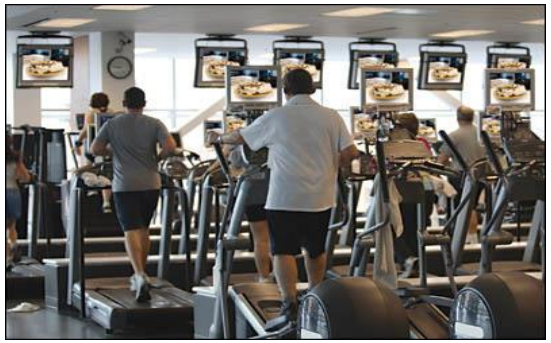


n =	72	22	10	20	30

Wong VW, J Hepatol 2013

Exercise

A recent large, cross-sectional study assessed the relationship between meeting/exceeding US national guidelines for physical activity and NAFLD severity



- Self-reported
- 813 patients
- Divided into 3 exercise categories based on time spent in activity and metabolic equivalents (METS):
  - Inactive (54%)
  - Moderate (20%):>150 min/week; Activities with MET values 3-5.9
  - Vigorous (26%):>75 min/week: Activities with MET values >6

Kistler KD, Am J Gastroenterol 2011;106:460-468

Exercise

- Vigorous exercise associated with decreased adjusted odds of having NASH
  - OR: 0.65 (0.43-0.98)

- Doubling recommended time spent in vigorous exercise (>150 min/week), associated with decreased adjusted odds of advanced fibrosis
  - OR:0.53 (0.29-0.97)

Younger age, higher education, higher income, lower BMI and no diabetes

Kistler KD, Am J Gastroenterol 2011;106:460-468

Exercise

- Optimal Intensity
  - Goal is to maintain a lifestyle change
  - Moderate exercise, burning ~400 kcal/session
    - 3 times/week
    - Improves insulin resistance
    - Overall energy expenditure achieved per work-out more important than intensity
      - » Training at 60% VO2max as effective as 80% VO2max
  - Weight loss
    - Need to work out for longer period of time

