



# **Current status of fatty liver disease nomenclature - implications for drug development**



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# Disclosures

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He has acted as consultant for Abbvie, Actelion, Aelin Therapeutics, AgomAb, Aligos Therapeutics, Allergan, Alnylam, Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol-Meyers Squibb, CSL Behring, Coherus, Echosens, Eisai, Enyo, Galapagos, Galmed, Genetech, Genfit, Gilead Sciences, Intercept, Inventiva, Janssens Pharmaceutica, Julius Clinical, Madrigal, Medimmune, Merck Sharp & Dome, NGM Bio, Novartis, Novo Nordisk, Promethera, Roche.

SF has been lecturer for Abbvie, Allergan, Bayer, Eisai, Genfit, Gilead Sciences, Janssens Cilag, Intercept, Inventiva, Merck Sharp & Dome, Novo Nordisk, Promethera, Siemens.



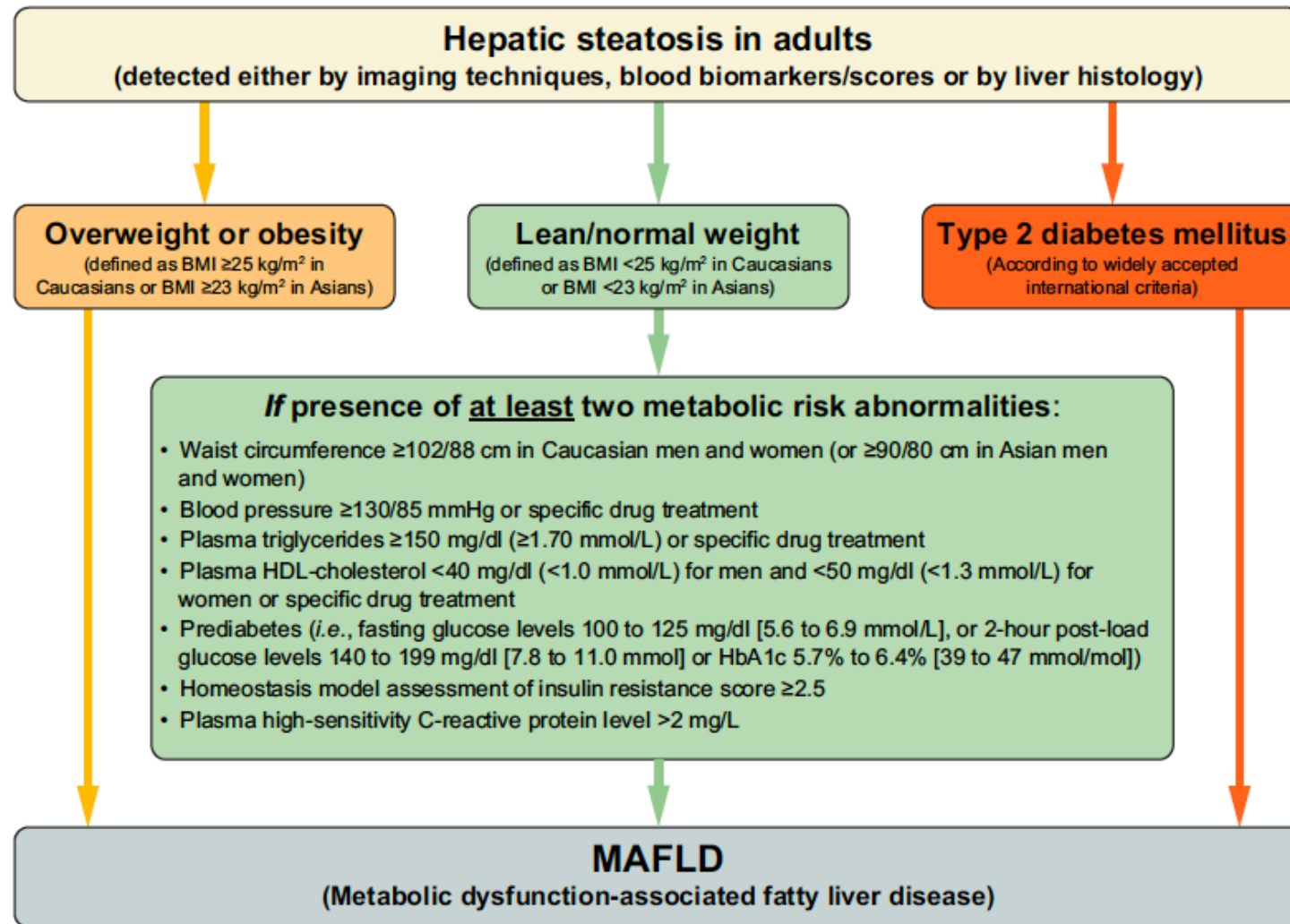
# Why changing the nomenclature?



