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Met-ALD Program

Liver Forum

Date: March 23, 2024

Co-Leads:

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Nikhil Vergis, *GSK*

Berkeley Public Health

Overall Goal

- *Recommendations for including patients with current or past harmful alcohol consumption in steatotic liver disease (SLD) drug development*

Vision

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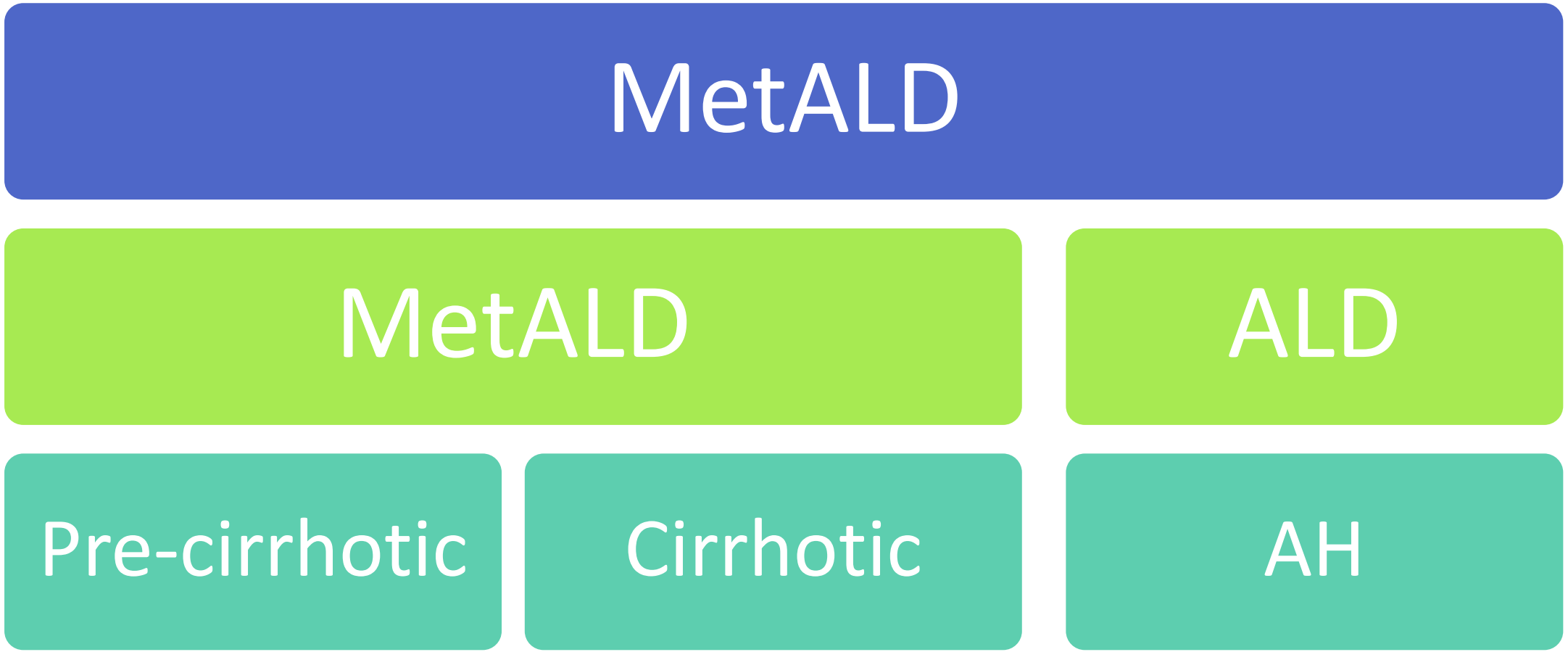
To progress into all forms of SLD with alcohol consumption



