SESSION 3

CLINICAL STATE OF THE ART LECTURE

Chair: Philippe Mathurin (France)

The clinical, pathophysiological and regulatory implications of alcohol consumption in nonalcoholic steatohepatitis

+

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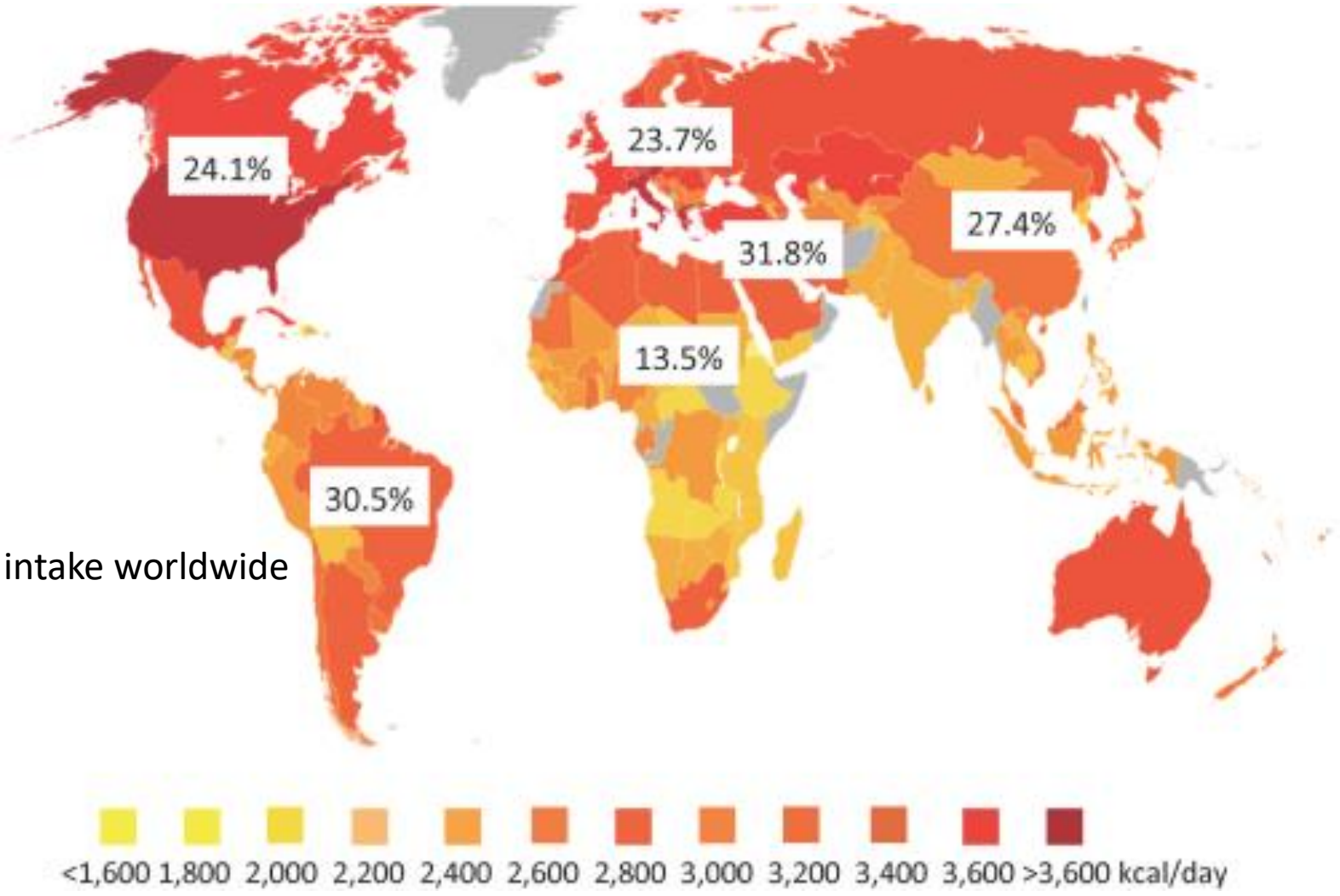
Conflicts of Interest

- President, Sanyal Biotechnologies
- Stock options: Genfit, Akarna, Tiziana, Indalo, Durect, Exhalenz, Hemoshear
- Advisor with compensation: Lilly, Pfizer, Novartis, Ardelyx, Salix, Hemoshear, NovoNordisk
- Advisor without compensation: Galectin, Intercept, Merck, Bristol Myers, Immuron, Gilead, Chemomab, Affimmune, Protalix, Nitto Denko, Cirius, Boehringer Ingelhiem
- Grants to institution: Gilead, Tobira, Allergan, Merck, Bristol Myers, Astra Zeneca, Immuron, Intercept, Novo Nordisk, Shire, Boehringer Ingelhiem, Cirius
- ALL OPINIONS EXPRESSED ARE MY PERSONAL OPINIONS

It was the best of times..it was the worst of times

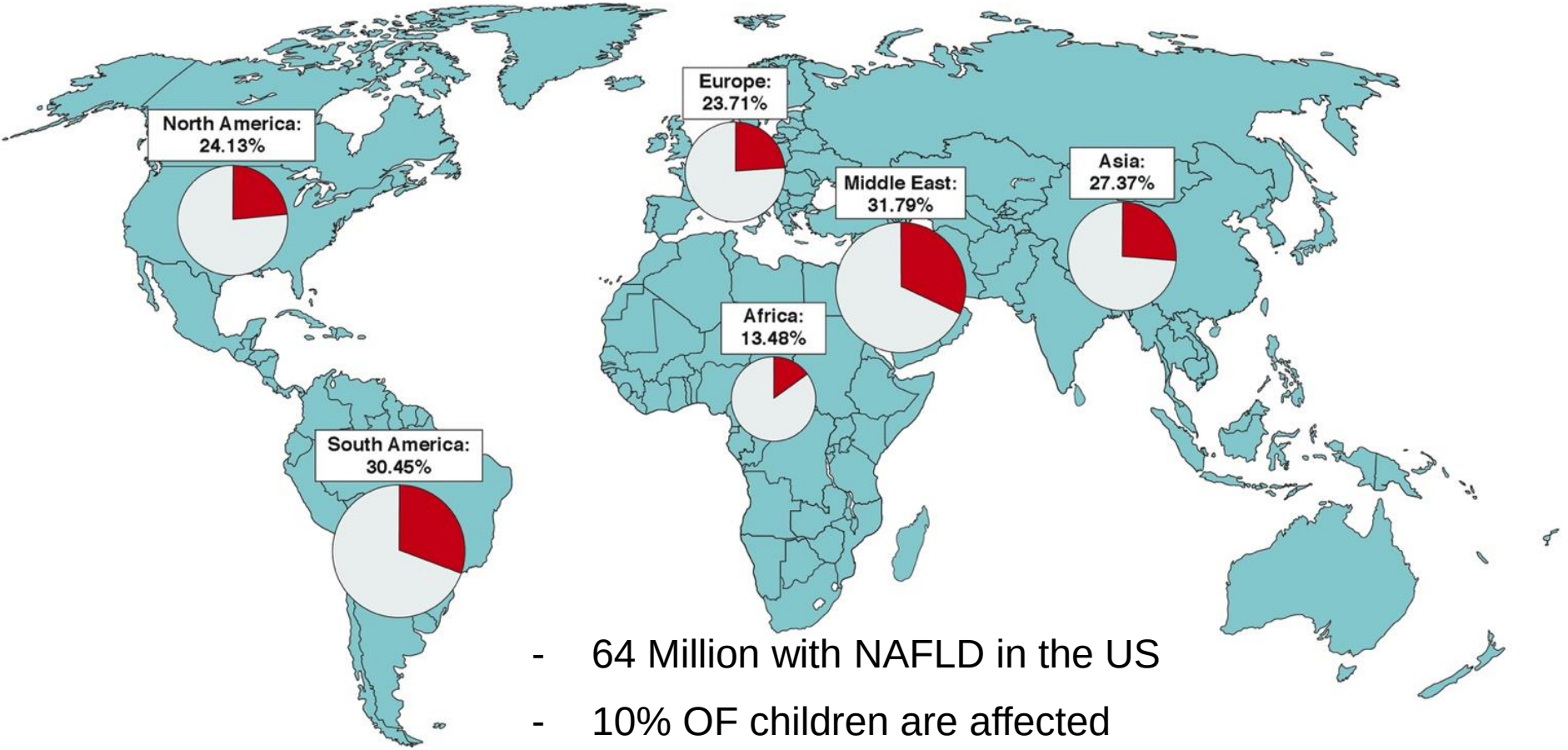
Caloric intake worldwide



Hepatology
Volume 64, Issue 1, pages 19-22, 4 APR 2016 DOI: 10.1002/hep.28524
http://onlinelibrary.wiley.com/doi/10.1002/hep.28524/full#hep28524-fig-0001

NAFLD: a global disease due to excess calories

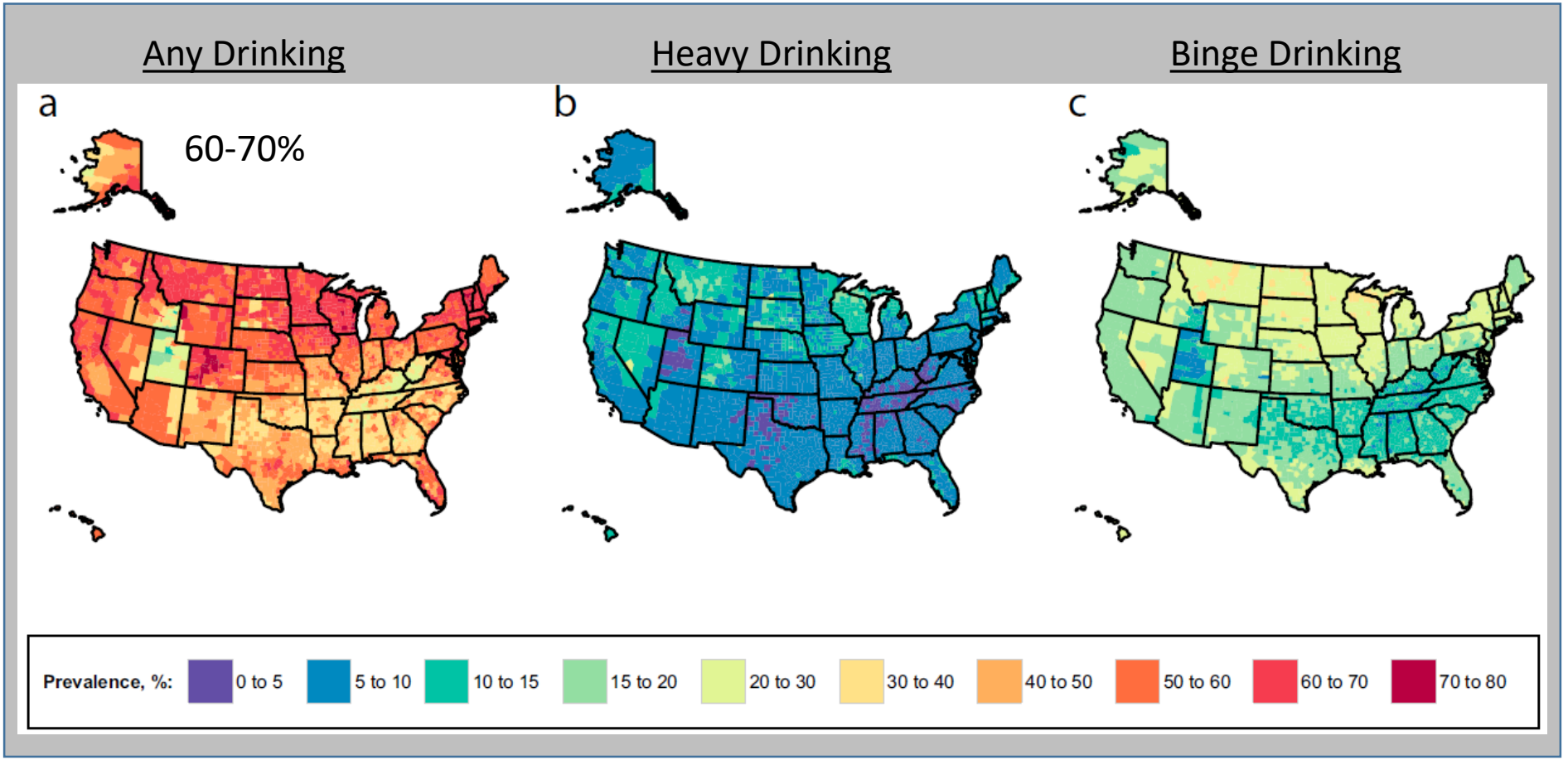
Prevalence data using a radiologic NAFLD diagnosis



- 64 Million with NAFLD in the US
- 10% OF children are affected
- Closely linked to global prevalence and trends for T2DM

