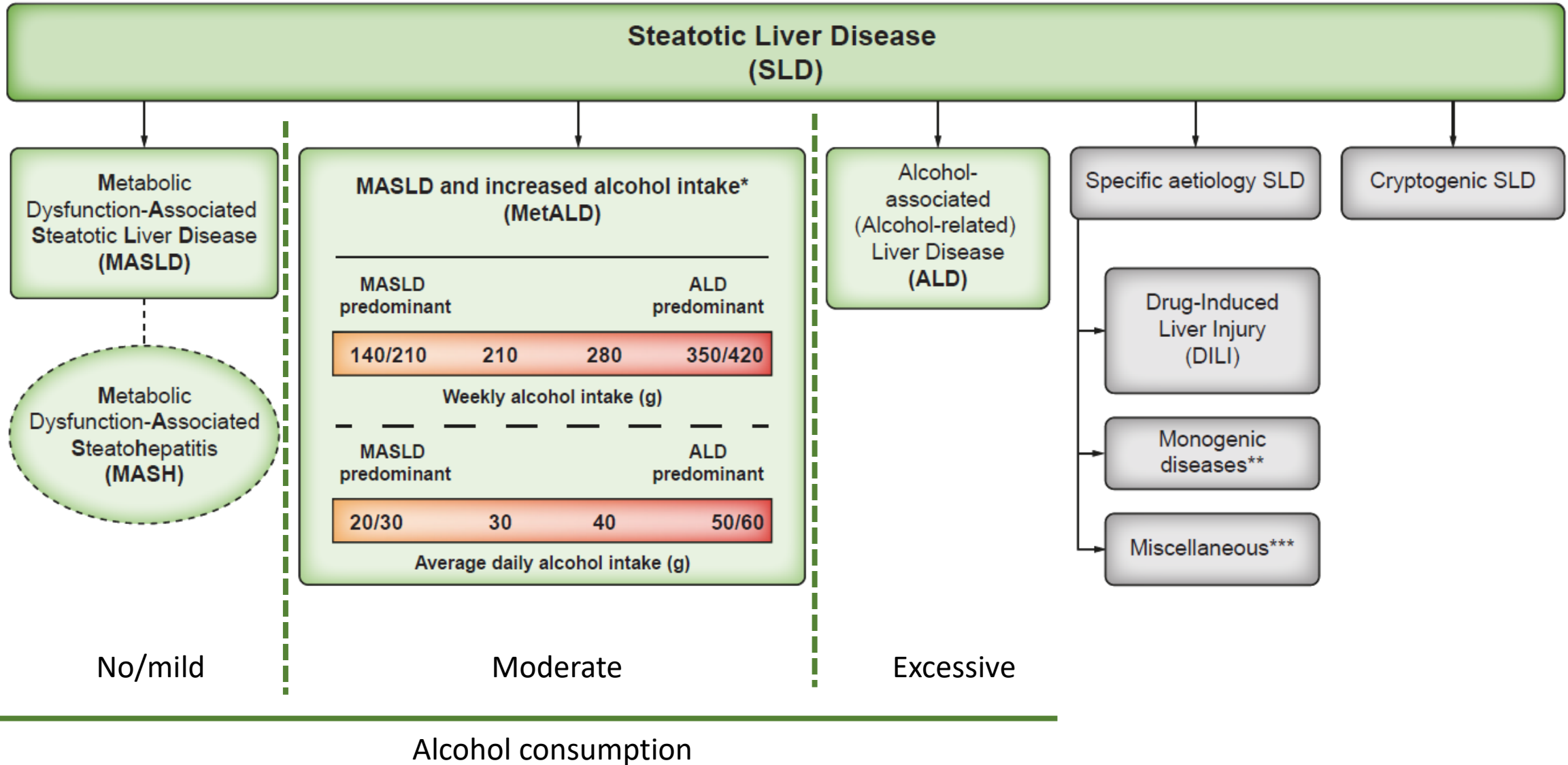


Debate: MetALD classification represents a major advancement in the field

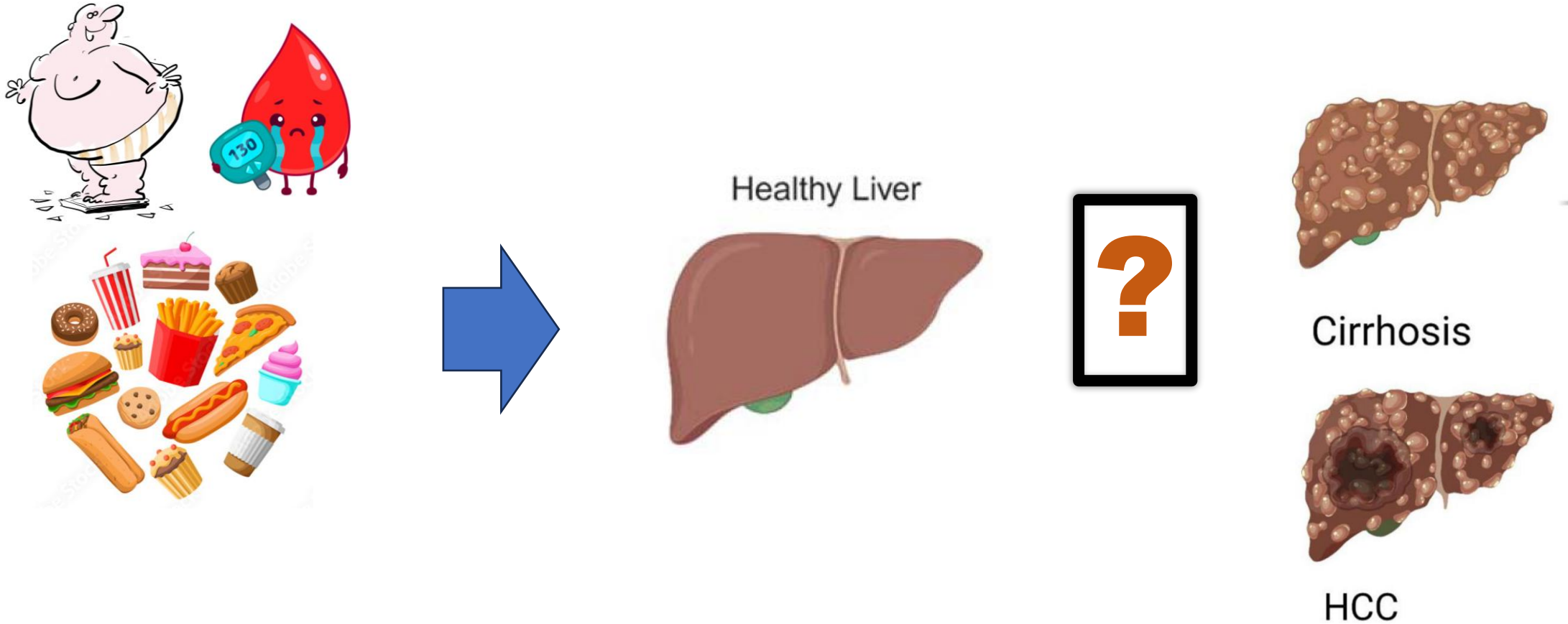
Paris MASH, September 5th, 2024

Vlad Ratziu, Sorbonne Université, Hôpital Pitié Salpêtrière,
Paris, France



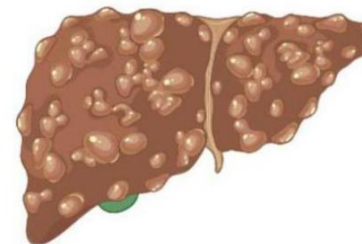
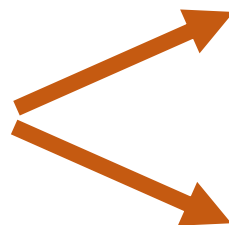
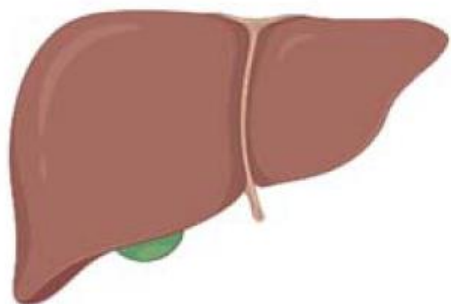


- Can MASLD alone (no alcohol consumption) induce liver cirrhosis and HCC ?

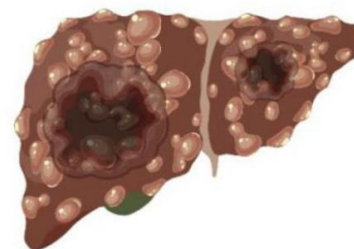




Healthy Liver



Cirrhosis



HCC

YES