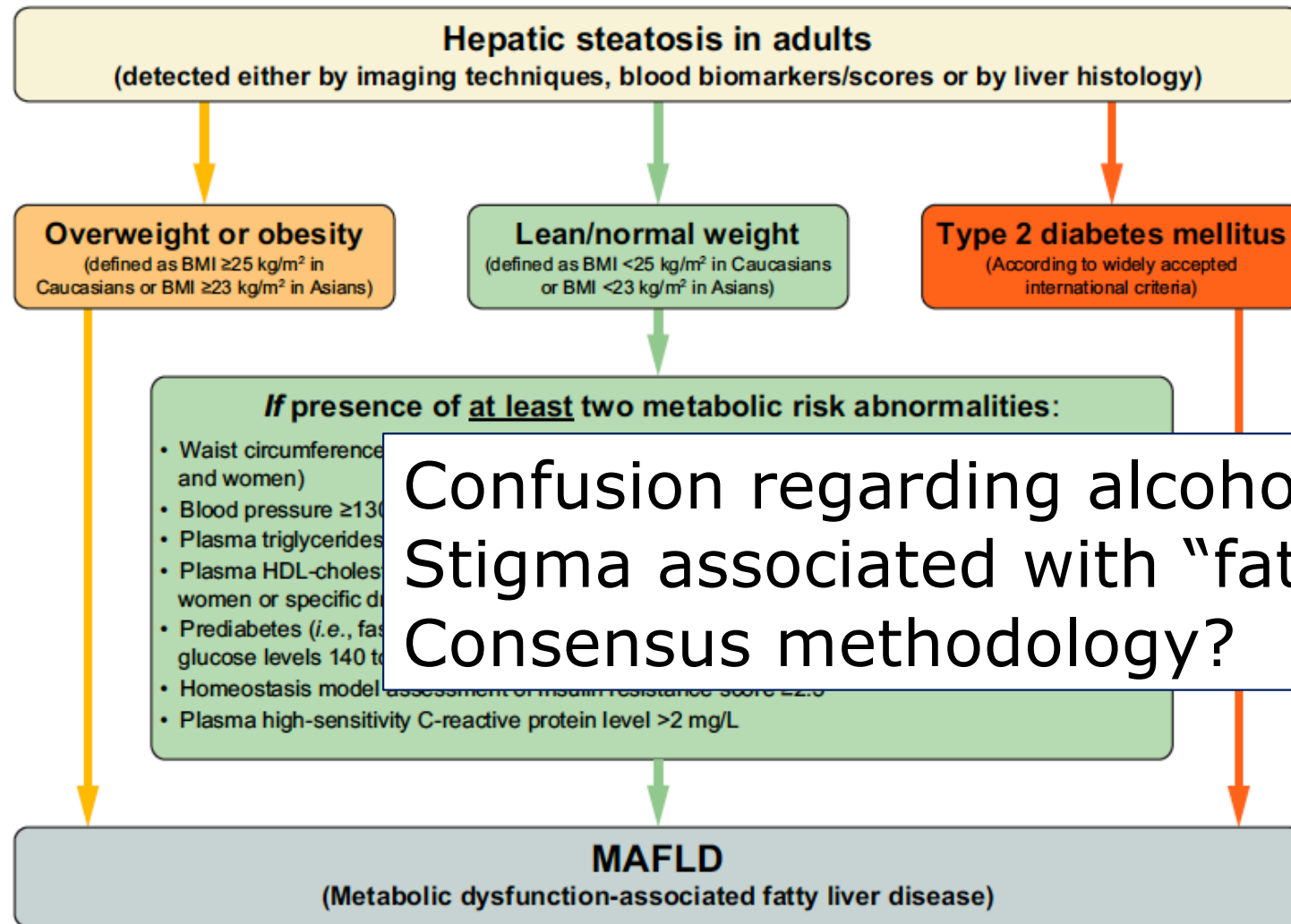
## **NAFLD =**

Steatosis in the absence of  
Alcohol consumption  
above threshold  
& Other known  
("secondary") causes of  
steatosis