Younossi ZM, Gastroenterology 2016

Prevalence of Alcohol Use in US

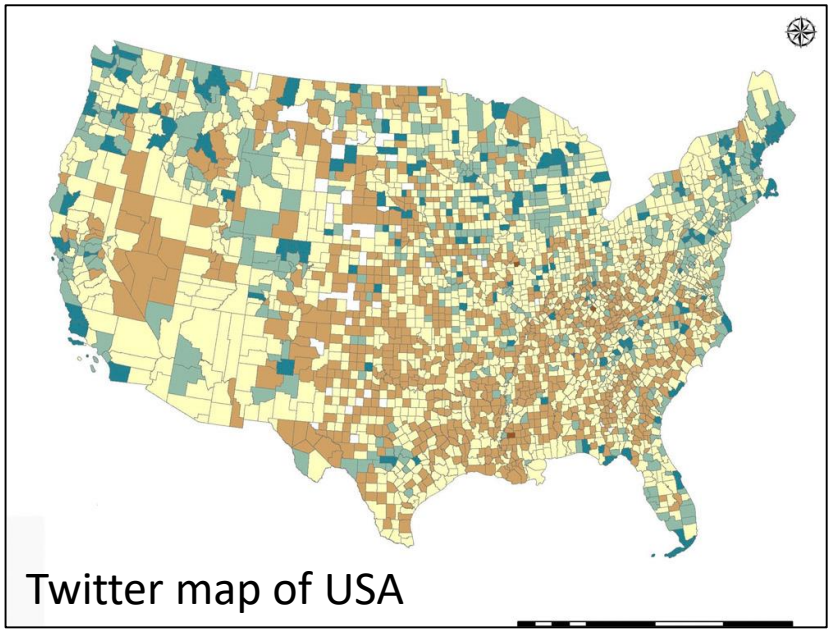


Dwyer-Lindgren, 2015 (Behavioral Risk Factor Surveillance System data)

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



Twitter map of USA

N= 80 million tweets
3140 counties

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


Duff
Livin'
La Vida
SoFa

Decoding the complexity of alcohol use and consumption behavior as it relates to end organ disease

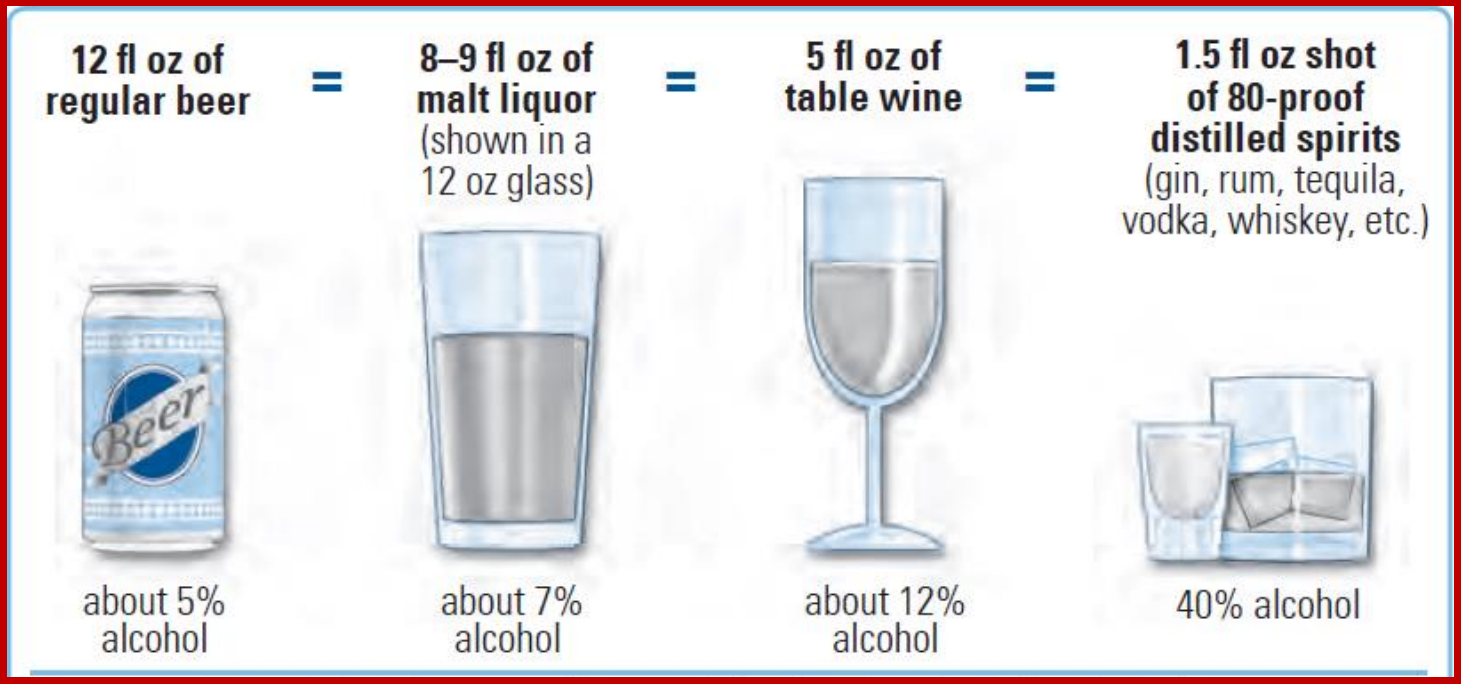
Alcohol use in society

- Experimental
- Recreational
- Situational
- Binge
- Habitual (dependency)

- Medicinal

What is a Standard Drink

1 Standard Drink = 14 g absolute ethanol



Rethinking Drinking, NIAAA; Clinician's guide, NIAAA.

Definitions

- Binge drinking:
  - 5 or more drinks in one session for men
  - 4 or more drinks in one session for women
- NIAAA consensus definition:
  - drinking to a blood alcohol level of 80 mg/dl (0.08) or higher in one session

Wechsler et al, *Psychol Addict Behav*. 2001;15:287–291.
NIAAA, 2004

Risk stratification based on risky drinking- *(drinking may be regular or episodic)*

Risk profile	< 3/occasion	5+/4+/monthy	5+/4+ weekly
none	Low/moderate	moderate	high
1-2	Low/moderate	moderate	high
> 3 or end organ damage	high	high	high

Risk factors: family history, childhood trauma, personality, mental disorders, age of initial drinking

TK Li, J Gas Hep, 2008

Alcohol Use Disorder (AUD): DSM 5

- Failure to fulfill major role obligations at work, school, or home
- Recurrent use in situations in which it is physically hazardous
- Continued use despite persistent social or interpersonal problems caused or exacerbated by alcohol
- Tolerance
- Withdrawal
- Larger amounts/longer period than intended
- Persistent desire or unsuccessful efforts to reduce or stop use
- Great deal of time spent obtaining, using or recovering
- Important activities reduced or given up
- Continued use despite persistent physical or psychological problems caused or exacerbated by alcohol
- Craving, or a strong desire or urge to use alcohol

Mild:
2-3 criteria

Moderate:
4-5 criteria

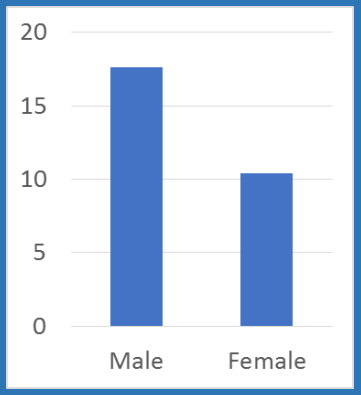
Severe:
6+ criteria

14% of US population met AUD criteria in last 12 months and 30% have AUD sometime in Their life- NESARC data