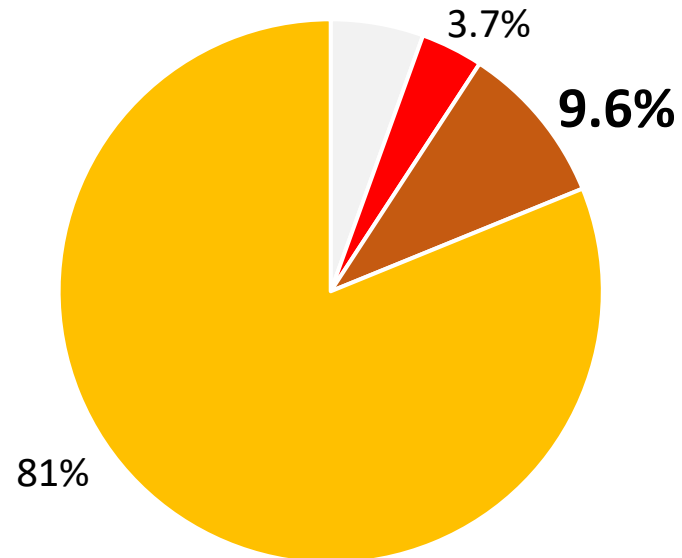
- **Can MASLD alone (no alcohol consumption) induce liver cirrhosis and HCC ?**
- **Do these MetALD patients really exist ?**

YES



Estimated prevalence of MetALD

NHANES 3, N=7980 → **SLD 22%**

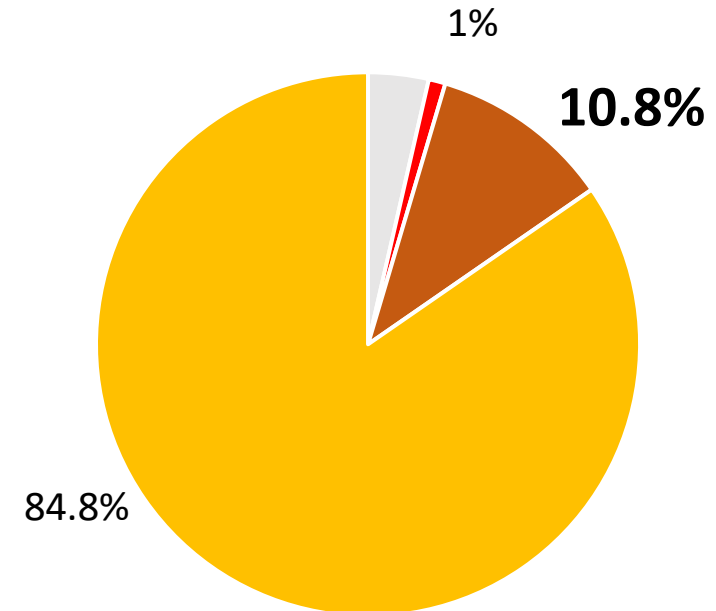


 **MetALD**

 **ALD**

 **MASLD**

UKBB, N=11217 → **SLD 28%**



- **Can MASLD alone (no alcohol consumption) induce liver cirrhosis and HCC ?** **YES**
- **Do these MetALD patients really exist ?** **YES**
- **Does the MetALD category has any prognostic relevance ?**

