



Intersection of Steatotic Liver Disease (SLD) and Alcohol-related Liver Disease (ALD)- Met-ALD

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Steatotic Liver Disease

Overarching term for the various aetiologies of steatosis

- Steatohepatitis continues to describe fatty inflammation in the liver
- The spectrum with respect to alcohol consumption is now:

Steatotic Liver Disease (SLD)

MASH*

Women: 0-20g/day

Men: 0-30g/day

Met-ALD

Women: 20-50g/day

Men: 30-60g/day

ALD

Women: >50g/day

Men: >60g/day

Stigma and inclusion

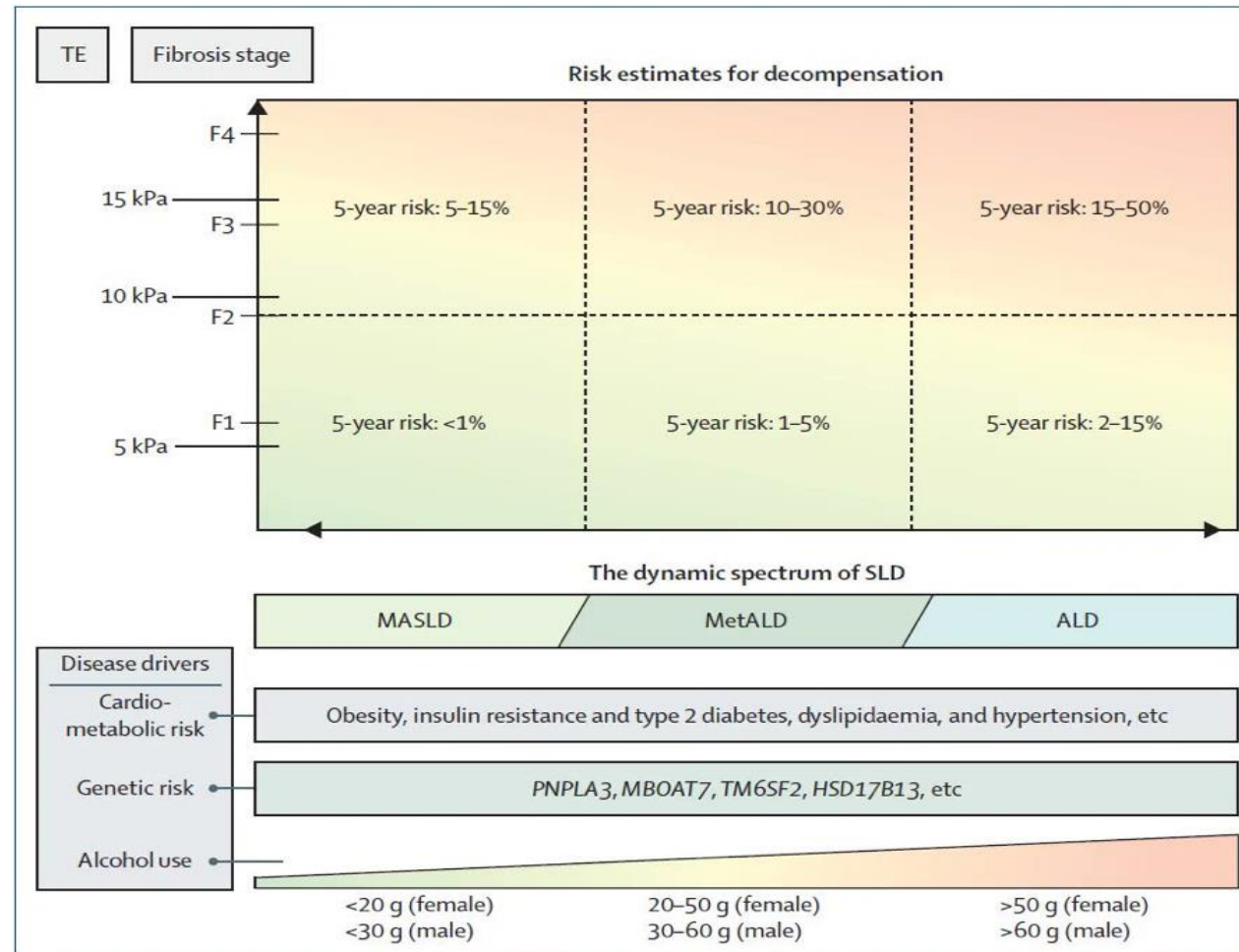
Progress in the stigma associated with obesity has not been matched with progress in the stigma associated with alcohol drinking

- >1/3 US population has NAFLD; 2/3 US population drink alcohol*
- FDA encourages inclusion of participants in clinical trials *“that better reflect the population most likely to use the drug if the drug gets approved”*
[Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry | FDA](#)
- Covert alcohol consumption is a risk to drug efficacy in NASH/MASH RCTs

*Williams 2011; Saad GALLUP well-being website; Browning 2004

Implications for clinical trial design

Key determinants are the clinical event rate of the subpopulation and/or the availability/variability of a surrogate biomarker that has been agreed by regulatory agencies



Isreaslen et al 2023

Figure: The dynamic spectrum of steatotic liver disease

Questions remain for drug development in Met-ALD

The unmet need and potential treatment benefit are commensurate with the work required

- Are the regulatory agencies aligned with the new definitions?
- Is there a need for new surrogate endpoints in Met-ALD?
- Documentation of clinical event rates (including placebo response rates) in various subpopulations within a clinical trial setting
- Prediction of alcohol drinking
- Reliability of self-reporting and/or biomarker quantification of alcohol drinking
- Quantification of metabolic co-morbidity
- Statistical analyses
- Dual effects of drug on liver and consumption of calories/ethanol
- Concomitant alcohol use disorder therapy

Liver Forum Met-ALD Working Group

Assemble experts in:

- MASH
- Cirrhosis
- Alcohol liver disease
- Alcohol use disorder
- Metabolic disorders
- Clinical trial design
- Statistics/analytics
- Patient reported outcomes

From:

- Academia, clinical research
- Industry
 - Pharmaceutical
 - Diagnostic
- Regulatory agencies
- Other government agencies
 - E.g. NIH
- Patient representatives
- Foundations/societies

Process

- Leadership
 - Academic, Industry co-chairs
- Working group
 - Ensure diverse representation
- Convening
 - Prioritize questions
 - Deliberate
 - And again
 - White paper