MASLD: Why the need to change again?

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Global Epidemiology of MASLD

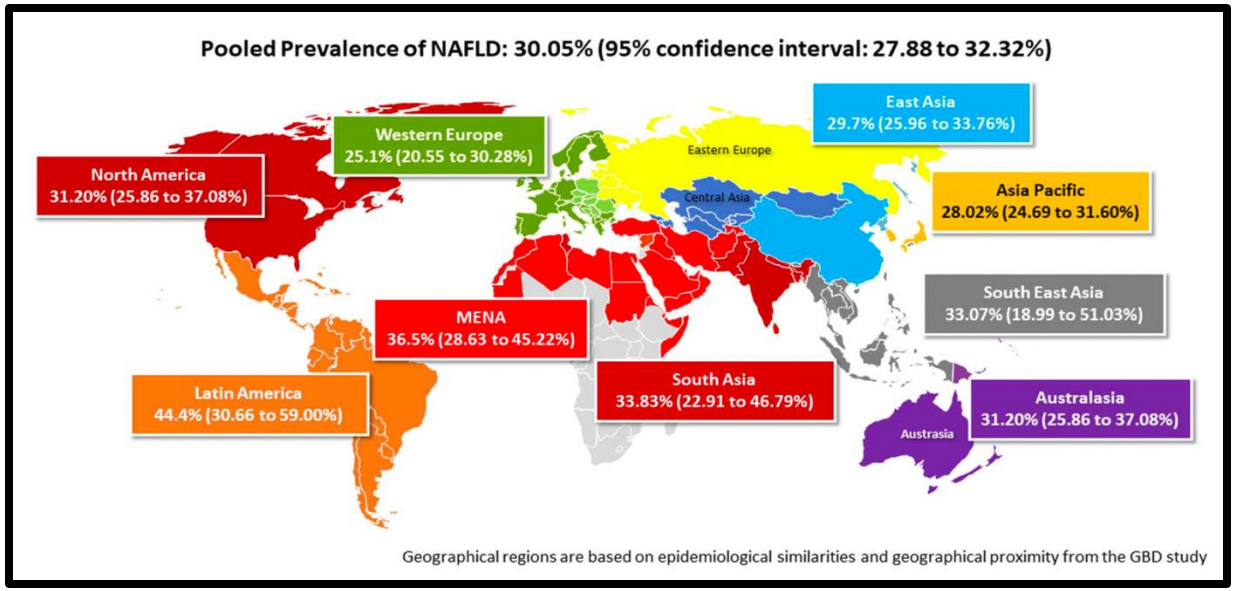
MASLD is the leading global cause of chronic liver disease

Estimated to **affect approximately 38.0% (33.71-42.49) of world's population: 1.66 billion (0.95–2.59)**

- Global MASH prevalence is 5.27% (SE: 2.63)
- Prevalence of **MASH among MASLD patients is 16.02% (3.24% - 52.08%)**

Data for the prevalence and incidence of MASLD in Africa are scarce

- **Earlier meta-analysis reported MASLD prevalence of 13.5% (95% CI 5.67–28.7)**
  - Ranging from 9% in Nigeria to 20% in Sudan – did not meet criteria for inclusion in recent meta-analyses
- Underestimate considering **increasing burden of NCDs**, esp **rising prevalence of obesity & type 2 diabetes**



NAFLD Prevalence: 2019 GBD

- **Latin America: 44.4%**
- **MENA: 36.5%**
- **South Asia: 33.8%**
- **South-East Asia: 33.1%**
- **North America 31.2%**
- **East Asia: 29.7%**
- **Asia Pacific: 28.0%**
- **Western Europe: 25.1%**

Hepatology 2023;77:1335; Nat Rev Gastroenterol Hepatol 2018; 15: 11
Lancet Gastroenterol Hepatol 2022;7:851

Global prevalence of MASLD among T2DM patients: 55.5% (95% CI: 47.3-63.7)