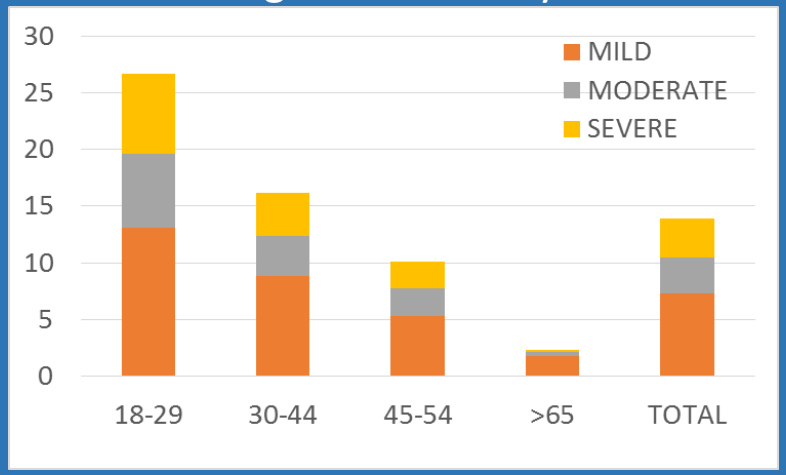
Alcohol Use Disorder Epidemiology

Males, younger age, lower SES and native Americans have higher rates of AUD

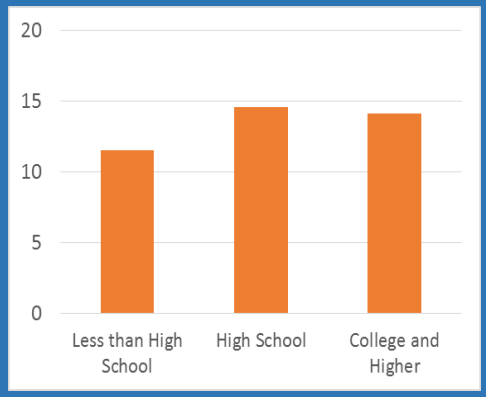
Sex



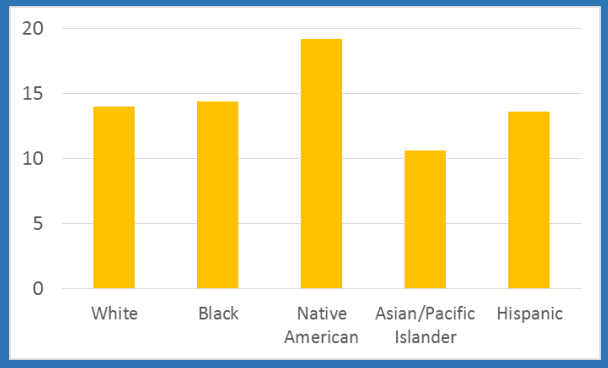
Age and Severity



Education Level



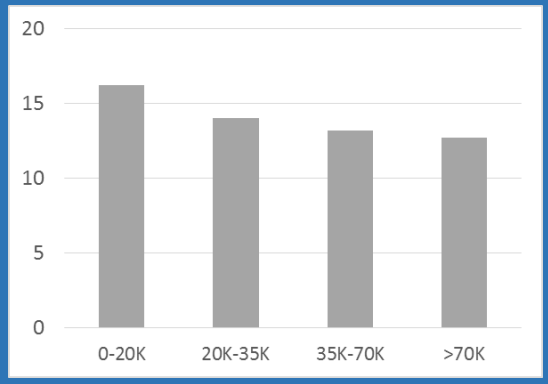
Race/Ethnicity

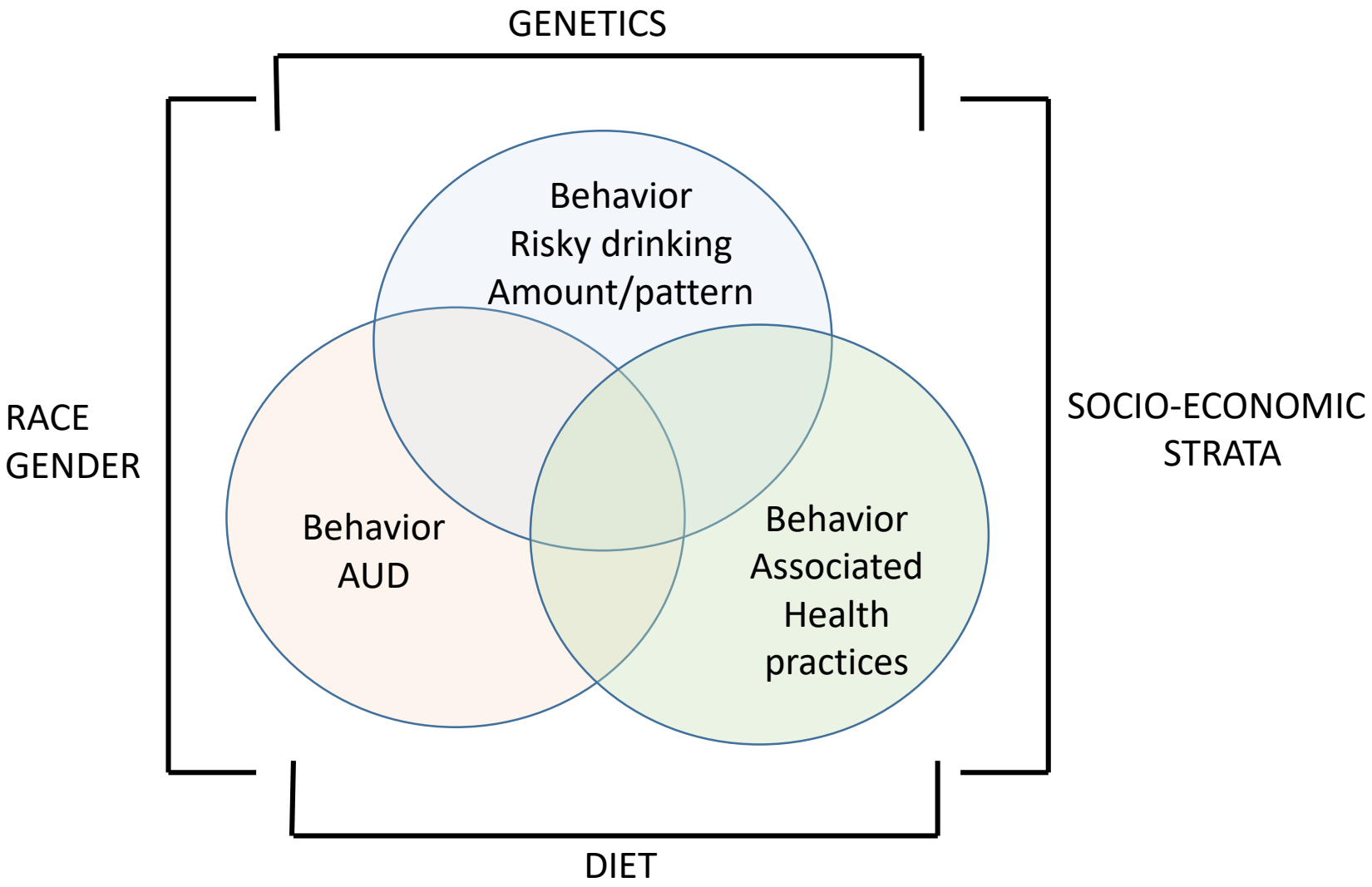


NESARC

Grant et al., JAMA Psychiatry 2015

Income

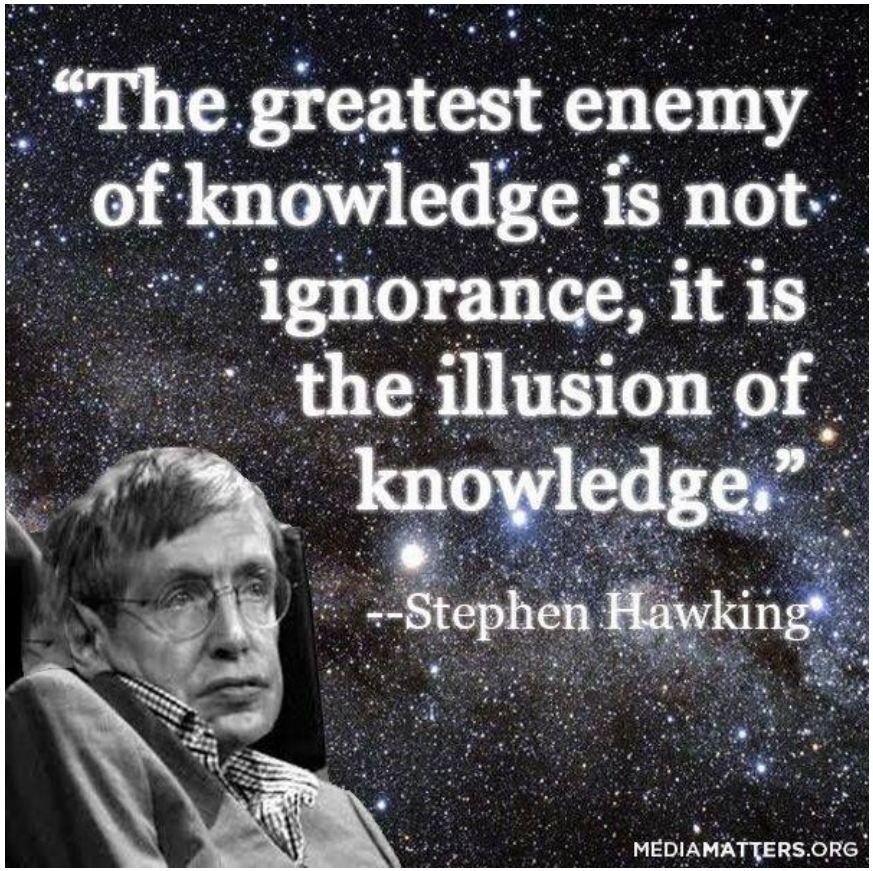



GENETICS
Behavior
Risky drinking
Amount/pattern
RACE
GENDER
SOCIO-ECONOMIC
STRATA
Behavior
AUD
Behavior
Associated
Health
practices
DIET

Take home messages

- Alcohol use is widespread and is contributing to declining life expectancy in the USA
- Ask the following questions (for health care providers):
  - do you consume alcohol
  - what is your beverage of choice
  - how much
  - how often
  - how often do you consume > 3, > 5 drinks
  - when did it start
- For Trials in NASH- AUDIT and timeline follow back

Pathophysiological relevance of alcohol consumption in NASH



Disease development and progression, response to treatment, impact on biomarkers used to define disease state and change in state

Pathogenesis of NASH

GENETICS

DIET

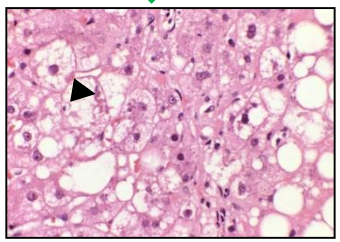
MICROBIOME

BEHAVIOR

SYSTEMIC INFLAMMATION-METABOLIC CHANGES (adipose tissue)

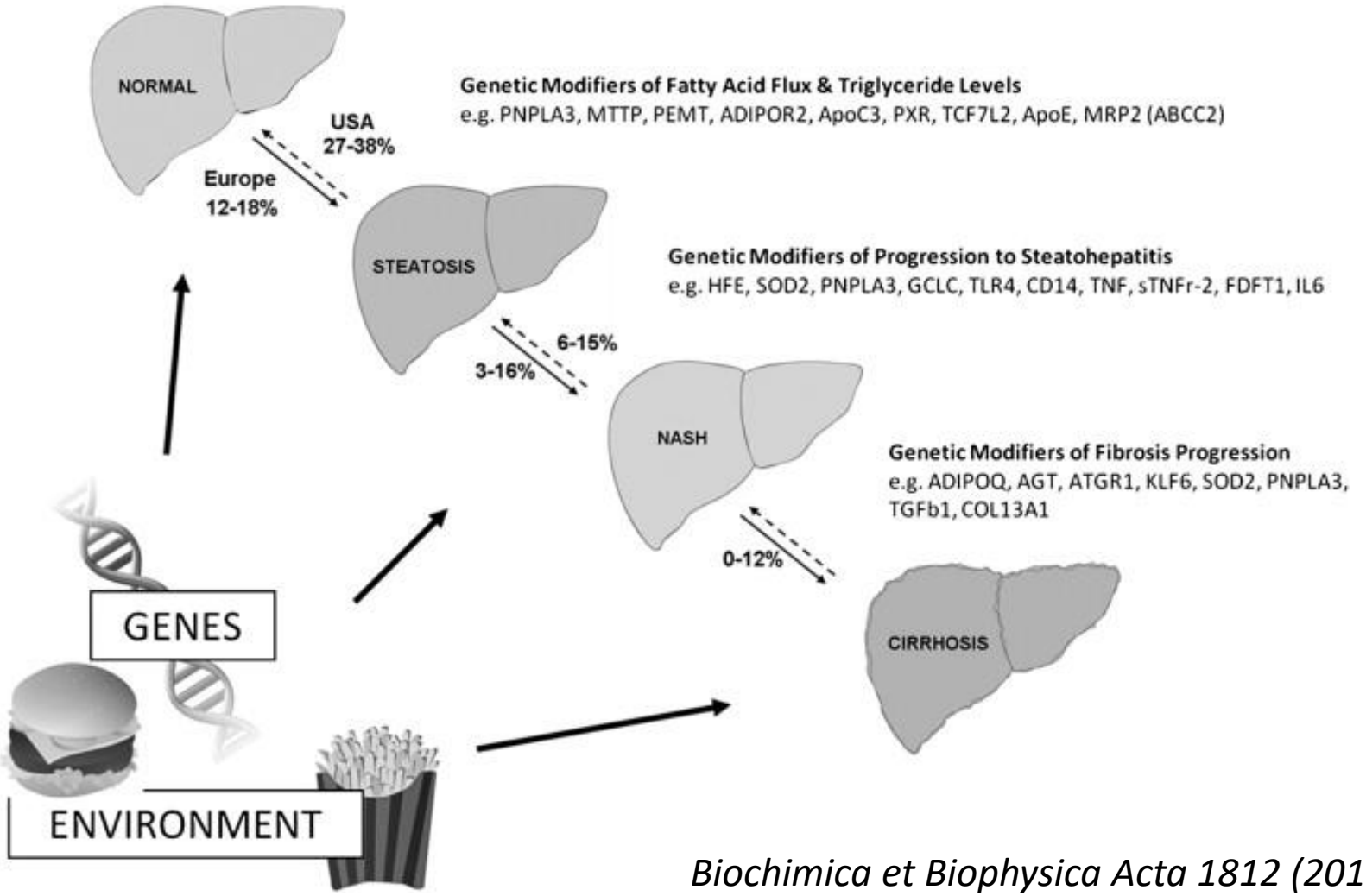
LIVER SPECIFIC CHANGES
(EPIGENETIC, TRANSCRIPTOMIC, PROTEOMIC, METABOLOMIC)
(CELL-CELL CROSSTALK)

NAFL vs NASH



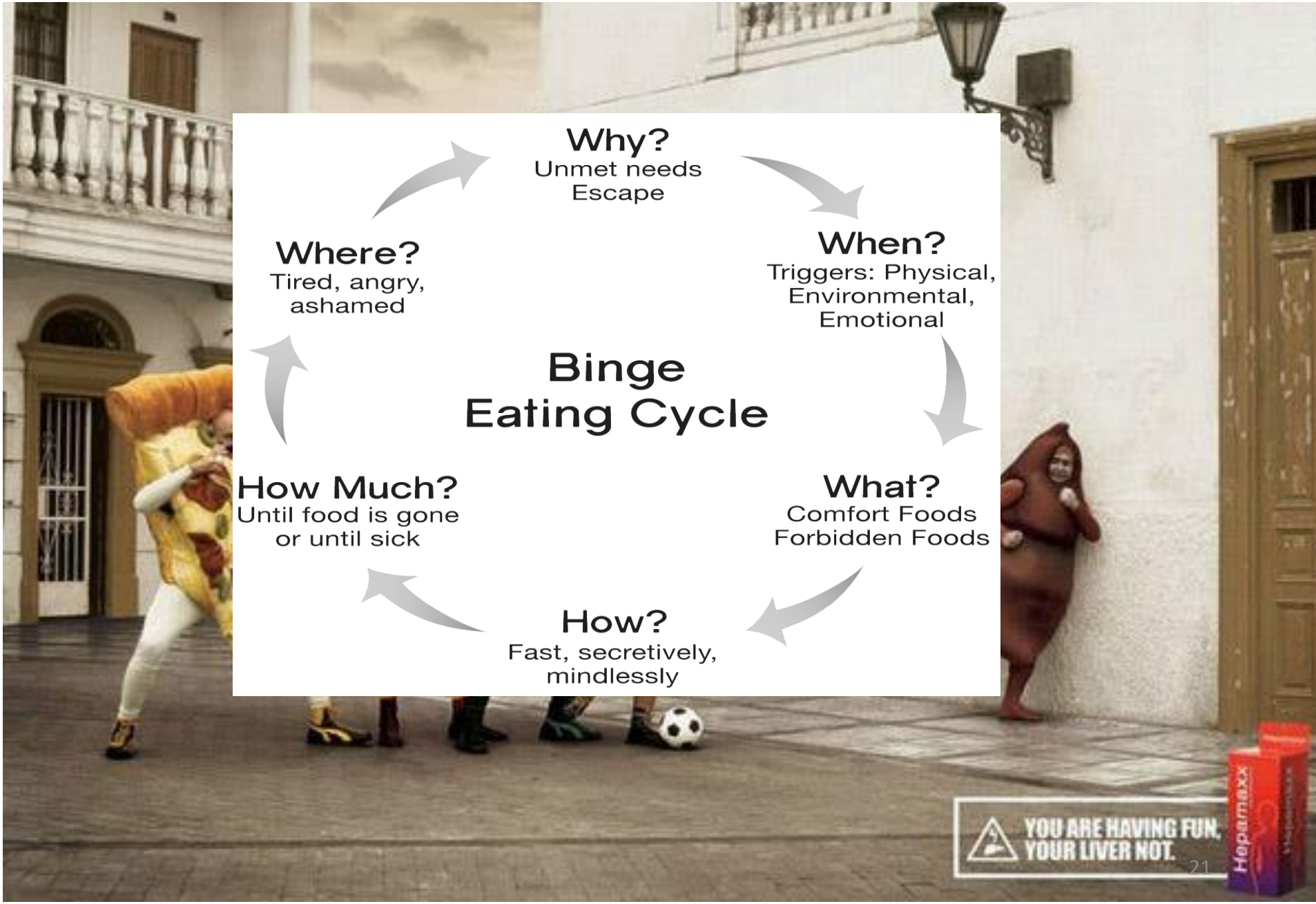
PROGRESSION TO CIRRHOSIS

Genetics influences the development and progression of NASH



Biochimica et Biophysica Acta 1812 (2011) 1557–1566

Pathophysiological implications



Binge Eating Disorder and Risk factors for Fatty Liver Disease

Hudson et al., Am J Clin Nutr 2010;91:1568–73

- 5 year follow-up 134 patients with binge-eating disorder and 134 with no history of eating disorders
- Frequency-matched for age, sex, and baseline body mass index (BMI)

	Binge-eating disorder		No binge-eating disorder	
Component	Subjects at risk[1]	Subjects with metabolic syndrome components[2]	Subjects at risk[1]	Subjects with metabolic syndrome components[2]
	n	*n* (%)	*n*	*n* (%)
Dyslipidemia	115	34 (30)	109	18 (17)
Hypertension	104	25 (24)	102	18 (18)
Type 2 diabetes	124	13 (10)	128	10 (8)
Any metabolic syndrome component	134	53 (40)	134	37 (28)
Two or more metabolic syndrome components	124	18 (15)	120	8 (7)
Three metabolic syndrome components	85	1 (1)	85	1 (1)