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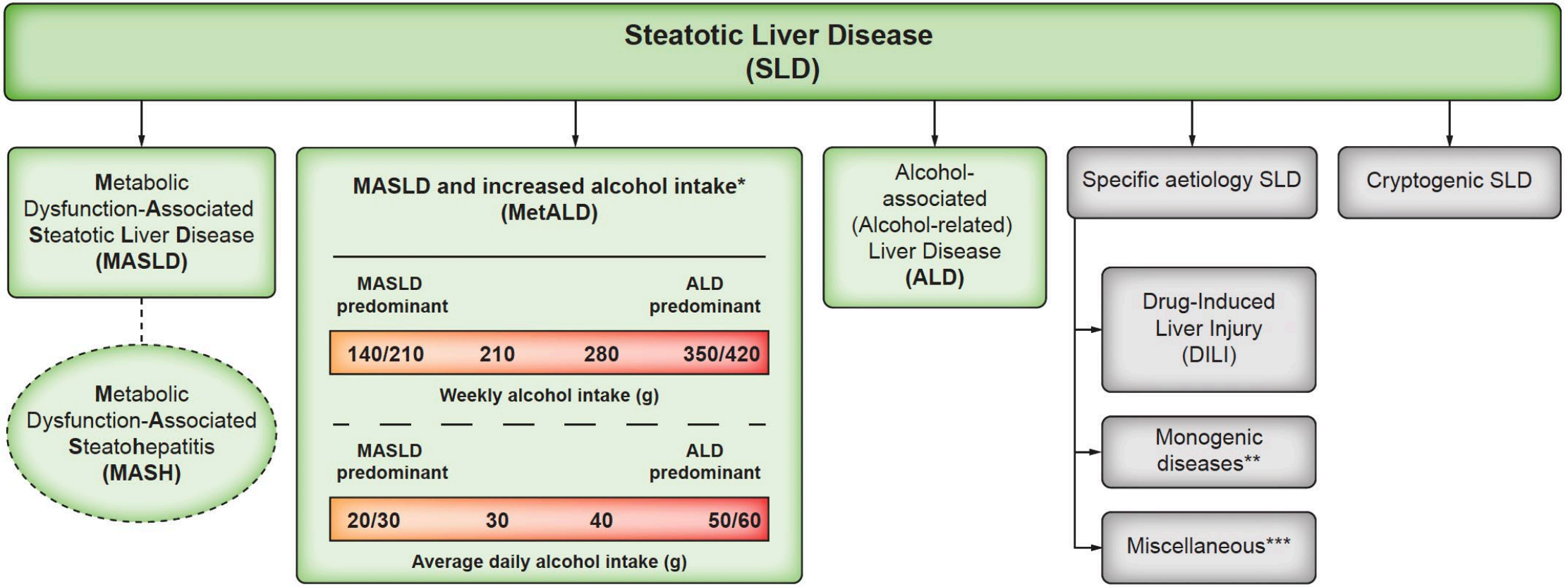