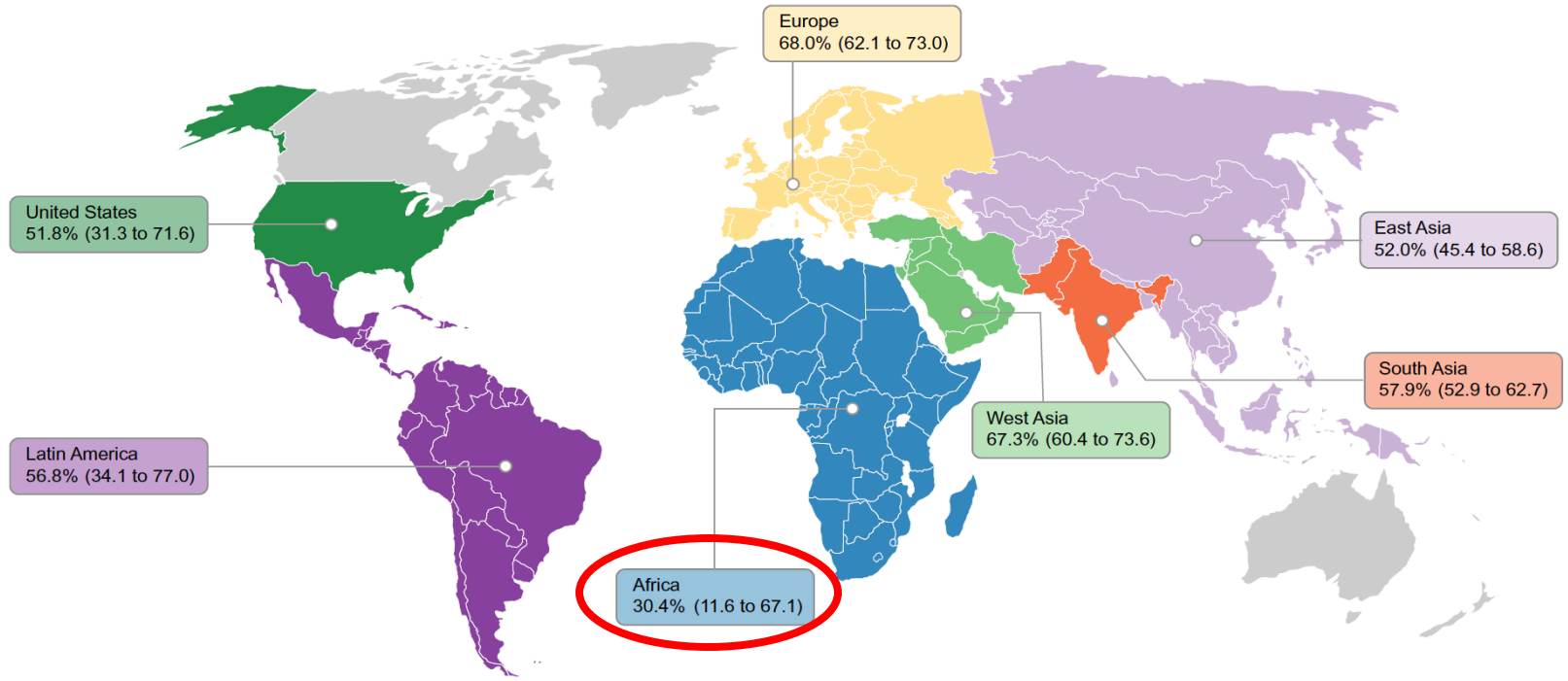


Fig. 2. Global and regional prevalence of NAFLD among patients with T2DM. H-MRS, proton magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus. NAFLD diagnosed by ultrasound or H-MRS. Data are displayed as prevalence (95% CI).

MASLD often precedes development of cardiometabolic risk factors, in particular type 2 DM

Prevalence of MASLD in patients with type 2 DM is >2-fold higher than in general population

- Global prevalence of MASH among patients with type 2 DM is 37.3%
- Patients with MASLD and type 2 DM undergoing liver biopsy, 17% have advanced fibrosis