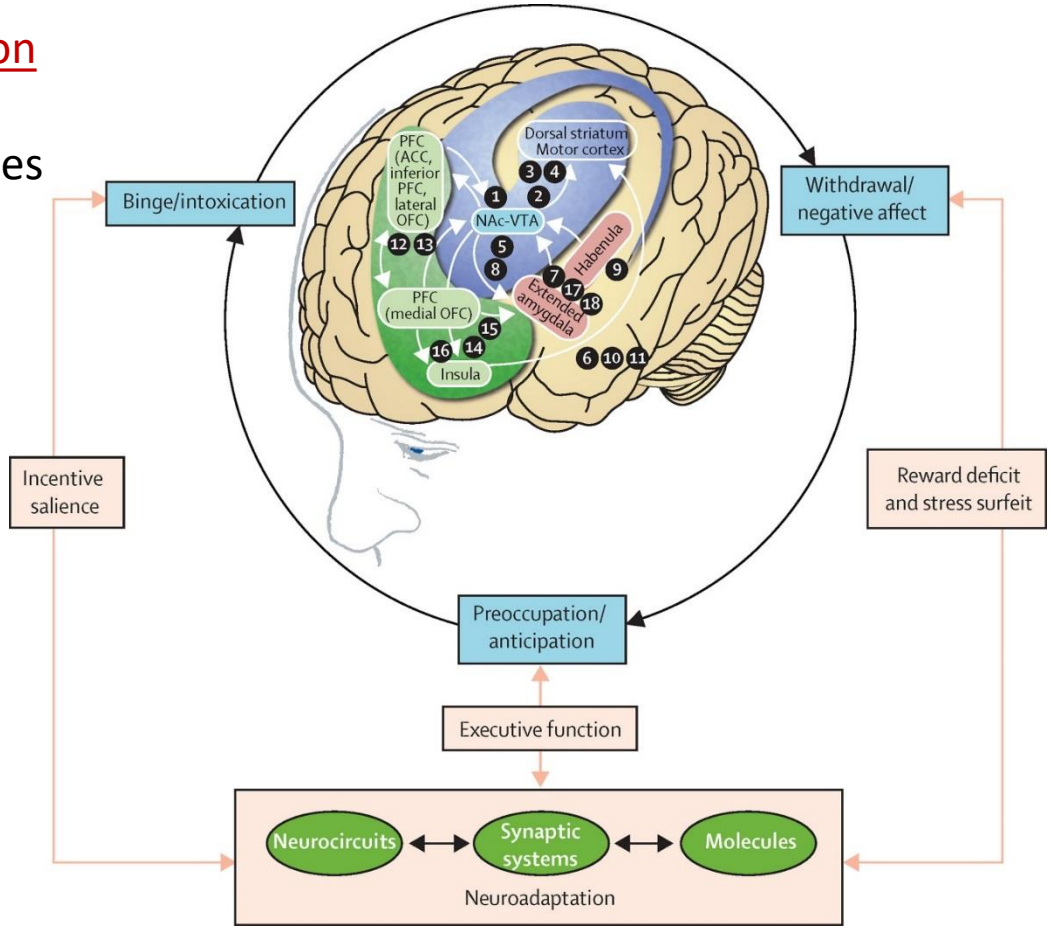
[1] Number at risk of developing a given component of the metabolic syndrome: for any component, represents the number lacking at least one component at baseline; for ≥2 components, represents the number lacking ≥2 components at baseline; and for 3 metabolic syndrome components, represents the number without any component at baseline.

[2] Number reporting new diagnosis of component or set of components during the follow-up interval.

Neurobiology of Addiction

Binge/Intoxication
- ↑ Dopamine
- ↑ Opioid peptides
- ↑ Serotonin
- ↑ GABA
- ↑ Acetylcholine

Preoccupation/ Anticipation
- ↑ Dopamine
- ↑ Glutamate
- ↑ Hypocretin
- ↑ Serotonin
- ↑ CRF



Koob, Volkow, 2017

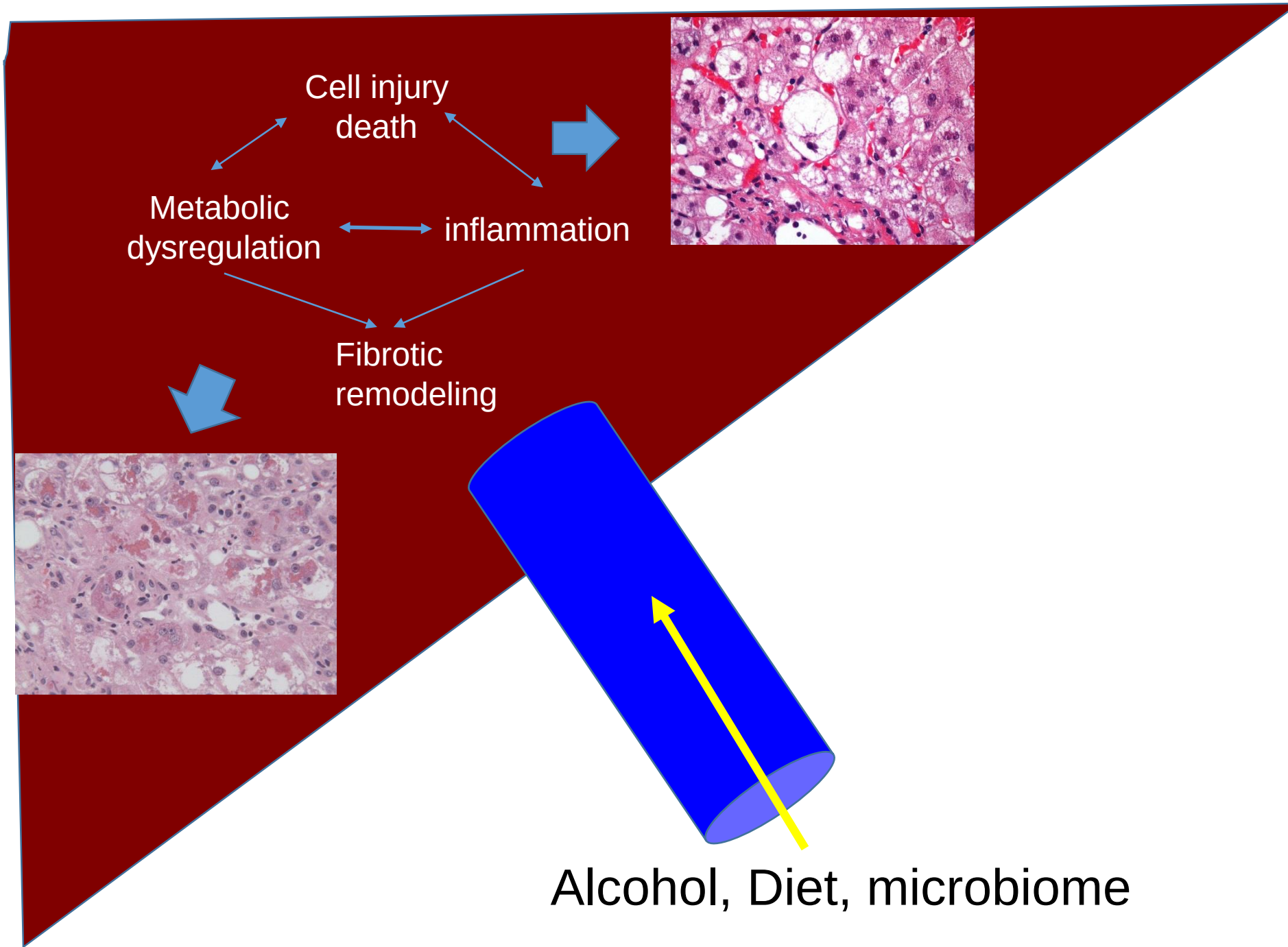
Withdrawal/ Negative Affect
- ↑ CRF
- ↑ Dynorphin
- ↑ Norepinephrine
- ↑ Hypocretin (Orexin)
- ↑ Substance P
- ↓ Dopamine
- ↓ Serotonin
- ↓ NPY
- ↓ Nociceptin
- ↓ Endocannabinoids
- ↓ Oxytocin

Alcohol as a source of calories

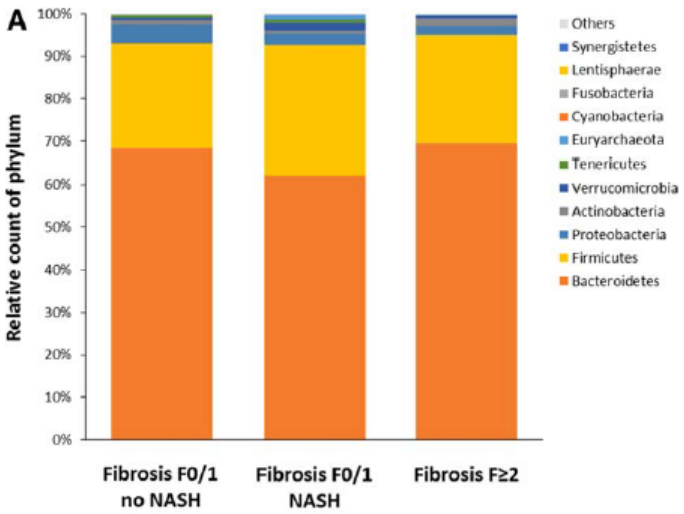
Calories	# drinks (1 unit=14 gm alcohol)	food
140	2	1 scoop ice cream
280	4	1 cheeseburger
420	6	1 large slice cheesecake
560	8	1 double cheese burger

- Alcohol (up to 4 drinks) increases appetite
- Alcohol increased high fat and high salt food intake
- Alcohol is oxidized preferentially
- This limits fat mobilization
- Clinical data on alcohol and weight gain are mixed

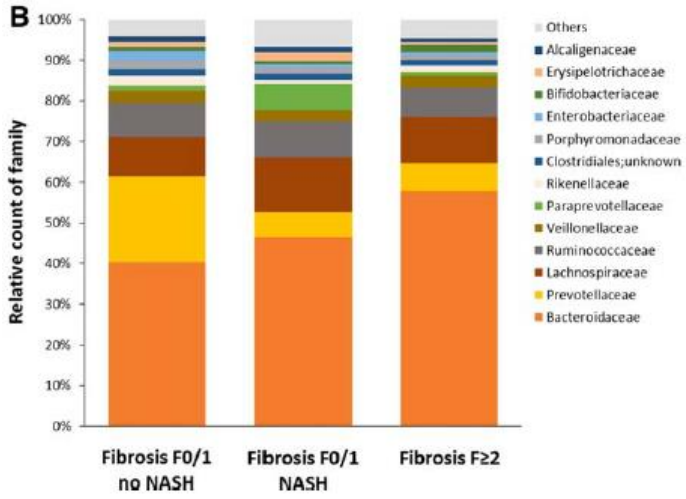
Traversy and Chaput, Curr Obes Reports 2015; 4(1): 122–130.


Cell injury
death
Metabolic
dysregulation
inflammation
Fibrotic
remodeling
Alcohol, Diet, microbiome

Taxonomic composition of the gut microbiota as a function of NAFLD severity



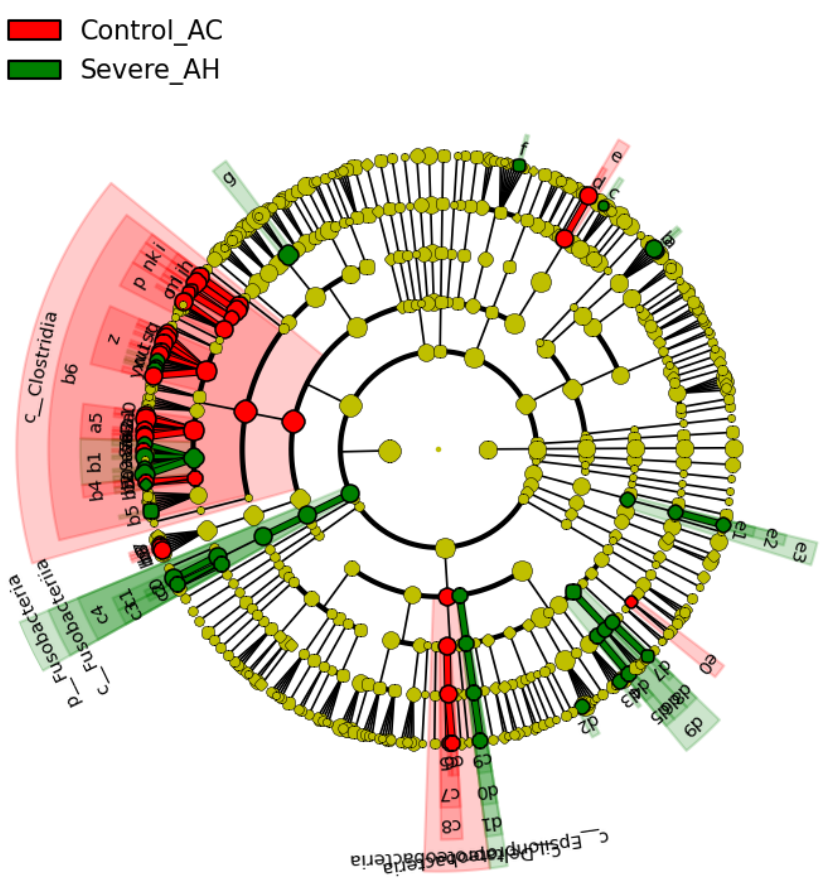
No significant difference was observed at the phylum level