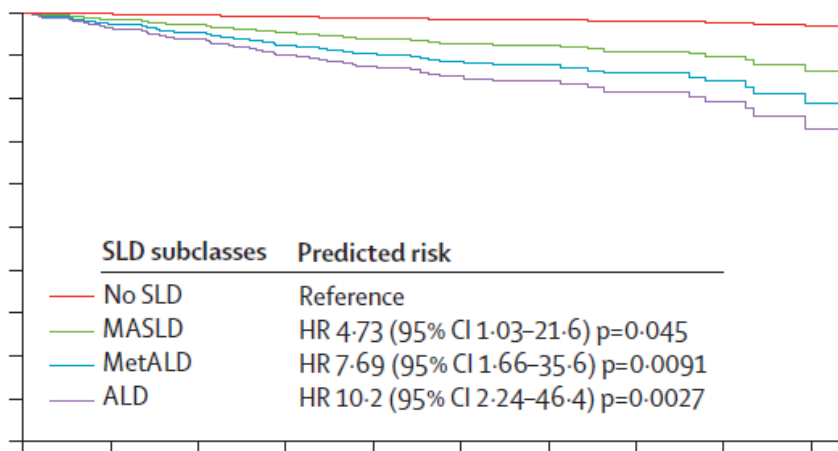
Validation of the new nomenclature of steatotic liver disease in patients with a history of excessive alcohol intake: an analysis of data from a prospective cohort study

Lancet Gastro Hep 2024

Mads Israelsen, Nikolaj Torp, Stine Johansen, Camilla Dalby Hansen, Emil Deleuran Hansen, Katrine Thorhauge, Johanne Kragh Hansen, Ida Villesen, Katrine Bech, Charlotte Wernberg, Peter Andersen, Katrine Prier Lindvig, Emmanuel A Tsochatzis, Maja Thiele, Mary E Rinella*, Aleksander Krag*, on behalf of the GALAXY consortium

| | MASLD (n=153) | MetALD (n=76) | ALD+ (n=86) | ALD-only (n=6) | No SLD (n=125) |
|--|-------------------------|-------------------------|-------------------------|----------------|----------------|
| Demographics | | | | | |
| Mean age (SD), years | 57 (10) | 60 (9) | 58 (9) | 49 (7) | 52 (12) |
| Liver parameters | | | | | |
| Significant fibrosis ($\geq F2$) | 105/153 (69%) | 39/73 (53%) | 40/85 (47%) | 4/5 | 0 |
| Risk of hepatic decompensation (HR, 95% CI) | 4.73 (1.03-21.6) | 7.69 (1.66-35.6) | 10.2 (2.24-46.4) | | 1 |

B Time without hepatic decompensation



The answer is YES !

- Can MASLD alone (no alcohol consumption) induce liver cirrhosis and HCC ? YES
- Do these MetALD patients really exist ? YES
- Does the MetALD category has any prognostic relevance ? YES
- OK, but this is simply because of the alcohol intake!