J Hepatol 2019;71:793

Epidemiology of NAFLD in sub-Saharan Africa

NAFLD cases in SAA

Western SSA

- **1990:** 8·4 per million
- **2017:** 23·2 per million

Central SSA

- **1990:** 2.3 per million
- **2017:** 6.2 per million

Southern SSA

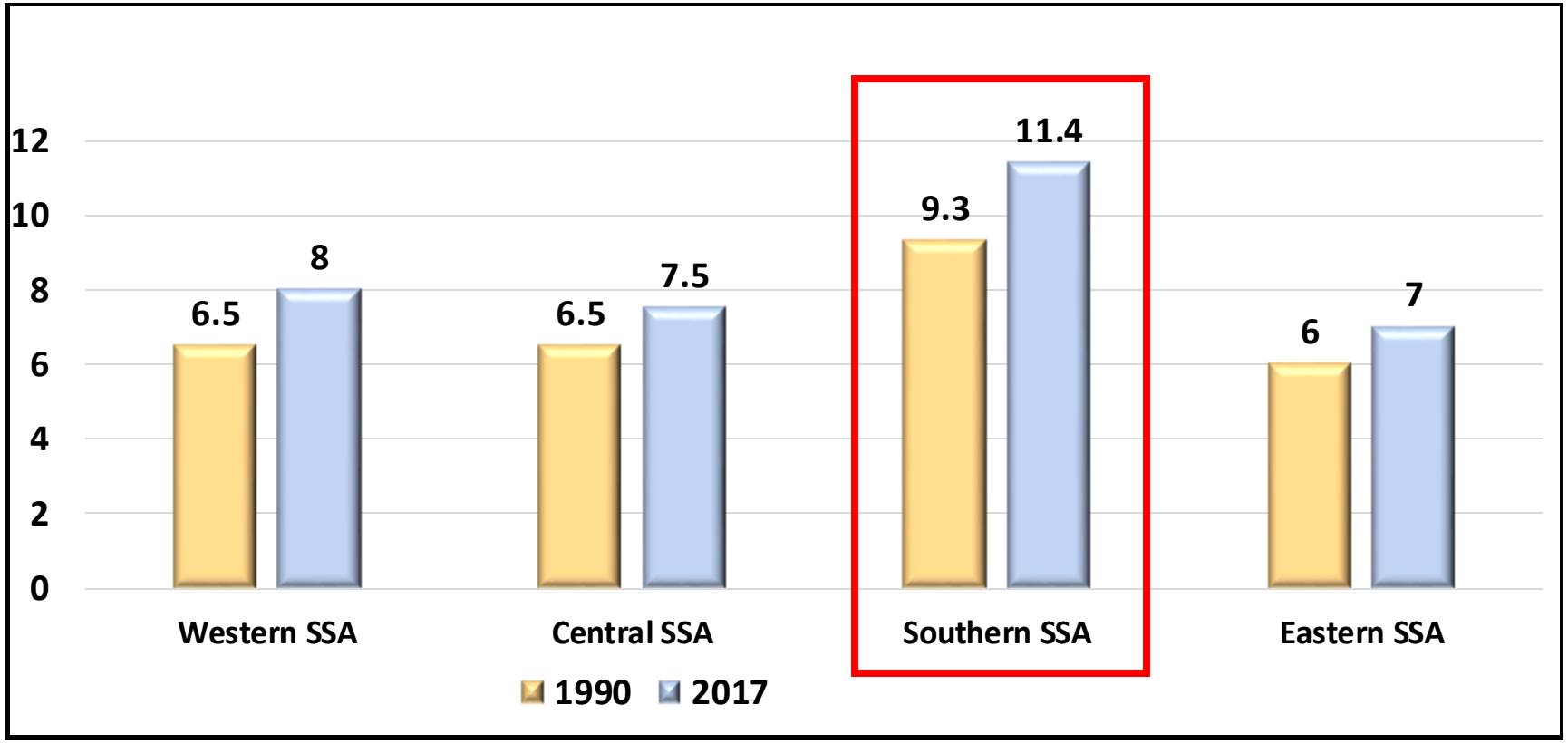
- **1990:** 3.7 per million
- **2017:** 8.1 per million

Eastern SSA

- **1990:** 7.1 per million
- **2017:** 18 per million

BMJ Open 2020; 10: e036663

GBD 2017 Study: Age-standardised prevalence of NAFLD in SSA



Obesity rates in southern SSA: Highest in SSA

SSA: MASLD and Non-Communicable Diseases

Sub-Saharan Africa, a middle-to-lower-income region, has varied evolving economies and increasing urbanization with pro-MASLD dietary and behavioural changes

Transition from infectious diseases of TB, malaria, and HIV to an increasing burden of non-communicable diseases