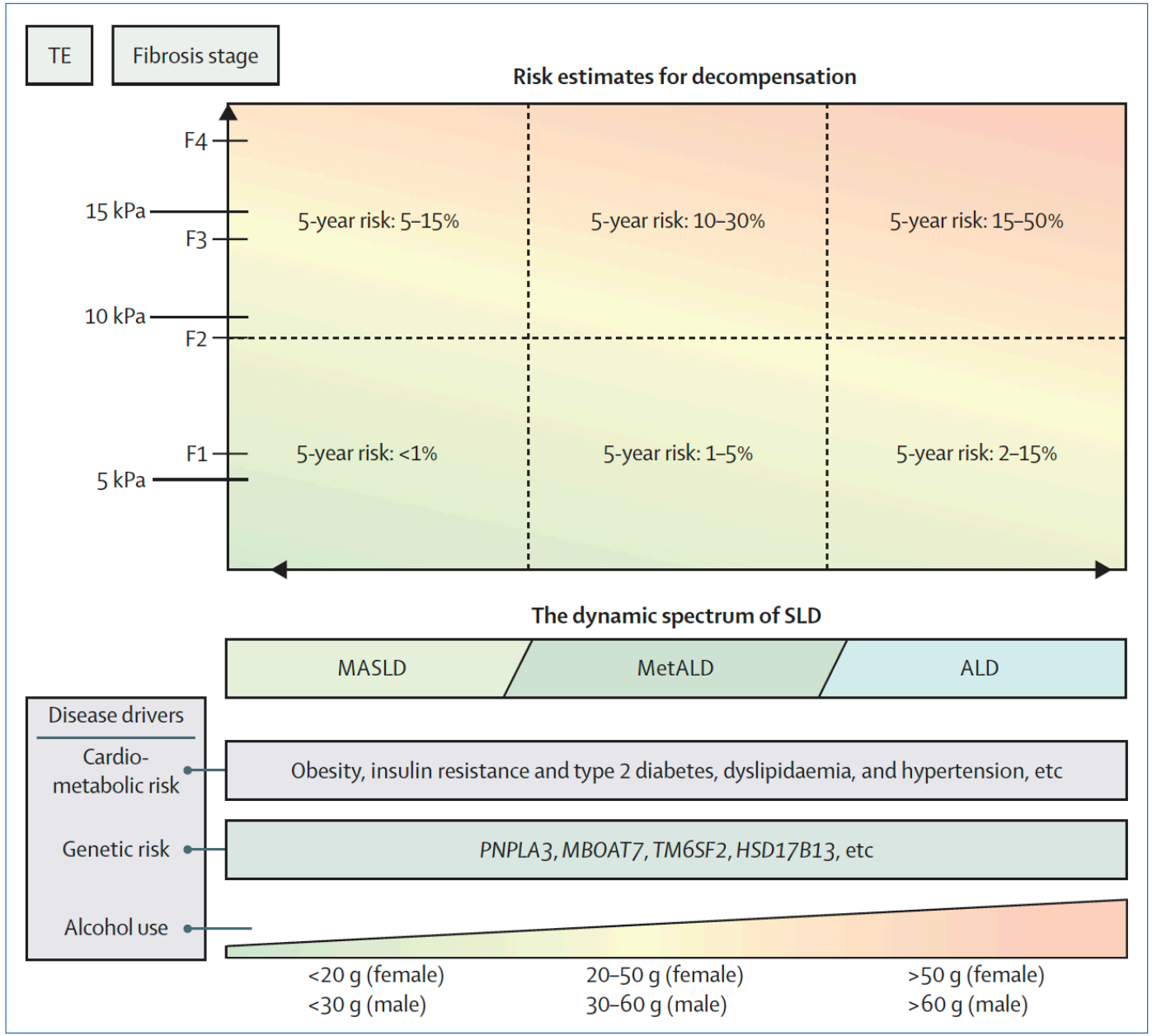
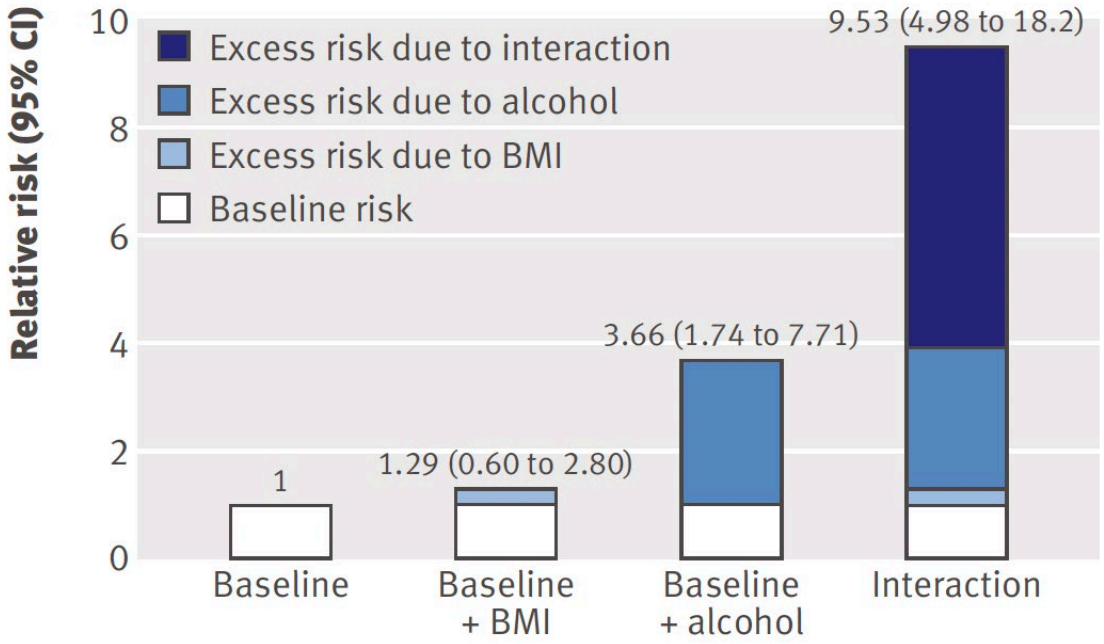