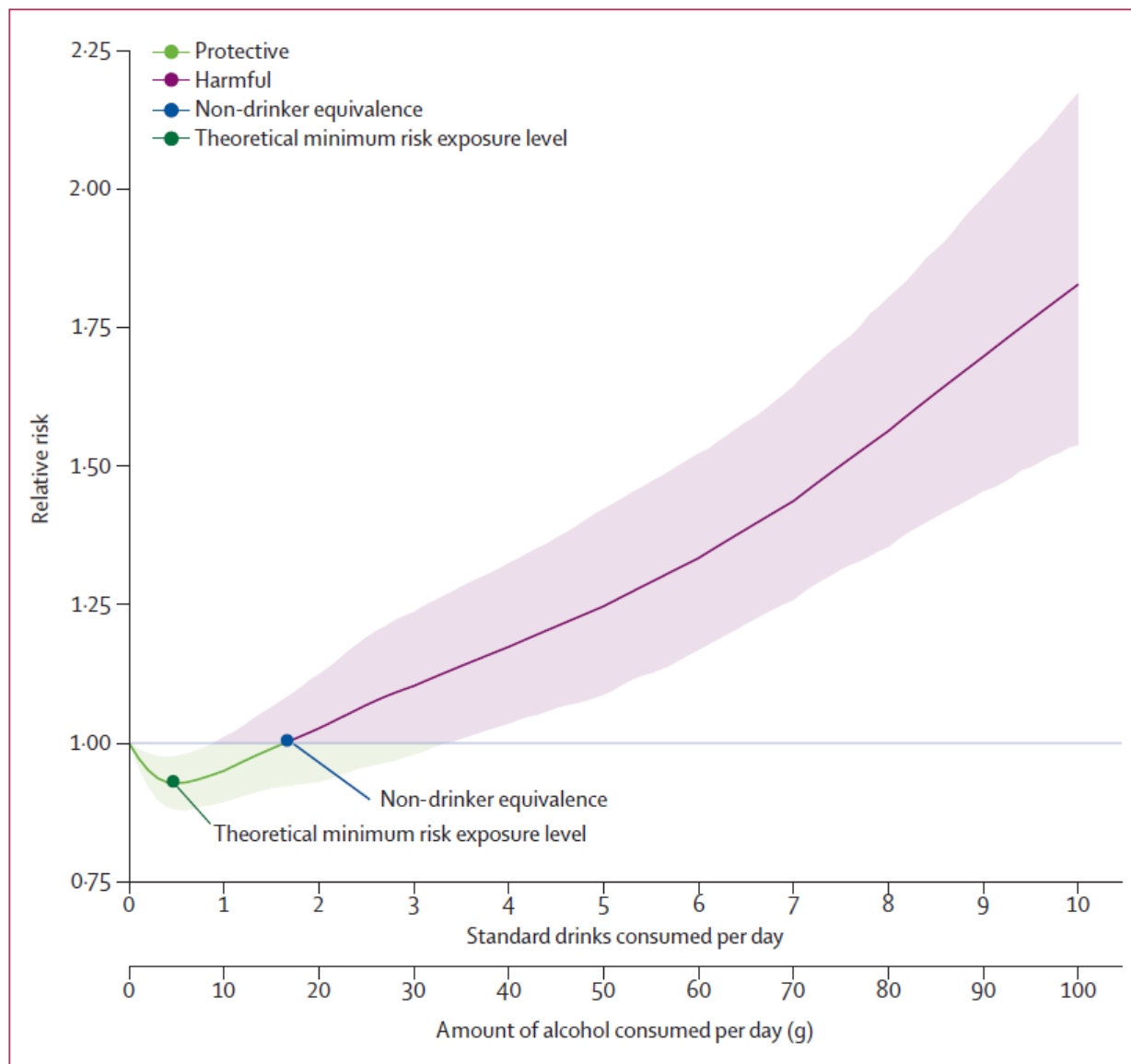


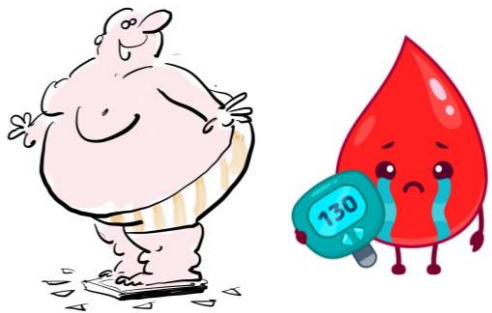
Figure 1: Exemplifying a weighted all-attributable cause alcohol relative risk curve

NIAA : 20-60 g/d equates « heavy alcohol use »

Canada's Guidance on Alcohol and Health:
« high-risk » alcohol drinking is ≥ 7 drinks per week !!

Does that imply that anything >20-30 g/day becomes ALD ??

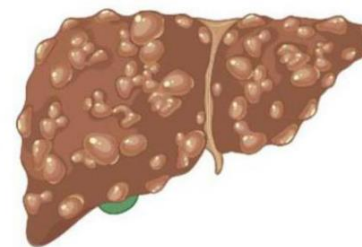
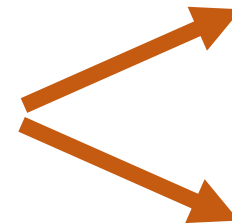
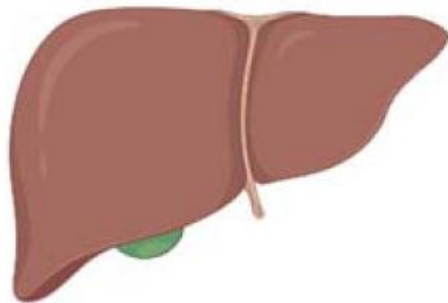
... and then there is no need for a MetALD category.



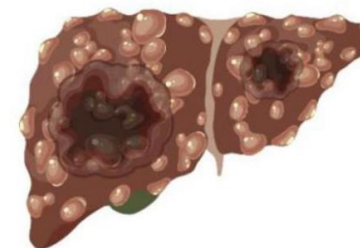
???