- Rising prevalence of obesity and type 2 diabetes
- Driven by overlapping challenges of food insecurity, nutritional transition, and associated increased consumption of calorie-dense foods and more sedentary urban lifestyles
- Africans with NCDs are younger by 10 years or more compared with people in other world regions with twice the risk of NCD-related mortality
- Burden of NCDs in all 4 SSA regions is higher than the global average
- SSA anticipated to experience largest global increase in NCD-related mortality

Lancet Glob Health 2019; 7: e1375; Lancet 2006;367: 1747; Nature 2018; 559: 507

Evolution of Fatty Liver Disease Nomenclature

NAFLD  **MAFLD**  **MASLD**

NAFLD: Need for a Name Change

Unified global approaches to nomenclature and disease definition are critical

- Increasing disease awareness
- Driving policy change
- Identifying those at risk
- Facilitating diagnosis and access to care

Language can

- Create or exacerbate stigma
- Marginalise segments of the affected population
- Contribute to health inequalities

History of Fatty Liver Disease Nomenclature

***" Nonalcoholic steatohepatitis"* first termed in 1980 by Jurgen Ludwig**

- Hepatic steatosis, hepatocyte injury, liver inflammation and fibrosis
- Associated with being overweight and obesity

Subsequently, the term non-alcoholic fatty liver disease (NAFLD)

- Used to describe histological spectrum of steatosis to steatohepatitis with its subtypes of NAFL and NASH
- Histological classification further expanded on by various scoring systems categorising steatosis, disease activity, and fibrosis
    - Brunt scoring system, NAFLD activity score (NAS), SAF score

Mayo Clin Proc. 1980;55:434; Liver. 1999;19:263; Hepatology 2005;41:1313; Hepatology. 2012;56