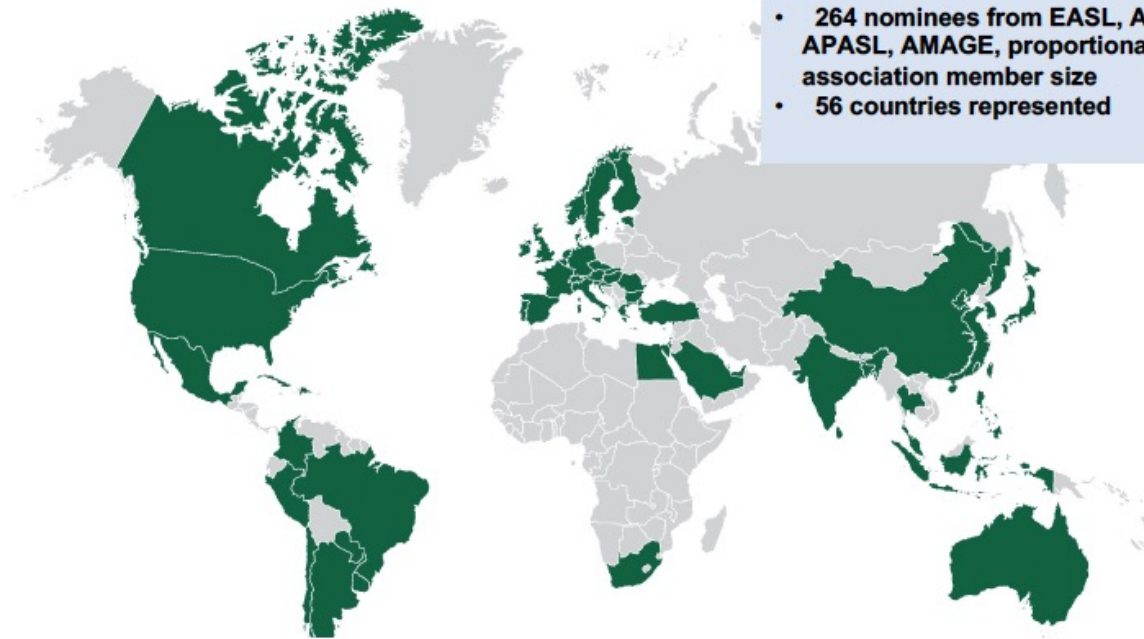
- Negative diagnosis
- No indication of the cause
  - Overweight/obesity
  - IR
  - Dyslipidaemia
  - ...
  - MetS
- Heterogenous
  - "lean" NAFLD/NASH
- Exclusionary
  - Reality: combined aetiology