Ryan AS, Aging Health, 2010

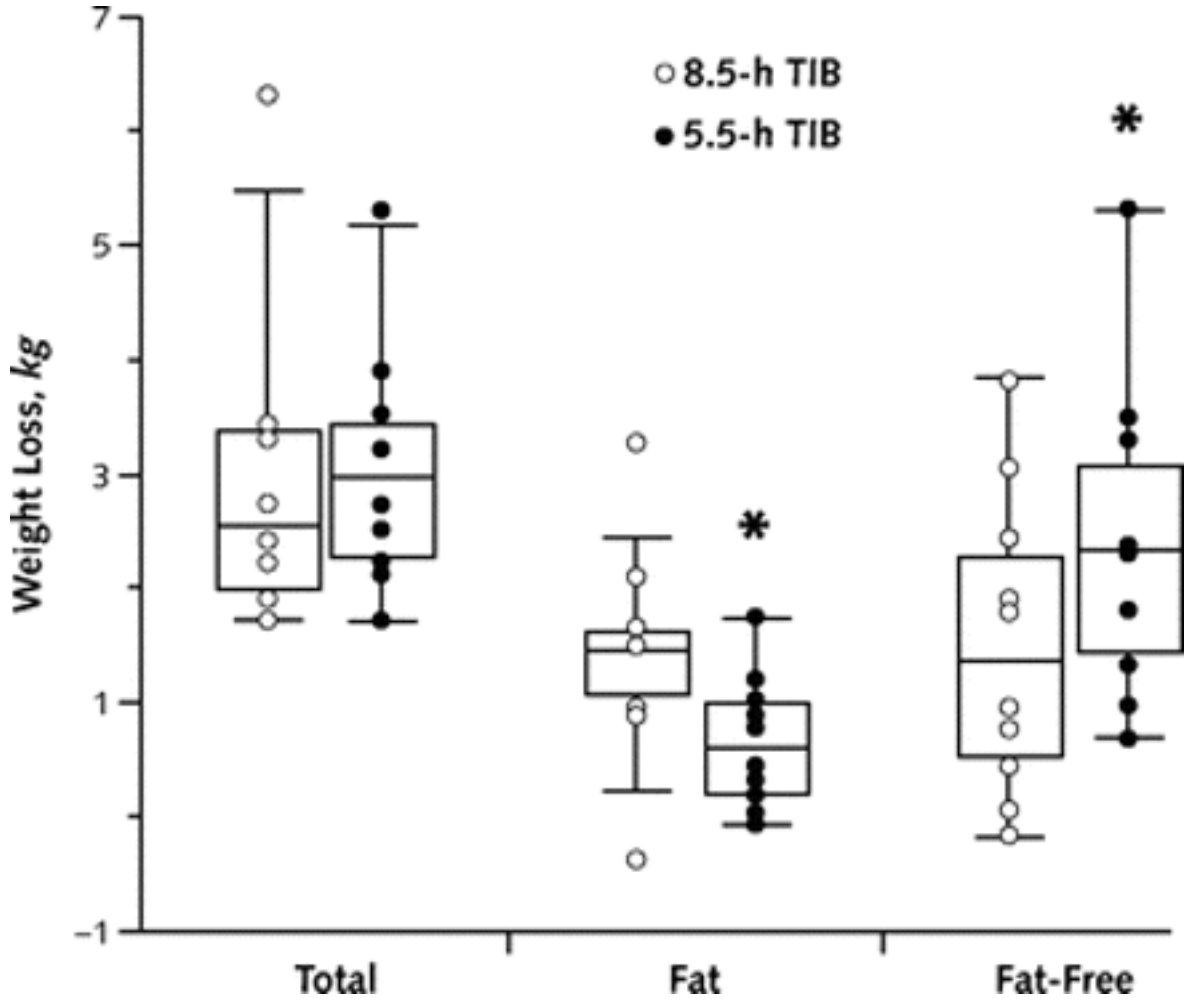
Sleep

10 overweight adults assigned to sleep 8.5 vs 5.5 hours each night for 14 days

Moderate caloric restriction

Lost same amount of weight (~6.6 pounds)

Sleep curtailment decreased proportion of weight lost as fat by 55% and increased loss of fat-free mass by 60%