MASLD: SPECTRUM OF DISEASE

NAFL
- Pure steatosis
- Steatosis and mild lobular inflammation

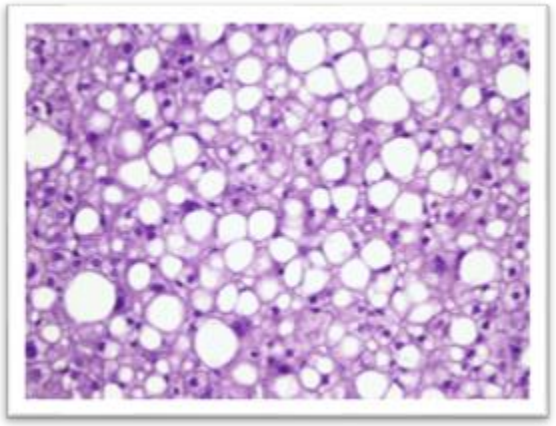
NASH

HCC

Early
F0/F1 fibrosis

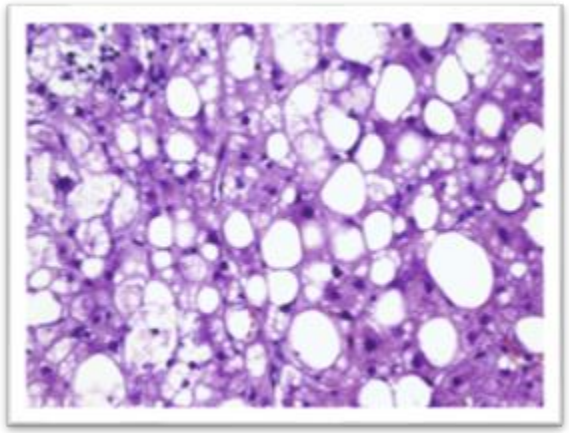
Fibrotic
≥F2 to ≥F3 fibrosis

Cirrhotic
F4 fibrosis



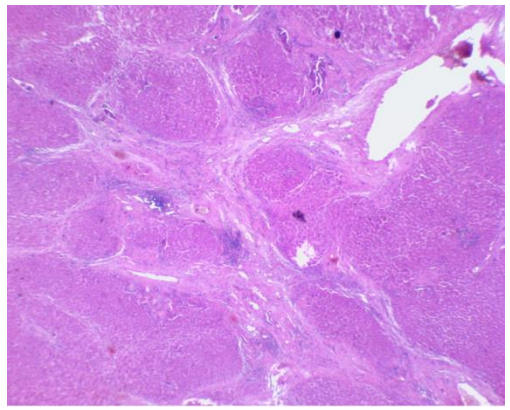
MAFL

Diffuse macro-vesicular steatosis >5% of hepatocytes



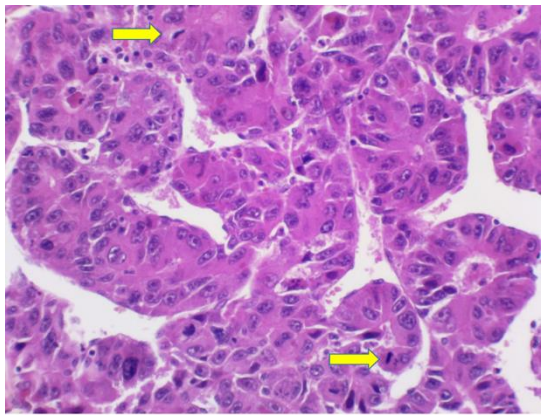
MASH

NAFL + lobular inflammation, hepatocyte ballooning, necrosis



Cirrhosis

Variably sized regenerative nodules surrounded by fibrous septa
Loss of steatosis



HCC

Thickened trabeculae of pleomorphic hepatocytes
Large irregular nuclei with conspicuous mitotic activity

J Hepatol 2016; 64:1388

Limitations of NAFLD nomenclature

- ***"Non-alcoholic"*** did not accurately capture what the aetiology of the disease was, and notably, the terms **"fatty"** has been considered to be stigmatising by some & **"non- alcoholic"** potentially disparaging to those who suffer from ALD
  - Diagnosis of exclusion

- ***Individuals with risk factors for NAFLD***, such as type 2 diabetes, who **consume more alcohol than the relatively strict thresholds** used to define **non-alcoholic nature** of the disease, were not adequately recognised by existing nomenclature and were **excluded from trials and consideration for treatments**

- **2020: *Eslam et al:*** Proposed the term: **Metabolic dysfunction–associated fatty liver disease (MAFLD),** which includes patients with fatty liver regardless of the amount and pattern of alcohol intake. **Allowed for dual pathology**