Eslam *et al.* J Hep 2020

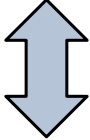


## Global NAFLD Nomenclature involvement

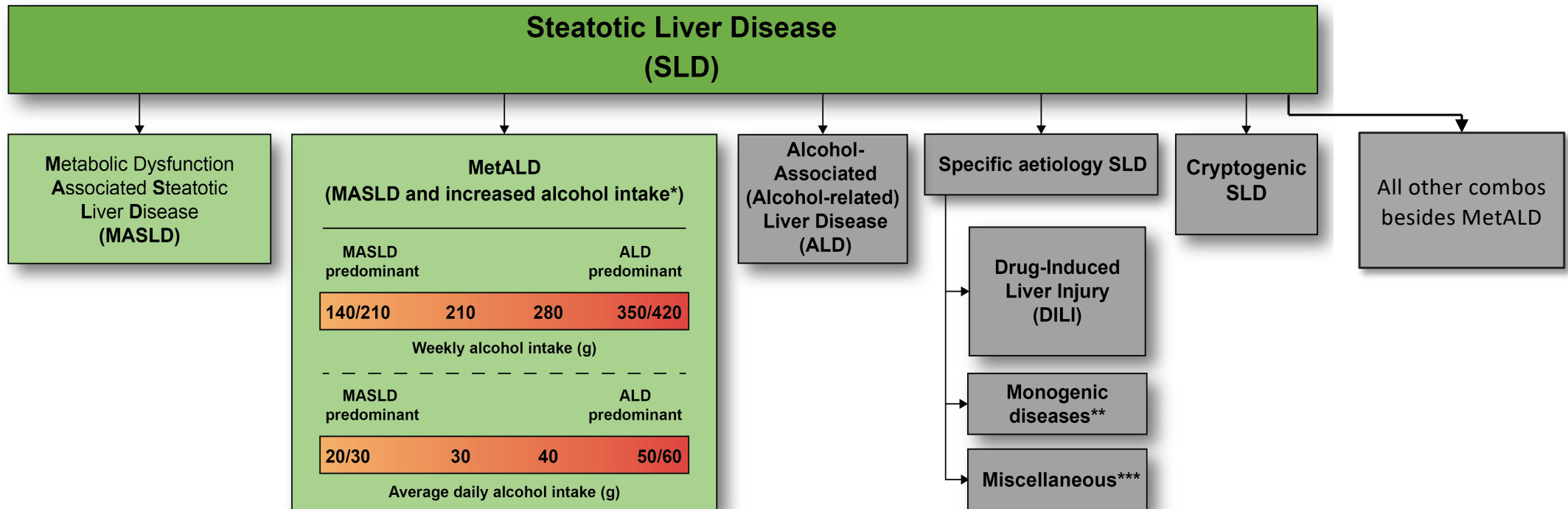


- 264 nominees from EASL, AASLD, ALEH, APASL, AMAGE, proportionate to association member size
- 56 countries represented

# Overarching term

- NAFLD = exclusionary
- 
- Clinical practice: many combo's
  - Mainly alcohol and metabolic
- Fatty liver = feature
  - Like "granulomatous hepatitis"
  - Long list of causes
    - 2 predominant ones

Rinella M... Francque S...Sanyal A *et al.* J Hep 2023



\*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

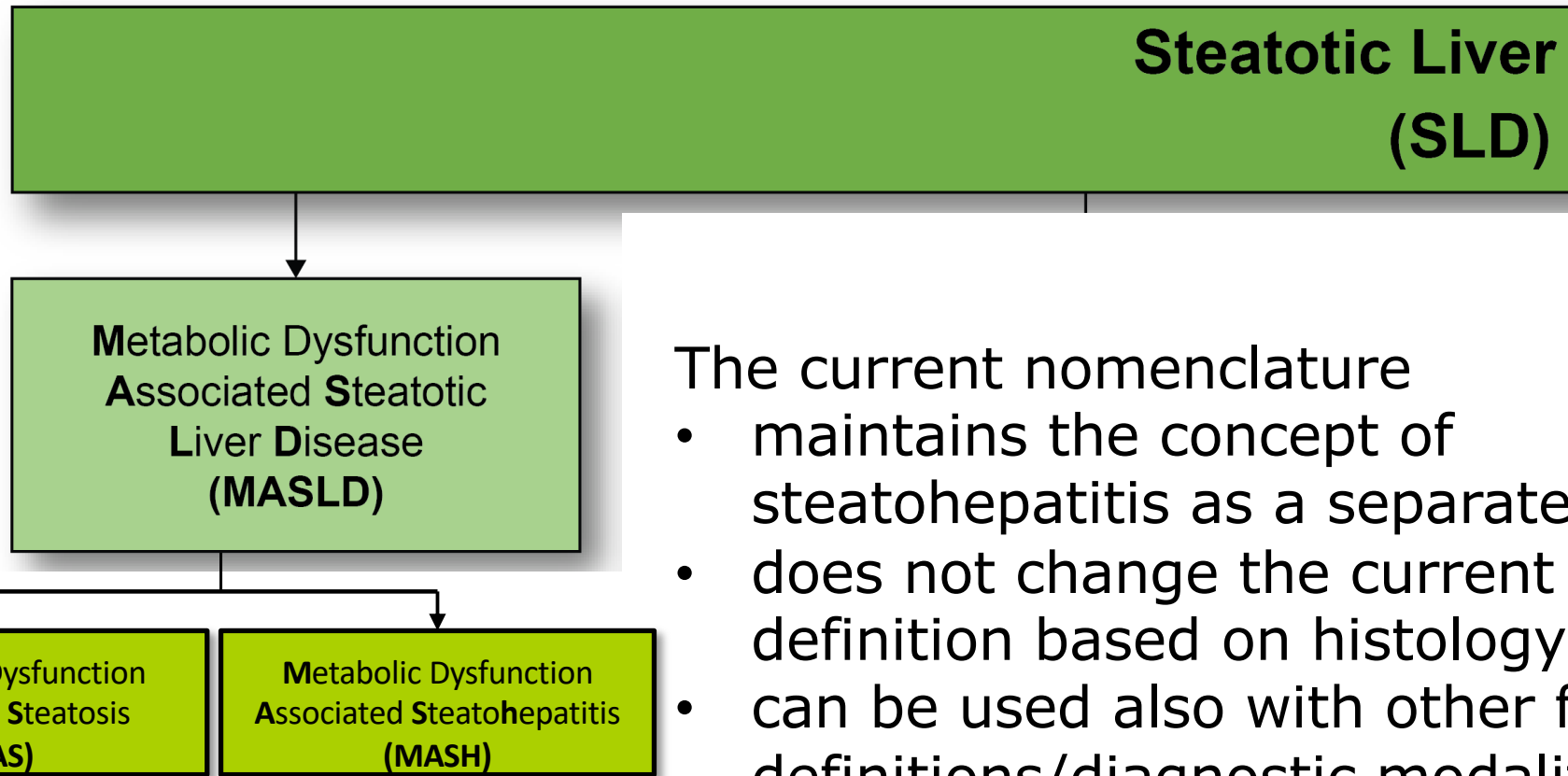
\*\*\*e.g. Hepatitis C virus (HCV), malnutrition, celiac disease



