



# VCU

Stravitz-Sanyal Institute for  
Liver Disease and Metabolic Health  
School of Medicine



# MetALD: An Emerging Diagnosis Changing ALD Care Before and After Transplant

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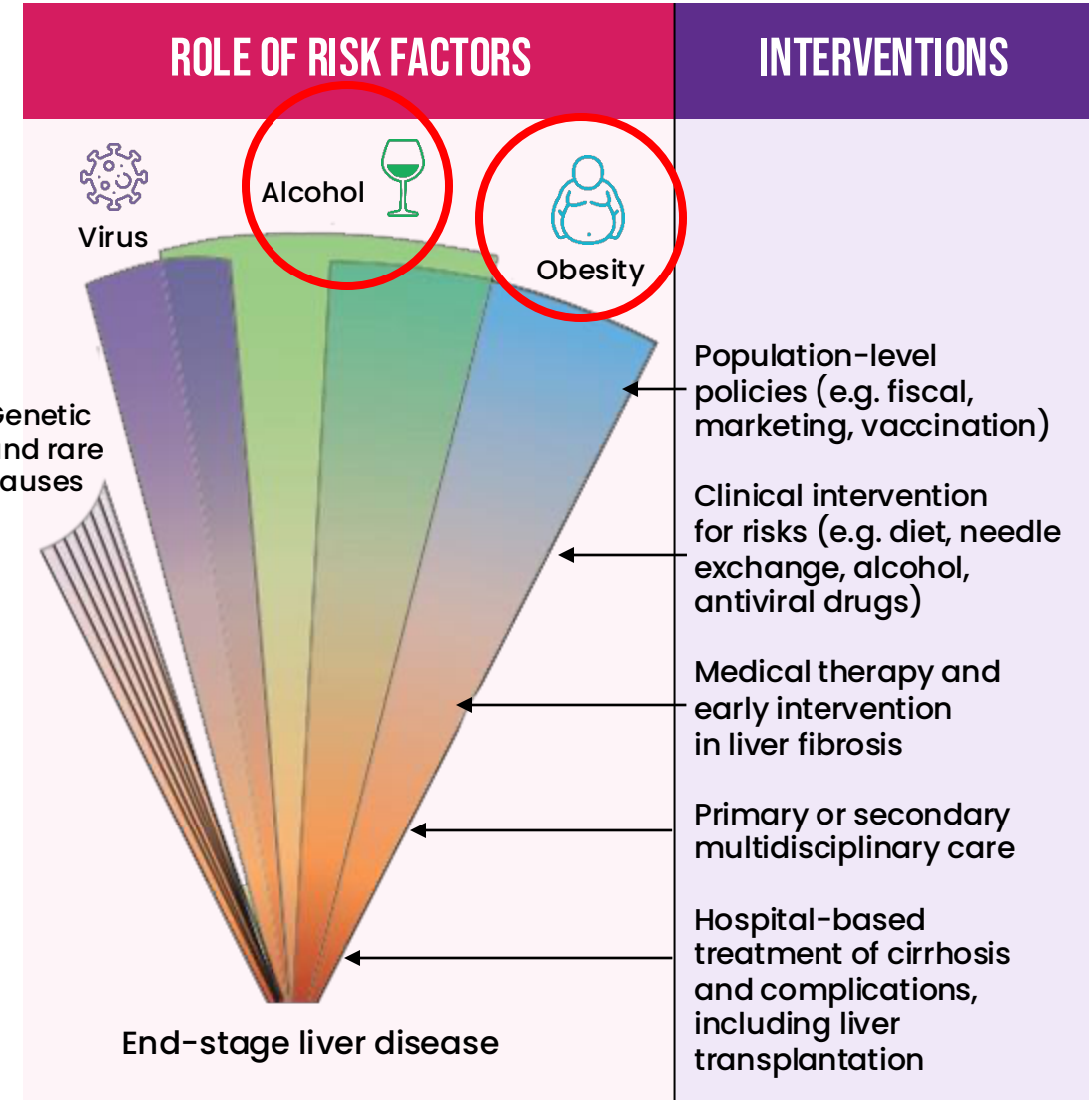
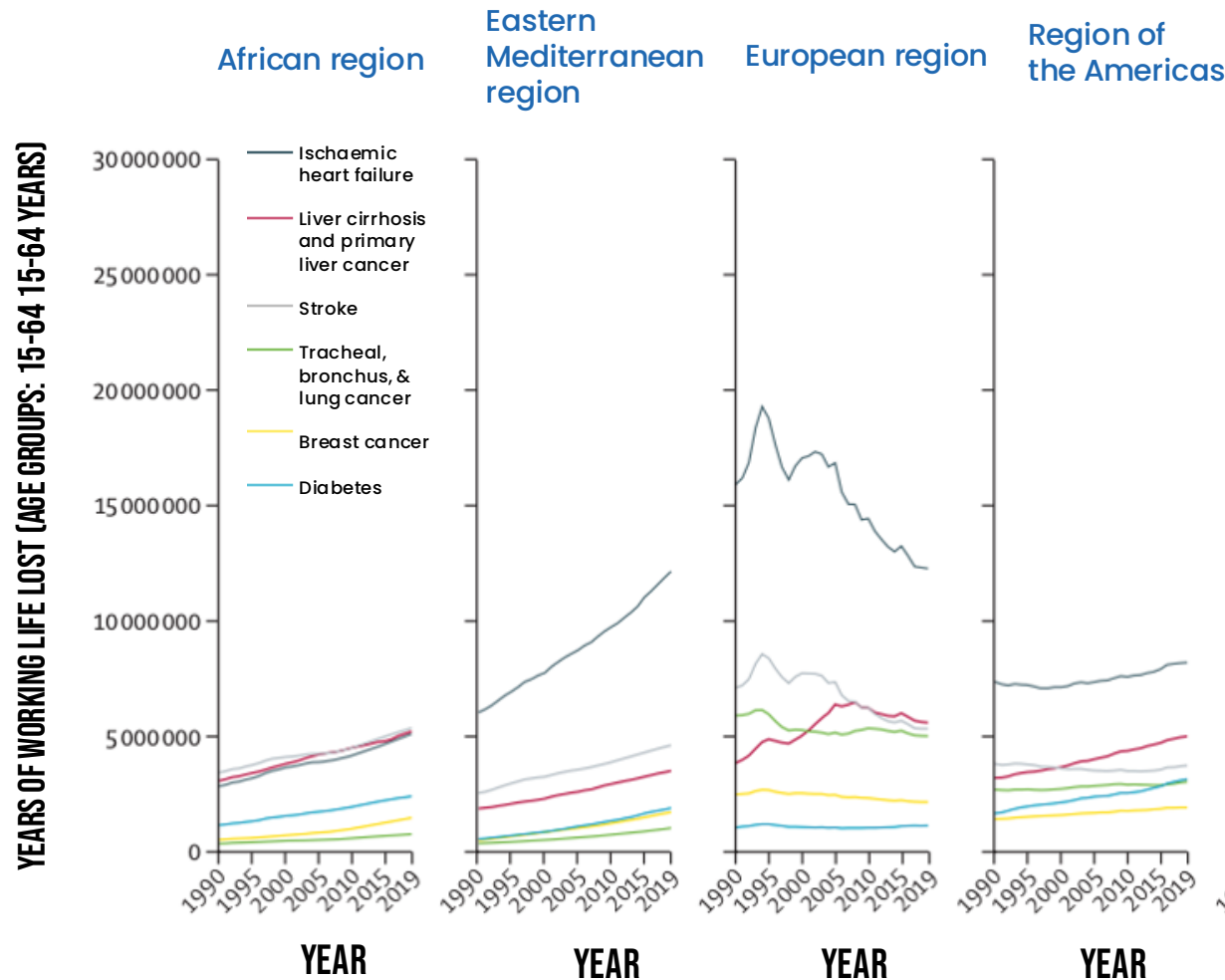
juanpablo.arab@vcuhealth.org

# Aims

- To understand the **epidemiology** of MetALD and ALD
- To discuss **differences and overlapping** features of MASLD and ALD
- To recognize the importance in distinguishing these phenotypes for **tailored clinical interventions**
- To discuss the impact of implementing **public health policies**



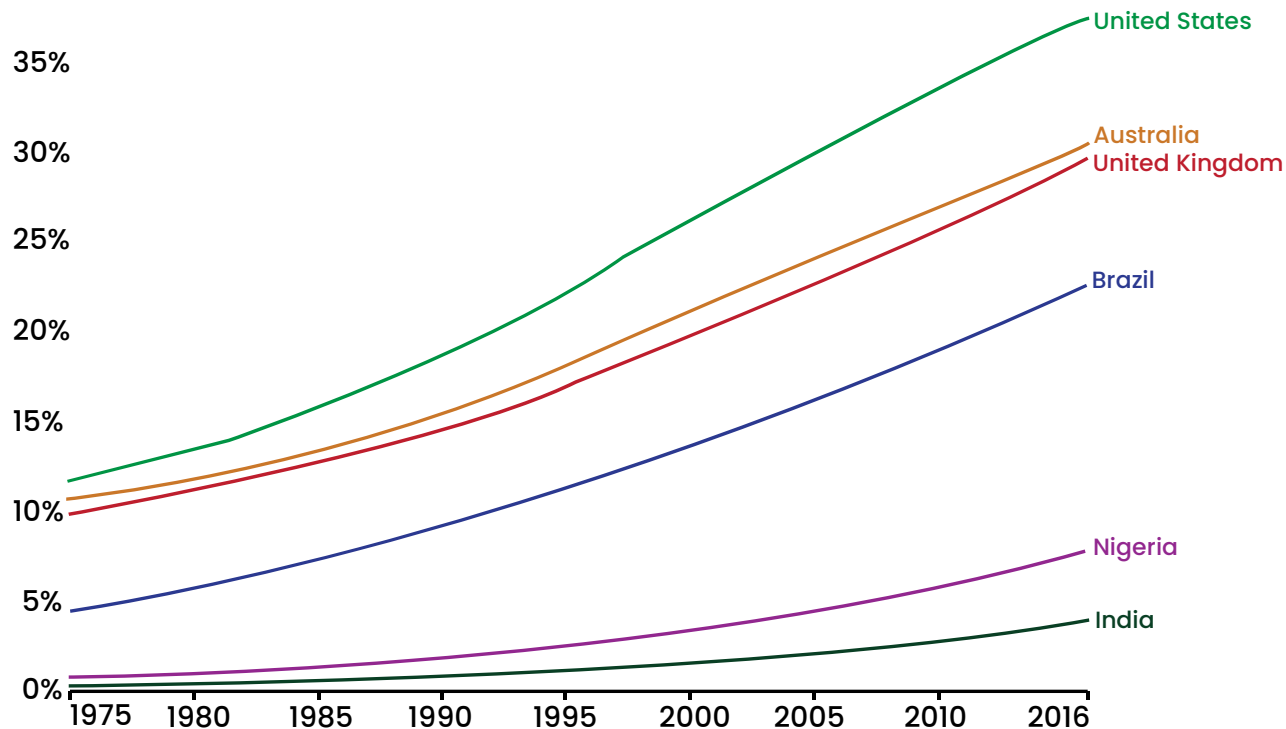
# Potential years of working life lost, and leading causes by WHO region



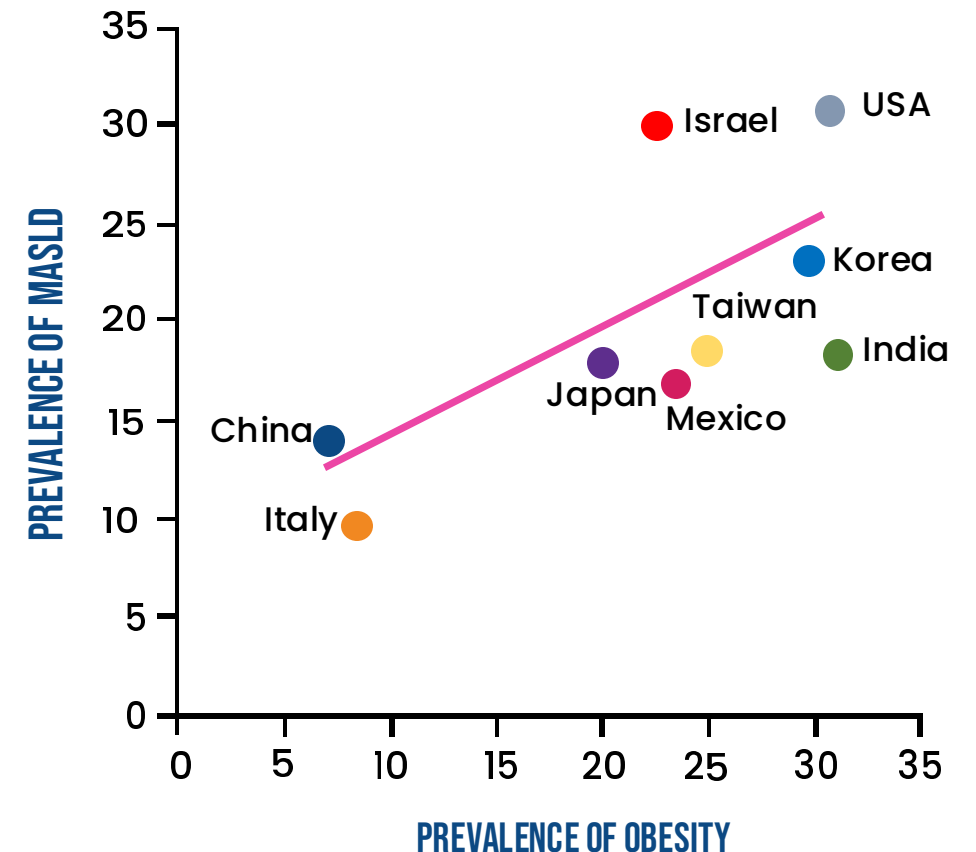
# OBESITY PREVALENCE AND RELATION TO MASLD

## SHARE OF ADULTS THAT ARE OBESE, 1975 TO 2016

Obesity is defined as having a body-mass index (BMI) equal to, or greater than, 30. BMI is a person's weight (in kilograms) divided by their height (in meters) squared.



<https://ourworlddata.org/obesity>



Lazo M. Semin Liver Dis. 2008



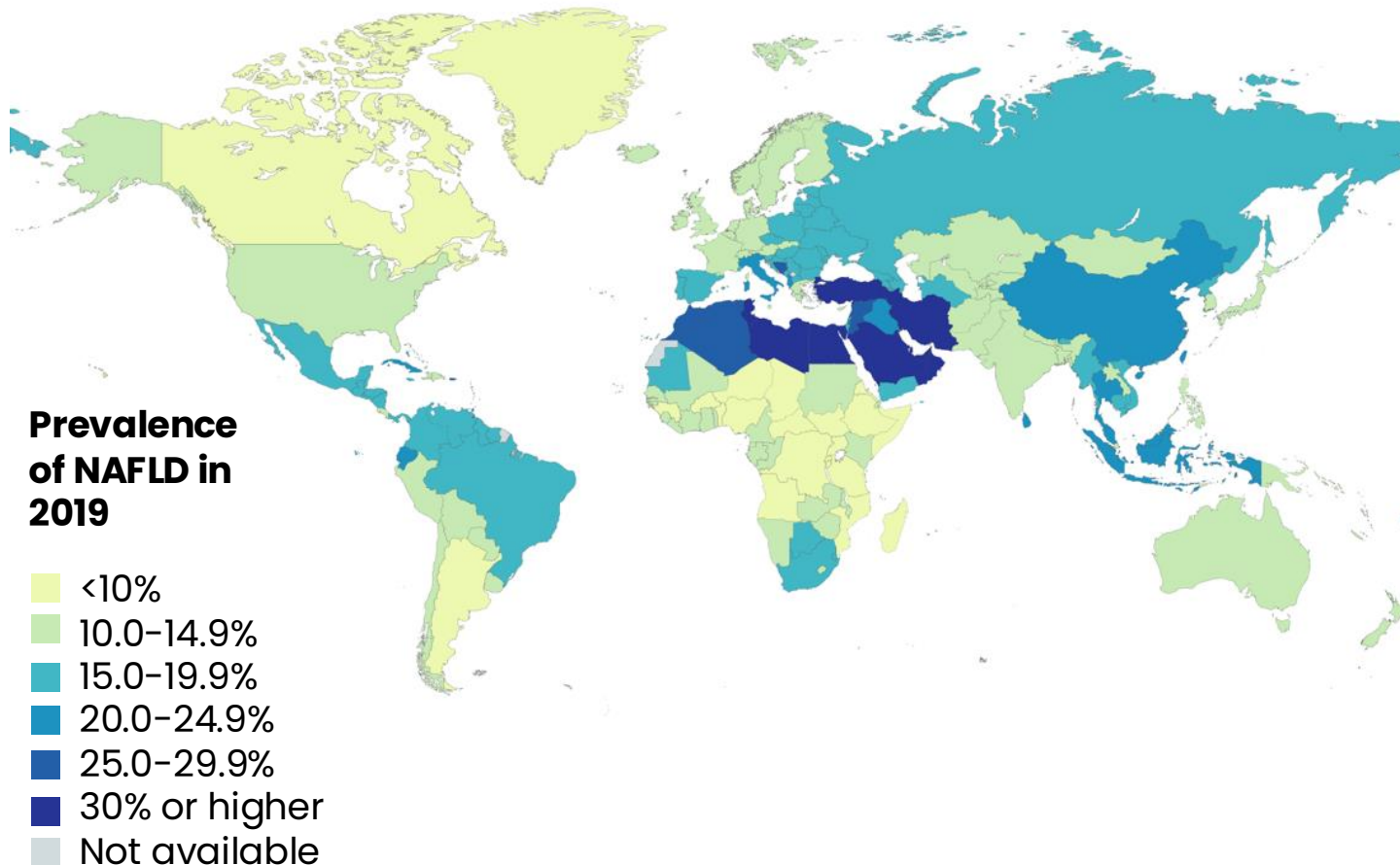
# PREVALENCE OF MASLD

Seminar

JOURNAL  
OF HEPATOLOGY

## GLOBAL BURDEN OF LIVER DISEASE: 2023 UPDATE

Harshad Devarbhavi<sup>1</sup>, Sumeet K. Asrani<sup>2,\*</sup>, Juan Pablo Arab<sup>3,4</sup>, Yvonne Ayerki Nartey<sup>5</sup>, Elisa Pose<sup>6</sup>, Patrick S. Kamath<sup>7</sup>



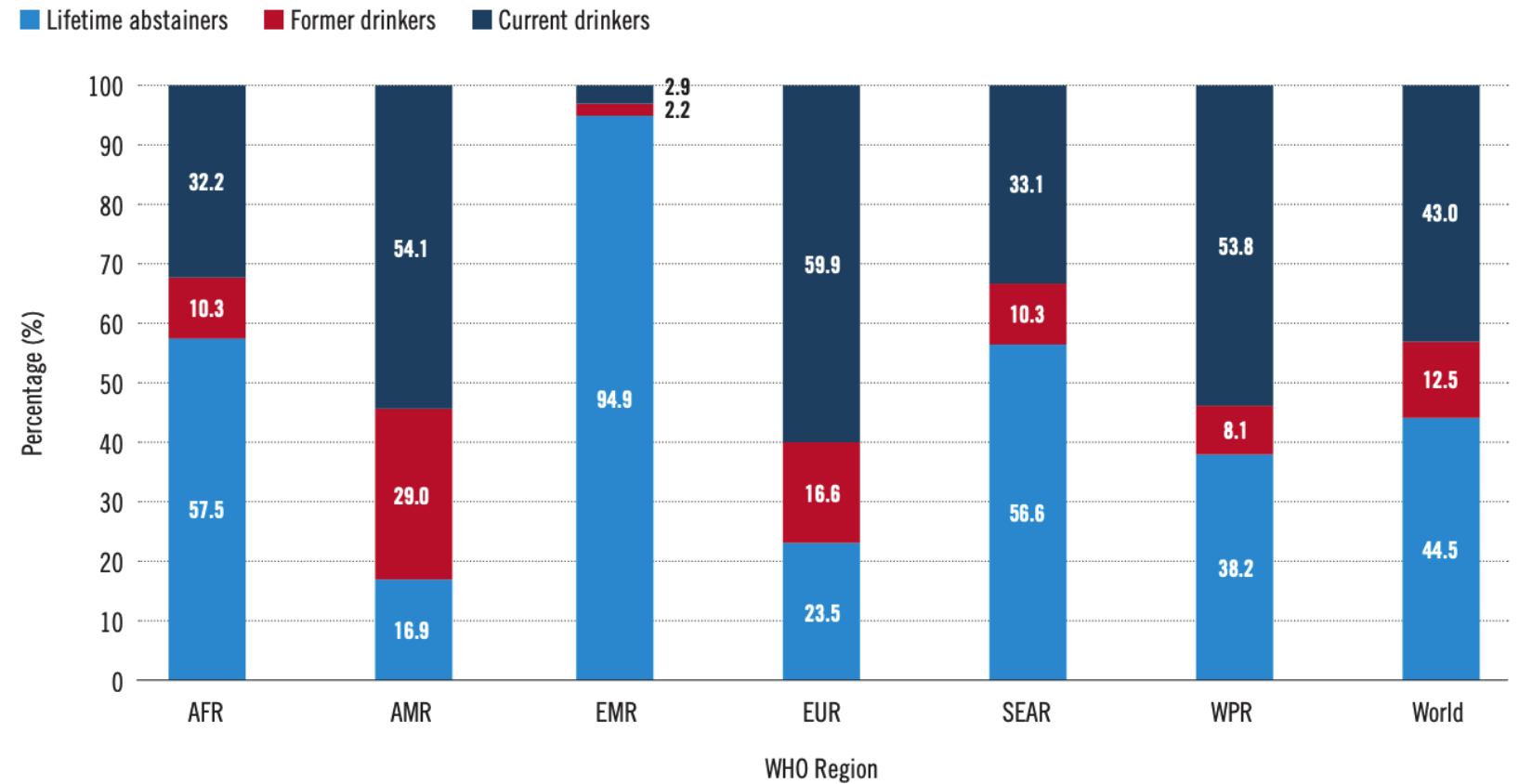
## MASLD:

- The worldwide **prevalence** of MASLD is **32.4%**.
- The percentage of **total deaths** from all causes attributable to MASLD increased from 0.10% to **0.17%**.
- MASLD represents the second-leading cause of **liver transplantation** and the leading cause among females.