Nedeltcheva AV, Ann Intern Med 2010

Treatment: Lipid Lowering Agents

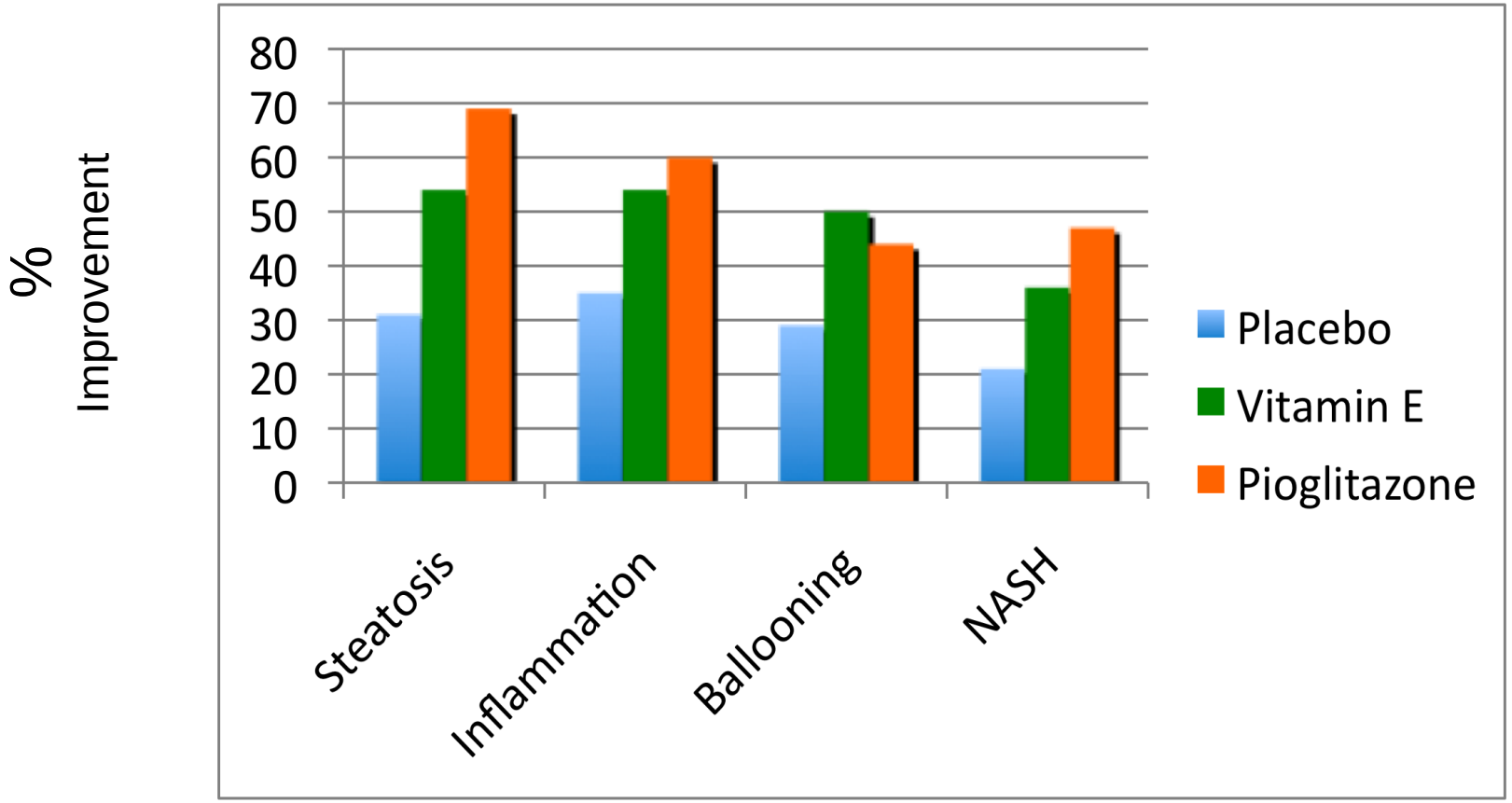
Study	Design (mts)	Meds	N	ALT	Hist
Laurin	Open label (12)	Clofibrate	16	-	-
Basaranoglu	RCT (1)	Gemfibrozil	46	+	NA
Horlander	Open label (12)	Atrovastatin	7	+	+
Kiyici	Open label (6)	Atrovastatin	27	+	NA
Hatzitolios	Open label (6)	Atrovastatin		+	NA
Gomez-Dominguez	Open label (12)	Atrovastatin	25	+	NA
Rallidis	Open label (7)	Pravastatin	5	+	+/-
Merat	RCT (6)	Probucol	30	+	NA

Statins are safe, improve ALT, not histology

Treatment: Insulin Sensitizing Agents

Study	N	Drug	Duration (months)	Design	ALT	Histology
Caldwell	10	Troglitazone	3-6	Open label	+	+
Acosta	8	Pioglitazone	2-12	Open label	+	N/A
Shadid	5	Pioglitazone	4.5	Open label	+	N/A
Sanyal	21	Pioglitazone + Vit E	6	RCT	+	+
Promrat	18	Pioglitazone	12	Open label	+	+
Tetri	30	Rosiglitazone	12	Open label	+	+
Belfort	55	Pioglitazone ± Diet	6	RCT	+	+
Marchesini	14	Metformin	4	Open label	+	N/A
Nair	15	Metformin	12	Open label	+	N/A
Bugianesi	55	Metformin	6	RCT	+	+
Uygun	17	Metformin	6	RCT	+	-
Duseja	7	Metformin	6	Open label	+	N/A
Schwimmer	10	Metformin	6	Open label	+	N/A