Steatotic Liver Disease
(SLD)
Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)
Metabolic Dysfunction-Associated Steatohepatitis (MASH)
MASLD and increased alcohol intake*
(MetALD)
MASLD predominant
ALD predominant
140/210
210
280
350/420
Weekly alcohol intake (g)
MASLD predominant
ALD predominant
20/30
30
40
50/60
Average daily alcohol intake (g)
Alcohol-associated (Alcohol-related) Liver Disease (ALD)
Specific aetiology SLD
Cryptogenic SLD
Drug-Induced Liver Injury (DILI)
Monogenic diseases**
Miscellaneous***



Israelsen, Lancet Gas Hep 2023

Why consider alcohol consumption?



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

HART BMJ 2010

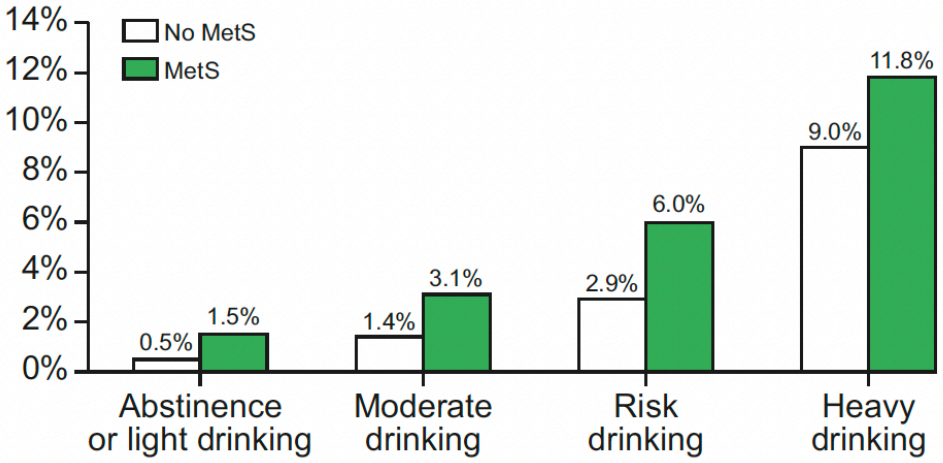


Fig. 2. Combined effects of alcohol and metabolic syndrome on liver-related outcomes. Cumulative 20-year incidence of severe liver-related outcomes (hospitalisation, cancer, or death), according to the baseline level of alcohol consumption and the absence/presence of MetS (data based on results reported in ref.[82]). MetS, metabolic syndrome.