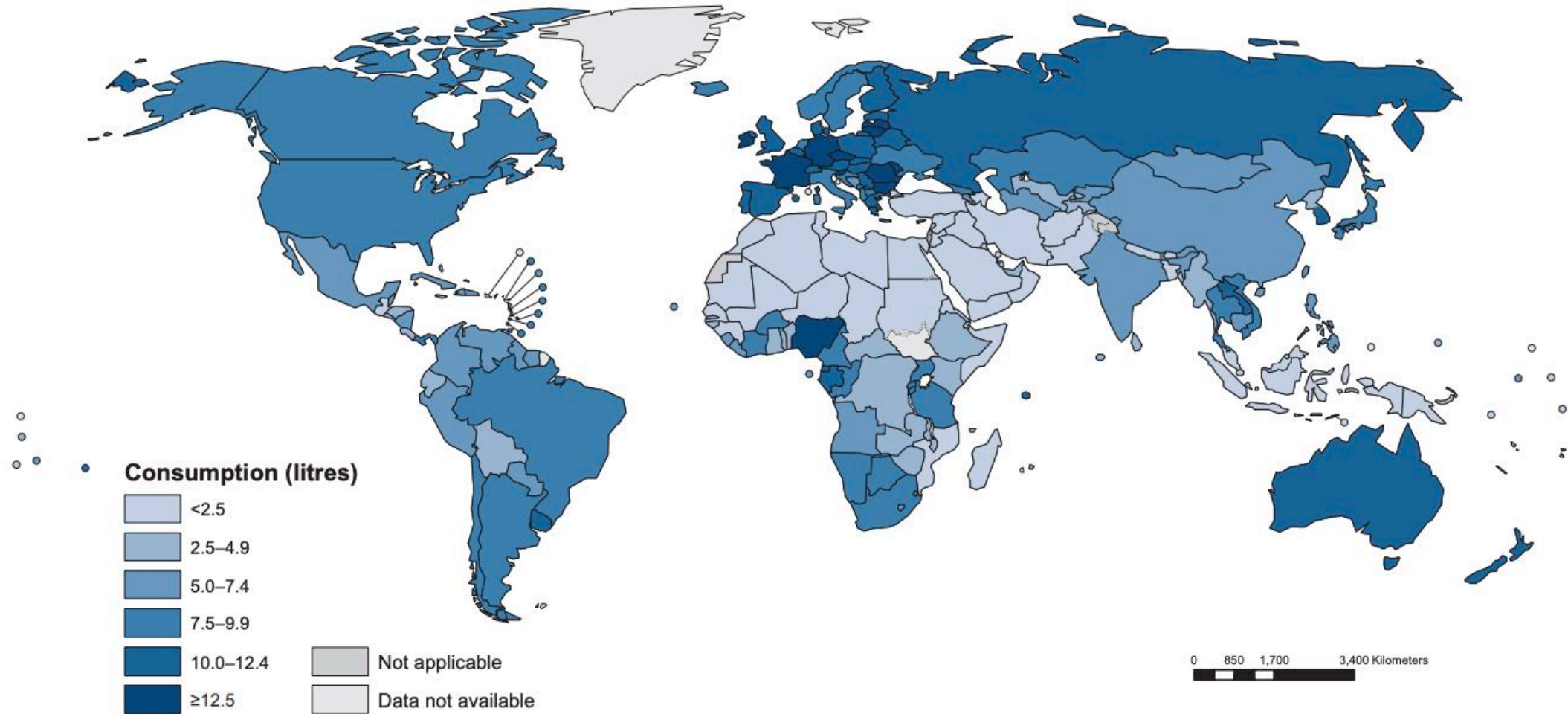
# Global Alcohol Consumption

Globally, 43% of the population currently drinks alcohol

- 1 African Region (AFR)
- 2 Region of the Americas (AMR)
- 3 South-East Asian Region (SEAR)
- 4 European Region (EUR)
- 5 Eastern Mediterranean Region (EMR)
- 6 Western Pacific Region (WPR)



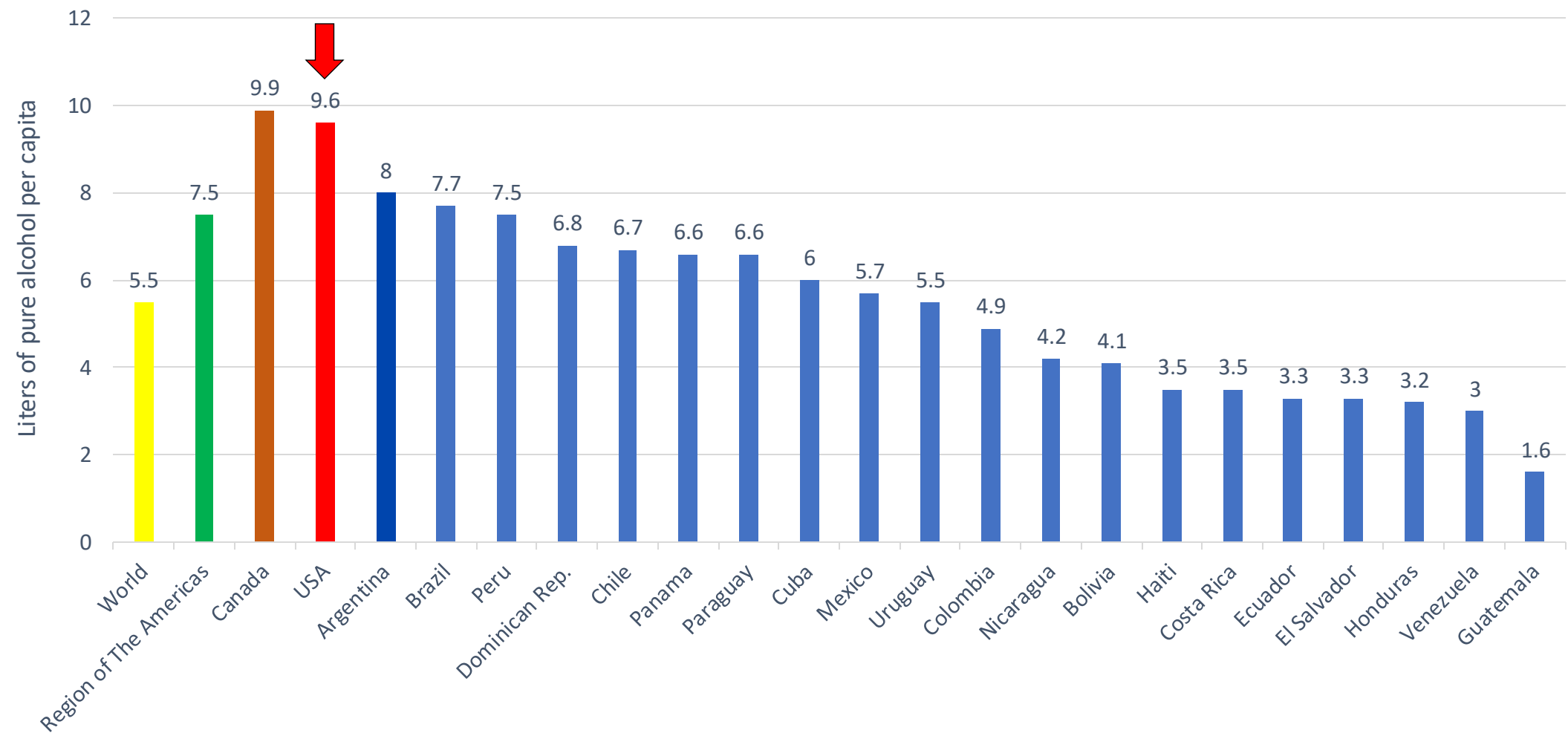
# Alcohol consumption per capita



Global status report on alcohol and health 2018. World Health Organization (WHO)

2024

EPIDEMIOLOGY

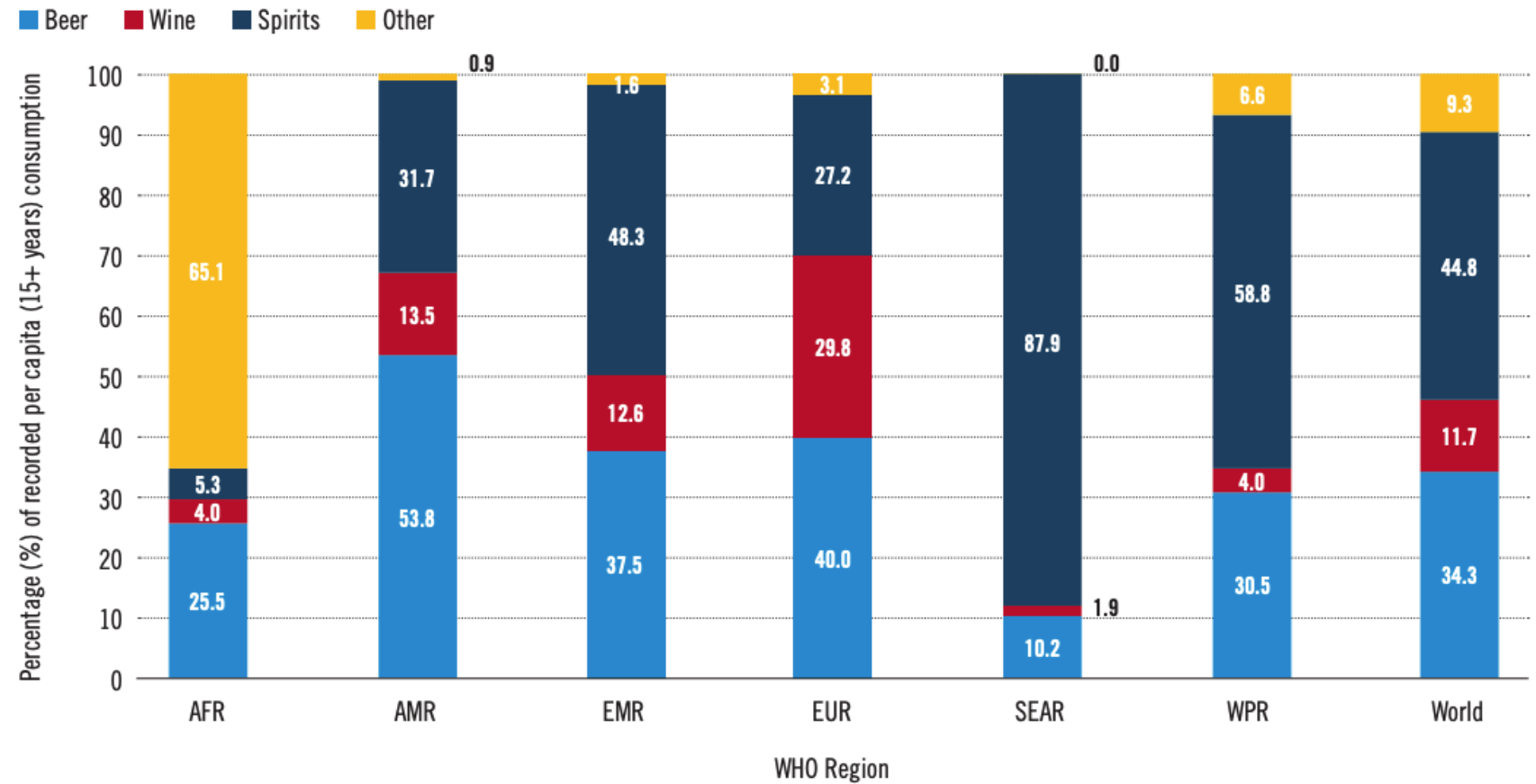


Global status report on alcohol and health 2024. World Health Organization (WHO)

# Type of alcohol consumed

## Worldwide:

1. Spirits (44.8%)
2. Beer (34.3%)
3. Wine (11.7%)

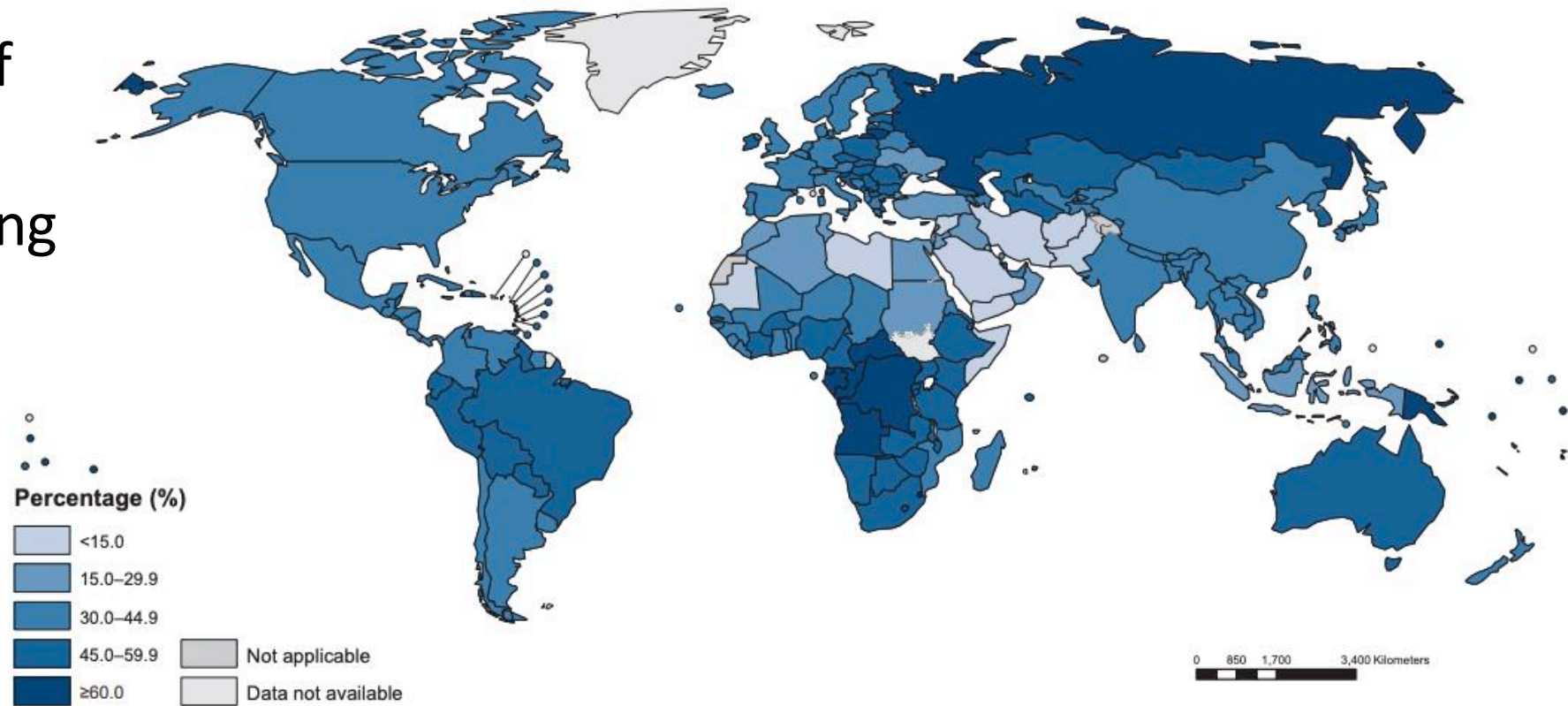




# Heavy Episodic Drinking

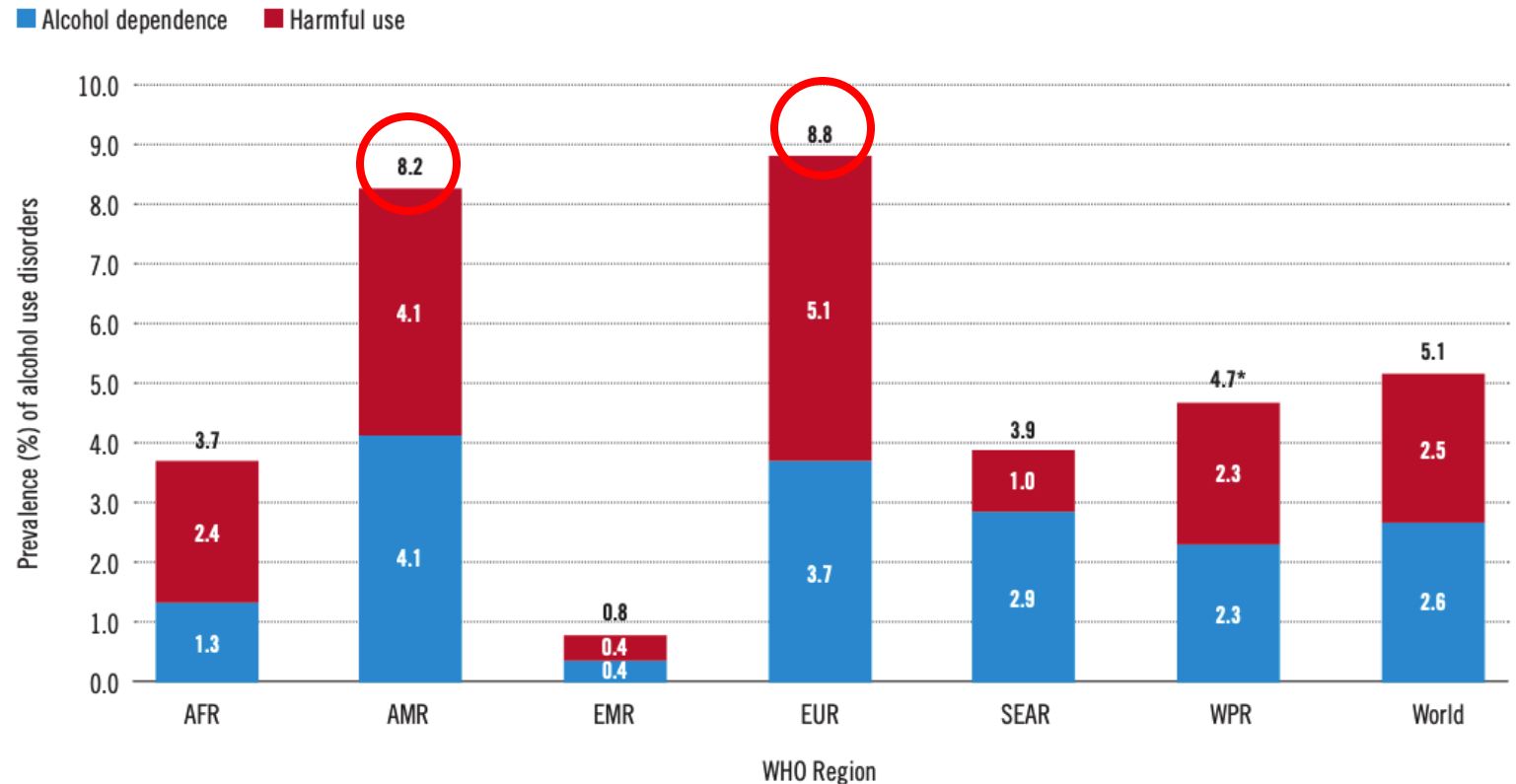
Prevalence (in %) of heavy episodic drinking\* (HED) among current drinkers (15+ years), 2016

*\*(defined as 60 or more grams of pure alcohol on at least one occasion at least once per month)*



# Prevalence of AUD

Prevalence of alcohol  
use disorders (AUDs) =  
**5.1%**

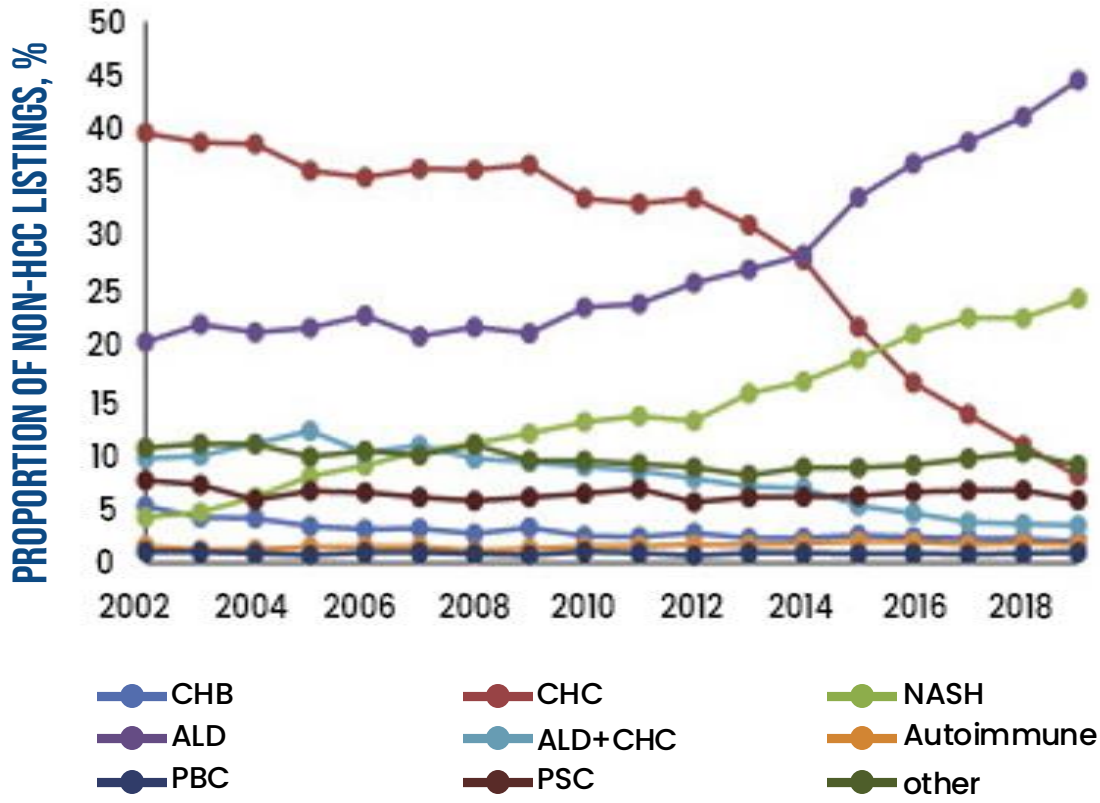


\* Note: The discrepancy between categories and total number can be explained due to rounding of numbers.