Pioglitazone and Vitamin E
PIVENS Trial



Sanyal AJ, New Engl J Med 2010

Summary of PIVENS findings

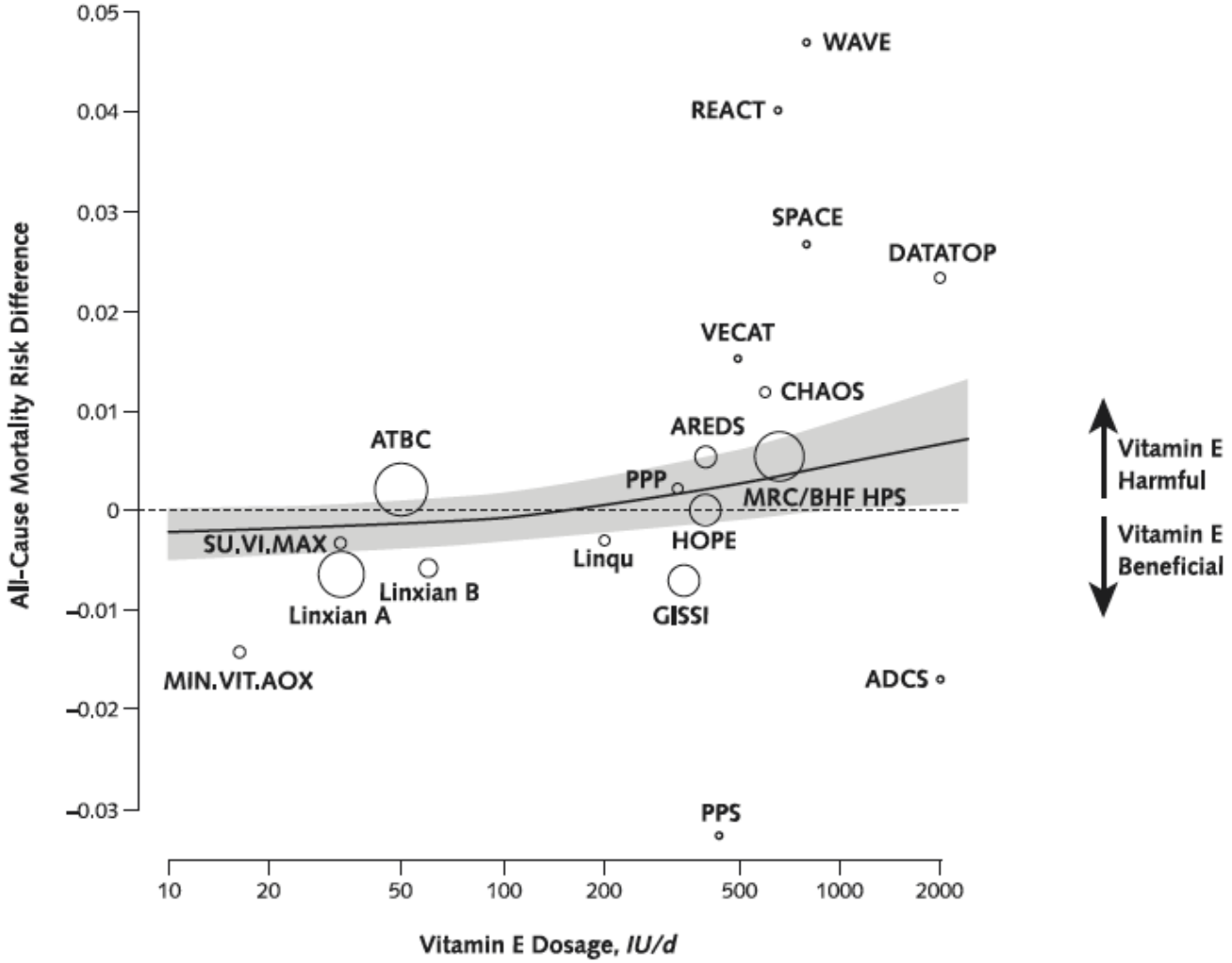
- Vitamin E effective over placebo for NASH
- Pioglitazone improved, IR, ALT, steatosis and inflammation, but not 1˚ outcome
- Only 34% (Pio) and 43% (Vit E) had histological response, neither improved fibrosis
- Cannot generalize to diabetics or cirrhotics

Why not empirically treat suspected NAFLD with vitamin E ?