ÅBERG JHEP 2023

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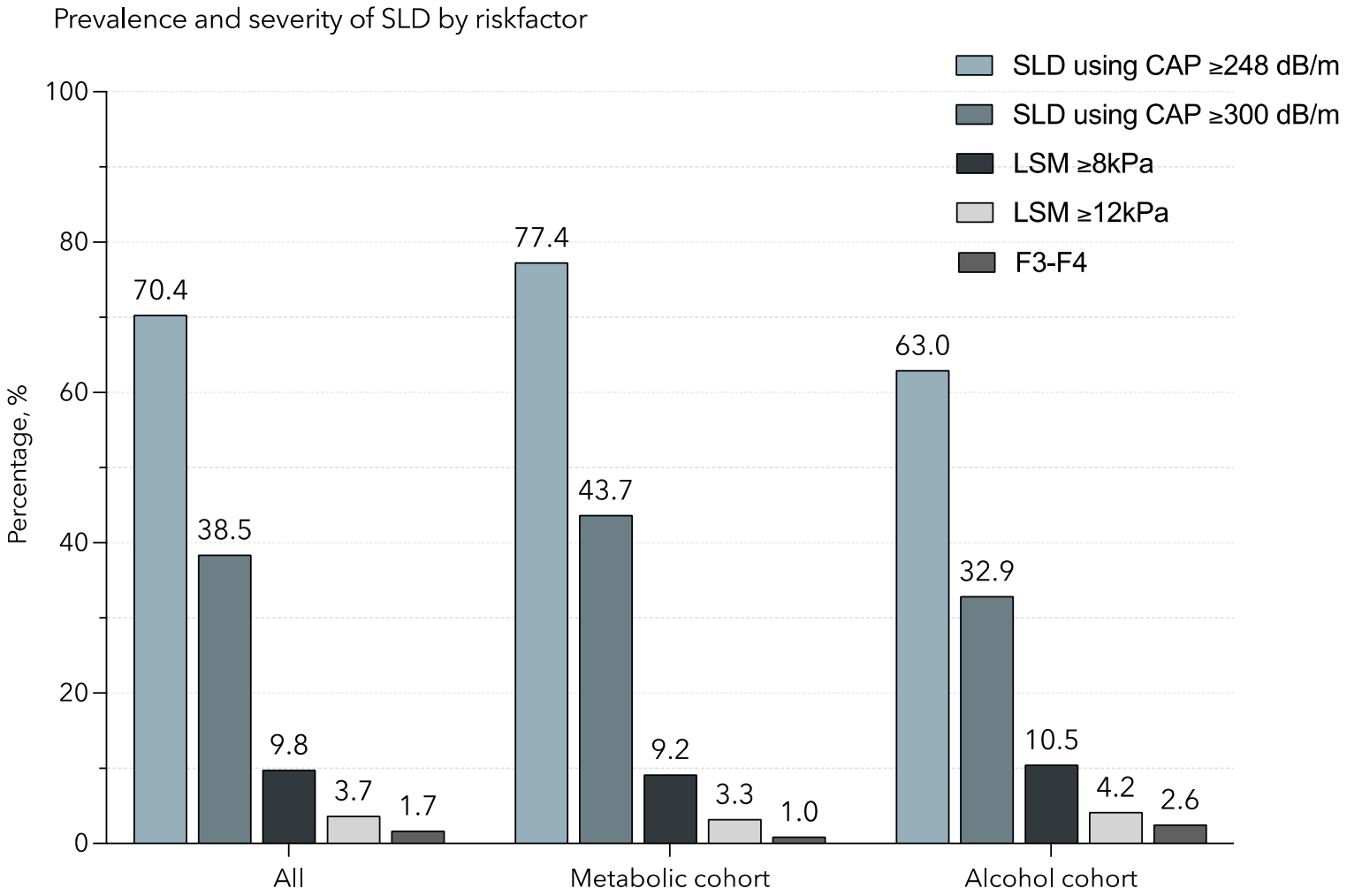

UNPUBLISHED DATA

Berkeley Public Health

Why consider alcohol consumption?

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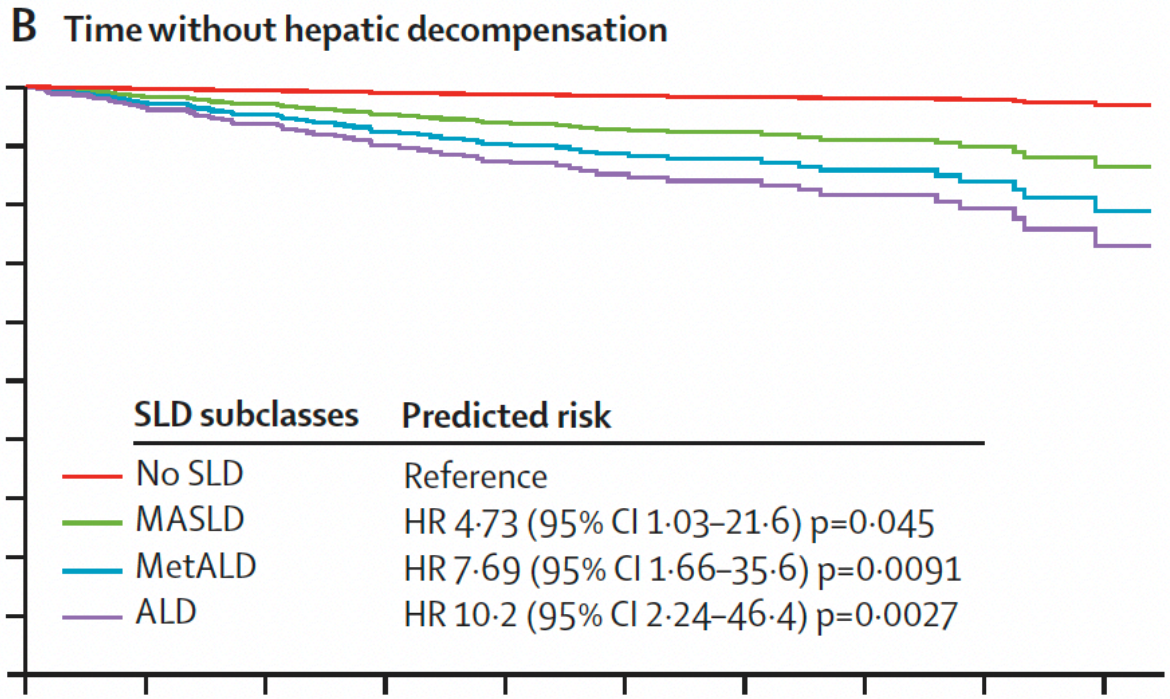