# TRENDS ON LIVER TRANSPLANTATION

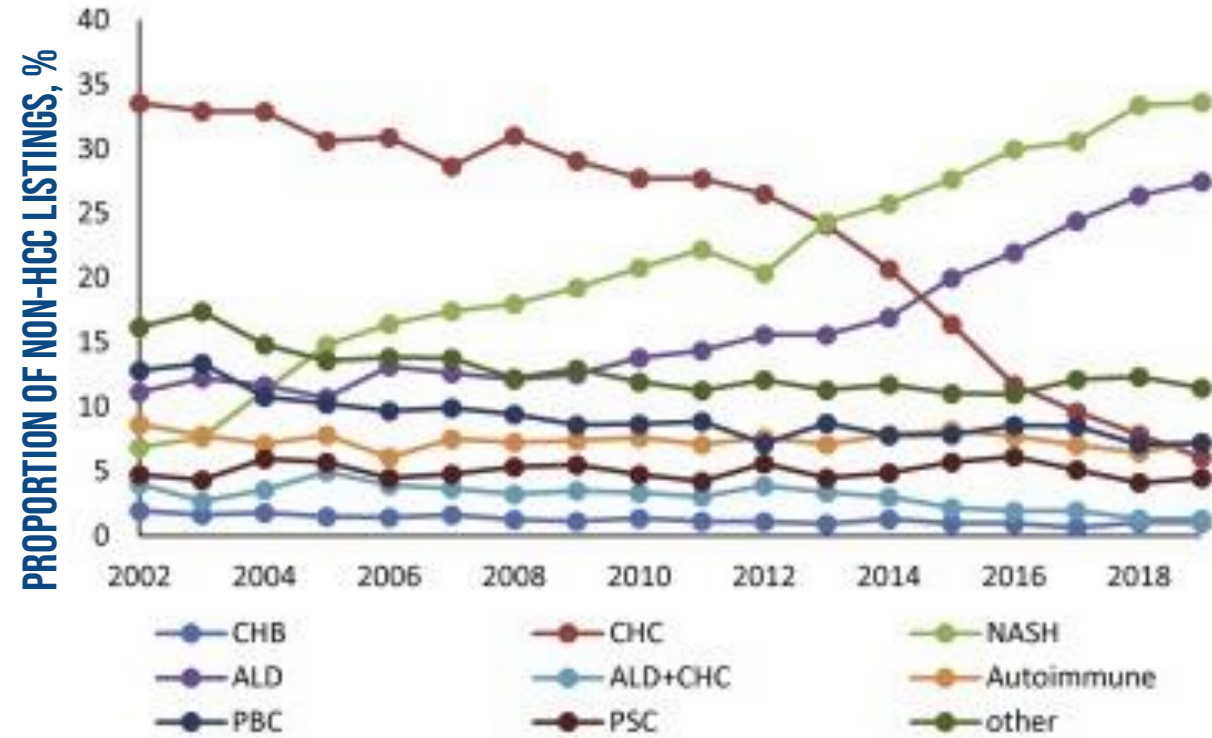
A

MALE

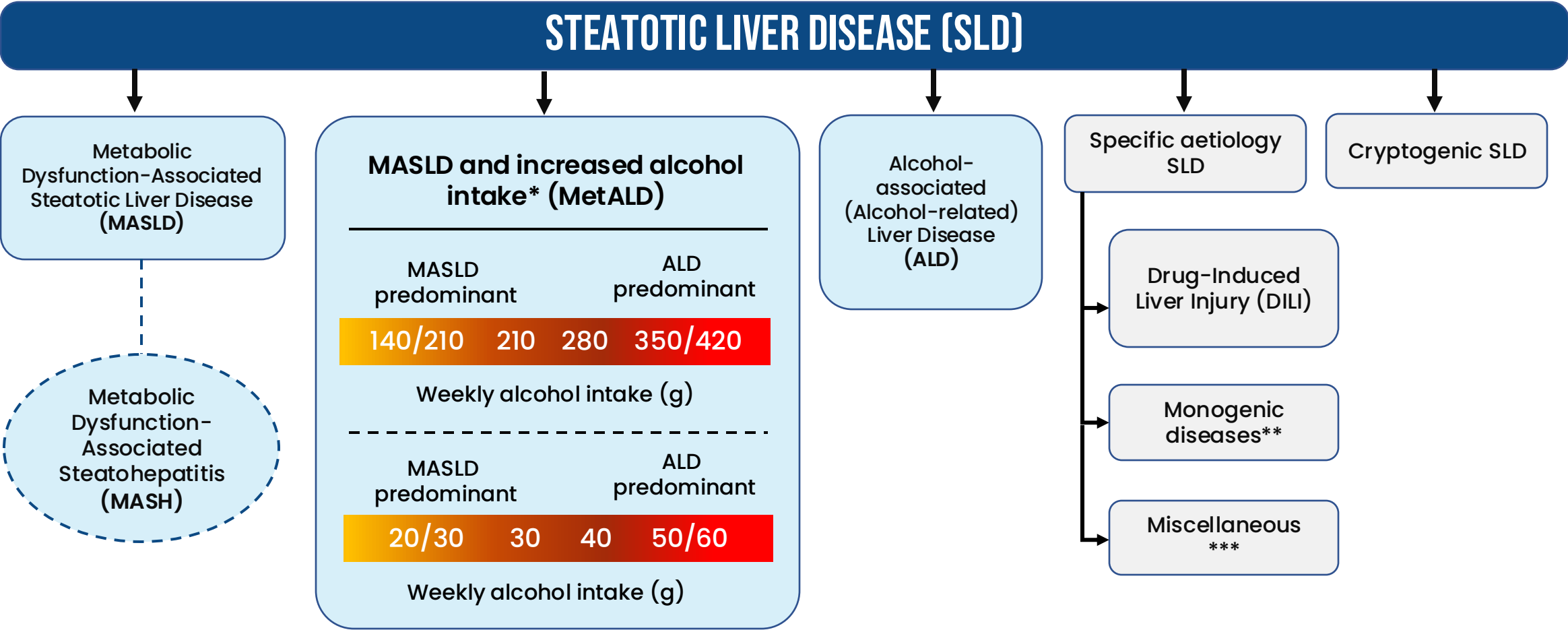


B

FEMALE



# NEW NOMENCLATURE: STEATOTIC LIVER DISEASE

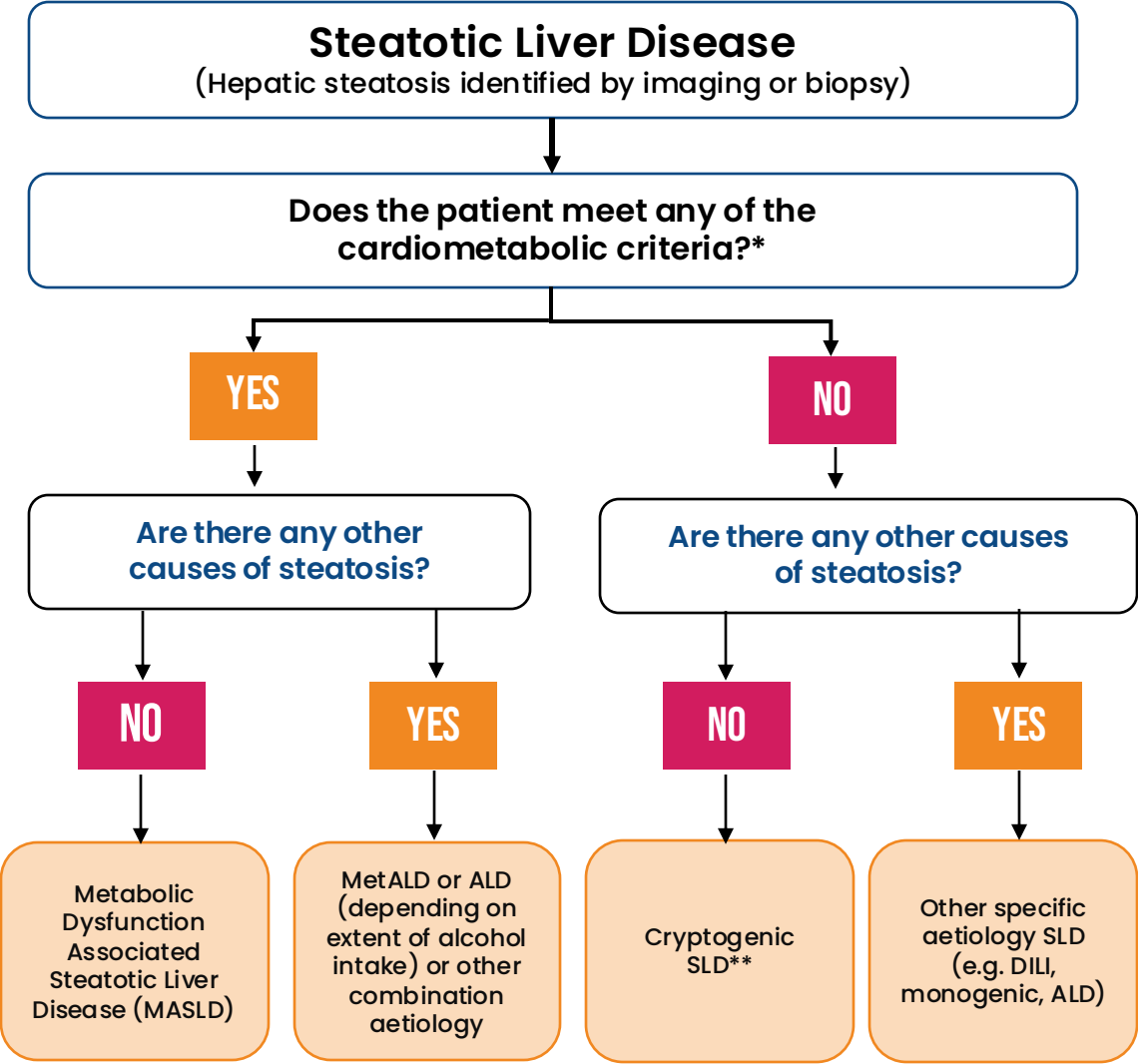


\*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)

\*\*e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism

\*\*\*e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

# NEW NOMENCLATURE: STEATOTIC LIVER DISEASE



## \*CARDIOMETABOLIC CRITERIA

### ADULT CRITERIA

At least 1 out of 5:

- ☐ BMI  $\geq 25$  kg/m<sup>2</sup> [23 Asia] OR WC  $>94$  cm (M) 80 cm (F) OR ethnicity adjusted equivalent
- ☐ Fasting serum glucose  $\geq 5.6$  mmol/L [100 mg/dl] OR 2-hour post-load glucose levels  $\geq 7.8$  mmol/L [ $\geq 140$  mg/dl] OR HbA1c  $\geq 5.7\%$  [39 mmol/L] OR type 2 diabetes OR treatment for type 2 diabetes
- ☐ Blood pressure  $\geq 130/85$  mmHg OR specific antihypertensive drug treatment
- ☐ Plasma triglycerides  $\geq 1.70$  mmol/L [150 mg/dl] OR lipid lowering treatment
- ☐ Plasma HDL-cholesterol  $\leq 1.0$  mmol/L [40 mg/dl] (M) and  $\leq 1.3$  mmol/L [50 mg/dl] (F) OR lipid lowering treatment

### PEDIATRIC CRITERIA

At least 1 out of 5:

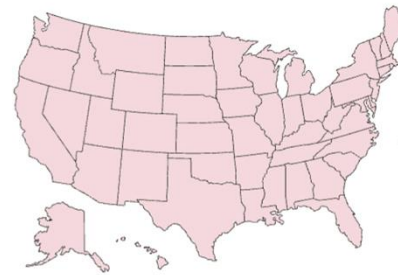
- ☐ BMI  $\geq 85$ th percentile for age/sex [BMI z score  $\geq +1$ ] OR WC  $>95$ th percentile OR ethnicity adjusted equivalent
- ☐ Fasting serum glucose  $\geq 5.6$  mmol/L [ $\geq 100$  mg/dl] OR serum glucose  $\geq 11.1$  mmol/L [ $\geq 200$  mg/dl] OR 2-hour post-load glucose levels  $\geq 7.8$  mmol [140 mg/dl] OR HbA1c  $\geq 5.7\%$  [39 mmol/L] OR already diagnosed/treated type 2 diabetes OR treatment for type 2 diabetes
- ☐ Blood pressure age  $<13$  yr, BP  $\geq 95$ th percentile OR  $\geq 130/80$  mmHg (whichever is lower); age  $\geq 13$  yr, 130/85 mmHg OR specific antihypertensive drug treatment
- ☐ Plasma triglycerides age  $<10$  yr,  $\geq 1.15$  mmol/L [ $\geq 100$  mg/dl]; age  $\geq 10$  yr,  $\geq 1.70$  mmol/L [ $\geq 150$  mg/dl] OR lipid lowering treatment
- ☐ Plasma HDL-cholesterol  $\leq 1.0$  mmol/L [ $\leq 40$  mg/dl] OR lipid lowering treatment



# Epidemiology

## Prevalence of Steatotic Liver Disease in the US: NHANES 2017-2020

**Background and Aims:** Following a Delphi consensus process, the term "steatotic liver disease" (SLD) was introduced to replace "fatty liver disease". Using the NHANES dataset from 2017-2020 we aimed to unveil the prevalence of SLD and its sub-categories in the US.



**SLD**

**37.87%**

(95% C.I: 35.1%-40.7%)

**MASLD**

**32.45%**

(95%C.I: 29.8%-35.2%)



**MetALD**

**2.56%**

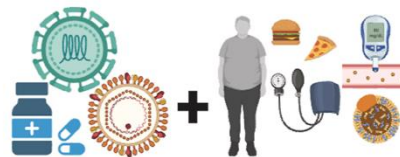
(95%C.I: 1.91%-3.41%)



**Other Combination  
Aetiology**

**1.14%**

(95%C.I: 0.88%-1.49%)



**ALD**

**1.17%**

(95%C.I: 0.71%-1.92%)



**Cryptogenic/  
Other**

**0.32%**

(95%C.I: 0.17%-0.61%)

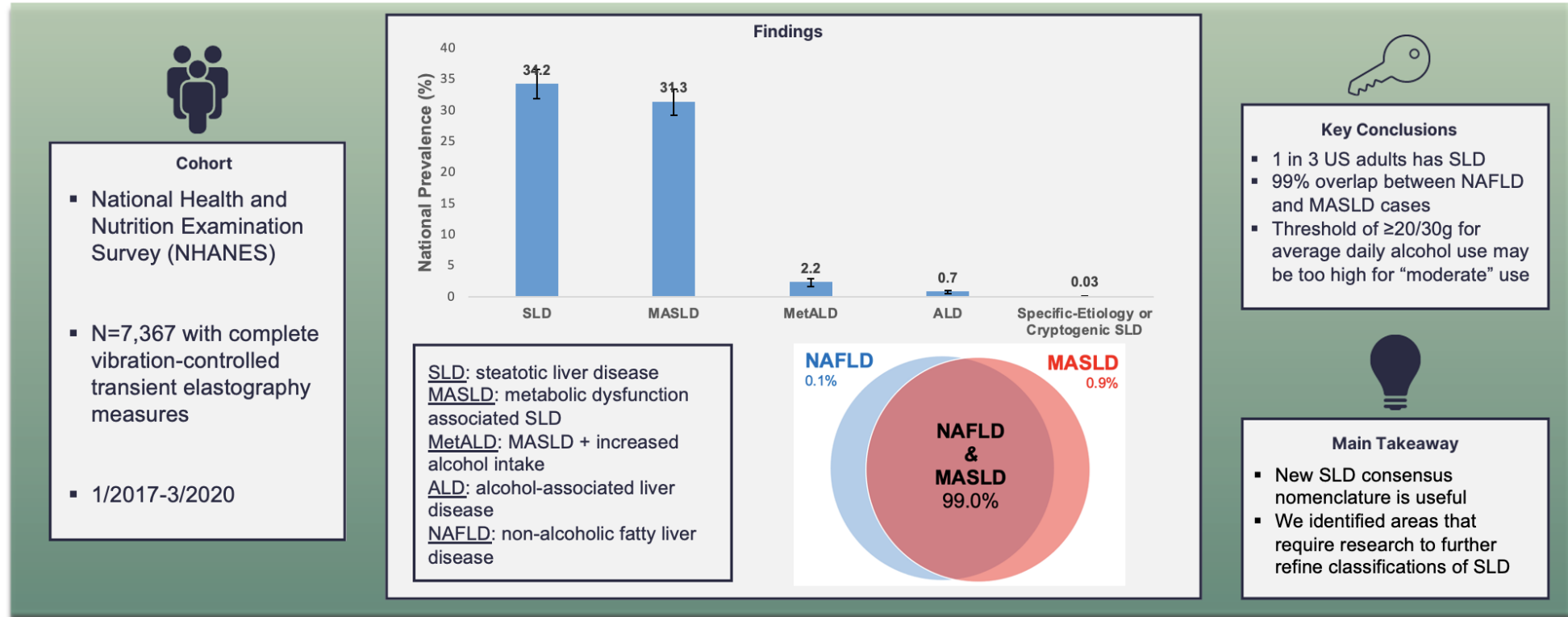


Clinical Gastroenterology  
and Hepatology

# Epidemiology

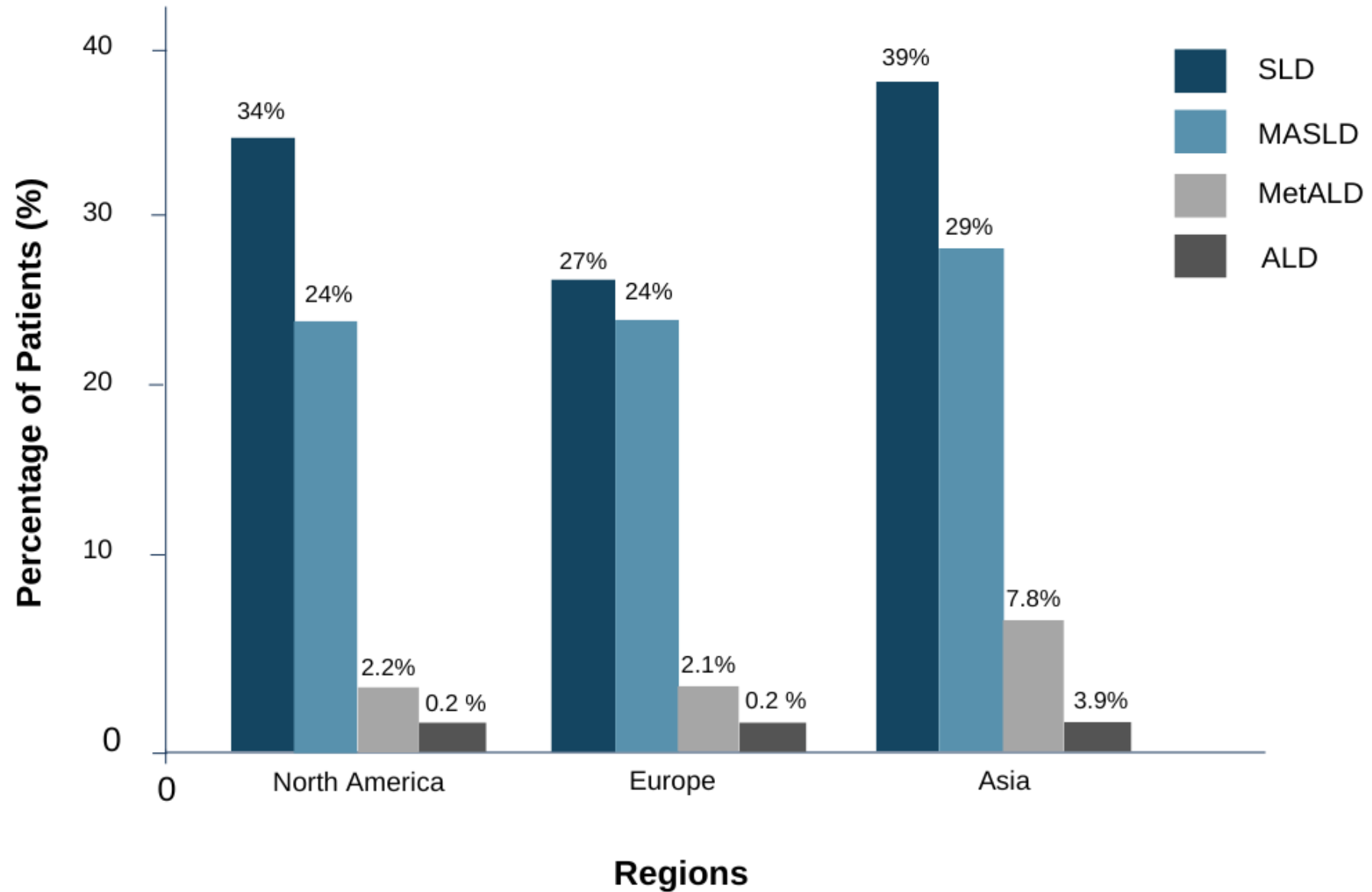
**SLD** 34.2% (95% CI  
31.9%–36.5%)  
**MASLD** 31.3%  
(29.2%–33.4%)  
**MetALD** 2.2%  
(1.6%–2.9%)  
**ALD** 0.7%  
(0.5–0.9%)