<h3>Adult Criteria</h3>	<h3>Pediatric Criteria</h3>
<p><b>At least 1 out of 5:</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> BMI <math>\geq 25</math> kg/m<sup>2</sup> [23 Asia] <b>OR</b> WC &gt; 94 cm (M) 80 cm (F) <b>OR</b> ethnicity adjusted</li> <li><input type="checkbox"/> Fasting serum glucose <math>\geq 5.6</math> mmol/L [100 mg/dL] <b>OR</b> 2-hour post-load glucose levels <math>\geq 7.8</math> mmol/L [<math>\geq 140</math> mg/dL] <b>OR</b> HbA1c <math>\geq 5.7\%</math> [39 mmol/L] <b>OR</b> type 2 diabetes <b>OR</b> treatment for type 2 diabetes</li> <li><input type="checkbox"/> Blood pressure <math>\geq 130/85</math> mmHg <b>OR</b> specific antihypertensive drug treatment</li> <li><input type="checkbox"/> Plasma triglycerides <math>\geq 1.70</math> mmol/L [150 mg/dL] <b>OR</b> lipid lowering treatment</li> <li><input type="checkbox"/> Plasma HDL-cholesterol <math>\leq 1.0</math> mmol/L [40 mg/dL] (M) and <math>\leq 1.3</math> mmol/L [50 mg/dL] (F) <b>OR</b> lipid lowering treatment</li> </ul>	<p><b>At least 1 out of 5:</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> BMI <math>\geq 85^{\text{th}}</math> percentile for age/sex [BMI z score <math>\geq +1</math>] <b>OR</b> WC &gt; 95<sup>th</sup> percentile <b>OR</b> ethnicity adjusted</li> <li><input type="checkbox"/> Fasting serum glucose <math>\geq 5.6</math> mmol/L [<math>\geq 100</math> mg/dL] <b>OR</b> serum glucose <math>\geq 11.1</math> mmol/L [<math>\geq 200</math> mg/dL] <b>OR</b> 2-hour post-load glucose levels <math>\geq 7.8</math> mmol [140 mg/dL] <b>OR</b> HbA1c <math>\geq 5.7\%</math> [39 mmol/L] <b>OR</b> already diagnosed/treated type 2 diabetes <b>OR</b> treatment for type 2 diabetes</li> <li><input type="checkbox"/> Blood pressure age &lt; 13y, BP <math>\geq 95^{\text{th}}</math> percentile <b>OR</b> <math>\geq 130/80</math> mmHg (whichever is lower); age <math>\geq 13y</math>, 130/85 mmHg <b>OR</b> specific antihypertensive drug treatment</li> <li><input type="checkbox"/> Plasma triglycerides &lt; 10y, <math>\geq 1.15</math> mmol/L [<math>\geq 100</math> mg/dL]; age <math>\geq 10y</math>, <math>\geq 1.70</math> mmol/L [<math>\geq 150</math> mg/dL] <b>OR</b> lipid lowering treatment</li> <li><input type="checkbox"/> Plasma HDL-cholesterol <math>\leq 1.0</math> mmol/L [<math>\leq 40</math> mg/dL] <b>OR</b> lipid lowering treatment</li> </ul>