- 70-75% have NAFLD, most isolated steatosis
- 50% of patients don’t respond to Vitamin E
  - liver enzymes are not reliable to assess quiescence or progression
- The long-term safety remains unknown
- Prostate cancer risk? (absolute increase 1.6 per 1000 person yrs)

Meta-analysis of Vitamin E – increased mortality?

- Different forms of Vitamin E
  - Natural vs synthetic
- Confounders not controlled for:
  - High dose Zn supplementation
  - Use of concomitant vitamin A
  - Smoking
- Trials not uniformly using Vit E as a treatment
- RCTs with no death excluded



Annals of Int Med, 2005

NO Pioglitazone for NASH

Improve[2]

- Insulin sensitivity
- ALT
- Steatosis
- Inflammation
- ? Ballooning

- Weight gain **(2–4.7 kg)**
- Cardiac toxicity[1]
- Fracture risk[2]
- ? Bladder cancer[3]

Pros

Cons

Meta-analysis of 19 trials (16,390 patients) with T2DM, pioglitazone[1]
- Death, MI, or CVA: 4.4% of pioglitazone vs 5.7% of control (*P* = 0.005)
- More CHF in pioglitazone (2.3%) vs control (1.8%) (*P* = .002), no effect on mortality

Abbreviations: ALT, alanine aminotransferase; CHF, congestive heart failure; CVA, cerebrovascular accident; MI, myocardial infarction; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

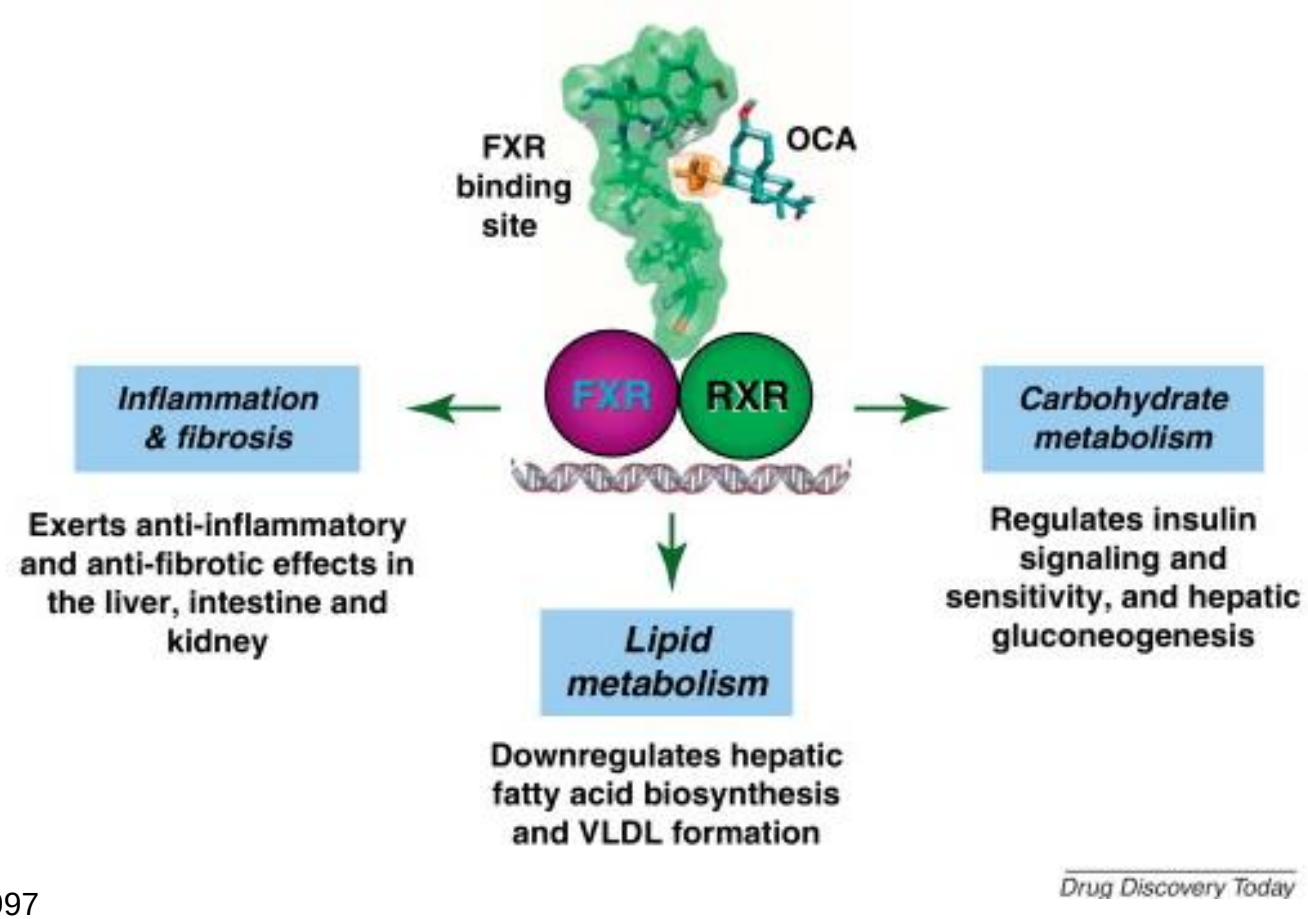
1. Lincoff AM, et al. *JAMA.* 2007;298:1180-1188. 2. Ratziu V. *Nat Rev Gastroenterol Hepatol*. 2013;10;646-685.
3. Lewis JD, et al. *Diabetes Care.* 2011;34:916-922.