## National Prevalence Estimates for Steatotic Liver Disease and Sub-Classifications using Consensus Nomenclature

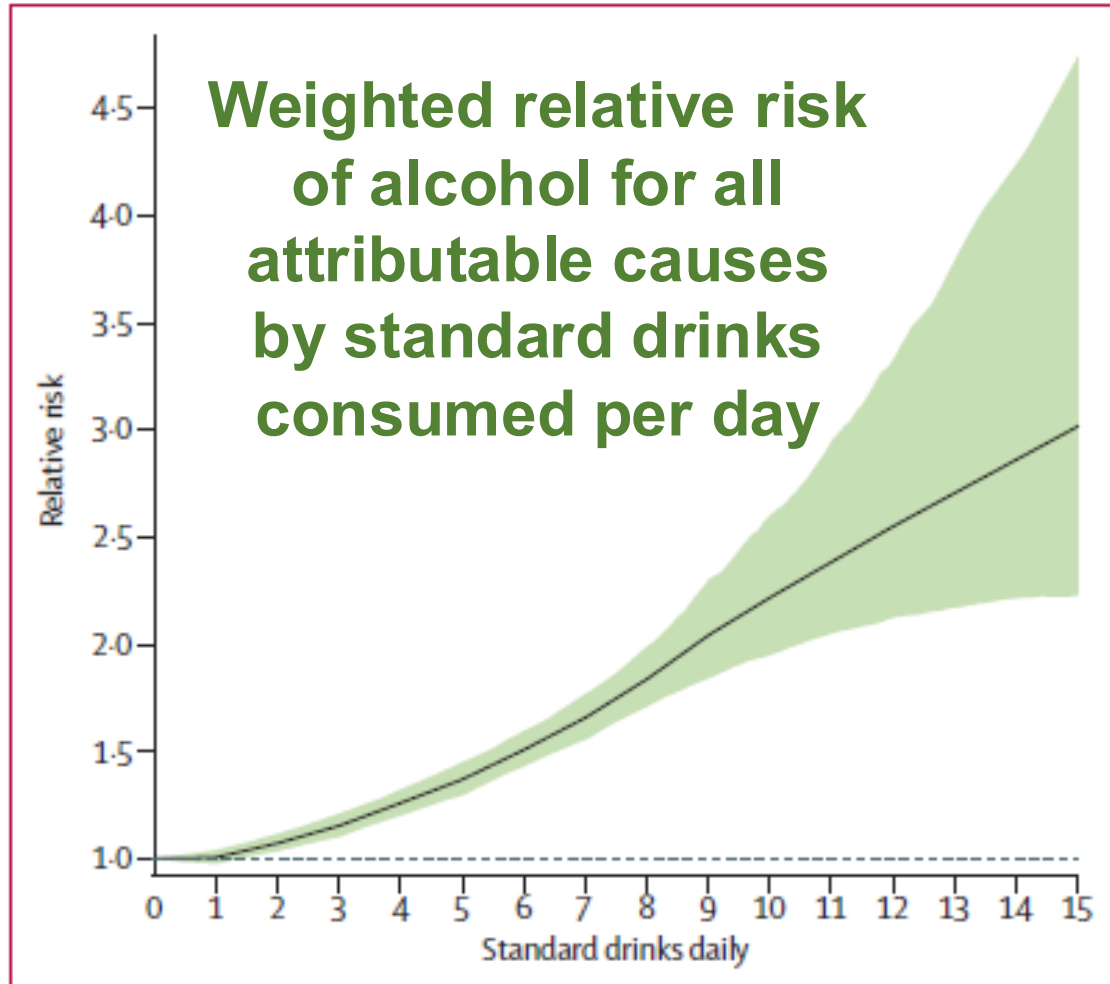


Lee BP, et al. *Hepatology*.

# HEPATOLOGY



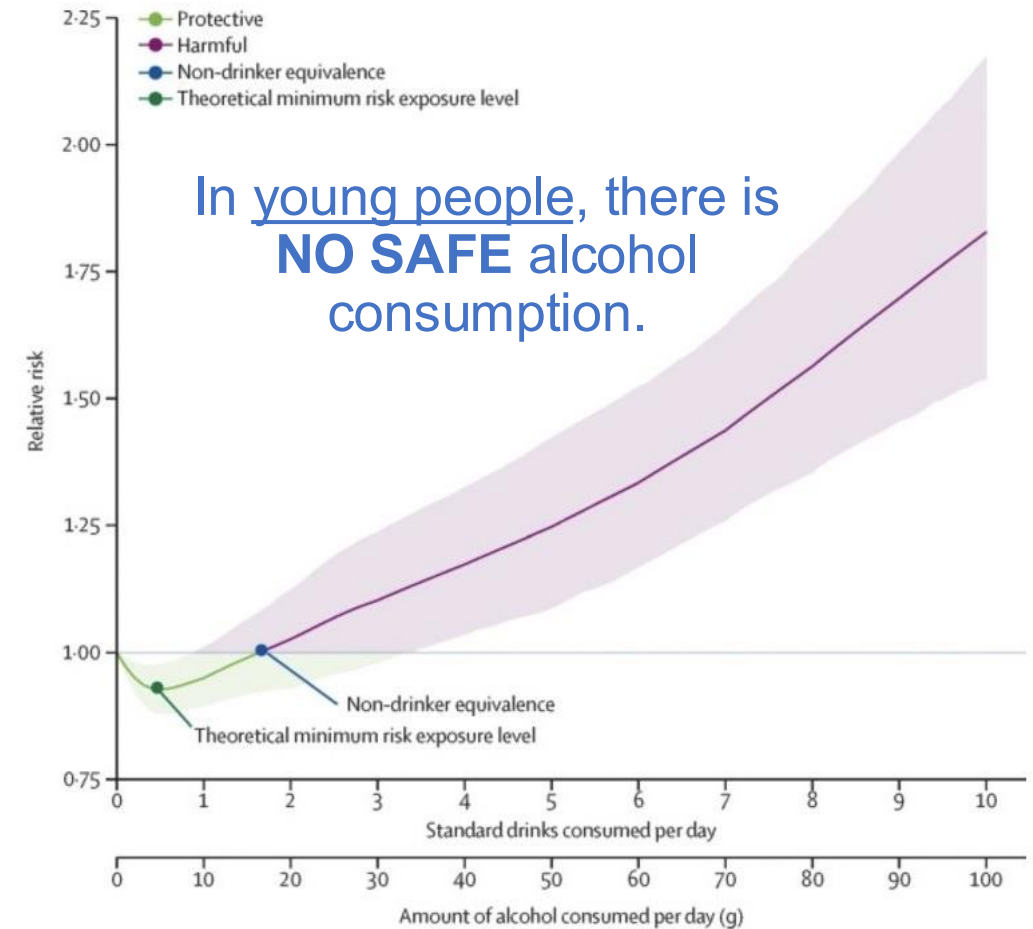
# Harmful Drinking



Lancet. 2018;392(10152):1015-35.

## Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020

GBD 2020 Alcohol Collaborators\*

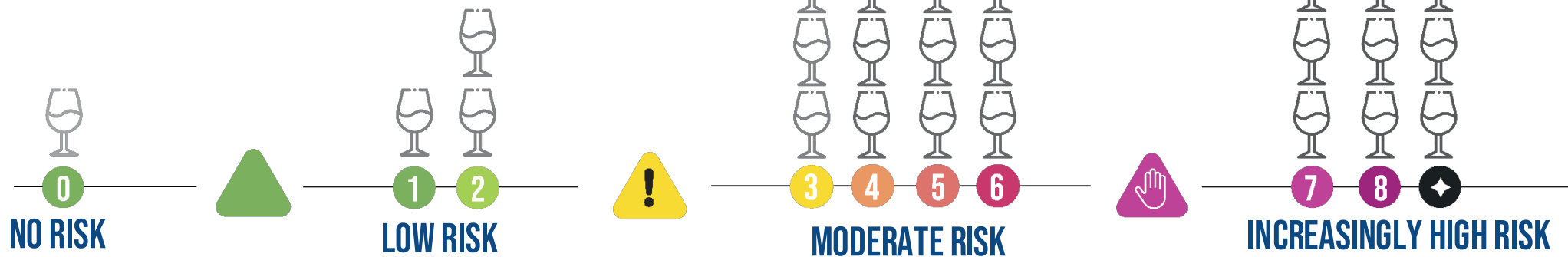


Lancet. 2022 Jul 16;400(10347):185-235. 20

# THE RISK OF ALCOHOL-CAUSED CONSEQUENCES

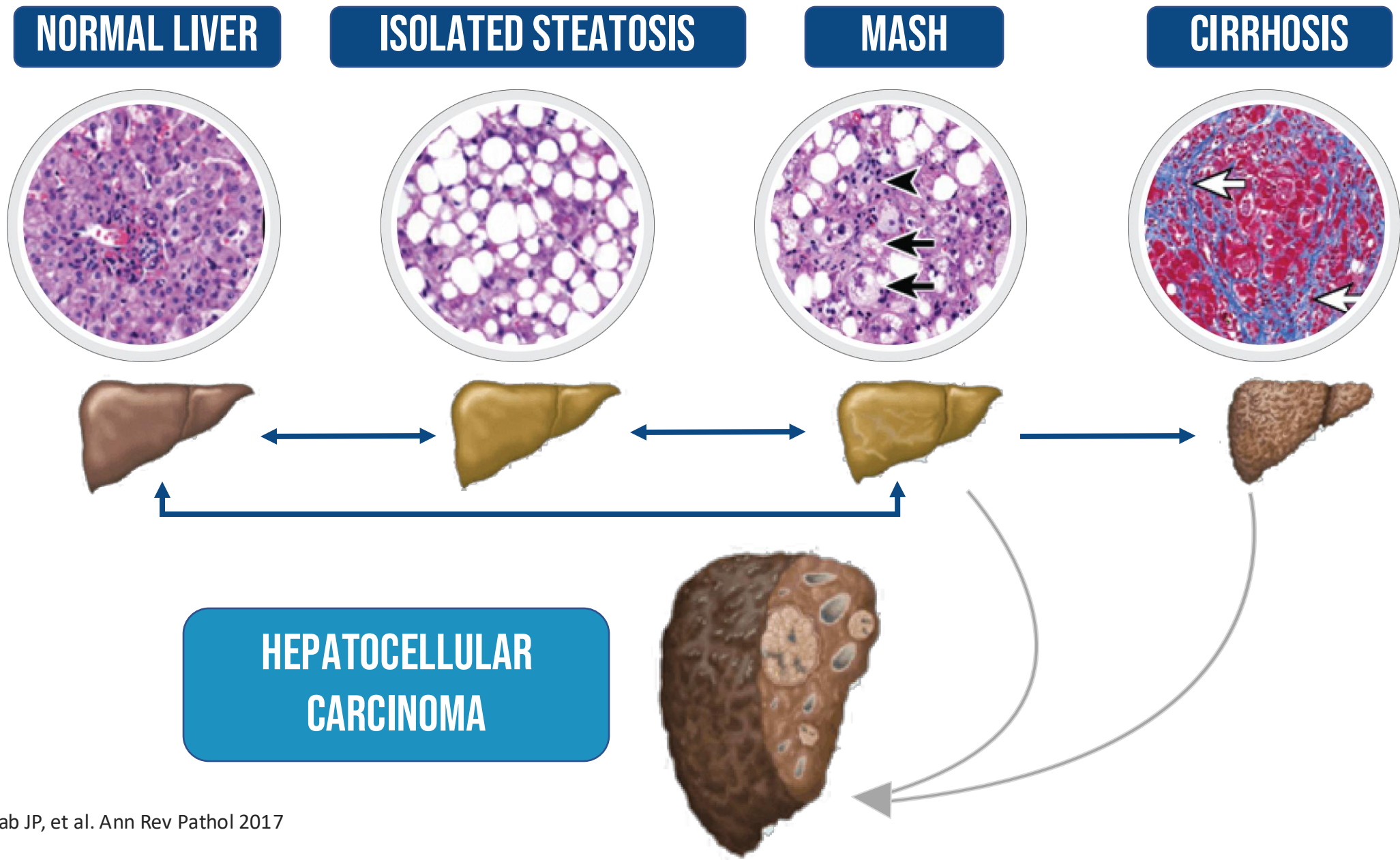
increases with the number of drinks you have **per week**