Significant differences appeared from the family level

Boursier J et al, Hepatology 2016

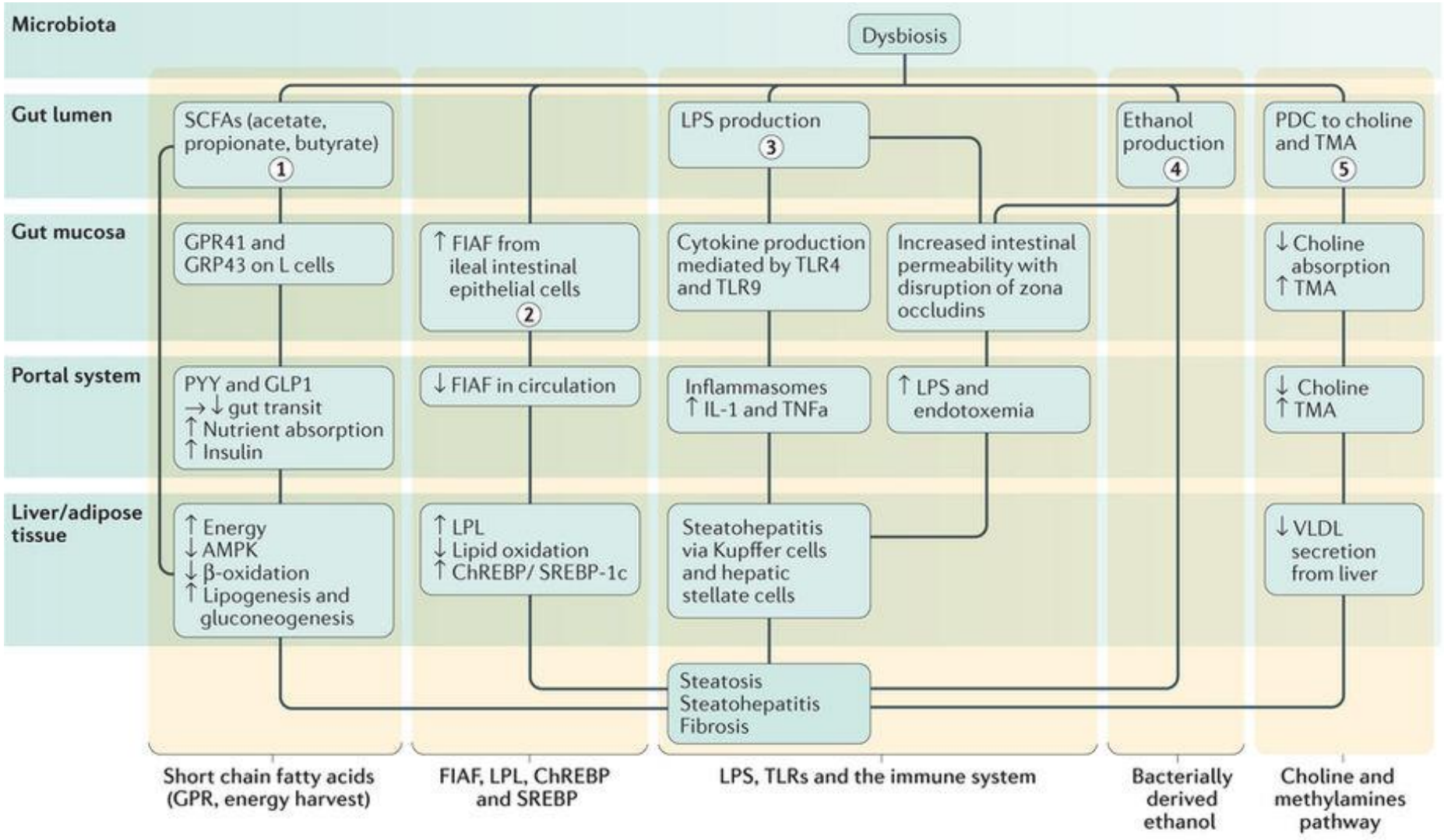
Failure to increase fusobacteria are associated with severe AH



a: g__Adlercreutzia
b: g__Atopobium
c: g__Porphyromonas
d: g__
e: f__Rikenellaceae
f: g__Capnocytophaga
g: f__Enterococcaceae
h: Other
i: Other
j: g__
k: f__
l: g__
m: g__Christensenella
n: f__Christensenellaceae
o: g__
p: f__Clostridiaceae
q: Other
r: g__
s: g__Blautia
t: g__Coprococcus
u: g__Dorea
v: g__Lachnospira
w: g__Oribacterium
x: g__Roseburia
y: g___Ruminococcus_
z: f__Lachnospiraceae
a0: Other
a1: g__
a2: g__Faecalibacterium
a3: g__Oscillospira
a4: g__Ruminococcus
a5: f__Ruminococcaceae
a6: Other
a7: g__Acidaminococcus
a8: g__Megasphaera
a9: g__Selenomonas
b0: g__Veillonella
b1: f__Veillonellaceae

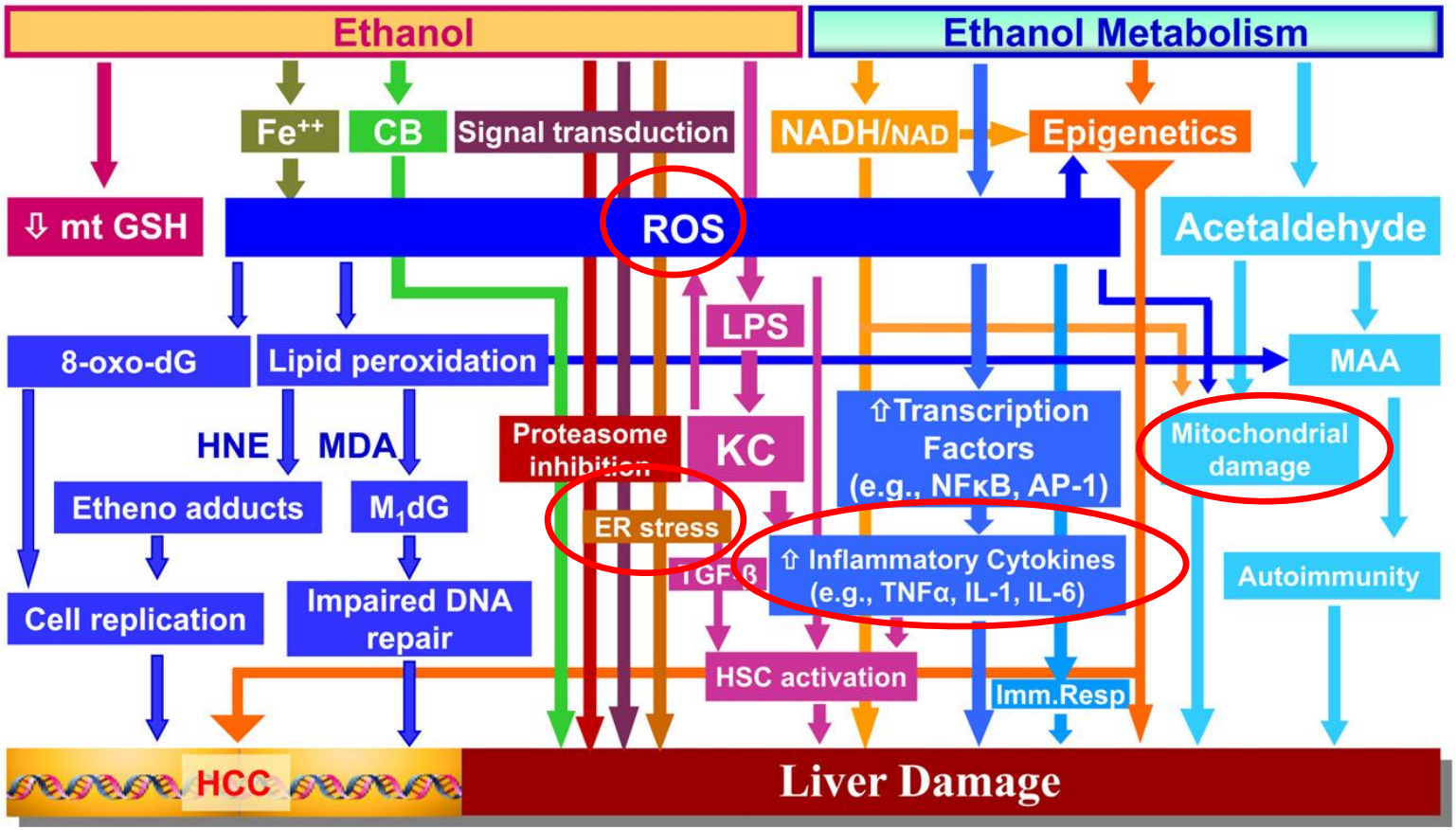
Puri et al, Hepatology 2017

Key mechanistic pathways involved in the gut–liver axis in NAFLD progression



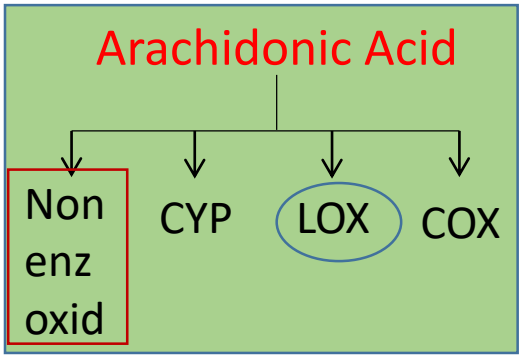
Nature Reviews | Gastroenterology & Hepatology

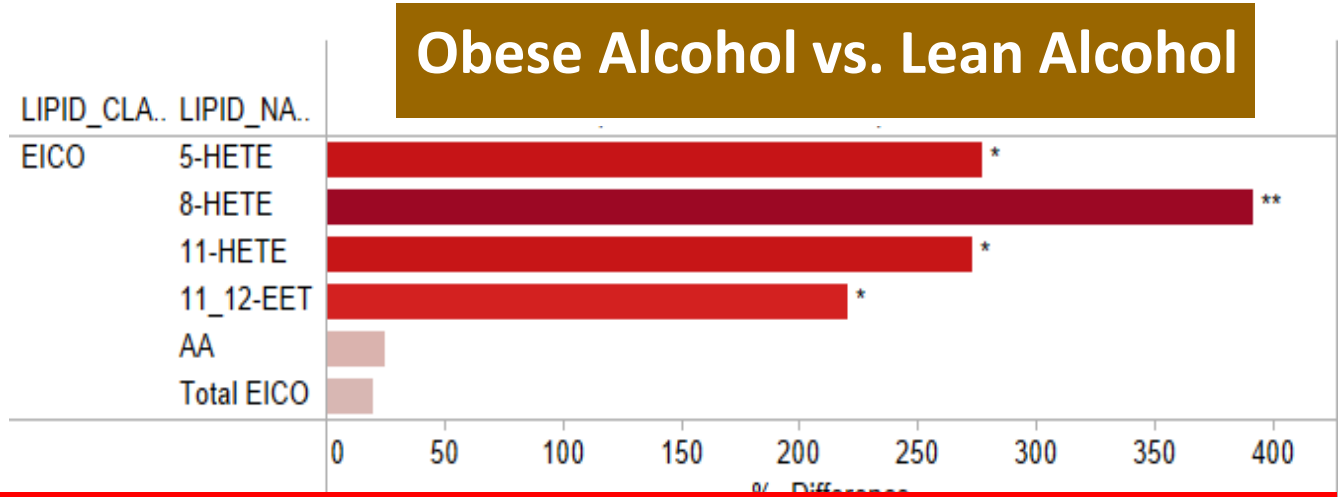
Alcoholic liver disease and NAFLD share many common pathways



Zakhari et al, Volume 28, Issue S1, August 2013 Pages 18–25

Eicosanoid: LOX and non-enzymatic oxidative pathway



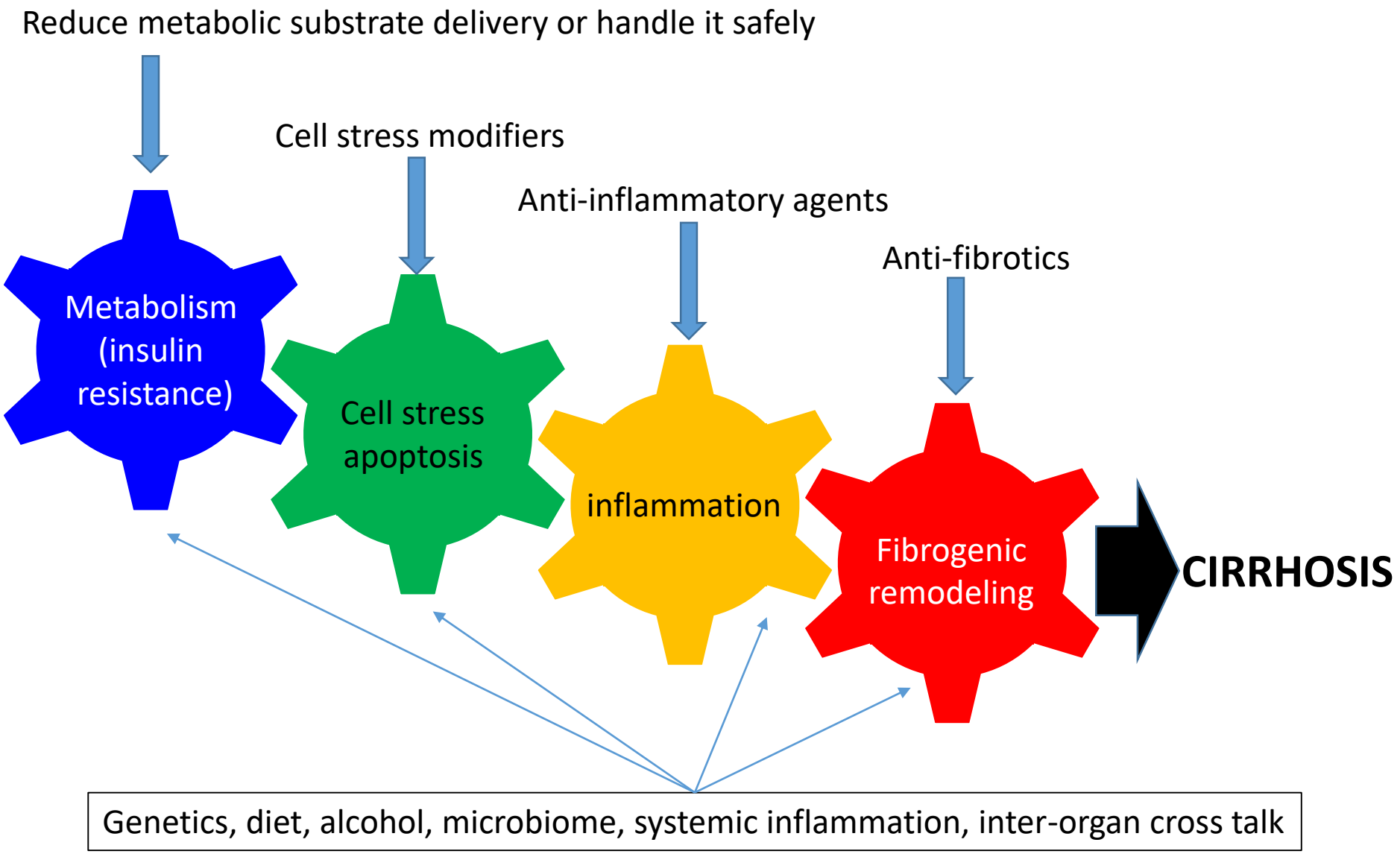


Compared to lean alcohol mice, alcohol use in obese mice results in significant increase in proinflammatory mediators of LOX pathway and non-enzymatic lipid peroxidation product 11-HETE