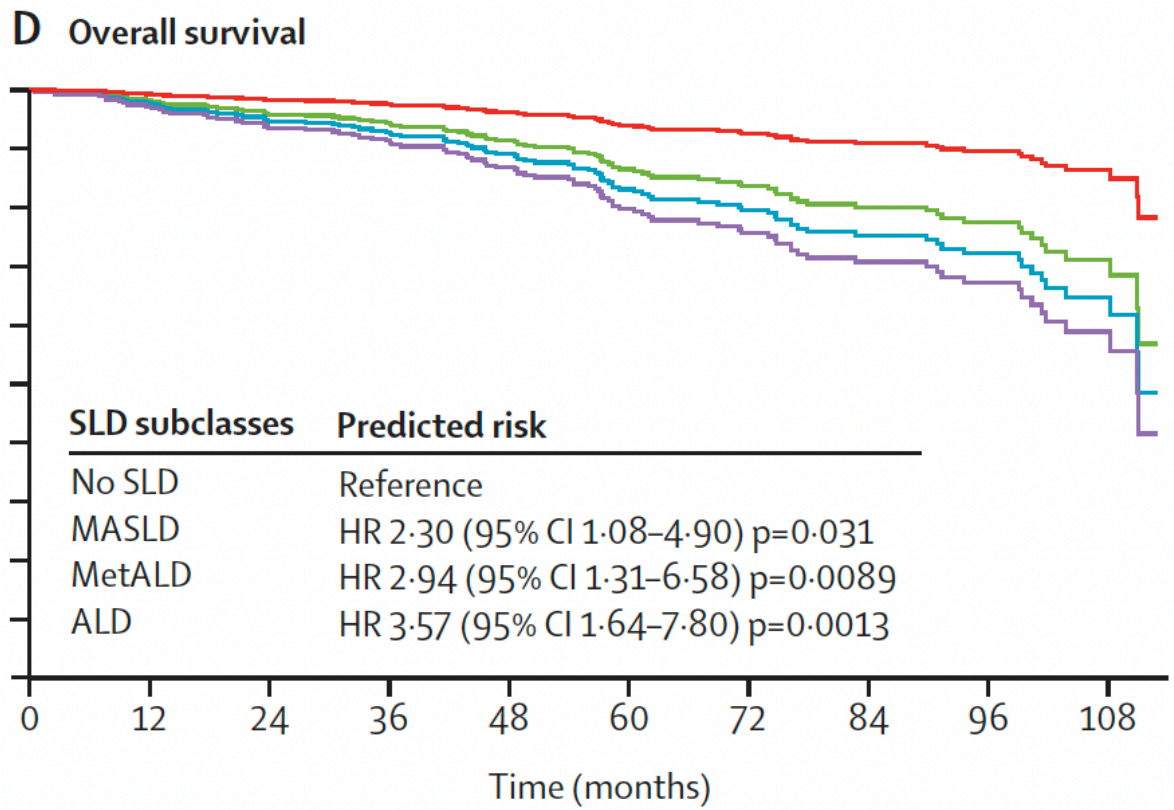

Israelsen, Lancet Gas Hep 2024

Scope of the MetALD Working Group

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Diagnosis
Lead: Maja

Drugs
Lead: Nikhil

Endpoints
Lead: Maja

Alcohol-use disorder
Lead: Nikhil

Diagnosis

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How should MetALD be diagnosed (eligibility for trial inclusion)?

1. Should patients be eligible for MetALD trials if they have a history of harmful alcohol drinking, but no present excess consumption? If so, what should be the minimum duration of excess use, min-max magnitude of use, and what should be the maximum period of abstinence/reduced drinking?
2. How to quantify present and prior duration and magnitude of alcohol intake when assessing eligibility for trial inclusion (alcohol biomarkers, standardized questionnaires, self-report)
3. Is metabolic dysfunction at inclusion a requirement for trial inclusion? If so, how many features, which features, of what severity, for how long, and independent of current alcohol drinking?