**“Even in small quantities,  
Alcohol is not good for your  
health”**

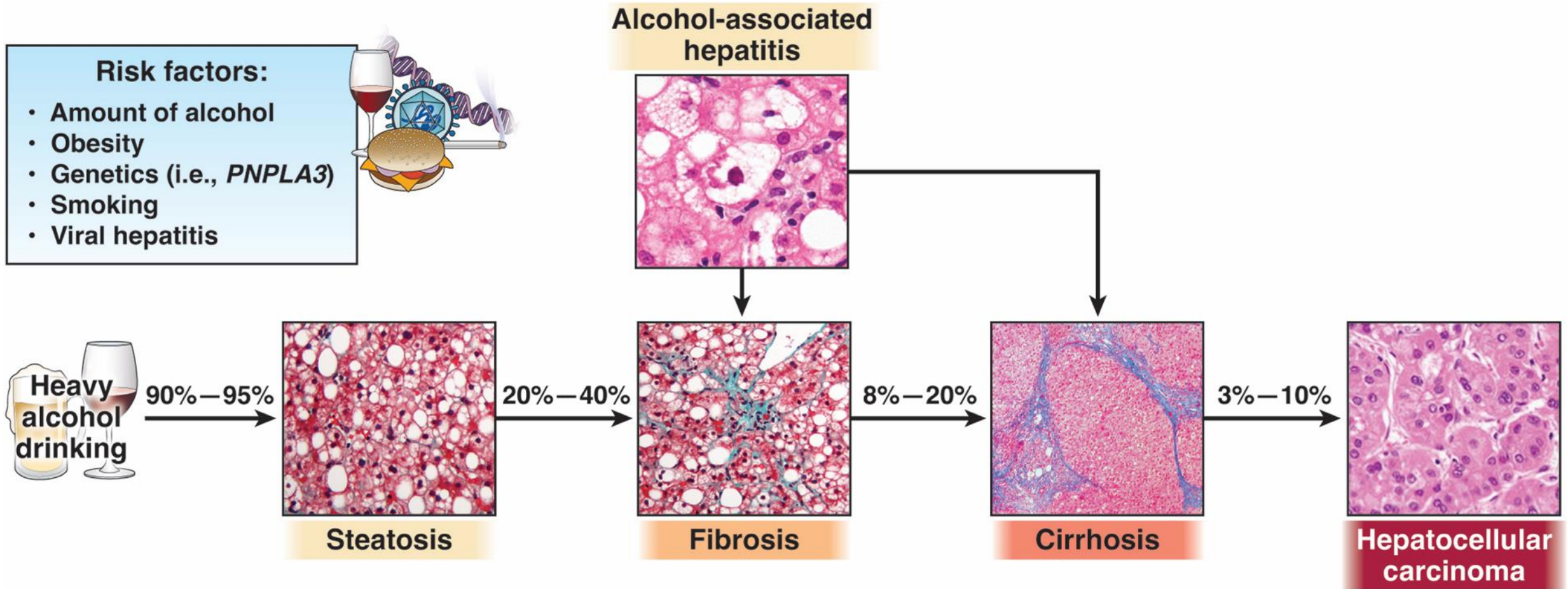




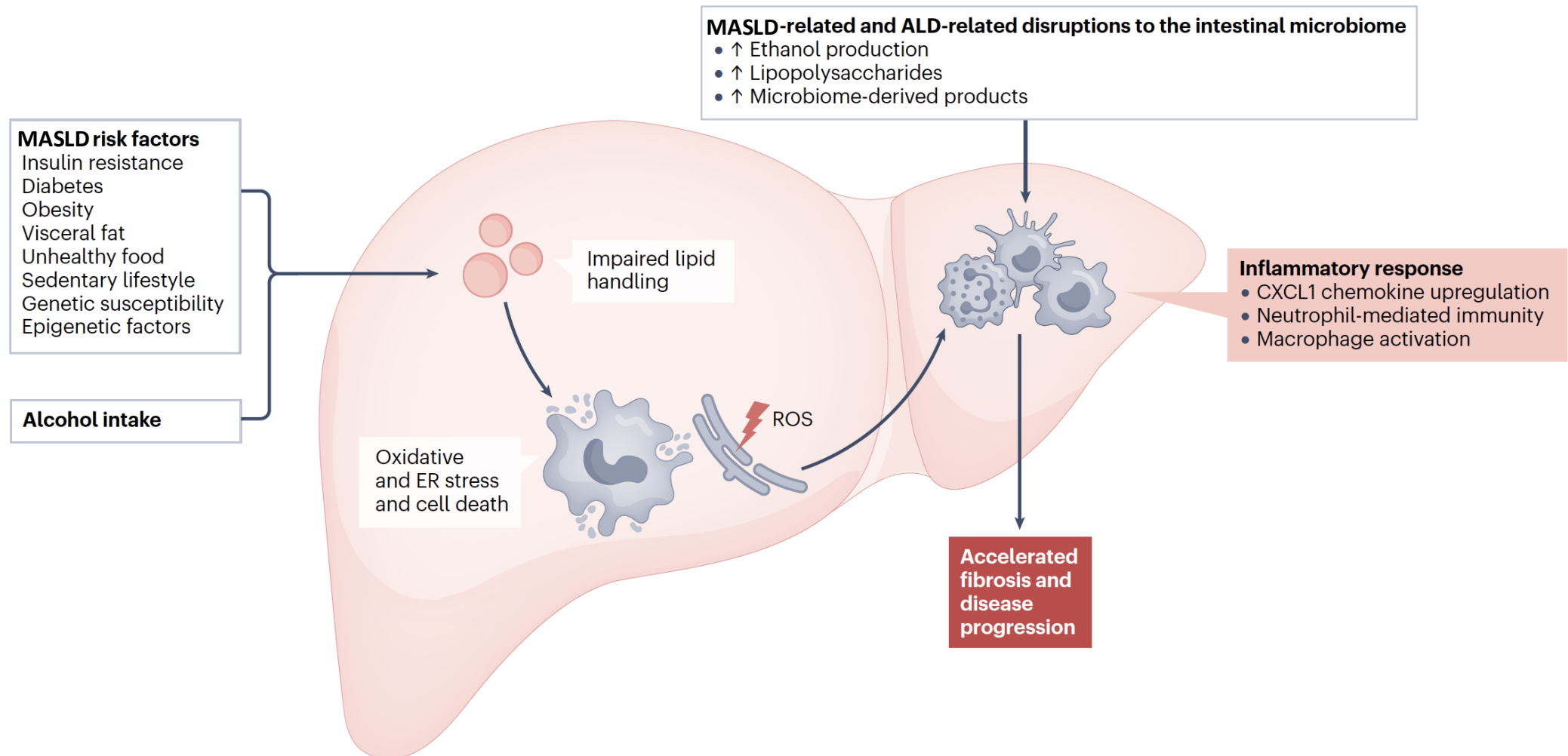
# MASLD: NATURAL HISTORY



# ALD: NATURAL HISTORY



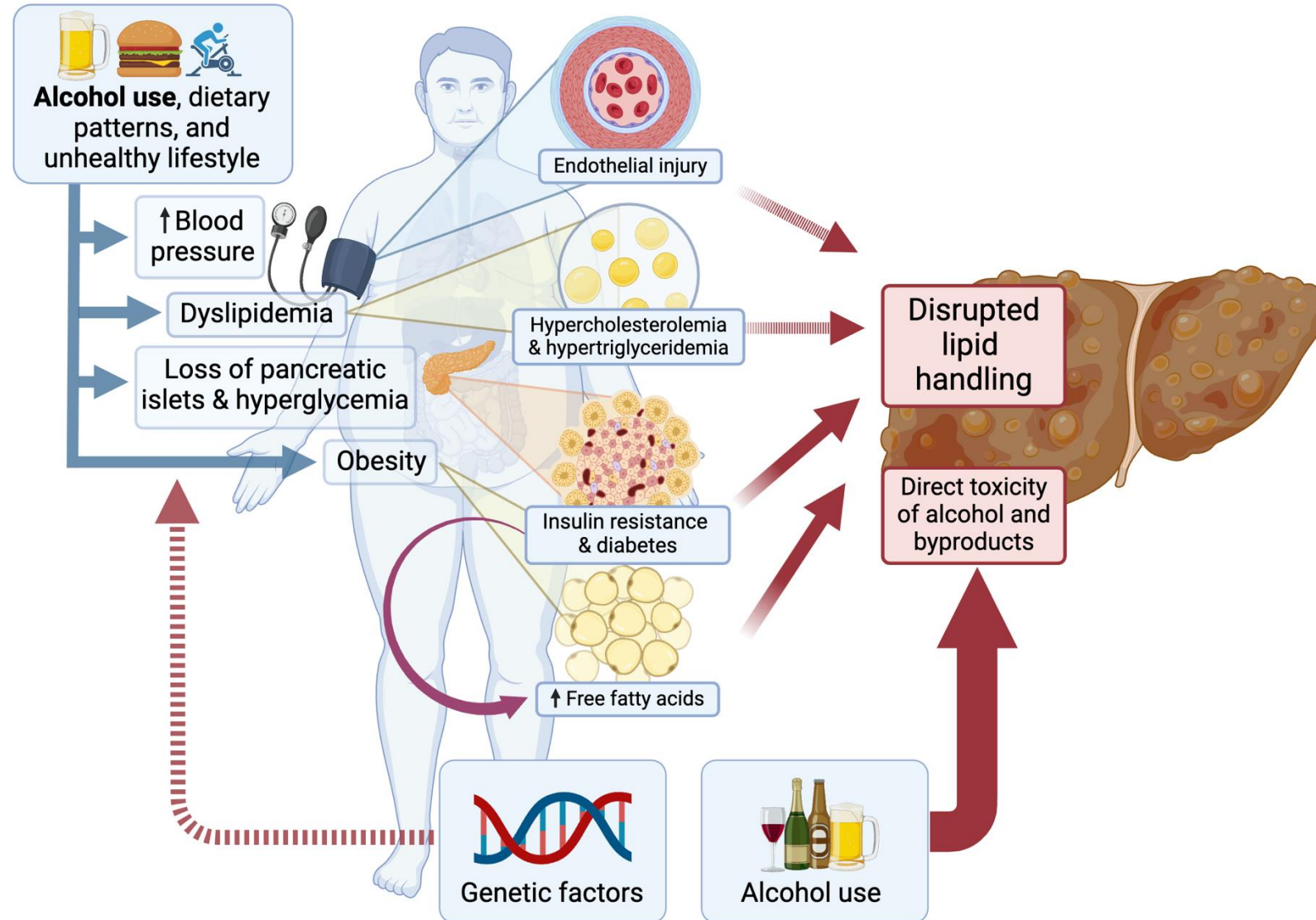
# Key pathogenic mechanisms in MetALD





# MetALD

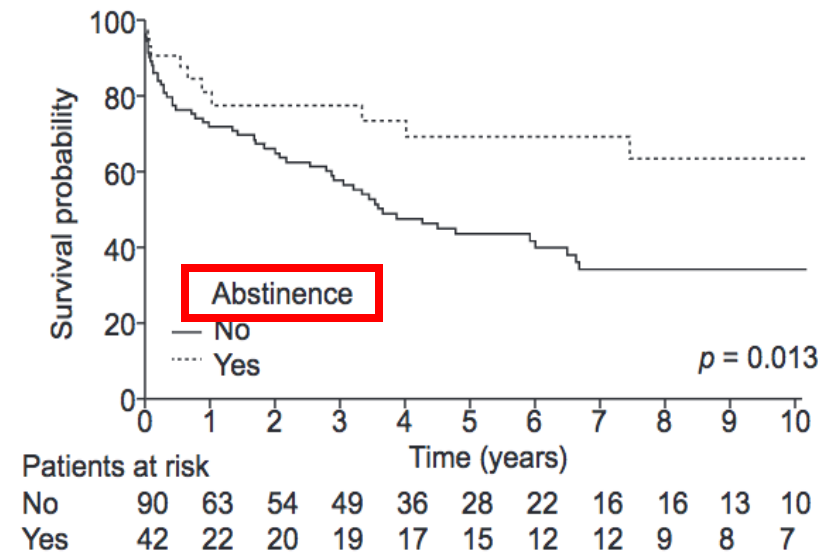
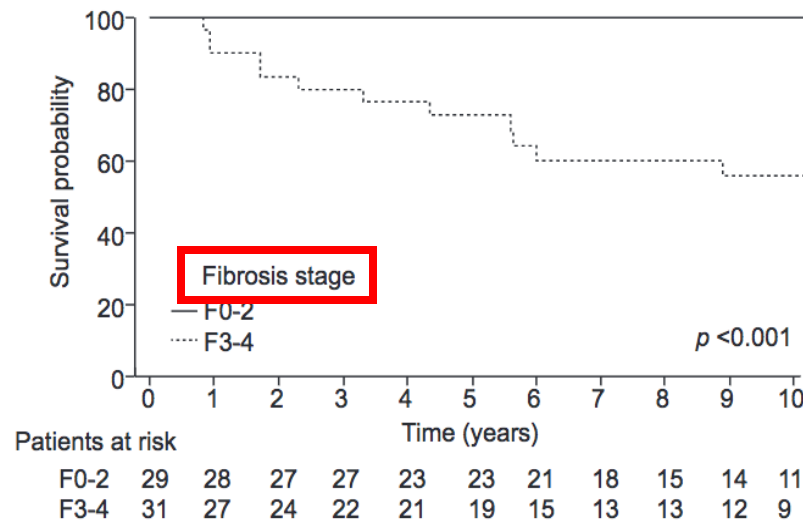
## The role of alcohol use and metabolic dysfunction in promoting liver disease development and progression



# PROGNOSIS

## Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease

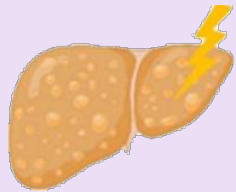
Carolin Lackner<sup>1,\*†</sup>, Walter Spindelboeck<sup>2,†</sup>, Johannes Haybaeck<sup>1</sup>, Philipp Douschan<sup>2</sup>, Florian Rainer<sup>2</sup>, Luigi Terracciano<sup>3</sup>, Josef Haas<sup>4</sup>, Andrea Berghold<sup>5</sup>, Ramon Bataller<sup>6</sup>, Rudolf E. Stauber<sup>2</sup>





# DETECTION OF ALCOHOL MISUSE IN MASLD

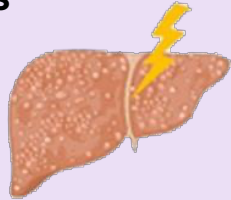
## FATTY LIVER DISEASE



Steatosis



Alcohol



Steatohepatitis



T2DM



Obesity



Diet



Cirrhosis

## METHODS



Questionnaire



Sample collection



AUDIT-C



MCV  
GGT  
CDT  
ANI



uEtG



hEtG  
FAEE

SCR for alcohol consumption  
+ metabolic characterization

## RESULTS & CONCLUSIONS

Moderate to excessive  
alcohol consumption in



28.6% of NAFLD patients  
25.0% of MAFLD patients

Optimal diagnostic means

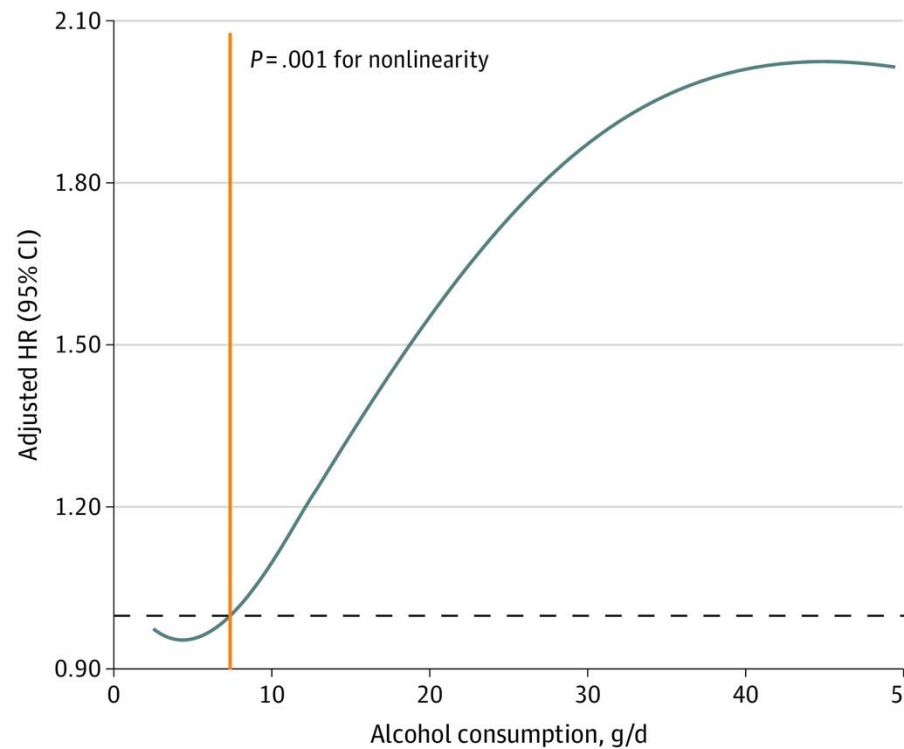


hEtG: AUC 0.927  
+ uEtG: AUC 0.754  
+ AUDIT-C: AUC 0.733

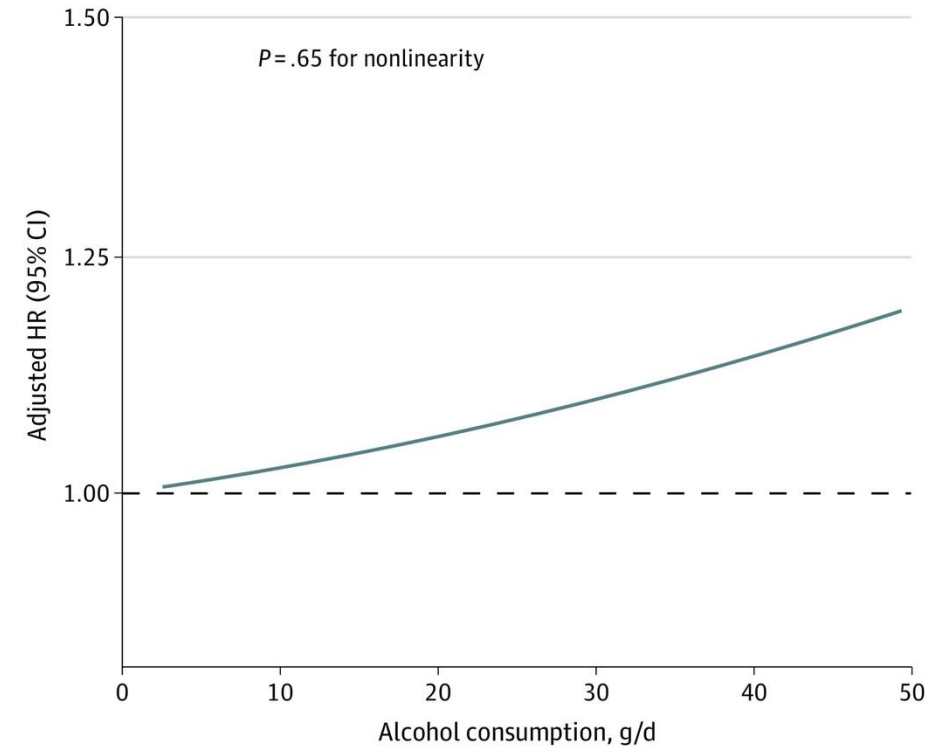
# Alcohol Intake Thresholds Among Individuals With Steatotic Liver Disease

“The recommended level of alcohol consumption was **less than 7.4 g/d** for individuals with SLD at lower risk for advanced fibrosis, which equals half a 12-oz (336-g) beer or half a glass of wine”.

**A** Low risk for advanced fibrosis (FIB-4 score <1.3)



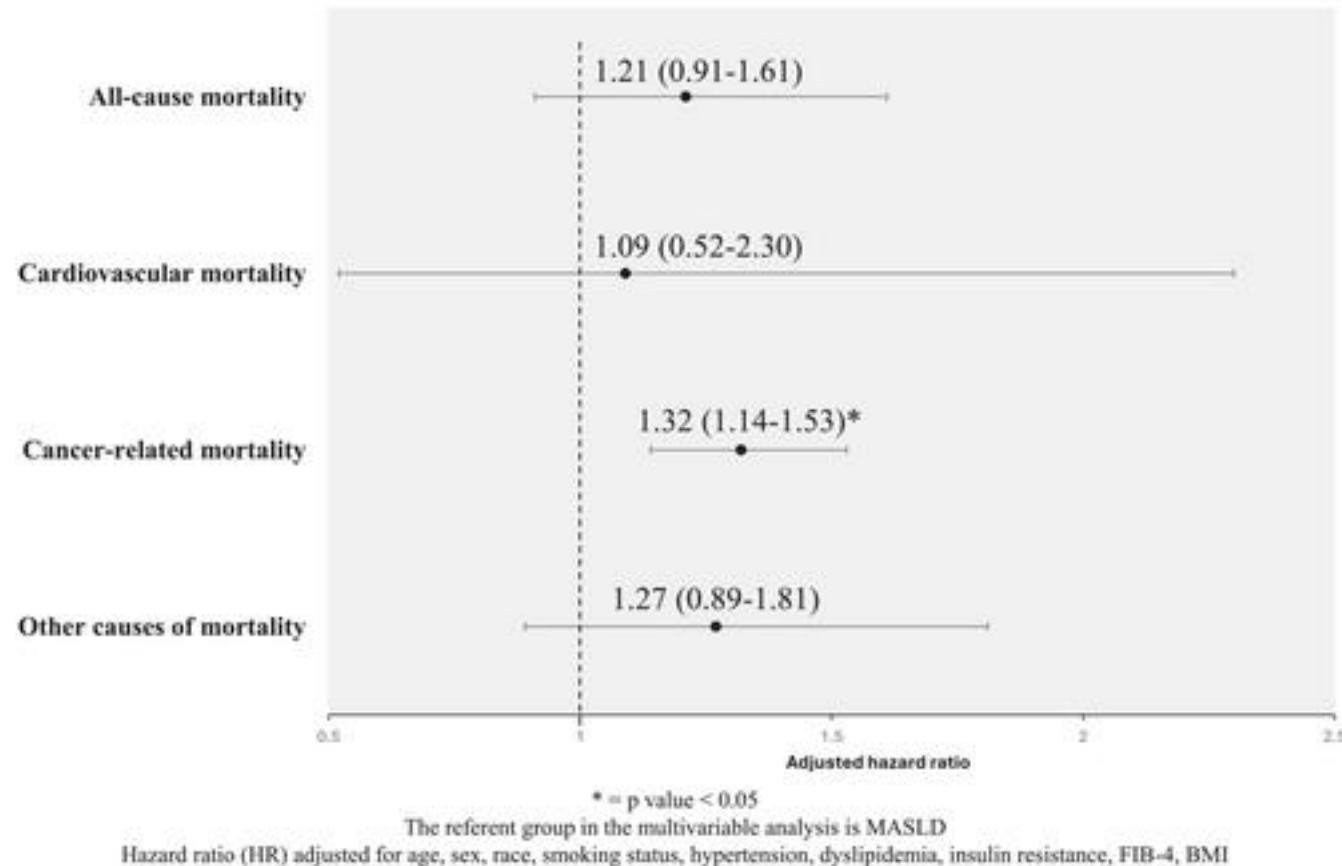
**B** Intermediate and high risk for advanced fibrosis (FIB-4 score  $\geq 1.3$ )

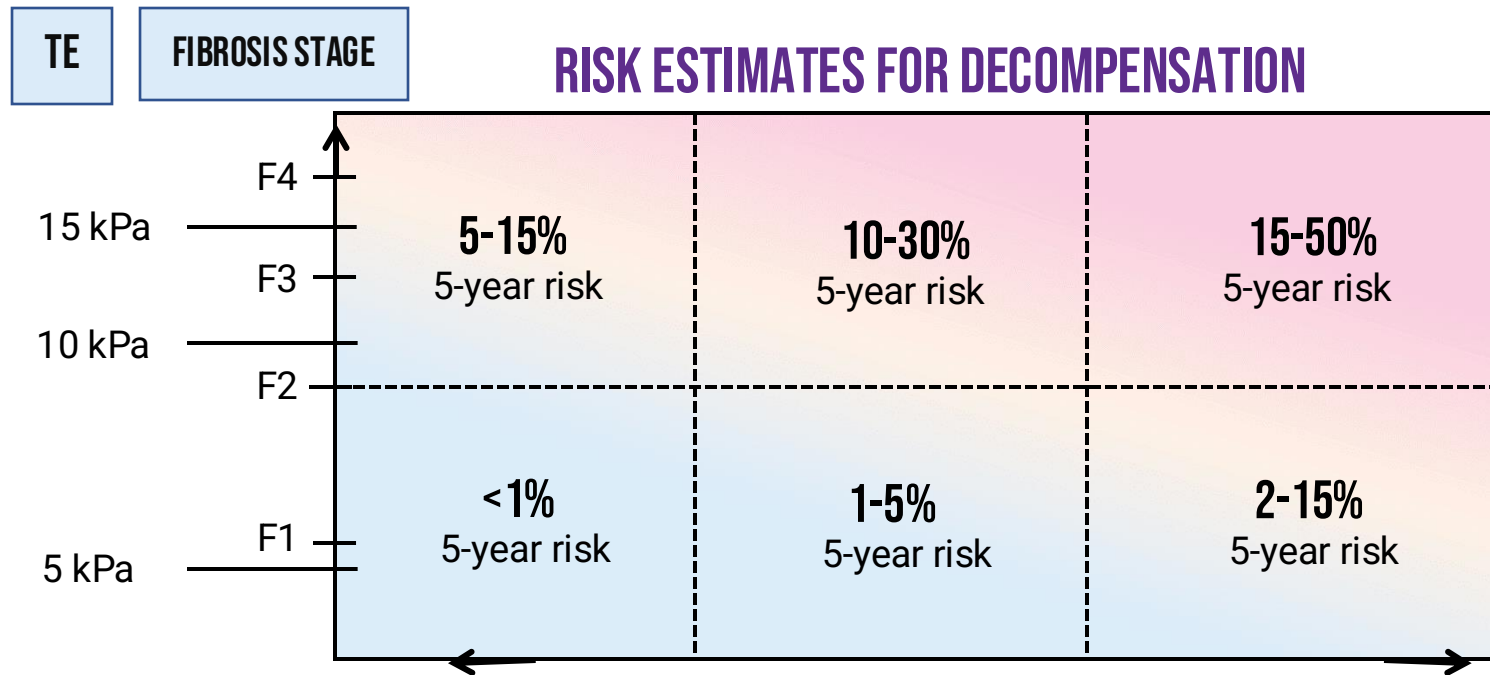


# Mortality outcomes in individuals with MASLD versus MASLD and increased alcohol intake

“MetALD patients were at increased risk of **cancer-related mortality** compared with patients with MASLD (**hazard ratio 1.32**; 95% confidence interval 1.14-1.53;  $p < 0.01$ )”.