No significant changes in CYP or COX pathways

Puri et al, J Lipid Res, 2016

Alcohol is a disease modifier/driver affecting multiple steps



Clinical and Regulatory implications

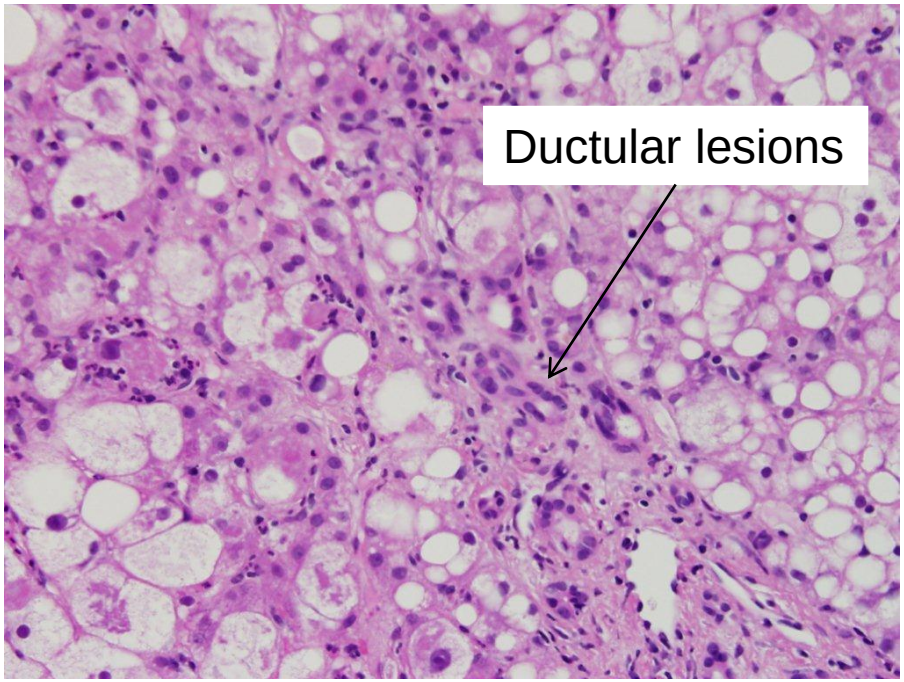
CURRENT NOMENCLATURE

Phenotype	Disease Activity	Disease Stage	Etiology/Associations
1. Steatosis **2. Steatohepatitis** **3. Indeterminate**	NAS: - Steatosis - Lobular inflammation - Ballooning SAF: - Steatosis - Lobular inflammation - Ballooning - Fibrosis	Fibrosis: - Stage 0: No fibrosis - Stage 1a: Mild peri-sinusoidal - Stage 1b: Moderate peri-sinusoidal - Stage 1c: Portal/Peri-portal - Stage 2: Peri-sinusoidal and portal/peri-portal - Stage 3: Bridging - Stage 4: cirrhosis	1. Insulin resistance 2. Alcohol 3. Lean NASH 4. PNPLA3+ 5. Drugs 6. Inherited disorders e.g. Weber-Christian, hypobetalipoproteinemia 7. Lipodystrophy 8. Short bowel 9. TPN 10. Jejuno-ileal bypass

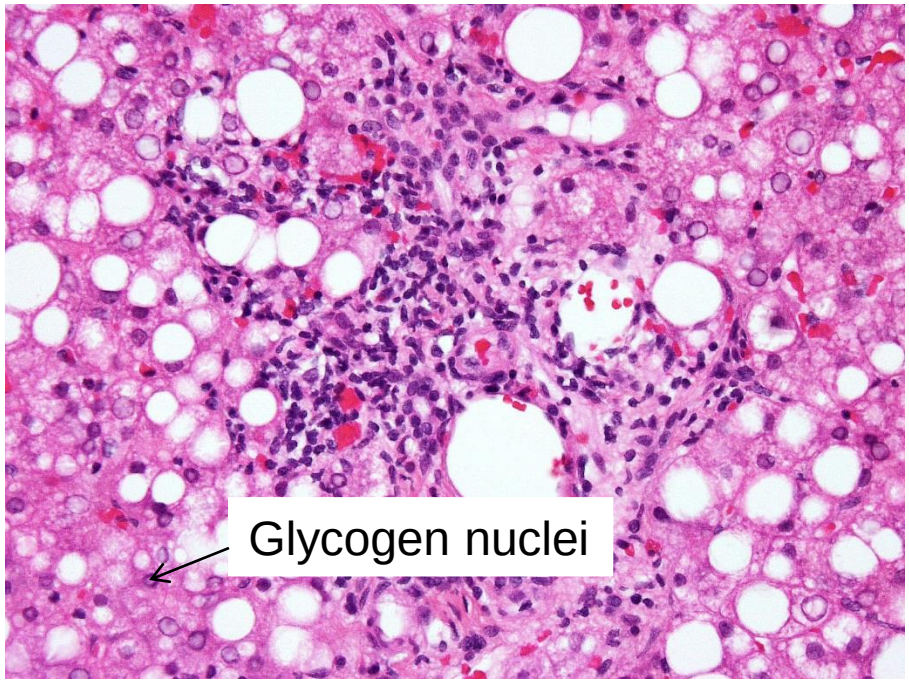
Siddiqui et al, Hepatology 2018

ASH vs NASH

ASH

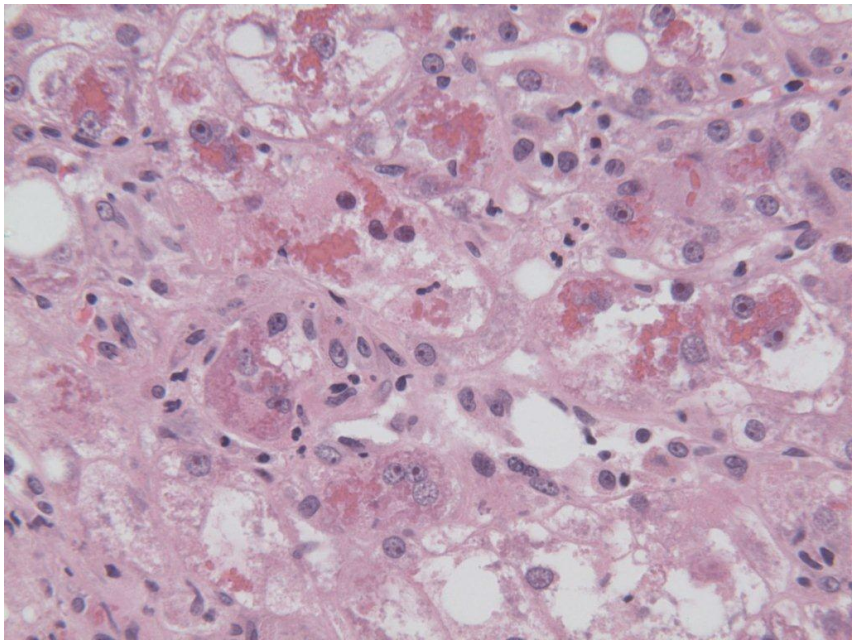


NASH

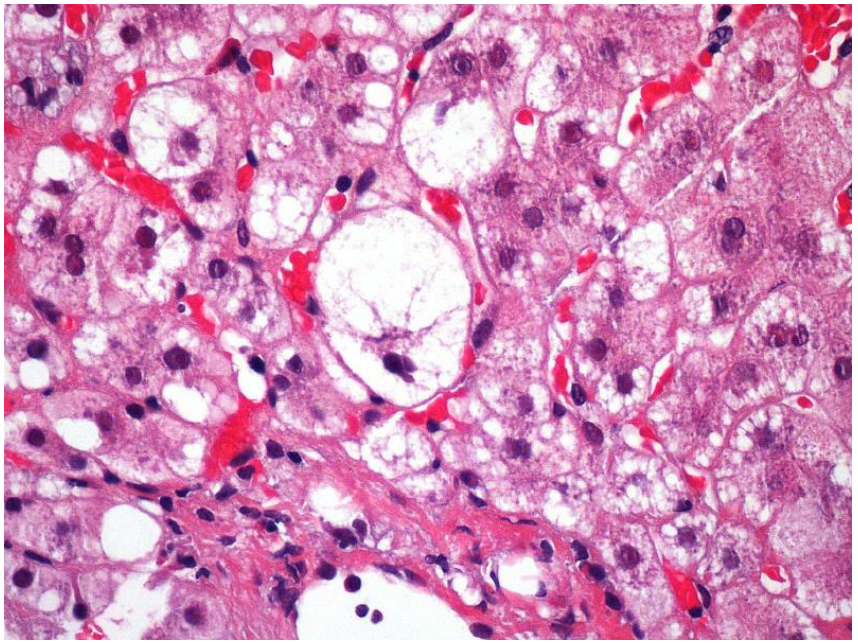


ASH vs NASH: Mallory-Denk bodies

ASH

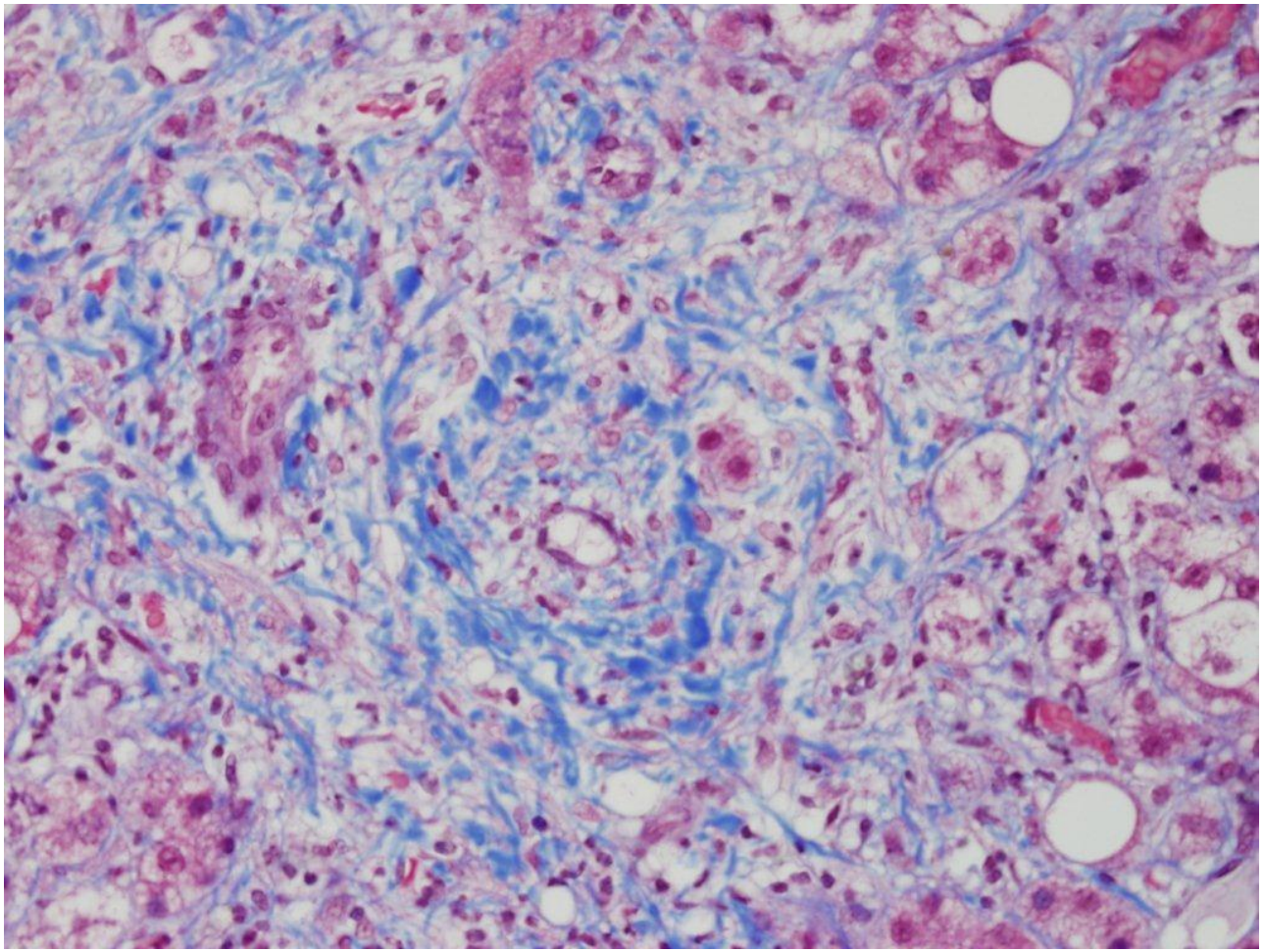


NASH



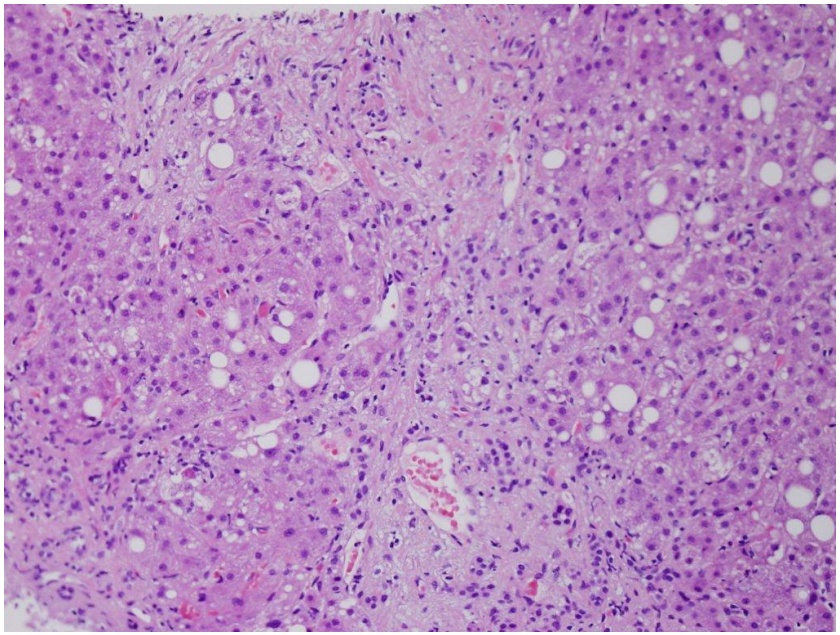
If you see large number of ballooned cells with Mallory bodies, it is more likely to be ASH