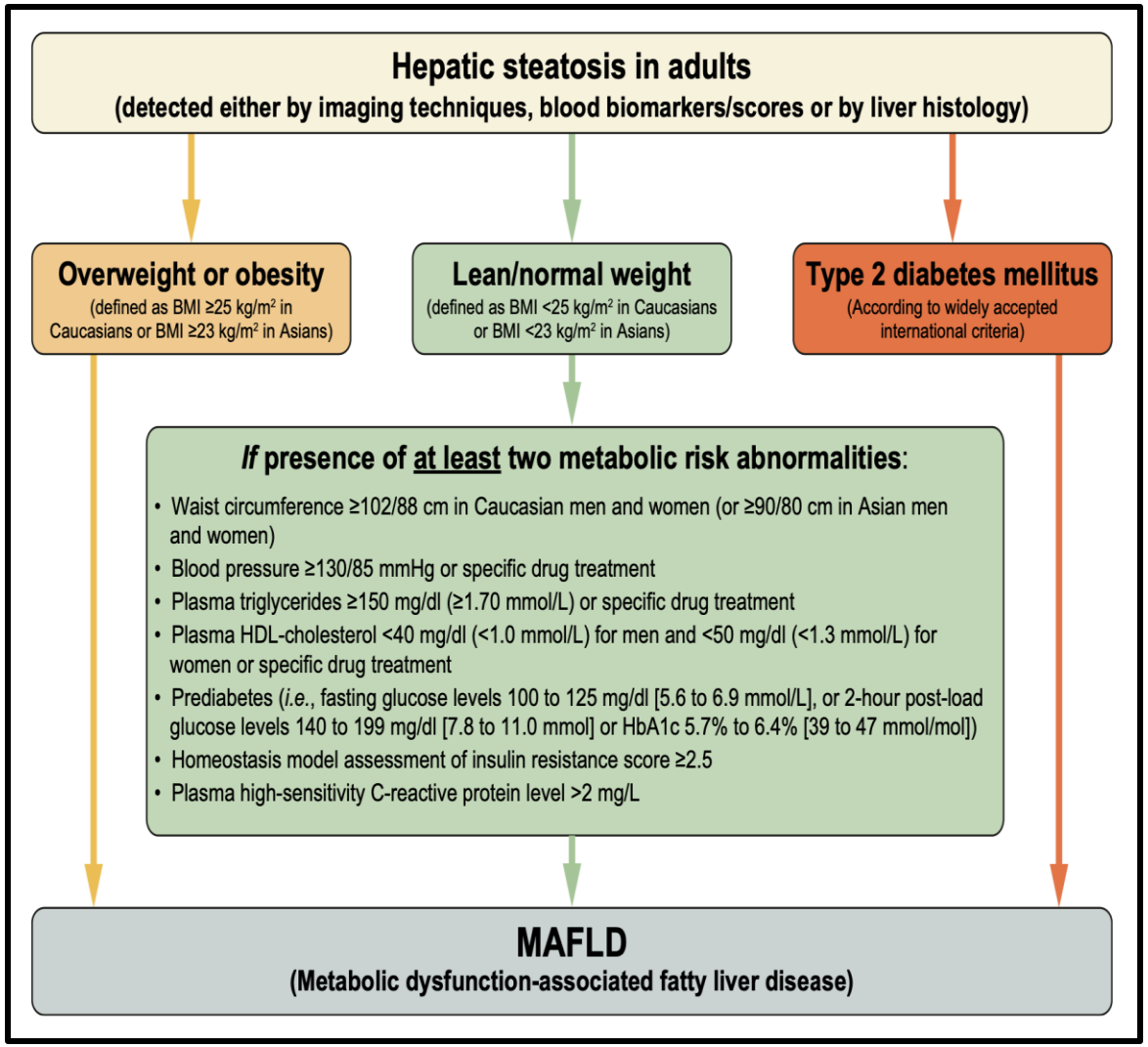
- ***MAFLD***: Evidence of hepatic steatosis by histology, imaging, or biomarkers or scores, in addition to **one of the following 3 criteria:** overweight or obesity, presence of type 2 diabetes, or ***evidence of metabolic dysregulation with at least 2 metabolic risk factors***

Gastroenterology 2020; 158: 1999

Limitations of the MAFLD nomenclature

Concerns were raised about

- Mixing of aetiologies
- Continued use of the term “fatty” considered stigmatising by many
- Restricting the population to those with 2 metabolic risk factors and allowance of more liberal alcohol use, thus impacting on the understanding of the natural history of the disease
  - >3 drinks per day in men and >2 drinks per day in women, or binge drinking (defined as >5 drinks in males and >4 drinks in females, consumed over a 2-hour period)
- Potential negative impact of changes in diagnostic criteria for the disease in terms of biomarker and therapeutic development



J Hepatology 2020;73:202

Multistep Delphi process: Consensus Document

Multi-stakeholder effort under the auspices of AASLD and EASL in collaboration with ALEH: Engagement with:

- Academic professionals from around the world, including hepatologists, gastroenterologists, paediatricians, endocrinologists, hepato-histopathologists, and public health and obesity experts
- Colleagues from industry
- Regulatory agencies
- Patient advocacy organisations

Hepatology 2023 1;78(6):1966; Ann Hepatol 2024;29(1):101133; J Hepatol 2023;79(6):1542

Multistep Delphi process: Consensus Document

5 essential areas to consider when revising nomenclature:

- Can shortcomings of the current nomenclature be addressed?
- How important is steatohepatitis in disease definitions and endpoints?
- How should the role of alcohol be considered?
- How would renaming affect disease awareness, clinical trials, and regulatory approval processes?
- Can a new name decrease heterogeneity and facilitate future advancements?