Overall and Cause-specific mortality associated with MetALD vs MASLD

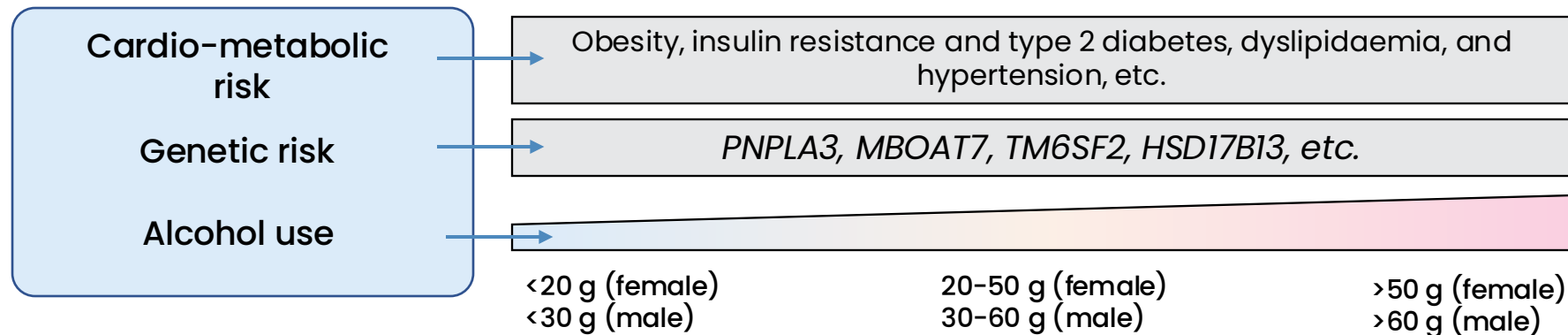




**THE DYNAMIC SPECTRUM OF SLD**

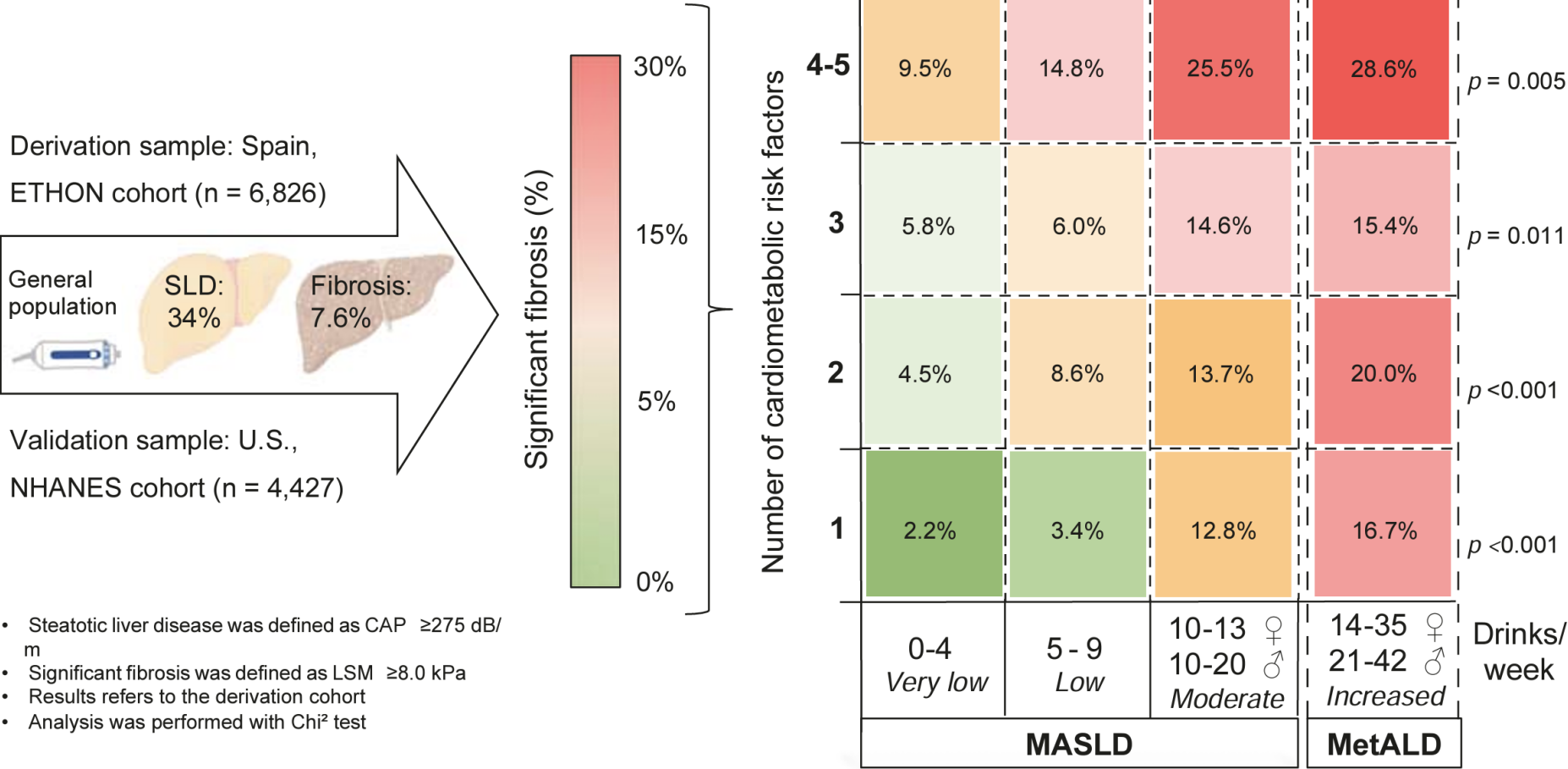


**DISEASE DRIVERS**



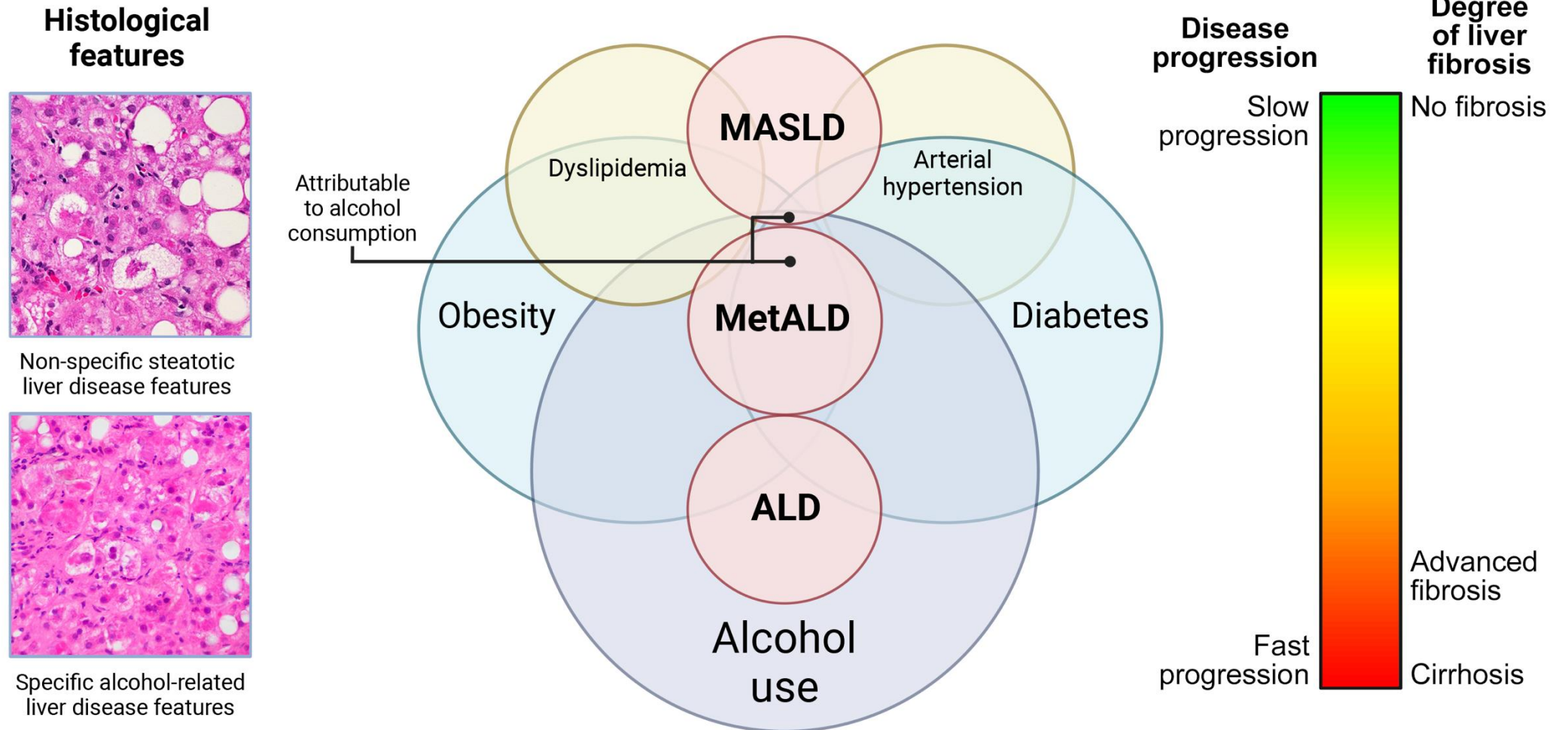
# MetALD

Low-to-moderate alcohol consumption is associated with **increased fibrosis** in individuals with **MASLD**



# MetALD

## The alcohol-attributable risk of steatotic liver disease





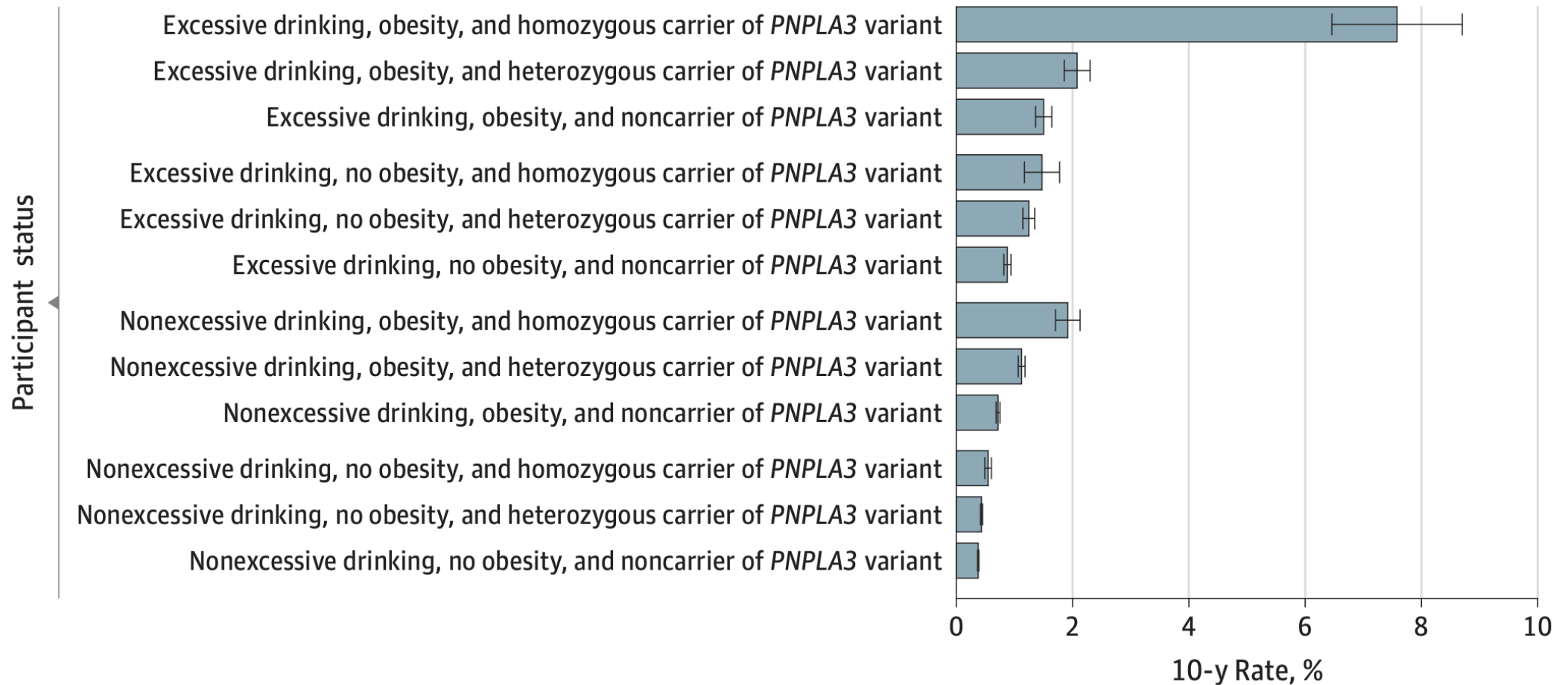
# Genes involved in dual-etiology

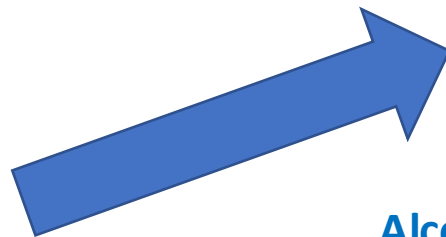
Gene	Protein name	Variant	Cytogenetic location	Pathway	Outcomes in NAFLD and ALD
<i>PNPLA3</i>	Patatin-like phospholipase domain-containing 3	rs738409 C>G	22q13.31	Lipid metabolism	The risk variant modulates liver fat deposition, disease severity and progression in terms of inflammation and fibrosis in NAFLD and ALD <sup>233,234</sup>
<i>TM6SF2</i>	Transmembrane 6, superfamily member 2	rs58542926 C>T	19p13.3-p12	Miscellaneous	The polymorphism was associated with increased hepatic triglyceride content and advanced hepatic fibrosis or cirrhosis in NAFLD and ALD <sup>234</sup>
<i>MBOAT7</i>	Membrane-bound O-acyltransferase domain-containing 7	rs641738 C>T	19q13.42	Lipid composition of cell membranes	The variant was identified as a risk factor for ALD and promotes fat accumulation in the liver and development of NAFLD, inflammation, fibrosis and HCC due to reduced protein expression <sup>235</sup>
<i>GCKR</i>	Glucokinase regulator	rs1260326 T>C	2p23.3	Lipid synthesis	The variant decreases circulating fasting glucose and insulin levels but increases the production of malonyl-CoA, thereby promoting hepatic fat accumulation by serving as a substrate for lipogenesis and by blocking fatty acid oxidation <sup>235</sup>
<i>HSD17B13</i>	17 $\beta$ -hydroxysteroid dehydrogenase 13	rs72613567 T>TA rs62305723 G>A	4q22.1	Lipid metabolism	HSD17B13 protects against liver inflammation, cirrhosis and HCC due to both dysmetabolism and alcohol; the risk variants are related to the modulation of inflammation and fibrogenesis <sup>236</sup>
<i>SOD2</i>	Superoxide dismutase 2, mitochondrial	rs4880 C>T	6q25.3	Oxidative stress	The risk variant was associated with more advanced fibrosis in NASH <sup>113,237,238</sup>

Genes are ordered according to relevance to clinical practice. ALD, alcohol-associated liver disease; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

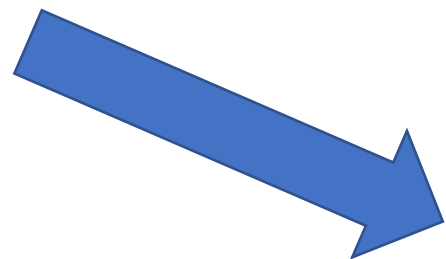
# Individual susceptibility: Cirrhosis

**A** Cumulative 10-year incidence rate of cirrhosis





**Alcohol-associated liver disease (ALD)**



**Alcohol use disorder (AUD)**

# ALCOHOL USE DISORDERS SCREENING: AUDIT

## ALCOHOL USE DISORDERS IDENTIFICATION TEST (AUDIT)

AUDIT is a comprehensive 10 question alcohol harm screening tool. It was developed by the World Health Organization (WHO) and modified for use in the UK and has been used in a variety of health and social care settings.

QUESTIONS	SCORING SYSTEM					YOUR SCORE
	0	1	2	3	4	
How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times per month	2 to 3 times per week	4 times or more per week	
How many units of alcohol do you drink on a typical day when you are drinking?	0 to 2	3 to 4	5 to 6	7 to 9	10 or more	
How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
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	
How often during the last year have you failed to do what was normally expected from you because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you needed an alcoholic drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
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	
How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
Have you or somebody else been injured as a result of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?	No		Yes, but not in the last year		Yes, during the last year	

Total AUDIT score

## SCORING

- 0 to 7 indicates low risk
- 8 to 15 indicates increasing risk
- 16 to 19 indicates higher risk,
- 20 or more indicates possible dependence

## ALCOHOL UNIT REFERENCE

One unit of alcohol

Half pint of "regular" beer, lager or cider


Half a small glass of wine

1 single measure of spirits

1 small glass of sherry


1 single measure of aperitifs

Drinks more than a single unit

2  
Pint of "regular" beer, lager or cider


3  
Pint of "strong" or "premium" beer, lager or cider

1.5  
Alcopop or a 275ml bottle of regular lager

2  
440 ml can of "regular" lager or cider

4  
440 ml can of "super strength" lager

3  
250ml glass of wine (12%)

2  
75cl Bottle of wine (12%)

# ALCOHOL USE DISORDERS SCREENING: AUDIT-C

SCORE	0	1	2	3	4
How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times per month	2-3 times per week	4+ times per week
How many units of alcohol do you drink on a typical day when you are drinking?	1-2	3-4	5-6	7-9	10+
How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in last year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily

Men and women

0-4

Men and women aged 65+

0-2

No action required

Men and women

5+

Men and women aged 65+

3+

These patients are at an increasing or higher risk of hazardous/harmful drinking. Provide a patient information leaflet with details about harm, benefit and cutting down to patients who drink above low-risk levels (but are not dependent).

Men and women

11+

These patients are potentially addicted/dependent to alcohol. Explain to the patient that the score indicates they may be drinking problematically and refer to local specialist services.

# Screening for AUD: How are we doing it?

	Number of patients
Diagnosis of non-alcoholic fatty liver disease	15 984 (1.00%)
Body-mass index recorded	
In past 12 months	421 785 (26.44%)
In past 5 years	932 618 (58.45%)
Patient's alcohol units recorded	
In past 12 months	281 309 (17.63%)
In past 5 years	723 279 (45.33%)
Received alcohol use disorders identification test	
In past 12 months	48 880 (3.06%)
In past 5 years	164 743 (10.33%)
Assessed for hepatitis C virus infection status	
In past 12 months	50 (<0.001%)
In past 5 years	118 (0.01%)
Data are n (%).	

**Table 1: Royal College of General Practitioners Research and Surveillance Centre data<sup>9</sup> on primary care activity for 1 595 450 patients**

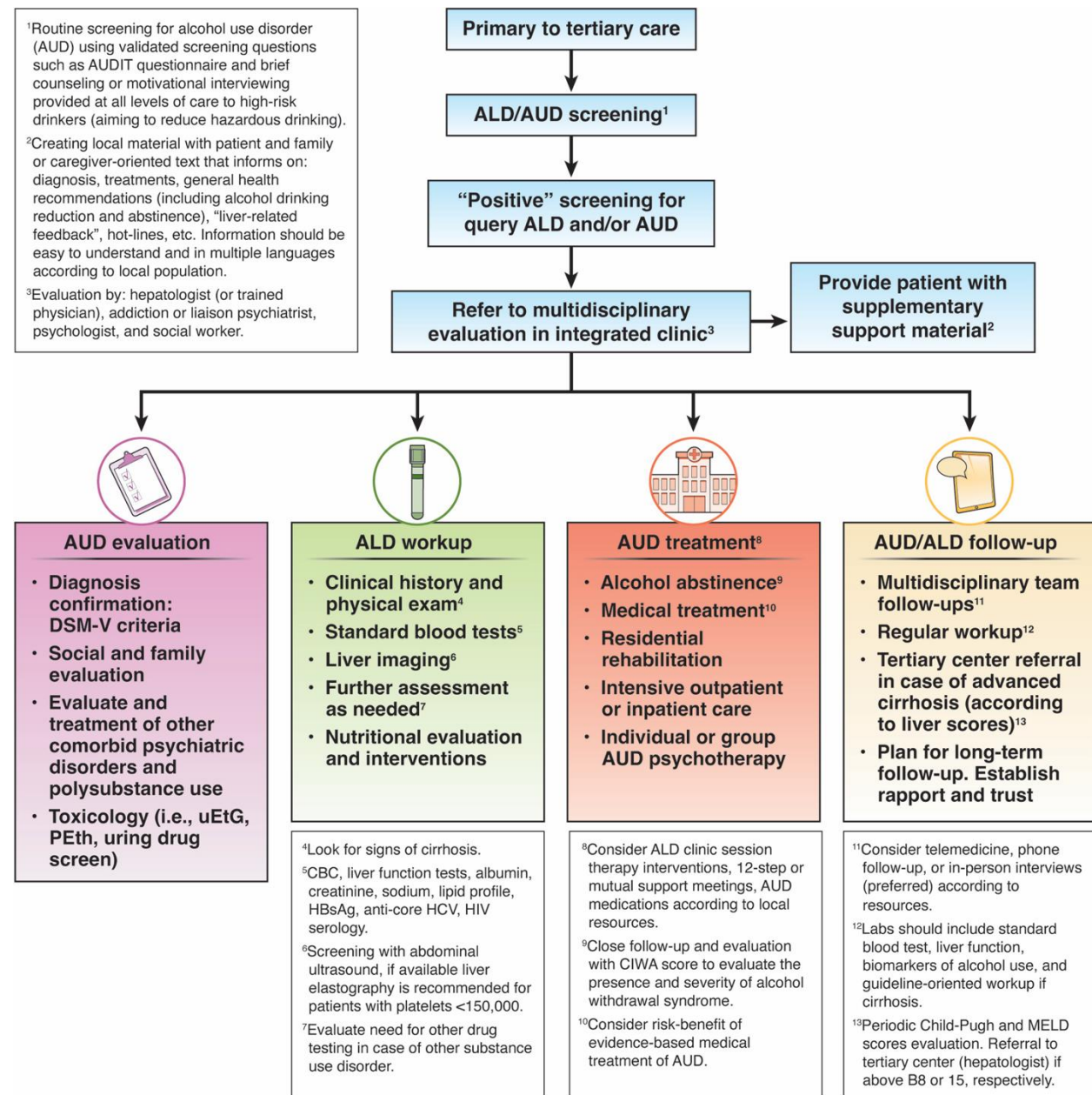
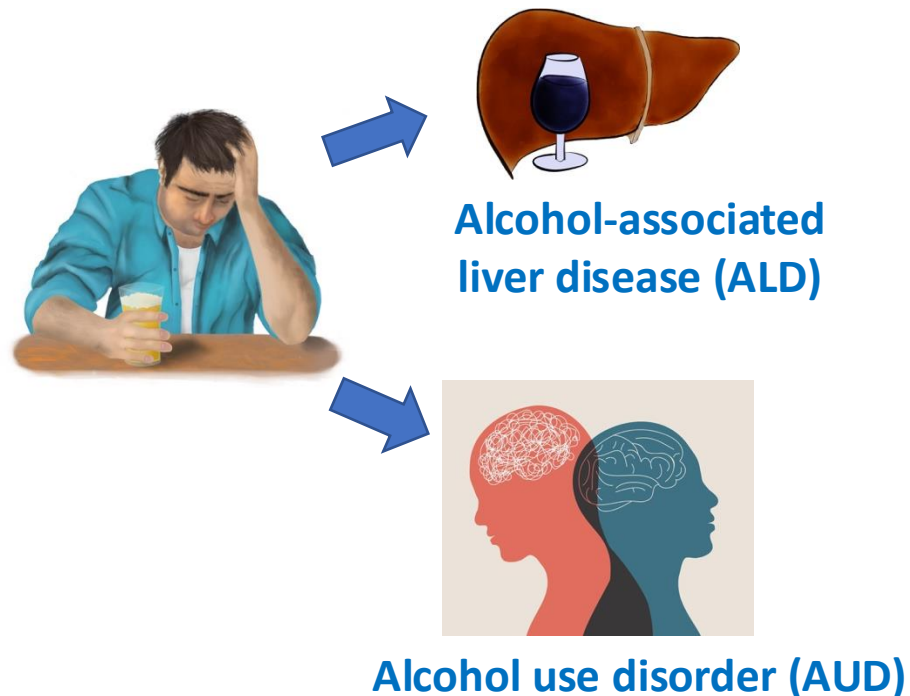


Table 1 | Available methods for detecting alcohol consumption in patients with ALD

Method	Population tested	Pros	Cons
Self-report, clinical interviews, questionnaires <sup>12–19,21,22</sup>	General population and ALD at all stages	Inexpensive and quick; it can be combined and validated with other biomarkers	Low accuracy in many clinical settings
Serum markers (ALT, AST, GGT and MCV) <sup>25,126,127</sup>	General population, ALD at all stages and patients with AUD	Inexpensive and readily available; AST to ALT ratio is a good indicator of chronic excessive alcohol use	Results are non-specific; many sources of false-positives, especially with advanced liver disease
Breath samples (for example, breathalysers or passive alcohol sensors) <sup>127,128</sup>	General population and patients with AUD	Accurate and rapid results	Only detects acute intoxication; sensitive to temperature and breathing pattern
Alcohol levels in saliva <sup>129</sup>	Patients with AUD	Inexpensive and quick	Cannot always predict blood alcohol content
Serum levels of ethanol or methanol <sup>127,130,131</sup>	General population, ALD and patients with AUD	Gold standard for detecting acute alcohol consumption	Rapid elimination in chronic heavy drinkers; quality of laboratory procedures influences results
Serum levels of CDT <sup>25,126,132</sup>	ALD pre-LT and post-LT and patients with AUD	Rare false positives; good indicator of relapse	Reflects more extended heavy drinking
Urine levels of EtG or EtS <sup>25,26,133</sup>	ALD pre-LT and post-LT	Results are easily determined; EtG: inexpensive, longer detection window than for ethanol	Short detection window compared to PEth
Hair testing (EtG or FAEE) <sup>134,135</sup>	General population, patients with AUD	Very specific marker of long-term alcohol use	Expensive; not widely available; collection can be difficult
Serum PEth <sup>24,25,27,136</sup>	ALD pre-LT and post-LT	Very specific; easy to collect; detect longer period of time than EtG or EtS	Expensive; not widely available
Transdermal sensors <sup>137–139</sup>	Patients with AUD	Allows continuous monitoring; tamper-resistant	Not clinically validated; expensive; technical difficulties

ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; CDT, carbohydrate-deficient transferrin; EtG, ethyl glucuronide; EtS, ethyl sulfate; FAEE, fatty acid ethyl esters; GGT,  $\gamma$ -glutamyl transpeptidase; LT, liver transplantation; MCV, mean corpuscular volume; PEth, phosphatidyl ethanol. Adapted from REF.<sup>140</sup>, Springer Nature Limited.