Healthy Liver



Cirrhosis



HCC

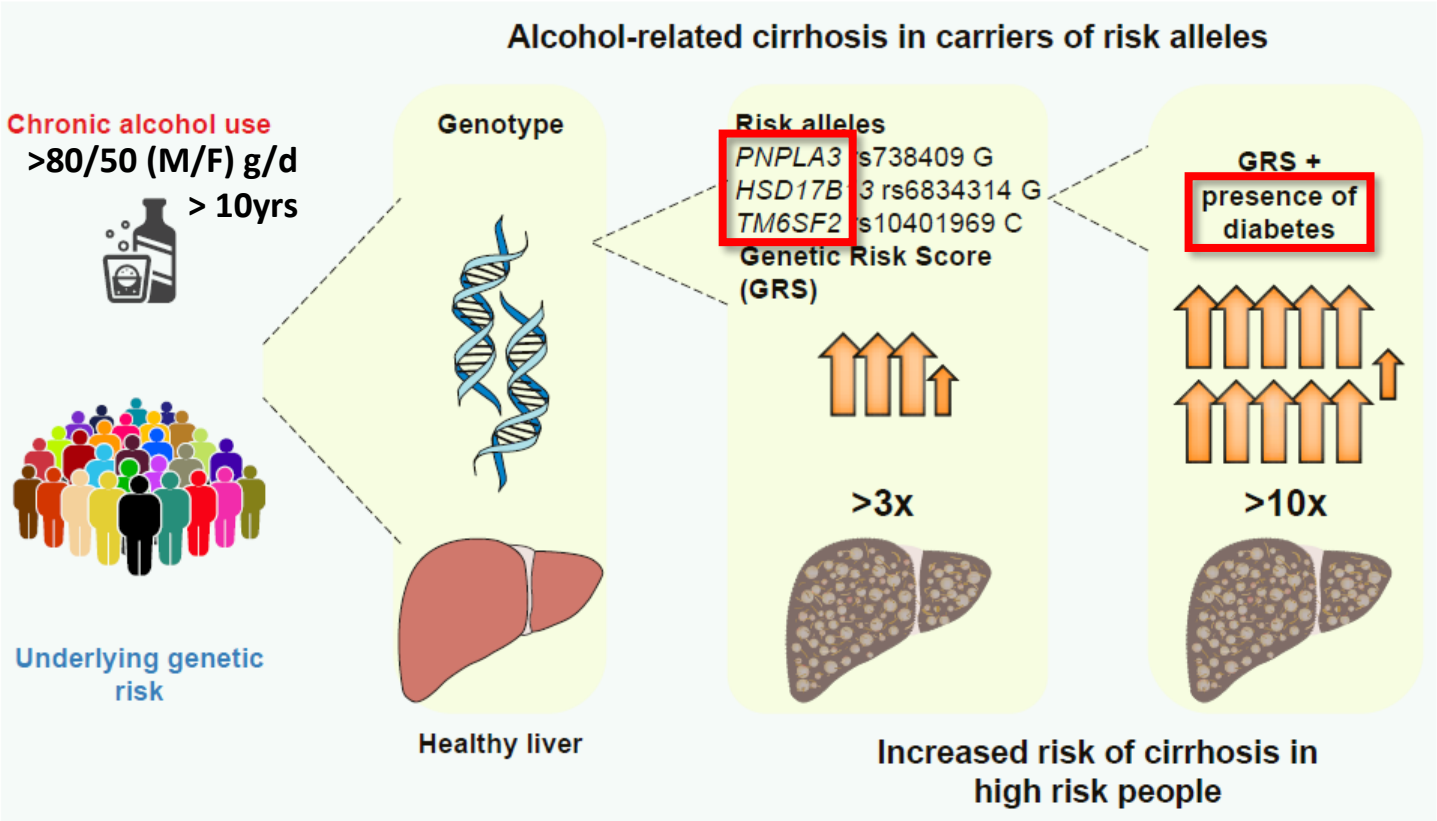
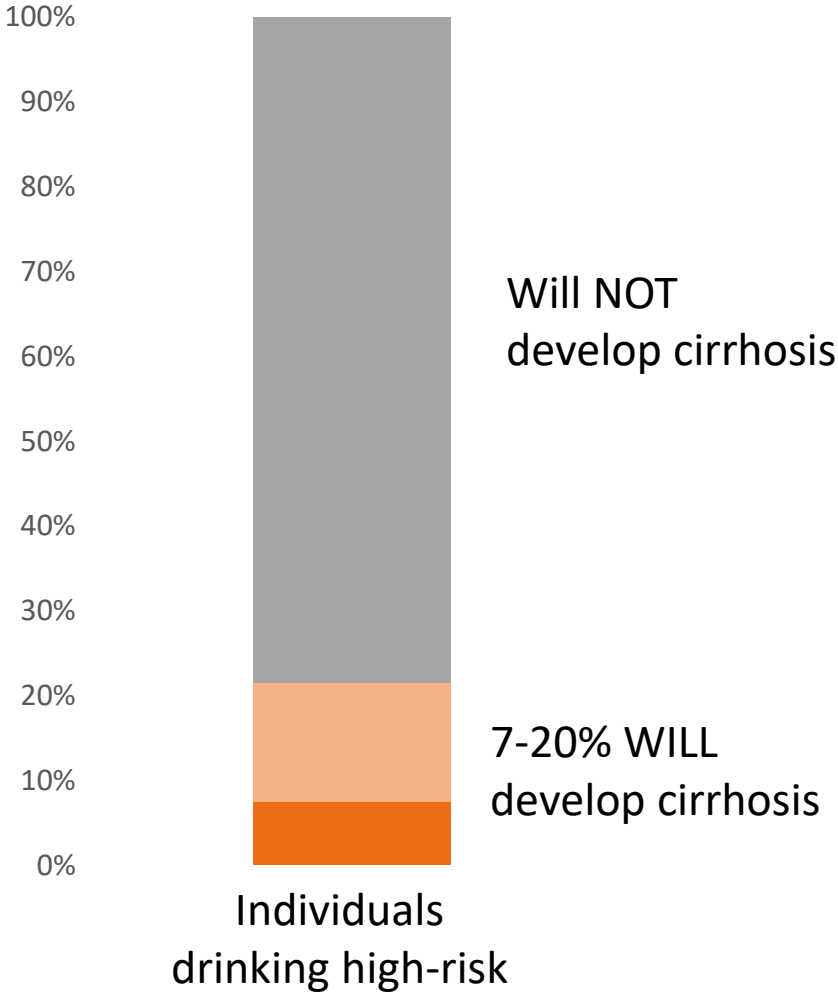


How many excessive drinkers develop cirrhosis?



A genetic risk score and diabetes predict development of alcohol-related cirrhosis in drinkers

John B. Whitfield^{1,*,#}, Tae-Hwi Schwantes-An², Rebecca Darlay³, Guruprasad P. Aithal⁴,



Same risk factors as MASLD...

Impact of alcohol and metabolic risk factors, on severe liver disease in the general population

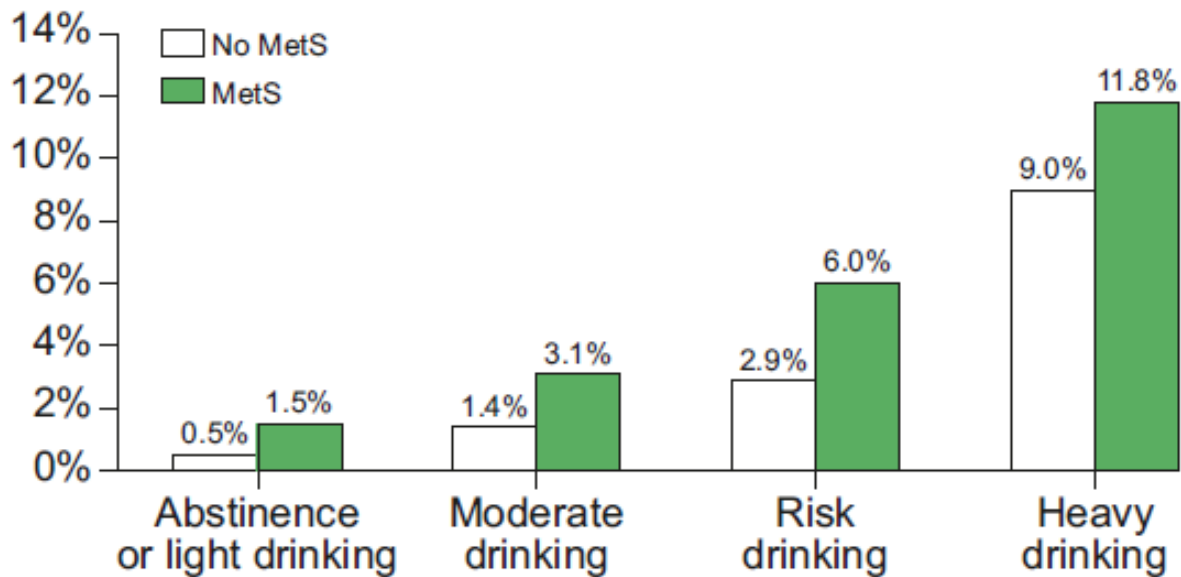
6732 subjects Finnish population,
mean follow-up 11.4 yrs
Liver events, n = 84