Hepatology 2023 1;78(6):1966; Ann Hepatol 2024;29(1):101133; J Hepatol 2023;79(6):1542

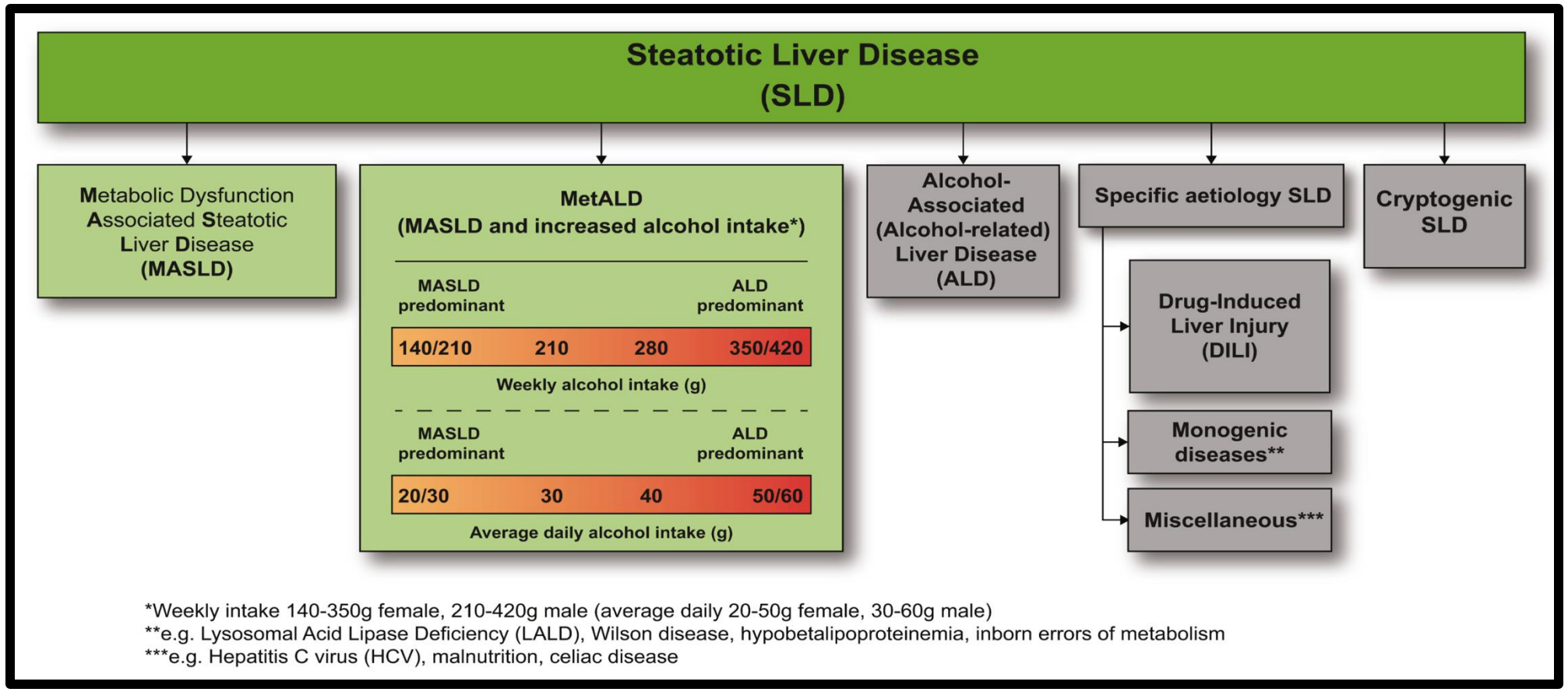
Multistep Delphi process: Consensus Document

Consensus was defined a priori as a supermajority (67%) vote

- An independent committee of experts external to the nomenclature process made the final recommendation on the acronym and its diagnostic criteria
- 236 panellists from 56 countries participated in 4 online surveys & 2 hybrid meetings
- Response rates across the 4 survey rounds were 87%, 83%, 83%, and 78%, respectively
- 74% felt that the current nomenclature was sufficiently flawed to consider a name change
- Terms “non-alcoholic” & “fatty” felt to be stigmatising by 61% & 66% respondents, respectively
- **Steatotic liver disease chosen as an overarching term to encompass various aetiologies of steatosis**
- **Steatohepatitis** felt to be important pathophysiological concept that should be retained
- **Metabolic dysfunction–associated steatotic liver disease: Chosen to replace NAFLD**
- **Consensus to change the definition to include the presence of at least 1 of 5 cardiometabolic risk factors**