Aligned with Alberti *et al.* Circulation 2009

Rinella M... Francque S...Sanyal A *et al.* J Hep 2023



- The current nomenclature
- maintains the concept of steatohepatitis as a separate entity
  - does not change the current definition based on histology
  - can be used also with other future definitions/diagnostic modalities



## A new era for steatotic liver Disease: Evaluating the Novel nomenclature in the UK Biobank

Kai Markus Schneider, Carolin V. Schneider

PII: S0168-8278(23)04985-1

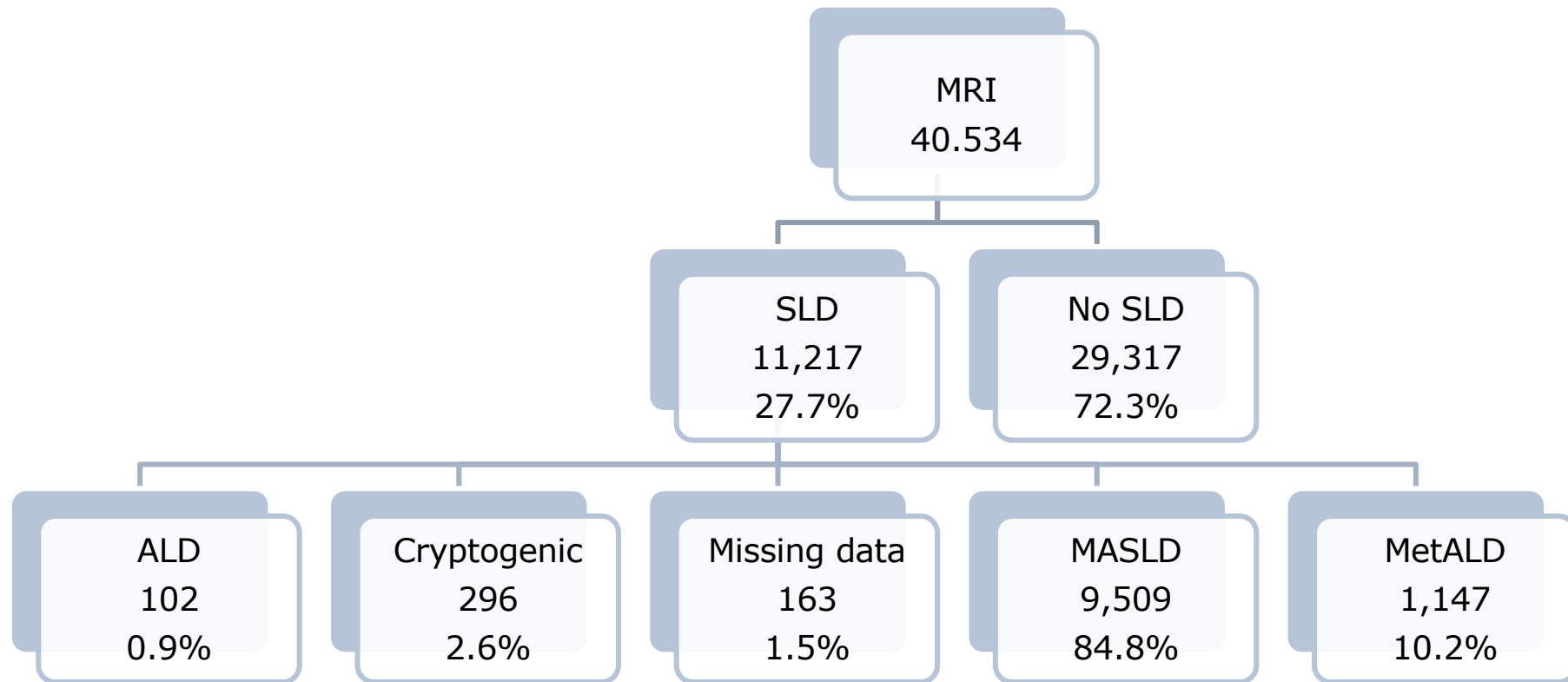
DOI: <https://doi.org/10.1016/j.jhep.2023.07.007>