HR for incident severe liver events

| | |
|----------|---------------------|
| Age | 1.02 (1.004-1.04) |
| Women | 0.55 (0.34-0.91) |
| Alcohol | 1.002 (1.001-1.002) |
| Diabetes | 2.73 (1.55-4.81) |
| LDL | 0.74 (0.58-0.93) |
| HOMA IR | 1.01 (1.004-1.02) |

Aberg, Hepatology 2018

Cumulative 20-year incidence of severe liver-related outcomes



In Aberg, J Hepatol 2023

Impact of alcohol and metabolic risk factors, on severe liver disease in the general population

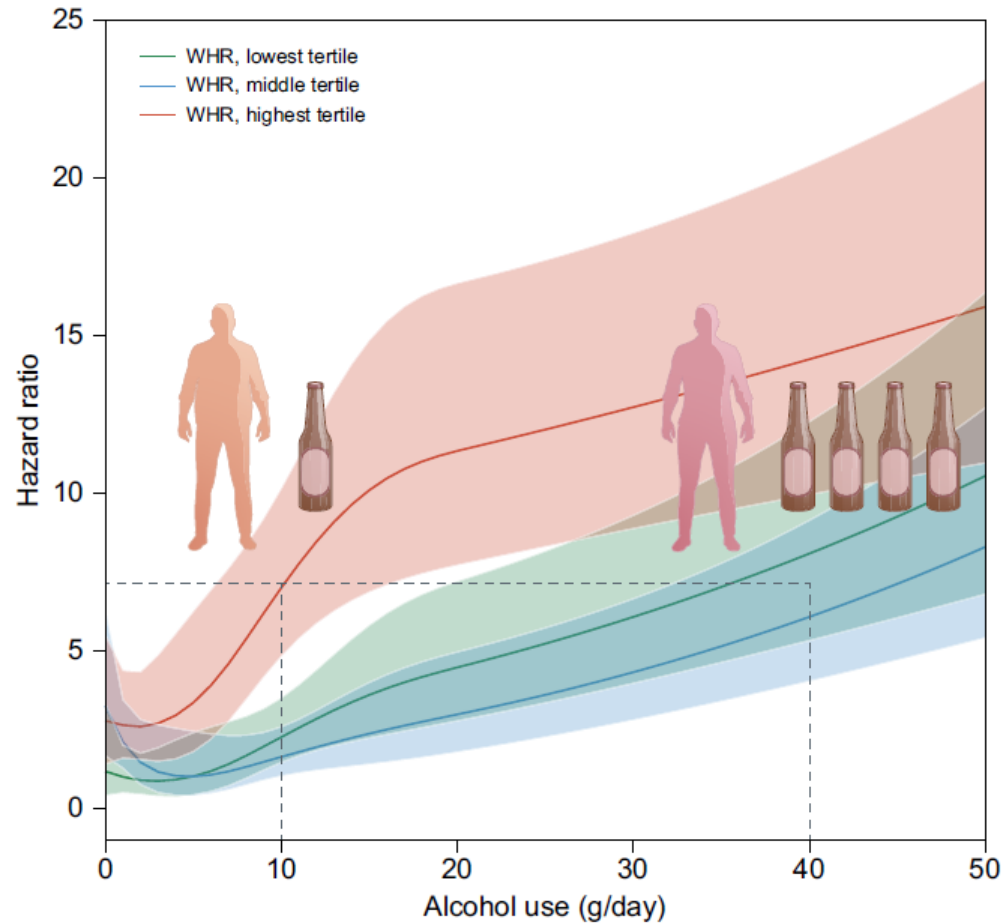
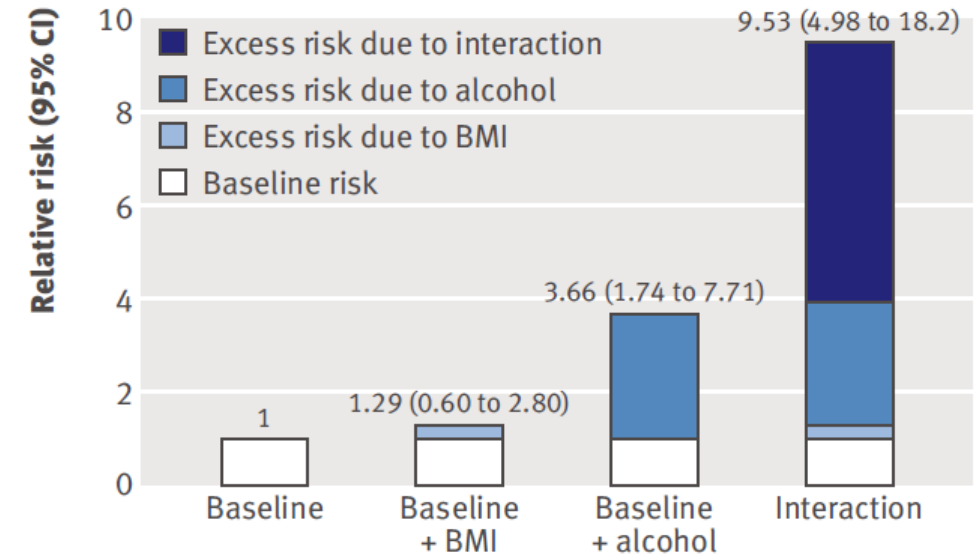


Fig. 3. Abdominal obesity increases alcohol-related liver toxicity by fourfold.