# INTEGRATED CARE



# PHARMACOLOGICAL THERAPY FOR ABSTINENCE

## Proven to be safe and efficient in ALD

Baclofen (10 mg TID; 80 mg QD max)

## Probably safe but not proven in ALD patients

Acamprosate (666 mg TID)

Naltrexone (PO: 50 mg QD IM: 380 mg monthly)

Nalmefene (Max daily dose: 1 tablet 18 mg)

Topiramate (300 mg QD)

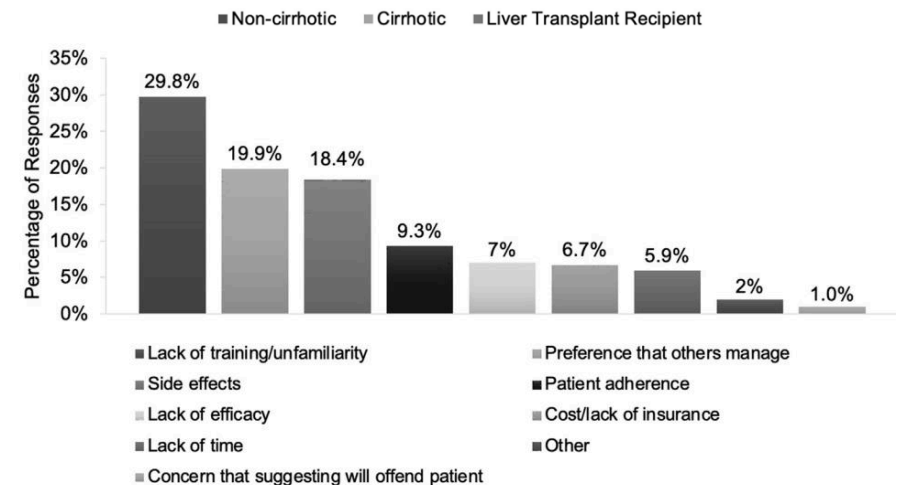
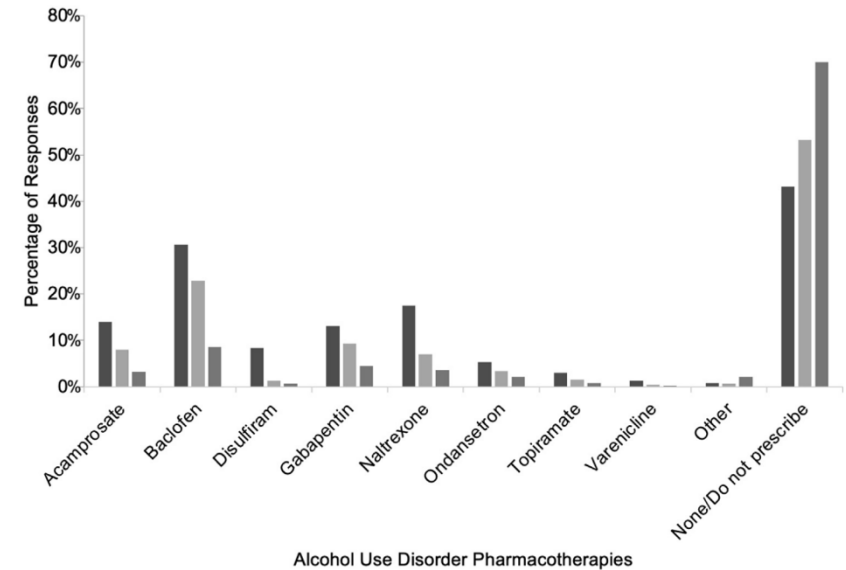
Gabapentin (900-1800 mg QD)

Varenicline (2 mg QD)

Ondansetron (1-16 mcg/kg BID)

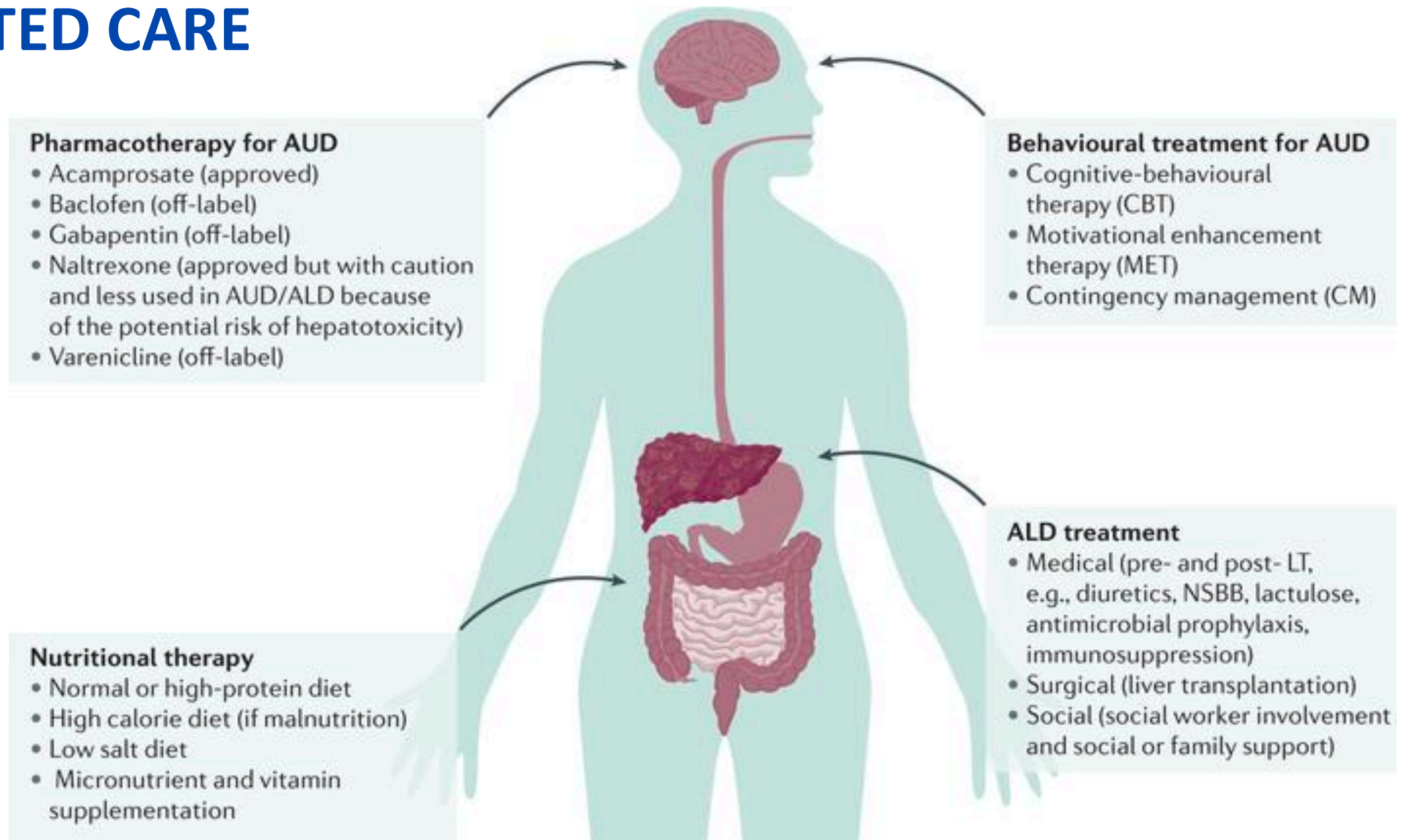
## Contraindicated medications in cirrhosis

Disulfiram

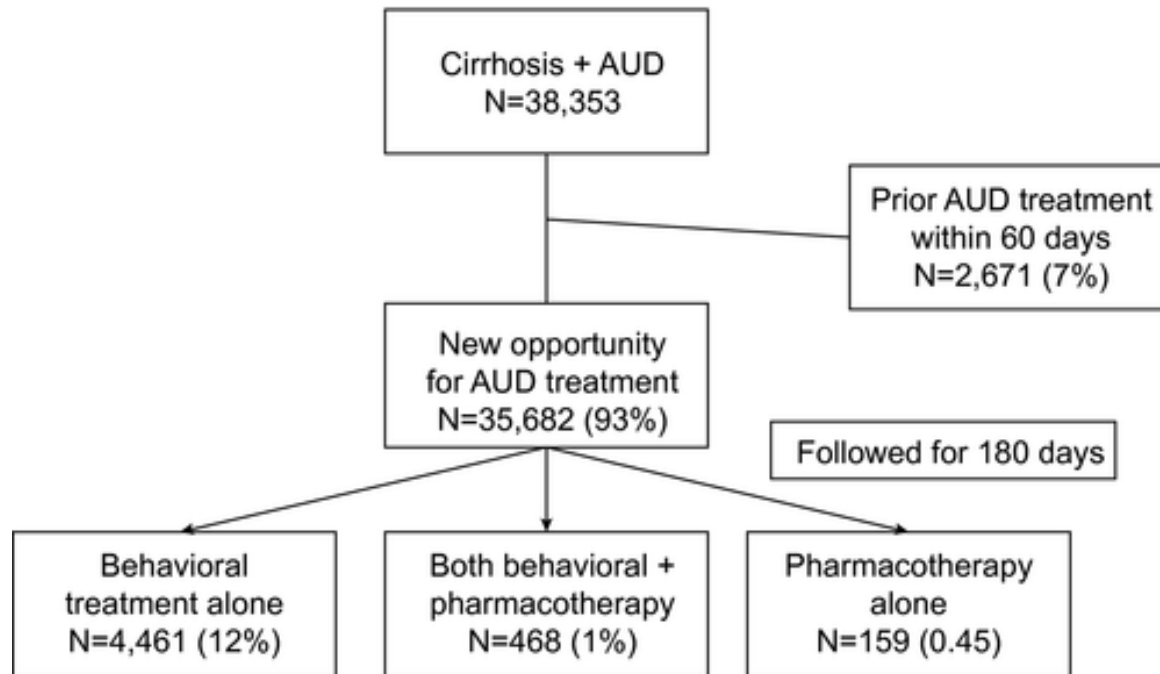




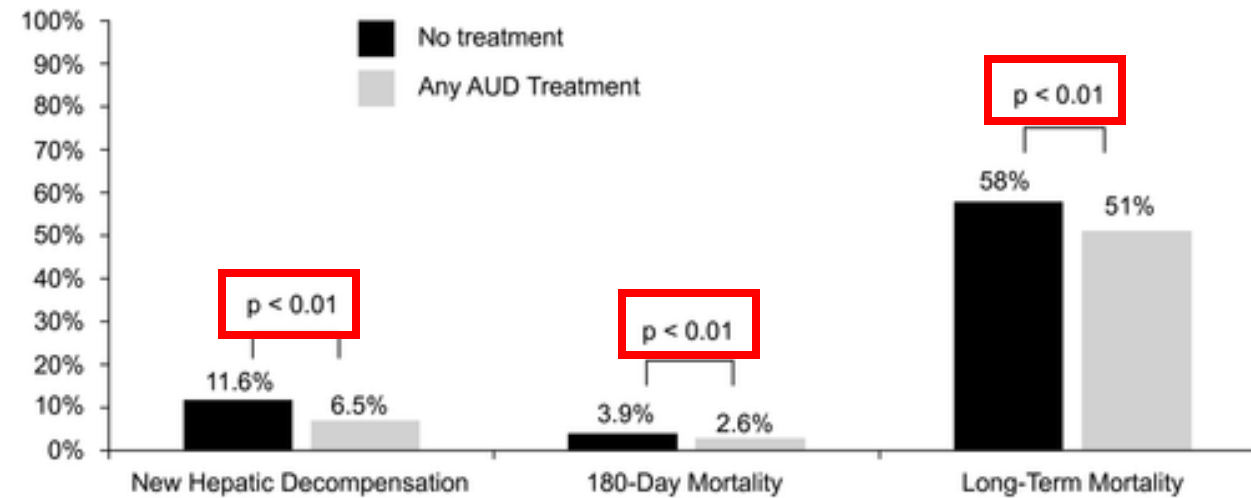
# INTEGRATED CARE



# PHARMACOLOGICAL THERAPY FOR ABSTINENCE



**1.5%!!!!**

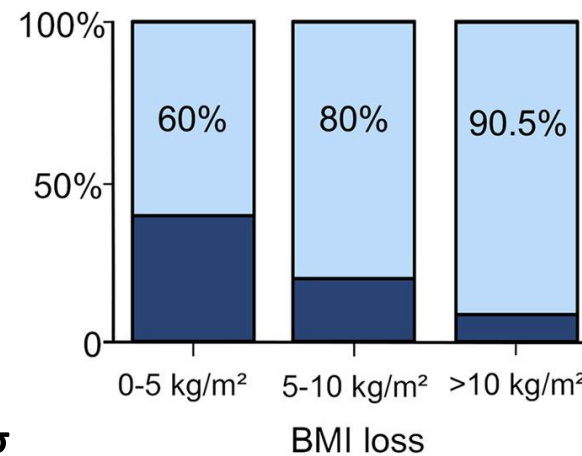


**AUD treatment  
improves survival**

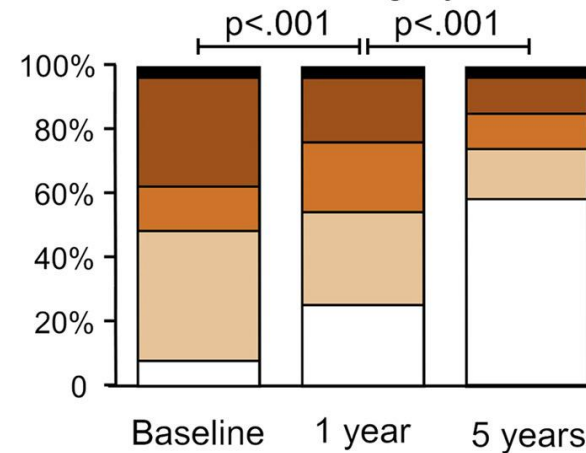
# Bariatric surgery and MASLD

- **MASH resolution in 84% of patients at 5 years.**
- **Reduction of fibrosis is progressive, beginning during the first year and continuing through 5 years.**

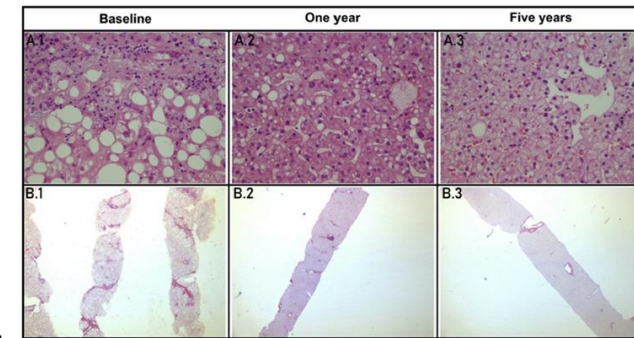
Resolution of NASH according to weight loss