Diagnosis (cont.)

4. What is the relevance of presence and severity of steatosis and fibrosis for trial inclusion eligibility, and what should be the reference non-invasive/invasive tests to diagnose those aspects?
   - Can compensated advanced chronic liver disease (cACLD) as defined non-invasively according to the Baveno VI consensus be used as a diagnostic inclusion criterium in phase 2 and 3 trials?
5. Is it important to distinguish MetALD from ALD at inclusion? If so, how should it be done, given the possible underreporting of alcohol, and the higher prevalence of dependence syndrome at higher levels of drinking?
6. What is the epidemiology and socioeconomic characteristics of MetALD, especially in terms of prevalence and disease severity, differences according to age groups, sex, and geography, presence and distribution of metabolic dysfunction?
7. How can diagnosis rates of MetALD be improved?

Endpoints

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Which primary and secondary endpoints are relevant to consider for phase 2 and 3 trials?

1. Can non-invasive biomarkers of steatosis and/or liver fibrosis be used as primary endpoints in phase 2 and 3 trials? If so, at which disease stages are non-invasive liver fibrosis tests relevant as primary endpoints: Severe fibrosis? Compensated cirrhosis? Decompensated cirrhosis?
2. Is liver histology mandatory for MetALD phase 2 and/or phase 3 trials?
   - If liver biopsy is performed in MetALD trials, are MetALD histological lesions similar to MASLD lesions, to ALD lesions, or different from the two?
   - Which histological score should be used: Kleiner & NAS-CRN, SALVE, SAF?
3. Can non-invasive biomarkers of liver function like the MELD, Child-Pugh, and MELD-Na scores be used as primary endpoints in phase 2 and 3 trials of decompensated MetALD cirrhosis?

Endpoints (cont.)

4. What defines a relevant change in non-invasive steatosis and fibrosis tests, liver enzymes, and liver function scores in small and large trials, respectively? According to disease severity and alcohol pattern:
    i. pre-cirrhotic;
    ii. compensated cirrhosis;
    iii. decompensated cirrhosis
    iv. abstinent patients;
    v. patients with ongoing alcohol use

Endpoints (cont.)

5. What are the required secondary endpoints in phase 2 and 3 trials, and how should they be measured?
   - Alcohol intake
   - Metabolic dysfunction
   - Liver dysfunction
   - Liver-related clinical events
   - Patient-reported outcome measures including HRQoL
   - Adverse events
6. At what disease severity and clinical trial phase should clinical benefit be the primary outcome in MetALD trials? If so, how should clinical benefit be defined?
   - pre-cirrhotic;
   - compensated cirrhosis;
   - decompensated cirrhosis

Drugs

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What would the ideal drug in MetALD look like?

1. What are the benefits of therapy, as described by harm-reduction, vs acceptable risks that are sought by prescribers, payers and patients for an effective drug in MetALD?
   a. liver-events vs reduction in alcohol drinking vs a reduction in metabolic risk factors
   b. pre-cirrhotic vs compensated cirrhotic vs decompensated cirrhosis
   c. abstinent vs patients with recent alcohol use
2. What routes of administration would be preferred by patients with MetALD?
3. What should the comparator arm be for patients with MetALD?
4. Which MASH drugs might be especially suitable for re-purposing? Is there a need for de novo (non-repurposed) drugs for MetALD?

Special considerations

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What are the unique considerations for a clinical trial involving MetALD participants?

1. Should patients with alcohol dependence be excluded from MetALD trials? If so, at what severity of dependence syndrome and how should dependence syndromes be evaluated?
2. What should the concomitant behavioral and/or pharmacotherapy be in MetALD trials for:
   - the metabolic dysfunction and
   - AUD
3. What is the preferred method of quantification of study alcohol consumption in:
   - the Screening period
   - the Treatment period
4. Can patients with psychiatric comorbidities be included in MetALD studies?
5. What methods ensure the highest rates of participant retention?
6. What safety safeguards should be in place within the protocol for MetALD trials?

Next steps

1. Discuss objectives at Liver Forum 16 and finalise shortly thereafter

2. Develop project proposals

3. Target outputs: position papers containing recommendations for Met-ALD drug development