Relative risks of contributions of BMI and alcohol to liver disease mortality (adjusted for all risk factors).

Relative excess risk due to interaction : 5,57
Synergy index : 2.89

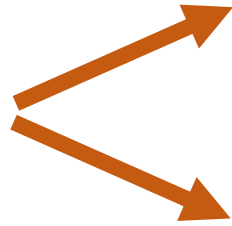
- Can MASLD alone (no alcohol consumption) induce liver cirrhosis and HCC ? YES
- Do these MetALD patients really exist ? YES
- Does the MetALD category has any prognostic relevance ? YES
- OK, but that is simply because of the alcohol consumption part! NO
- Well, then, what have we been doing about these patients ?
 - Natural history studies ? - excluded!
 - NASH/MASH therapeutic trials ? - excluded!
 - ArLD trials ? - excluded !
 - AAH trials
 - LT in ALD cirrhosis
 - Treatment of AUD
 - Antifibrotics ??

- Can MASLD alone (no alcohol consumption) induce liver cirrhosis and HCC ? YES
- Do these MetALD patients really exist ? YES
- Does the MetALD category has any prognostic relevance ? YES
- OK, but that is simply because of the alcohol consumption part! NO
- Well, then, what have we been doing about these patients ? Nothing specifically...
- Should the MetALD definition be refined ?

The ascertainment of alcohol consumption – multiple uncertainties

- Recall bias
- Patient underreporting
- Not accounting for variations drinking patterns
- Not accounting for life course consumption changes
- Not accounting for length of exposure/abstinence

Is the requirement of exposure to a single MRF sufficiently specific in case of MetALD ?



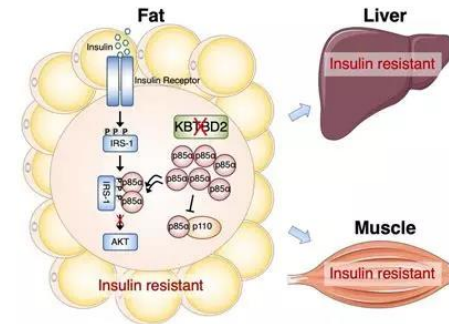
Arterial HTN



Visceral adiposity



Hyper TGemia



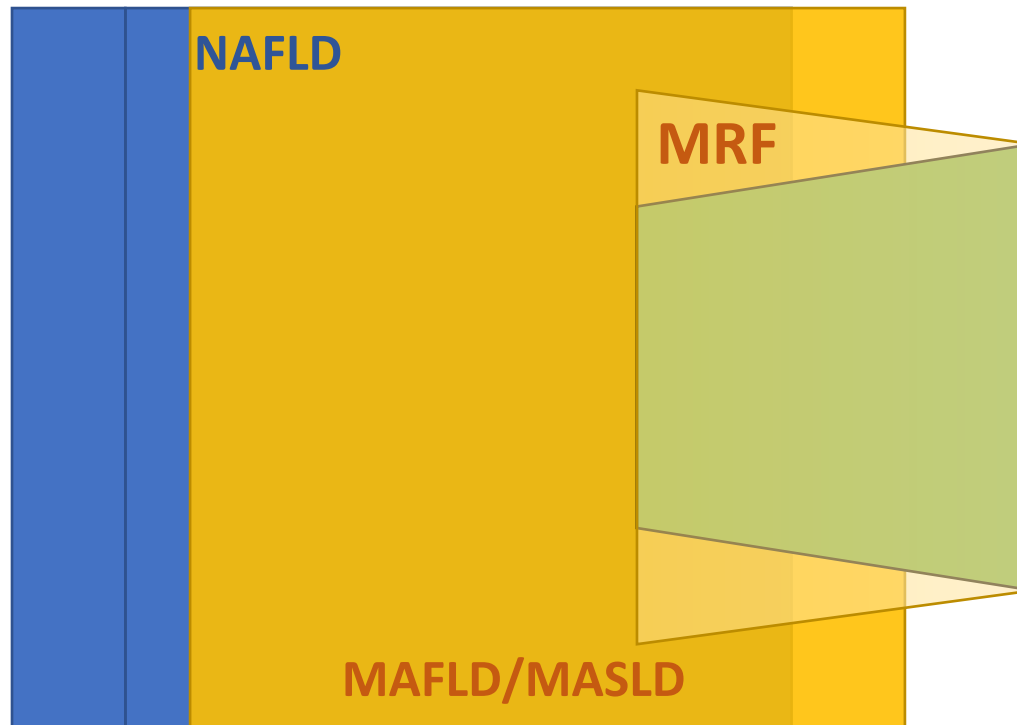
Insulin resistance



Stricter criteria : e.g. an adiposity-based and a glycemic dysregulation based criteria ?

The issue of thresholds...

« Lean »
NASH



Alcoholic liver disease

nature reviews gastroenterology & hepatology

<https://doi.org/10.1038/s41575-023-00822-y>

Review article

Check for updates

The intersection between alcohol-related liver disease and nonalcoholic fatty liver disease

Luis Antonio Díaz¹, Juan Pablo Arab^{1,2,3}, Alexandre Louvet^{4,5,6}, Ramón Bataller⁷ & Marco Arrese¹✉

Effects of harmful alcohol consumption on the liver

Harmful alcohol consumption is the leading cause of cirrhosis worldwide, accounting for up to 50% of patients, and is an important contributor to the global liver disease burden^{14,17}. Alcohol intake can be broadly classified as mild (up to 20 g (women) and 30 g (men) per day), moderate (21–39 g (women) and 31–59 g (men) per day), or heavy (≥ 40 g (women) and ≥ 60 g (men) per day)⁹. However, harmful thresholds of alcohol consumption are ill-defined and overlap in the literature.