Reference: JHEPAT 9239

To appear in: *Journal of Hepatology*

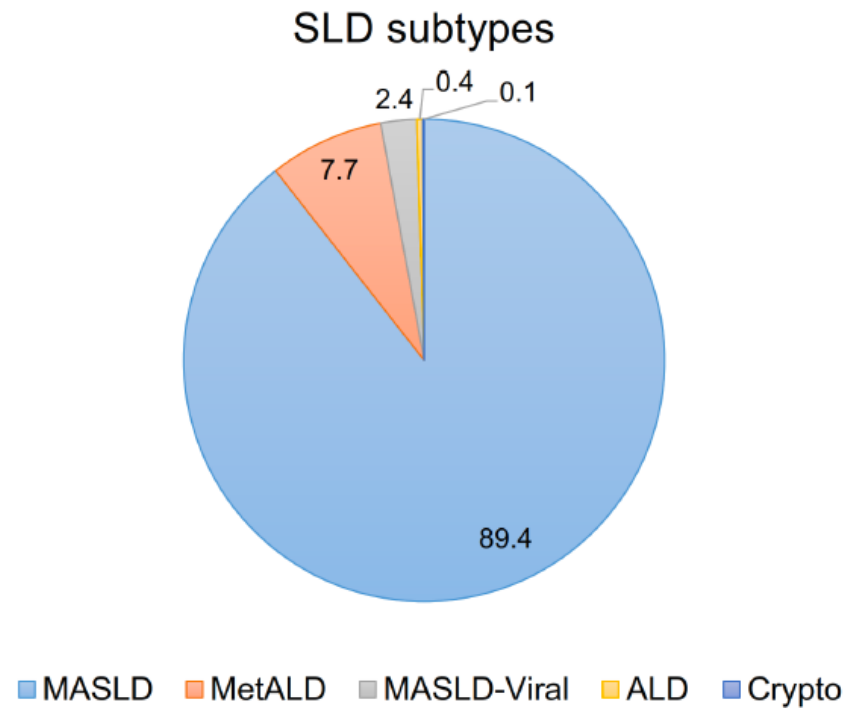
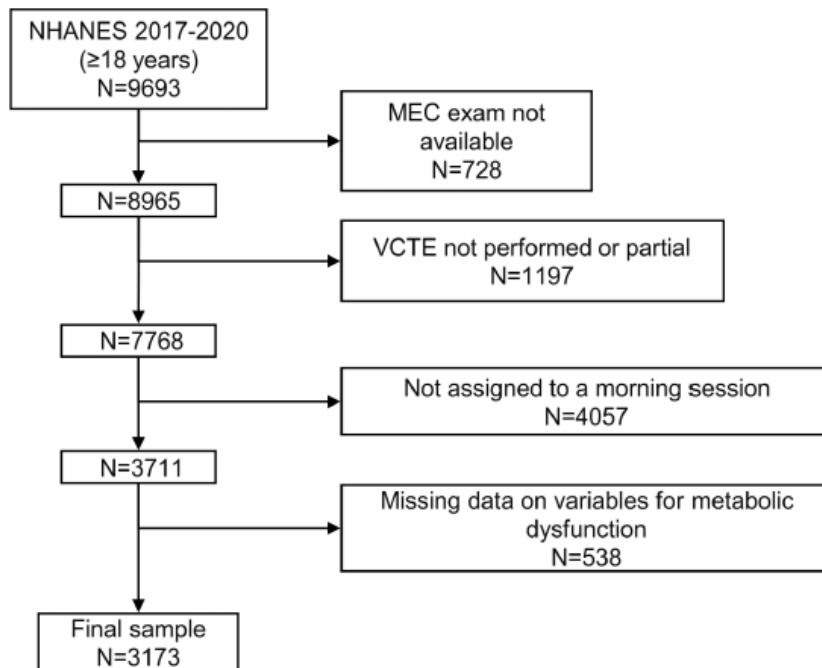
Received Date: 26 June 2023