Courtesy of Mary Rinella, MD.

Obeticholic acid

Semi-synthetic bile acid derivative

Farnesoid-X Receptor (FXR) agonist

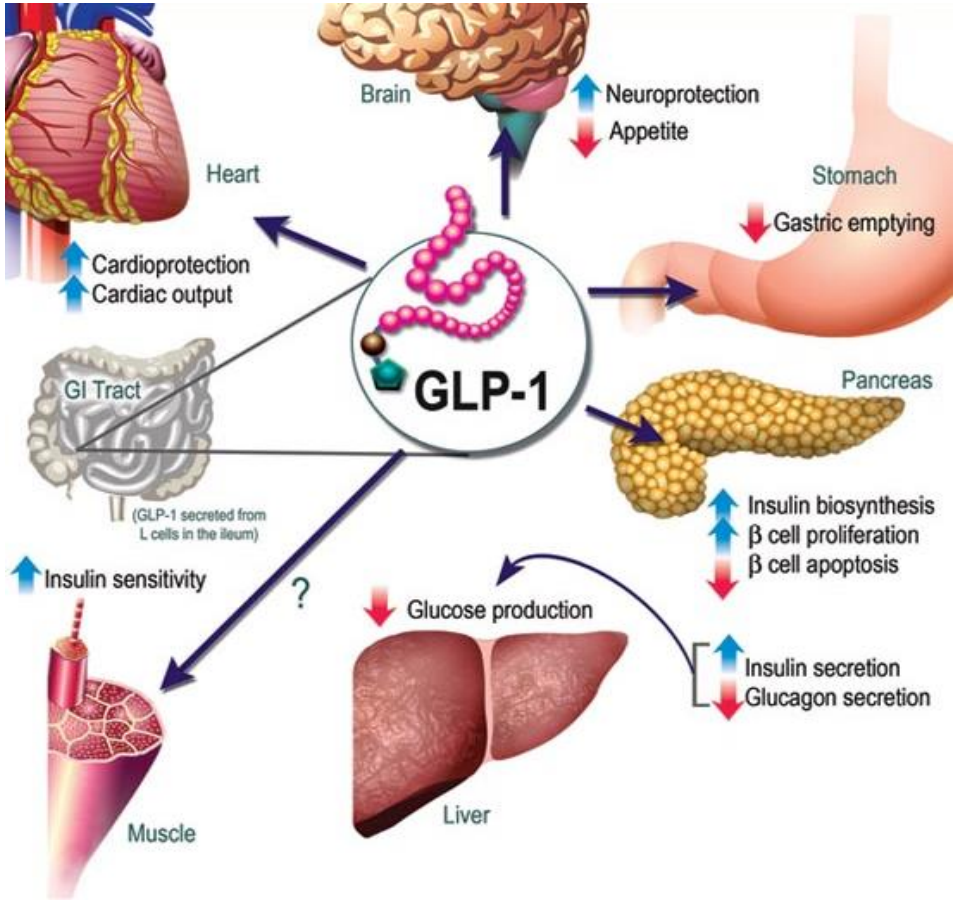


Adorini L, Drug Dis Today 2012;17:988-997

Glucagon-Like Peptide-1 Analogue: Liraglutide

GLP-1

- Controls serum glucose
  - Induces insulin secretion
  - Reduces glucagon secretion
- Induces weight loss, suppression of appetite and delayed gastric emptying