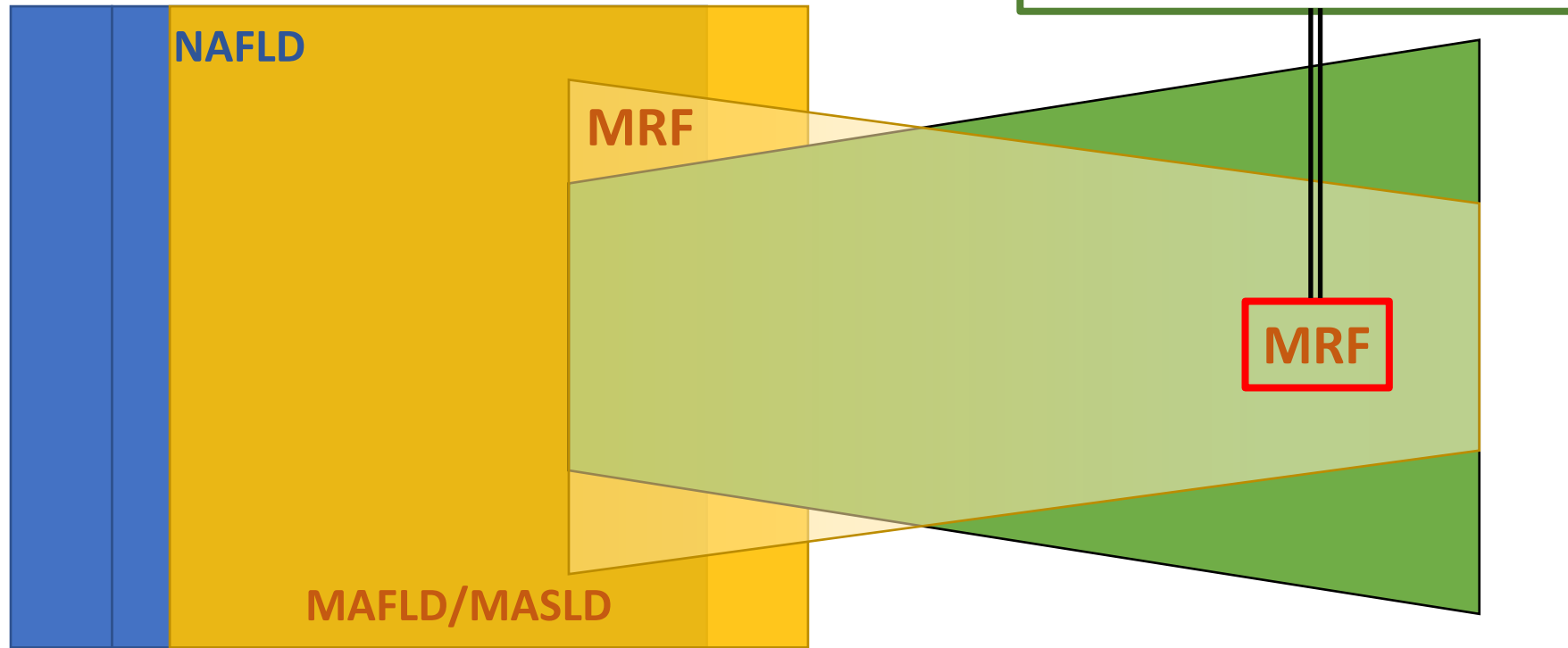
Secondary causes
of steatosis

20/30-50 g/day?

Moderate or already heavy ?

MRF as a modifier of ArLD ?!

« Lean »
NASH



↓
Secondary causes
of steatosis

↔
20/30-50 g/day?
↓
Moderate or already heavy ?

??

Risk of cirrhosis in heavy drinkers is increased by metabolic risk factors

Excess Weight Risk Factor for Alcoholic Liver Disease

Sylvie Naveau,¹ Vincent Giraud,¹ Eric Borotto,¹ Alain Aubert,¹ Frédérique Capron,² and Jean-Claude Chaput¹

TABLE 1. Epidemiological and Clinical Characteristics of Patients According to the Presence of Excess Weight for At Least 10 Years

| | Overweight Patients | Nonoverweight Patients | P |
|--|---------------------|------------------------|-------|
| Number of patients | 172 | 1,432 | |
| Presence of cirrhosis (%) | 103 (60) | 505 (35) | <.001 |
| Females (%) | 41 (24) | 366 (26) | NS |
| Age (y) | 56 ± 9 | 46 ± 12 | <.001 |
| Total duration of alcohol abuse (y) | 26 ± 12 | 22 ± 13 | <.01 |
| Alcohol intake over the last 5 years (g/d) | 121 ± 73 | 117 ± 78 | NS |

Overweight for at least 10 years : x 2,15 risk of cirrhosis*

*: after adjustment on all independent factors

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ARTICLE

Obesity, Diabetes, Coffee, Tea, and Cannabis Use Alter Risk for Alcohol-Related Cirrhosis in 2 Large Cohorts of High-Risk Drinkers

John B. Whitfield, PhD, FRCP¹, Steven Masson, FRCP², Suthat Liangpunsakul, MD³, Sebastian Mueller, MD, PhD⁴,

Diabetes (OR:3.68 [2.7-5.1]) and pre-morbid BMI increase the risk of cirrhosis

In conclusion

- MetALD is a useful classifier because, epidemiologically, it reflects a real group of people
 - MetALD is a SLD subclass entirely ignored because of the tyranny of thresholds...
 - Alcohol intake influences disease progression in (MA)SLD and MRF influence fibrosis progression in ArLD within a spectrum fraught with strong individual variability
 - Which opens the prospect of individualized therapy
-
- Patients with MetALD should be given treatment on par with those with MASLD and diabetes/obesity/metab syndrome
 - We do have drugs for MASH but not for ArLD; some drugs for MASH reduce the desire for alcohol
 - The MetALD category is long overdue and creates a space for better understanding and management of this complex condition



In conclusion

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"No, it's not water. You seem to
be retaining food."