Accepted Date: 2 July 2023

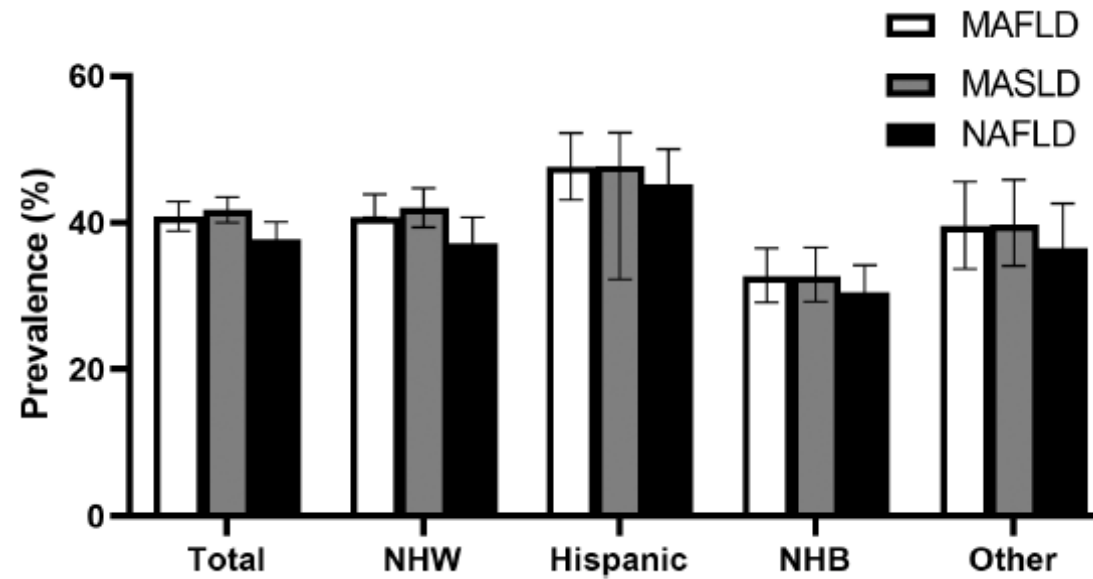


Schneider M, Schneider V. J Hep 2023

- 42.1% SLD based on CAP™ > 274 dB/m
- 90% met at least 1 CMRF



Ciardullo S *et al.* Liv Int 2023



Ciardullo S *et al.* Liv Int 2023



# Implications for research and clinical practice

- Better characterisation of all factors contributing to SLD and liver disease severity
- Better study the additive effect/synergistic effects on disease course
  - Few studies so far on role of metabolic factors as co-factors in viral hepatitis, ALD
- Appropriate management of all causes



# Implications for drug development?



- Current evidence
  - Minor or no impact
    - Populations largely overlap
    - NAFLD = MASLD only + cryptogenic
    - NASH = MASH
      - histological framework has not changed





# Implications for drug development?



- Future trials
  - Minor or no impact
    - Positive diagnosis:
      - Slightly reduced heterogeneity by excluding cryptogenic SLD
    - In- and exclusion criteria define the population
      - Exclusion criterion on alcohol implies MASLD only
        - » Equals NAFLD (except cryptogenic SLD)
    - NIT as endpoints
      - Not many data yet but likely little or no impact for the same reasons
  - MetALD as a separate patient population to study



# Take home messages

- Positive name + diagnosis and non-stigmating
- Look for and treat all potential causes
- NAFLD and MASLD only largely overlap
  - Cryptogenic SLD is only difference and a small fraction
- MetALD defines a separate group of patients
- Impact on existing literature and ongoing studies is minor
- Helps improving design of new studies



# Take home messages

- MetALD clearly defines a separate group of patients
- Impact on existing literature and ongoing trials is minor
- Helps improving design of new studies
  - Role of different factors combined
  - including studies for MetALD emerging as a separate area of research