Perazzo H, et al. *Liver Int.* 2016;Oct 11. [Epub ahead of print].

LEAN Study: Liraglutide in Overweight NASH Patients Without Cirrhosis

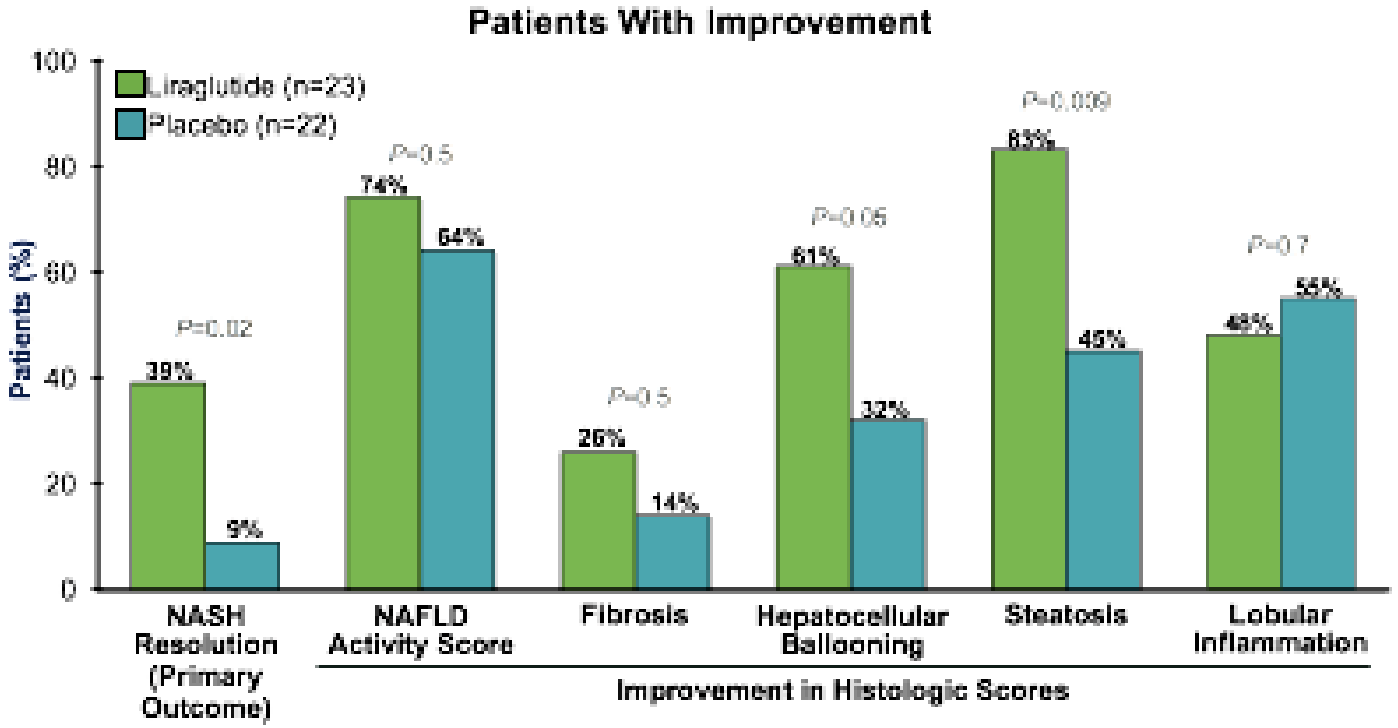
Phase 2 (n=52) (UK, 4 sites)