Evolution of Fibrosis after Bariatric Surgery



Histological Evolution of NASH and Fibrosis after Bariatric Surgery



**A:** Upper panel  
H&E staining,  
(X400)

**B:** Lower panel  
Sirius Red  
staining, (X25)

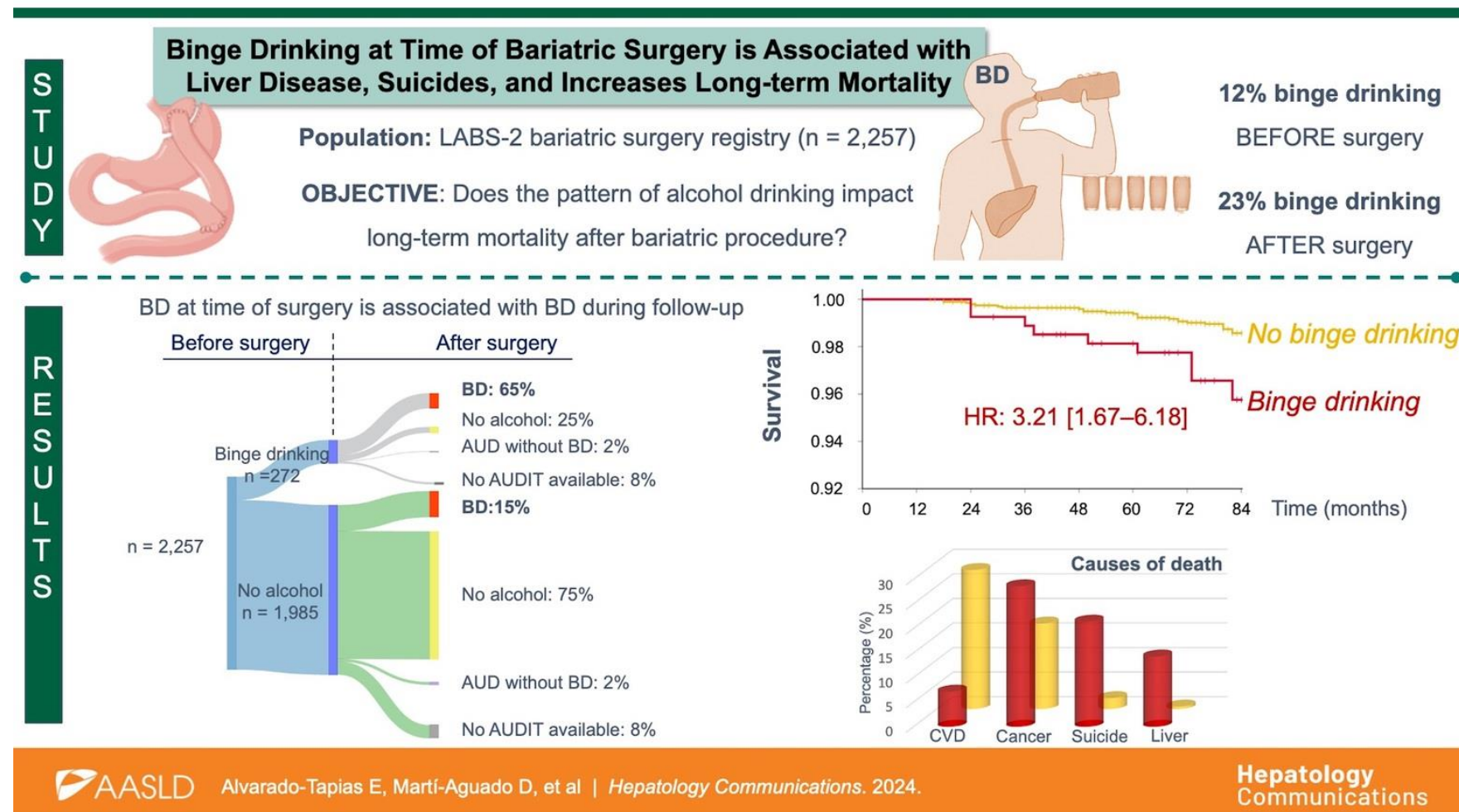
Gastroenterology



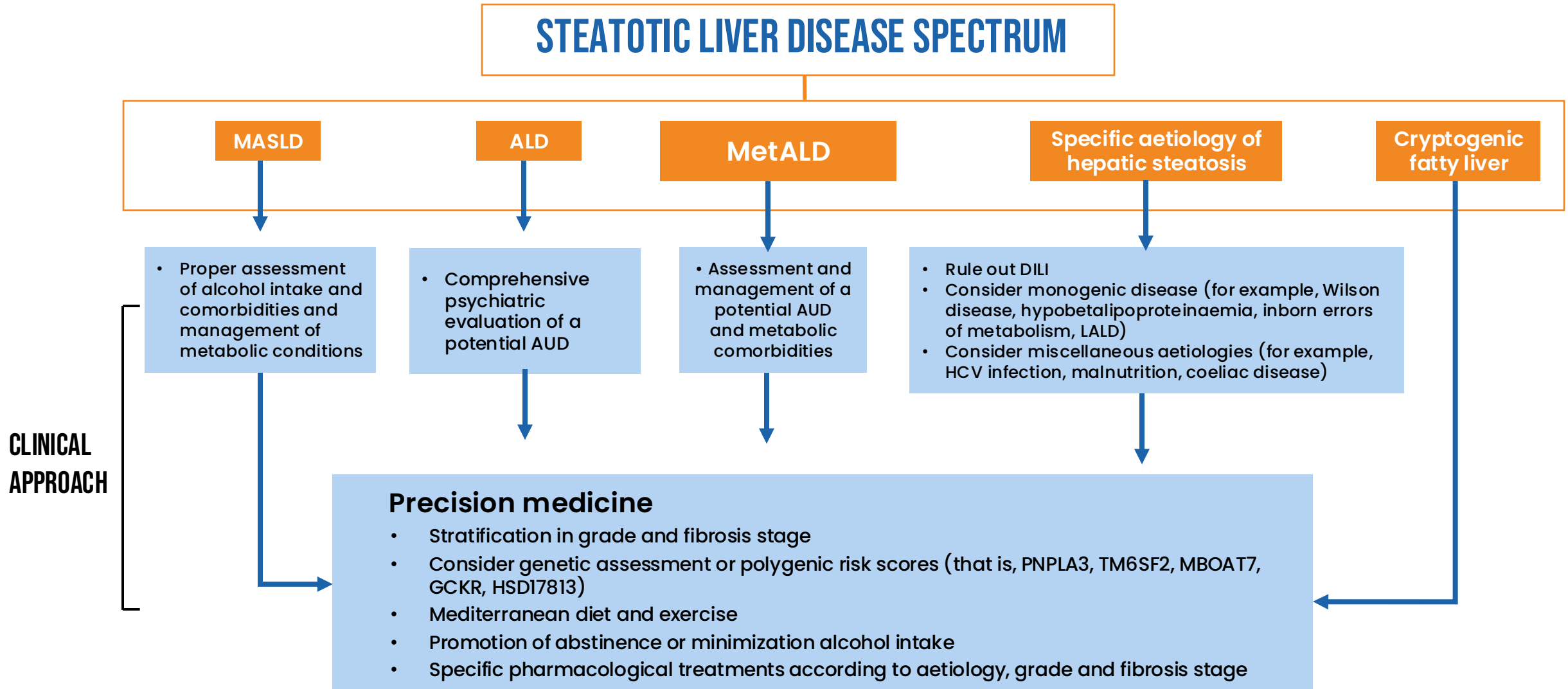
# Bariatric surgery and AUD

**Binge drinking at time of bariatric surgery is associated with:**

- Liver disease
- Suicides
- Increases long-term mortality



# CLINICAL CONSIDERATIONS FOR MANAGEMENT



# PHP Alcohol Global: Development of a Preparedness Index

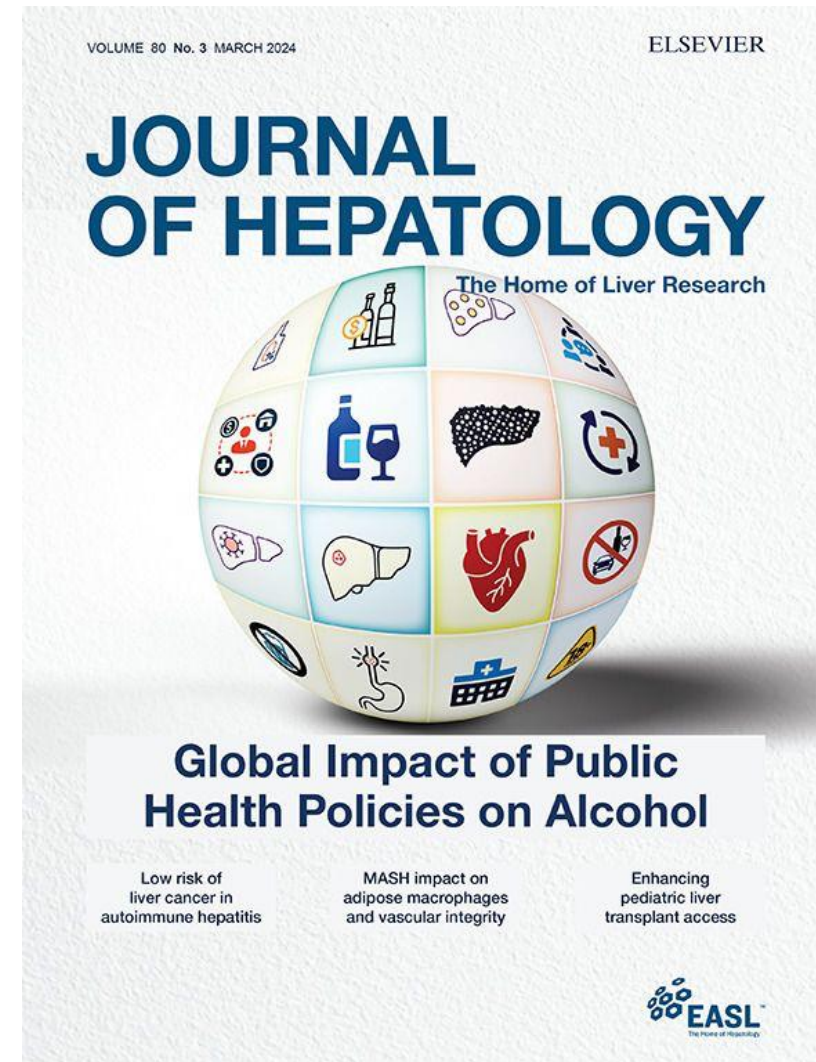
**169 countries**

Africa (50), America (35), Asia (33),  
Europe (46), Oceania (5)

**Median GDP per capita: US\$ 6,146**

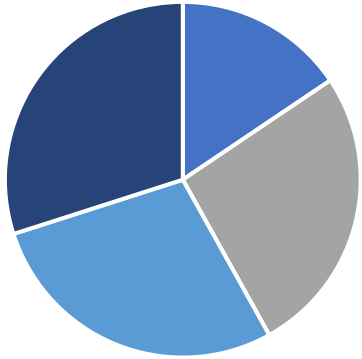
**Median alcohol per capita: 6.6 liters**

- Recorded: 4.7 liters
- Unrecorded 1.2 liters



## Alcohol preparedness index (API) to assess public health policies on alcohol worldwide

Income level



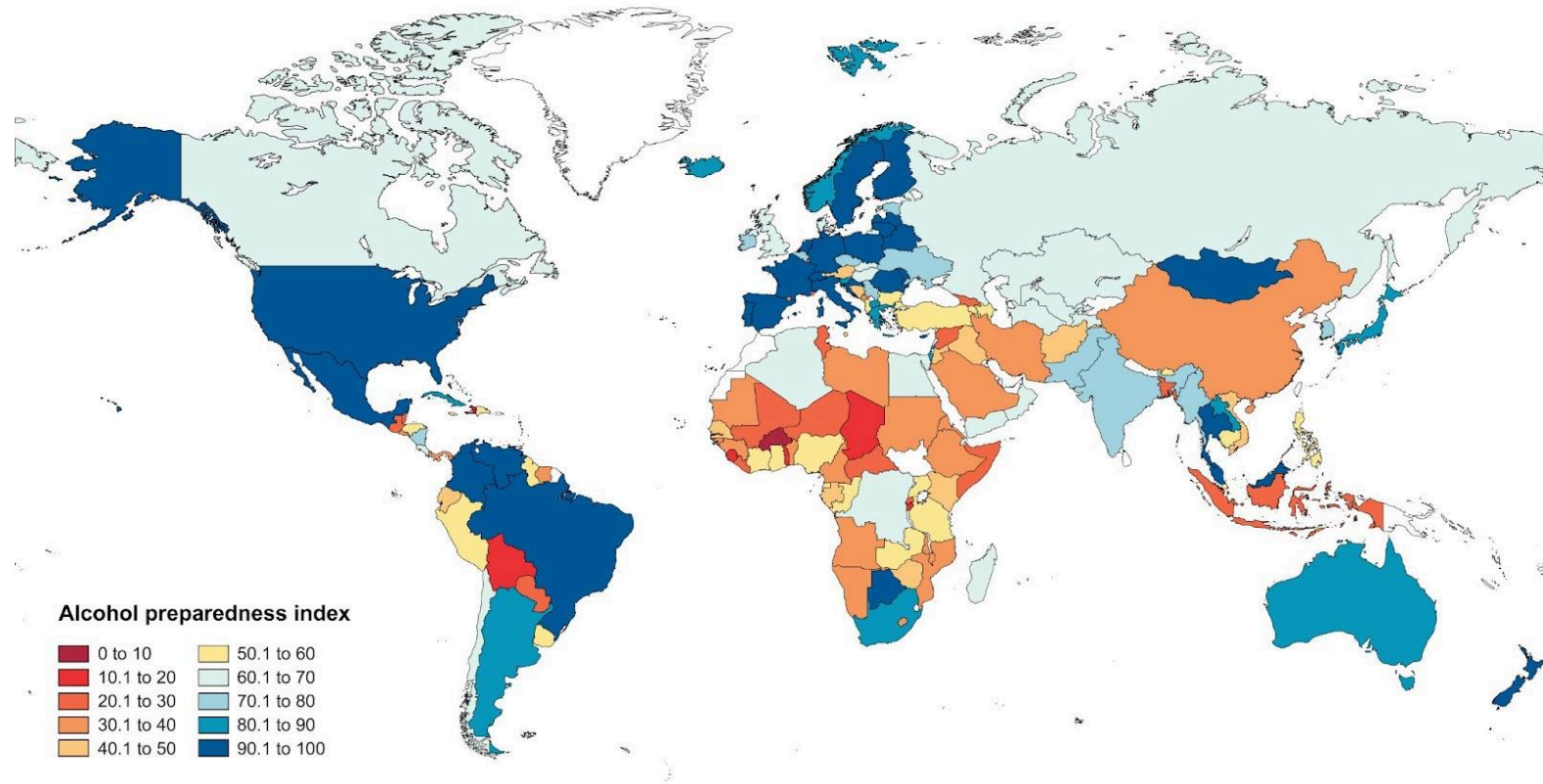
■ Low      ■ Lower-middle  
■ Upper-middle   ■ High

Median score  
54 [34.9-76.8]

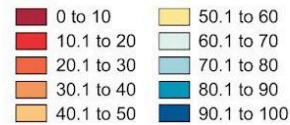
Important heterogeneity in  
the establishment of PHP:

Highest: Europe

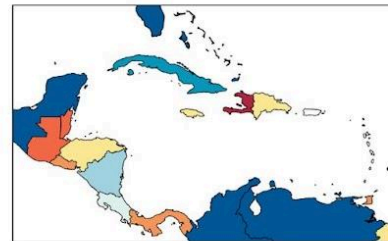
Lowest: Africa



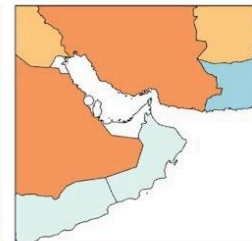
Alcohol preparedness index



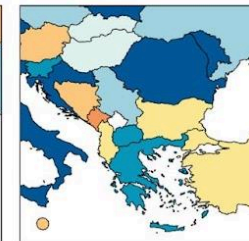
Caribbean and central America



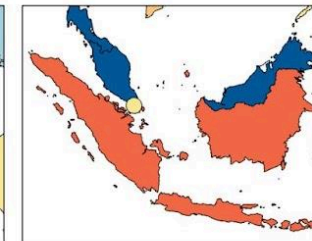
Persian Gulf



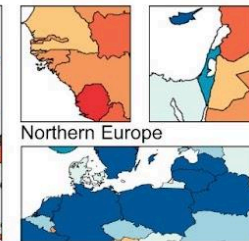
Balkan Peninsula



Southeast Asia



West Africa



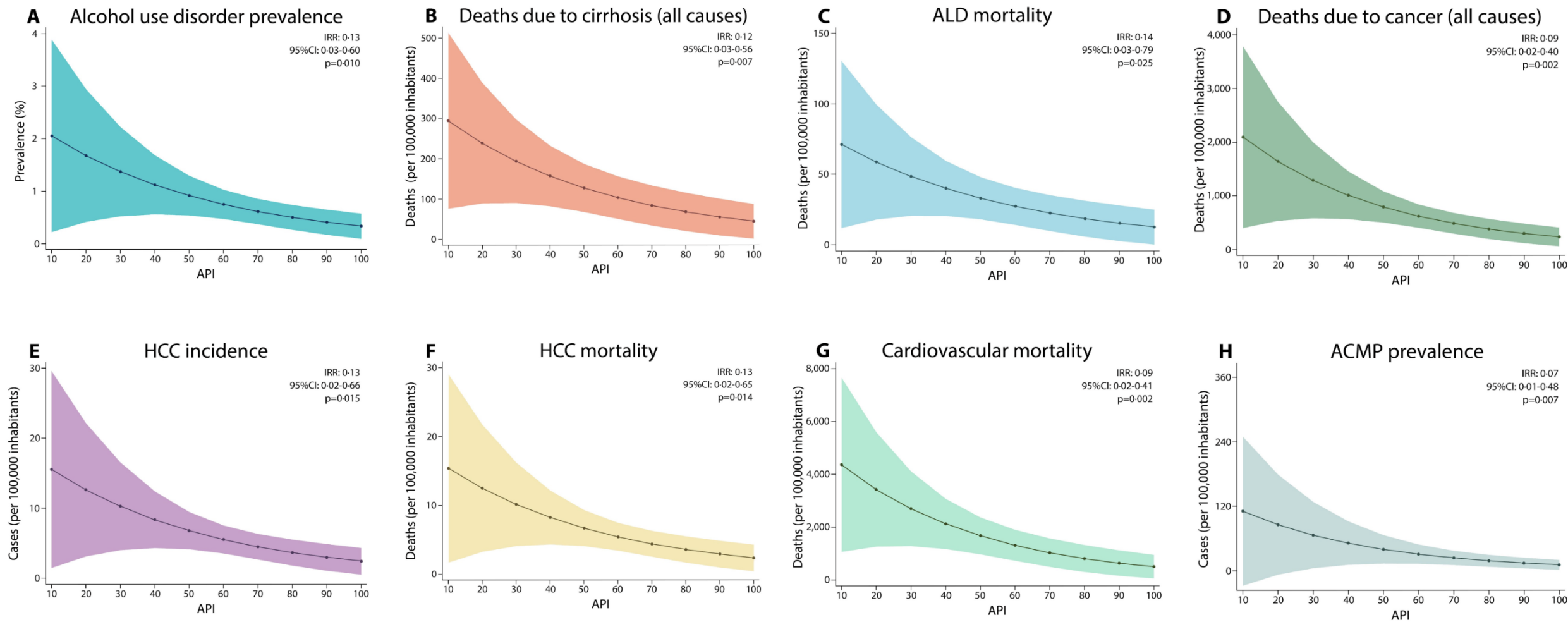
Eastern Mediterranean



Northern Europe

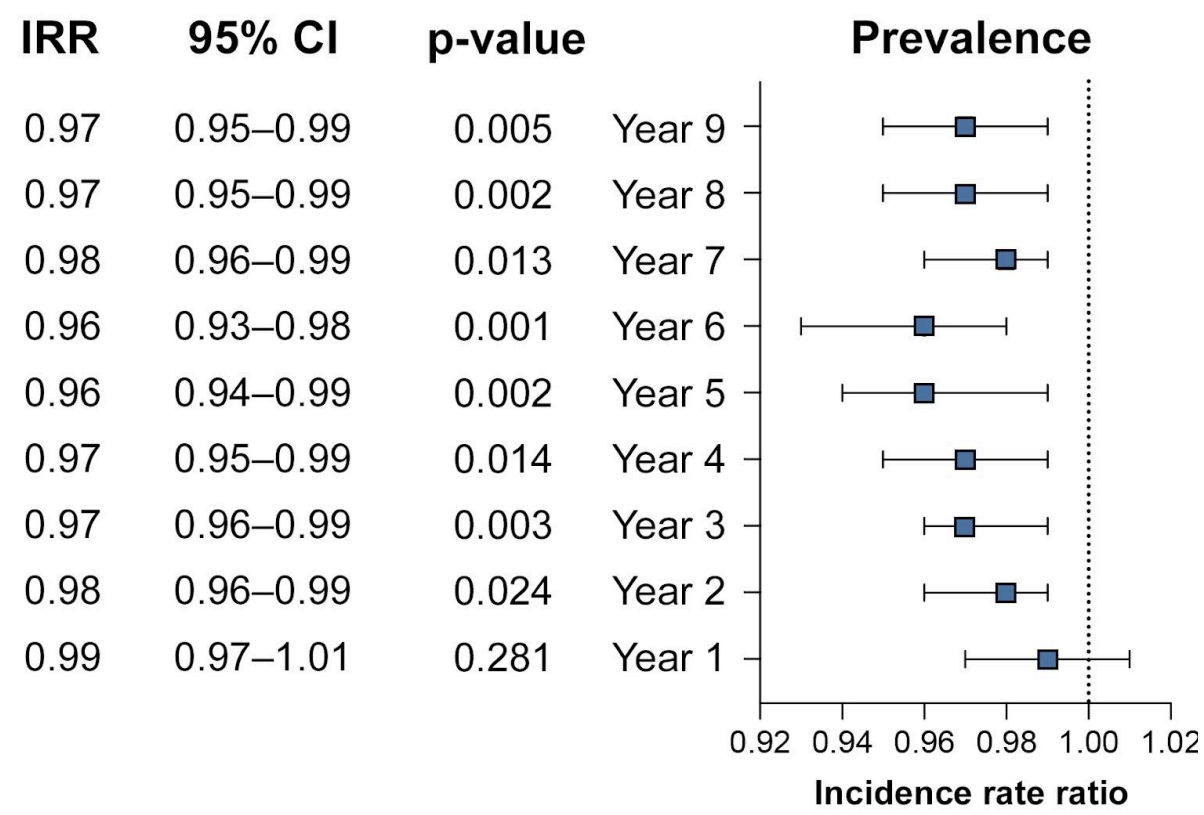




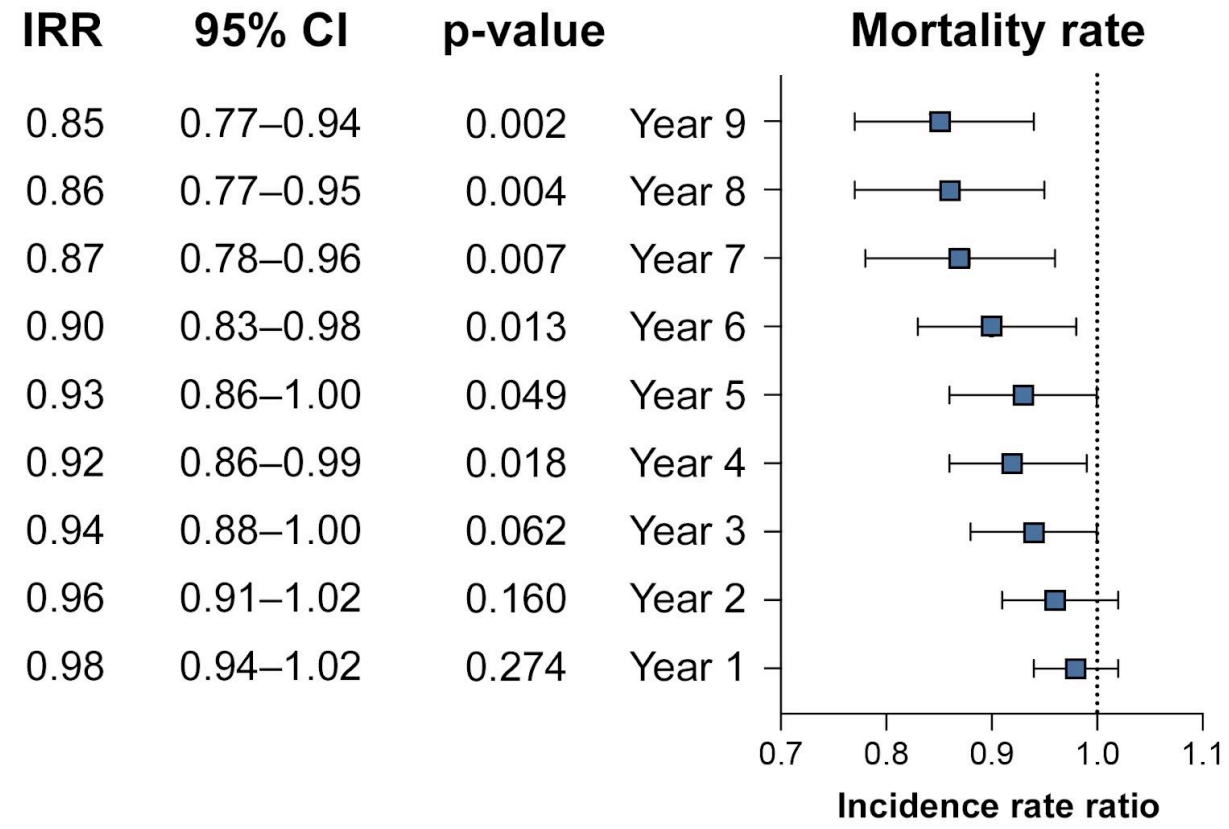




Association between alcohol-related PHP and AUD prevalence rate over time



Association between alcohol-related PHP and ALD mortality rate over time



# Take home messages

- **MASLD and ALD** are the leading causes of chronic liver disease worldwide
  - They are frequently overlapped
- New definition: **MetALD**:
  - MASLD and increased alcohol intake: 140–350 g and 210–420 g per week for women and men
- Identifying **under-reported alcohol consumption** in patients with presumed MASLD using standardized questionnaires and alcohol biomarkers is highly desirable
- Promotion of **abstinence or minimization of alcohol intake** should be recommended in addition to diet and exercise
- MetALD needs a whole-society approach and implementation of PHP.