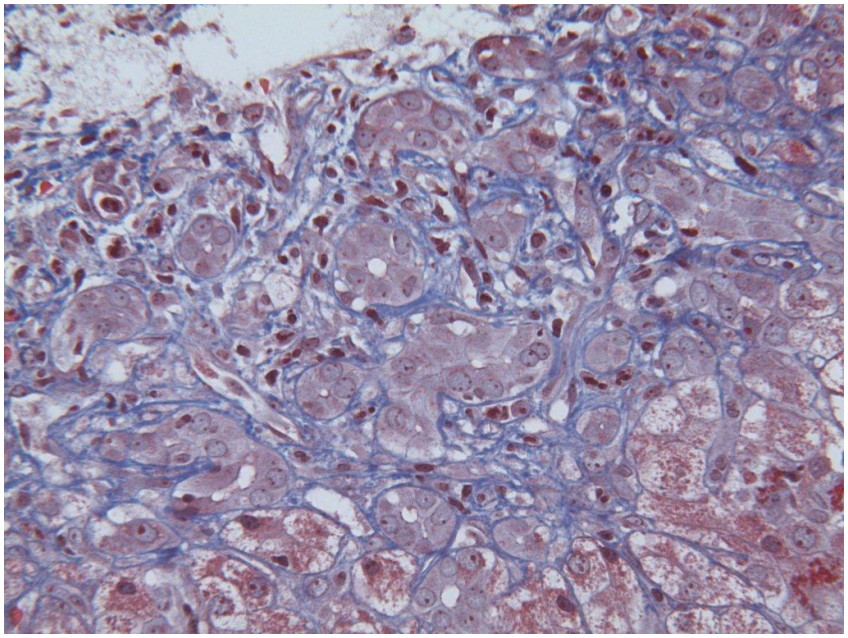
Obliterative venulitis: feature of ASH



Courtesy: Dr. Elizabeth Brunt

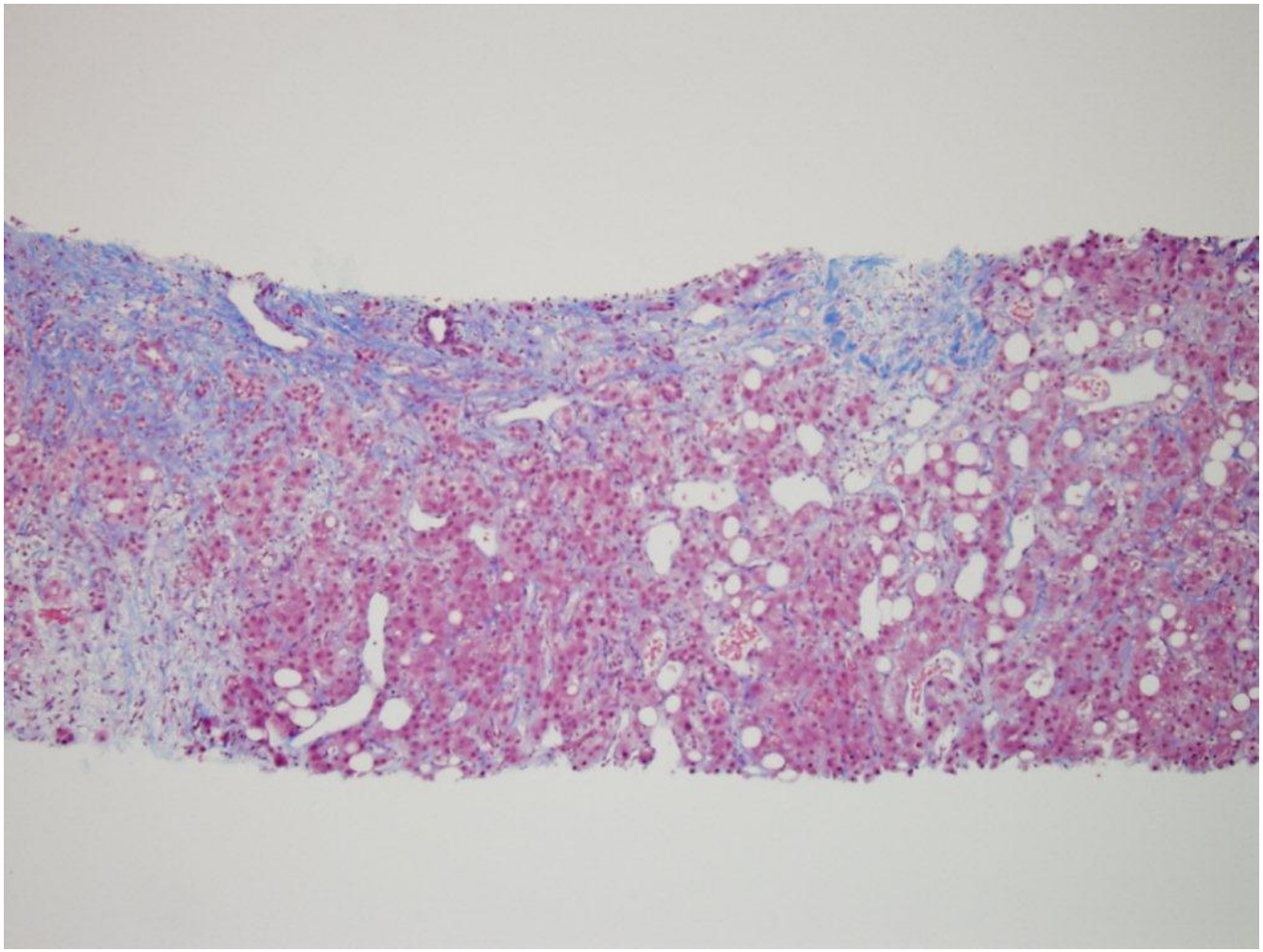
ASH: rosettes and fibro-obliterative disease