Double-blind, placebo-controlled
Histologic evidence of definite NASH
(steatosis >5%, hepatocyte ballooning, lobular inflammation)
Liver biopsy within 6 months of entry
Stable type 2 diabetes allowed
No Child-Pugh B/C cirrhosis

Liraglutide 1.8 mg/day sc (n=26)

Placebo (n=26)

Week 0 **48**

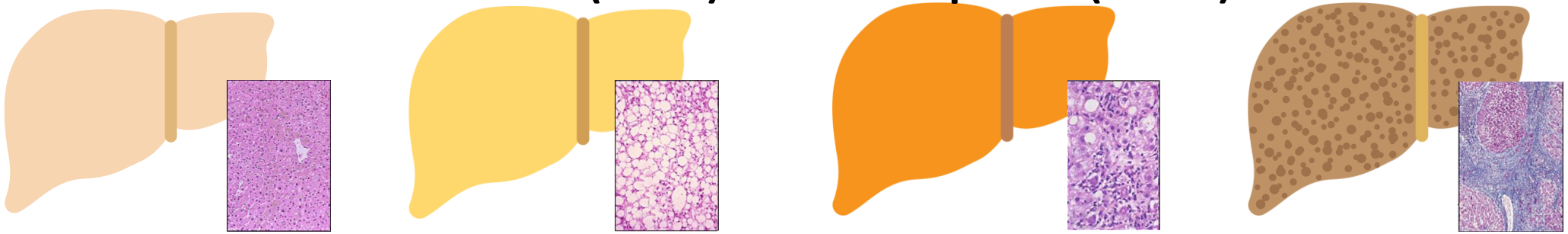


LEAN: Liraglutide Efficacy and Action in NASH.
Patients stratified by diabetes status.
Primary endpoint (week 72, ITT):
Improvement in liver histology without worsening of fibrosis.
Improvement: disappearance of hepatocellular ballooning.
Worsening of fibrosis: any increase in Kleiner fibrosis stage.

Armstrong MJ, et al. *Lancet.* 2016;387:679-690.

Examples of NASH Treatments in Phase II or III Investigations

NAFLD



Targets related to insulin resistance and/or lipid metabolism → **Targets related to lipotoxicity and oxidative stress** → **Targets related to inflammation and immune activation** → **Targets related to cell death (apoptosis and necrosis)** → **Targets related to fibrogenesis and collagen turnover**

PPARγ:	Pioglitazone
GLP-1:	Liraglutide, semaglutide
ACC:	GS-0976,PF-05221304
SCD1:	Aramchol
FGF21:	BMS-986036
THR-β:	MGL-3196, VK2809

PPARα/∂:	**Elafibranor**
PPARα/∂/γ:	Lanifibranor
FXR:	**OCA,** GS-9674, tropifexor
FGF19:	NGM282
MPC:	MSDC-0602K

CCR2/5: Cenicriviroc (inflammatory target but affects fibrosis)

P2X7R:	SGM-1019

ASK1: Selonsertib (cell death target but affects fibrosis)

Caspase:	Emricasan

Galectin:	GR-MD-02

Bold = phase III
Some agents have multiple targets

Slide credit: clinicaloptions.com

Summary

- NAFLD is part of a systemic inflammatory process and other diseases (cardiovascular) are associated
- More prevalent than previously estimated
  - Hispanics and diabetics at particular risk
- Biopsy is required for research studies not practical in clinical practice, steatosis benign from hepatic point of view, NASH can progress to cirrhosis
- Smoking and excess alcohol are bad, but coffee and sleep likely good

Summary

- Weight loss goal of 10% is best for immediate first level histopathology improvement
- Moderate exercise may not be enough to effect change in NASH. Vigorous exercise for >150 min/week ideal
- Vitamin E may be considered for patients with proven NASH with caveats (use natural Vit E)
- Statins are safe and effective for lipid disorders, not NASH
- Bariatric surgery is an expensive solution
- Dietician visits for all patients
- Consider weight loss contract
- Fructose free diet
- Vegetarian diet preferred
- Mediterranean diet optimal
- Stop use of plastic water bottles, containers, bisPhenols

Thank You!

GiSH