Courtesy of Dr. Elizabeth Brunt

Central to portal fibrosis in ASH

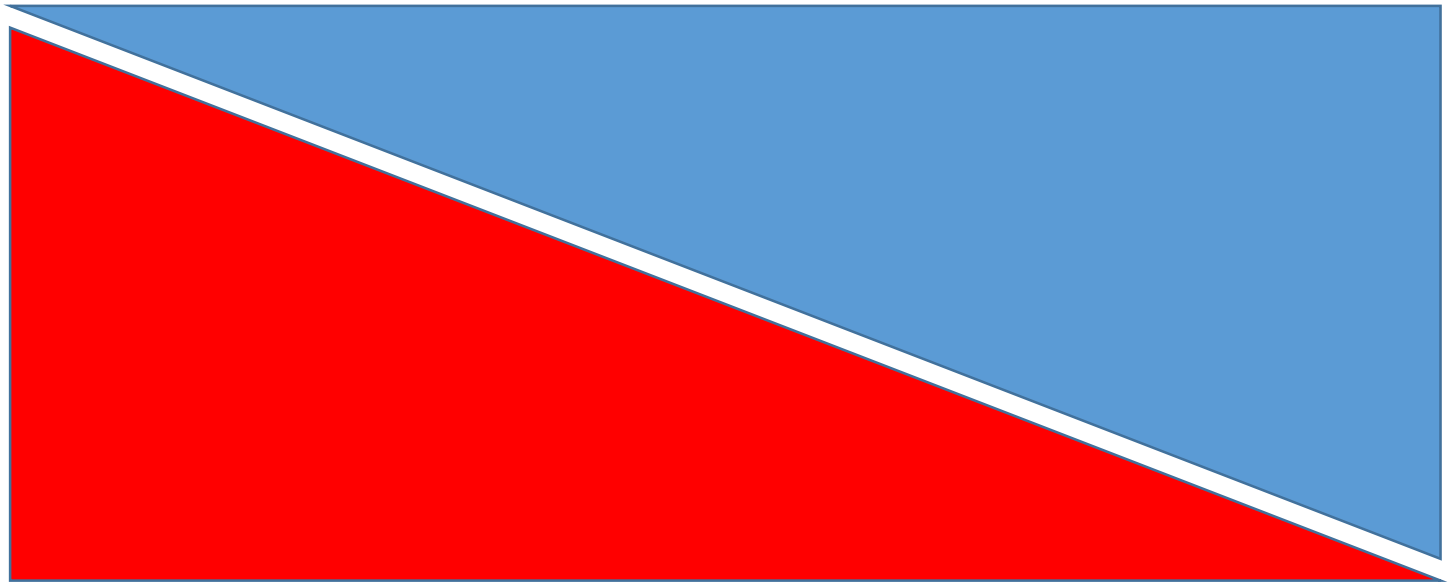


Courtesy Dr. Elizabeth Brunt

ASH and NASH: when can we call it steatohepatitis of mixed etiology

PURE NASH

PURE ASH

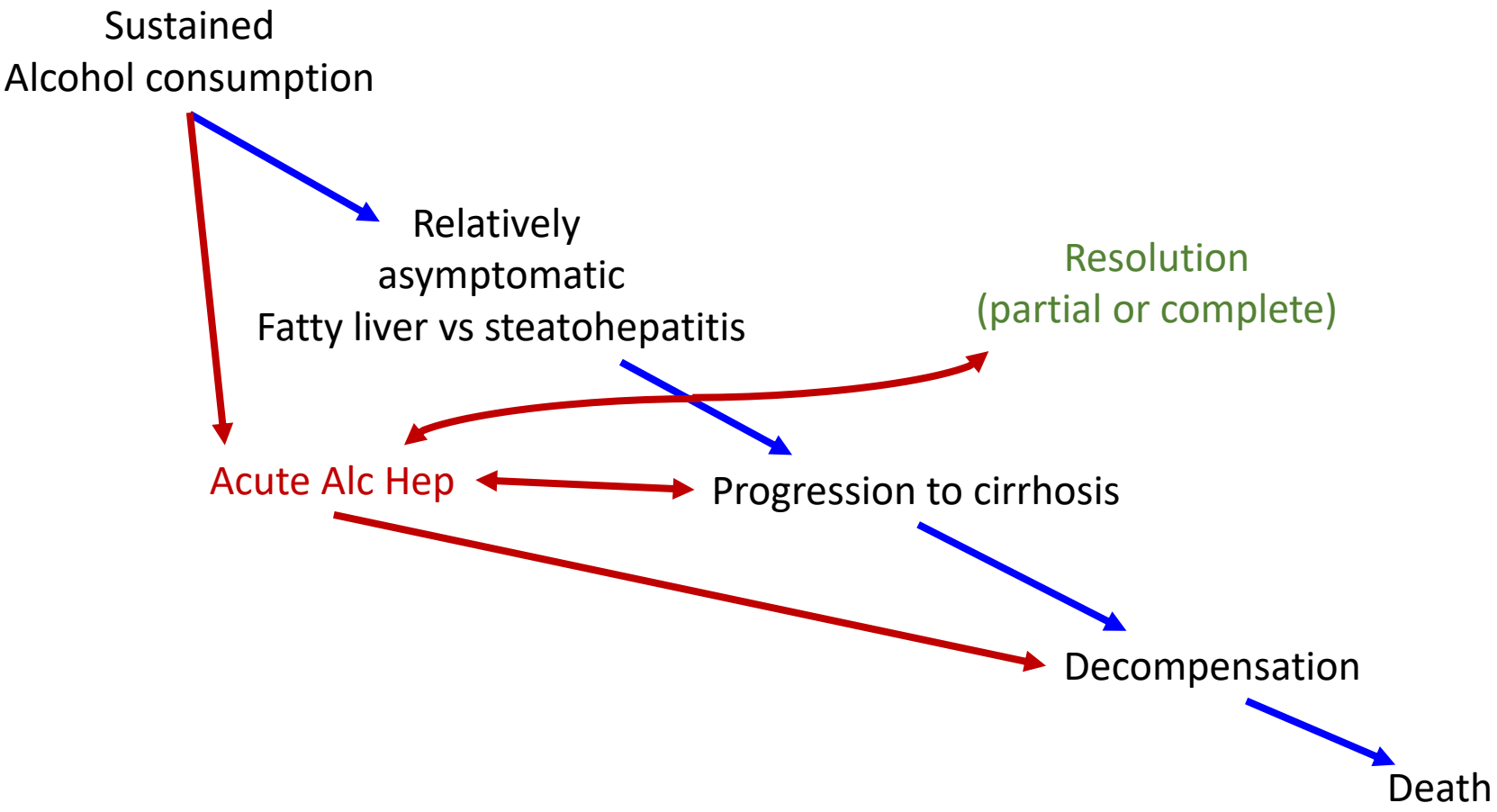


Glycogen nuclei common
Infrequent ballooning

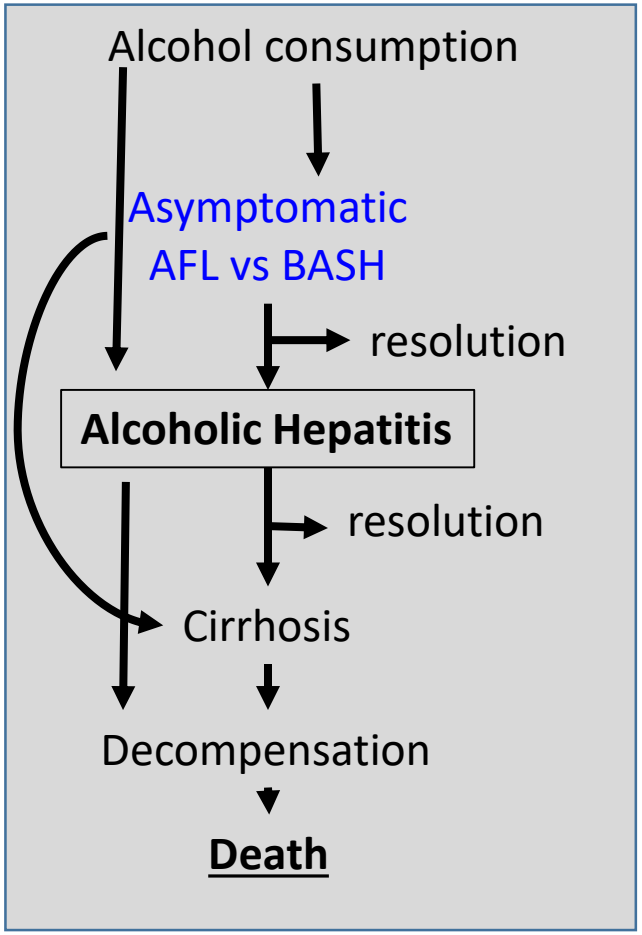
Loss of glycogen nuclei
Frequent ballooning
Increasing M-D bodies

Cholestasis
Rosettes
Central vein obliteration
Biliary proliferation

The course of alcohol related steatohepatitis



Alcohol consumption and obesity are major drivers of development of fatty liver



Those with a high BMI and high alcohol consumption Had greatest prevalence of fatty liver- Dionysus Study

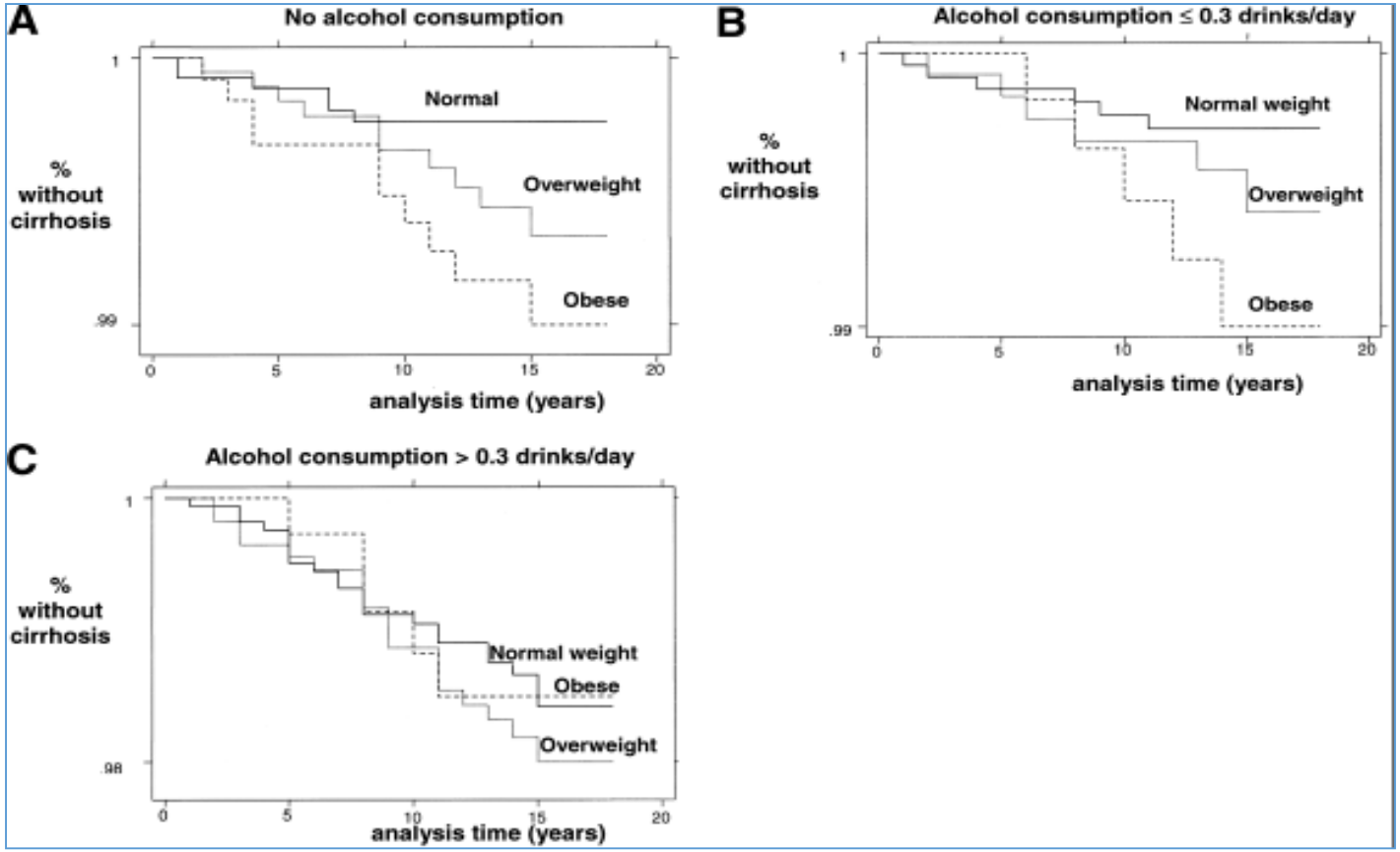
Risk factors for FLD development
(no FLD at baseline)

	Fatty liver	P value
Age	1.1	n.s.
Male gender	0.99	n.s.
BMI	1.1	n.s.
ethanol	1.17	0.01

Principal risks are cardiovascular/cancer

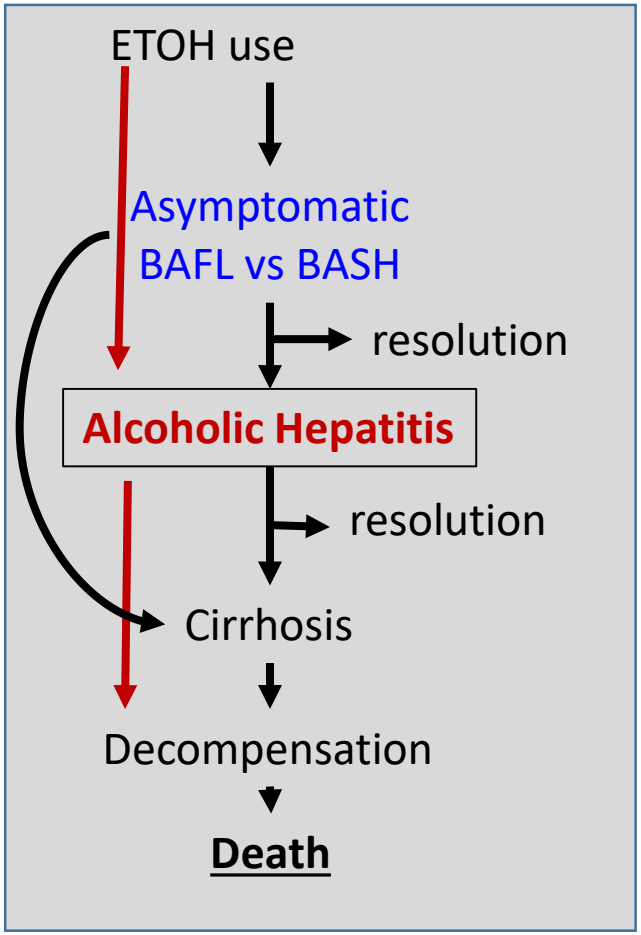
Bedogni et al, Hepatology, 2007; 46:1387-1391

Alcohol Intake, Obesity and Cirrhosis-Related Death or Hospitalization



Ioannou et al., Gastroenterology. 2003;125:1053-9

Objectives of clinical trials and defining endpoints (Asymptomatic or mildly symptomatic AFL or ASH)



What we know:

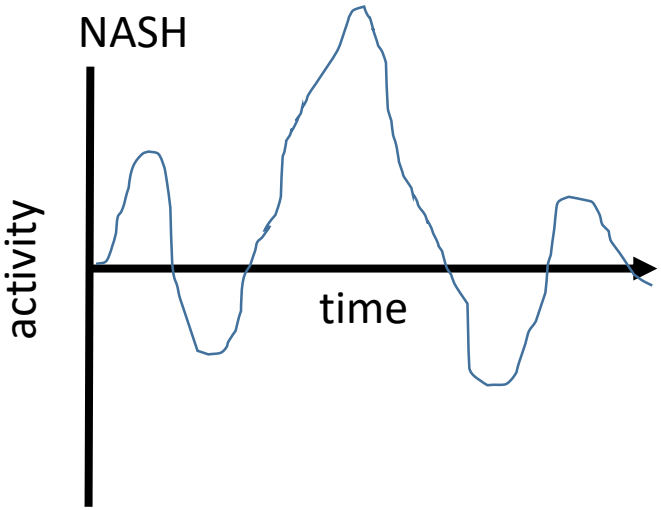
- Many patients with ETOH use have this
- There is interaction with obesity
- Resolution vs progression depends on abstinence
- No immediate liver related clinical outcomes

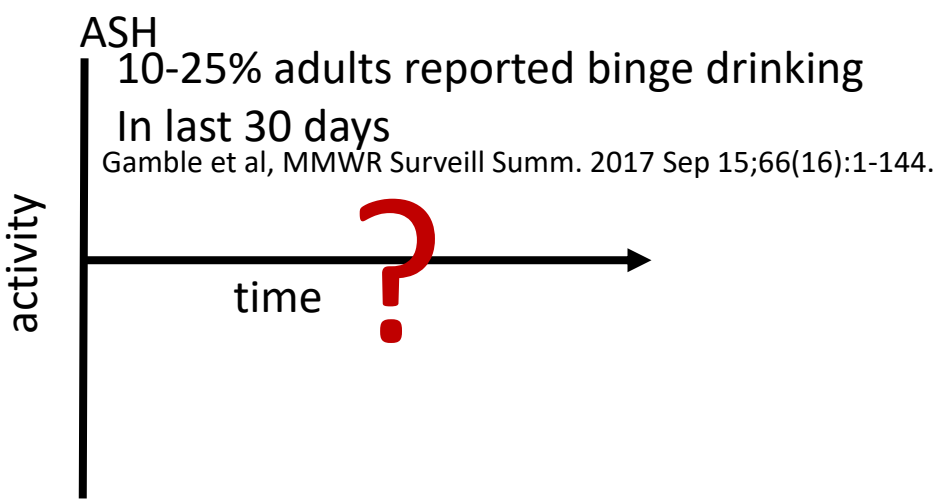
Primary focus has to be decreased ETOH intake

Key endpoints (surrogate endpoints):

- Reduction in heavy drinking days
- Reduction in WHO risk profile
- Improvement in histology
- *? Improvement in liver stiffness*

There is an unmet need to better understand the role of modest alcohol consumption in NASH





NASH CRN data
Centaur trial
Gilead 105/106 trials

→ Disease activity and fibrosis waxes and wanes spontaneously

NASH CRN data
GOLDEN

→ Disease activity direction drives fibrogenic remodeling

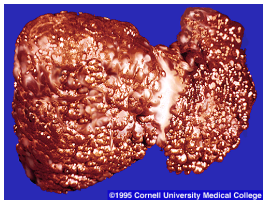
Modest alcohol consumption has modest effects on NASH

Histologic change	Alcohol abstinent Mean adjusted change N=117	Modest alcohol Mean adjusted change N= 187	P value
Steatosis	-0.48	-0.29	0.03
Ballooning	-0.25	-0.13	0.4
Lobular inflammation	-0.26	-0.26	0.9
NAS	-0.9	- 0.73	0.16
Portal inflammation	+0.18	+0.1	0.27
Fibrosis	+0.05	+ 0.1	0.65

- Adjusted for baseline histology
- Histology read blinded
- Formal prospective alcohol questionaires used to quantify consumption

Ajmeera et al, Clin Gastroenterol Hepatol. 2018 Mar 14. pii: S1542-3565(18)30094-6. doi: 10.1016/j.cgh.2018

Clinical trials for cirrhosis due to NASH or Mixed etiology must be considered in the context of when intervention is planned



Terlipressin
Pivotal trials

MELD: < 10 11-14 ≥ 15

Clinically Significant Portal Hypertension (HVPG > 10 mm Hg)

LACE
- Ascites/SBP/HRS
- Encephalopathy
- HCC
- Variceal bleed

Sepsis
ACLF
MOD

Future trials must incorporate patient reported outcomes and caregiver related outcomes

THANK YOU FOR YOUR ATTENTION

- Need to better define study populations with respect to disease drivers and clinical profile
- Better prediction biomarkers and drug development tools
- Refinement in trial endpoints