Multi-society Delphi Consensus Statement on New Fatty Liver Disease Nomenclature

Hepatology 2023 1;78(6):1966-1986



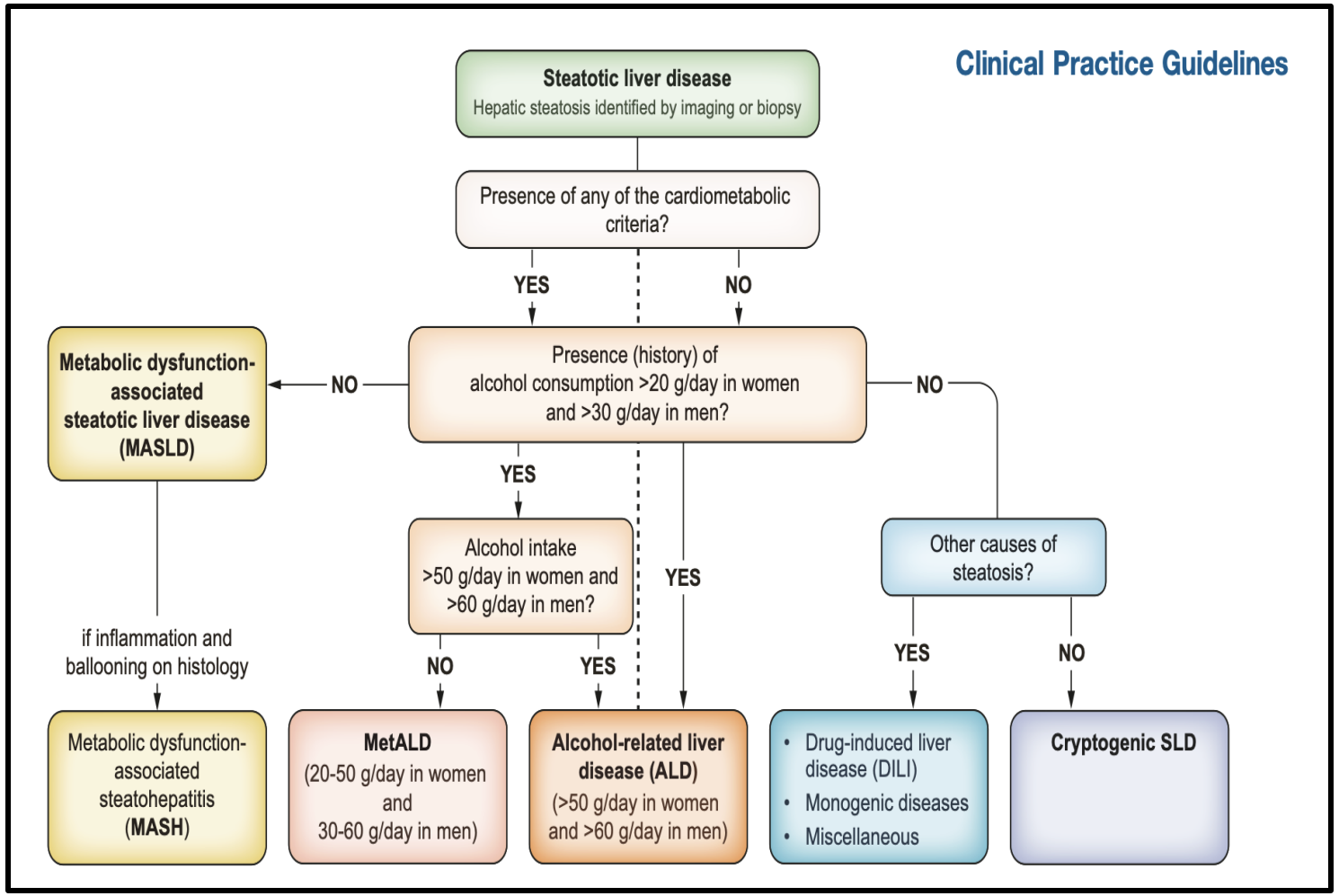
Steatotic Liver Disease diagnosed histologically or by imaging

MASLD: Defined as presence of hepatic steatosis in conjunction with one CMRF and no other discernible cause

MetALD: There is a continuum across the spectrum in which the contribution of MASLD and ALD will vary

Multiple aetiologies of steatosis can coexist: MASLD + autoimmune hepatitis or viral hepatitis

AASLD and EASL–EASD–EASO Clinical Practice Guidelines



Paediatric Criteria

At least 1 out of 5:

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

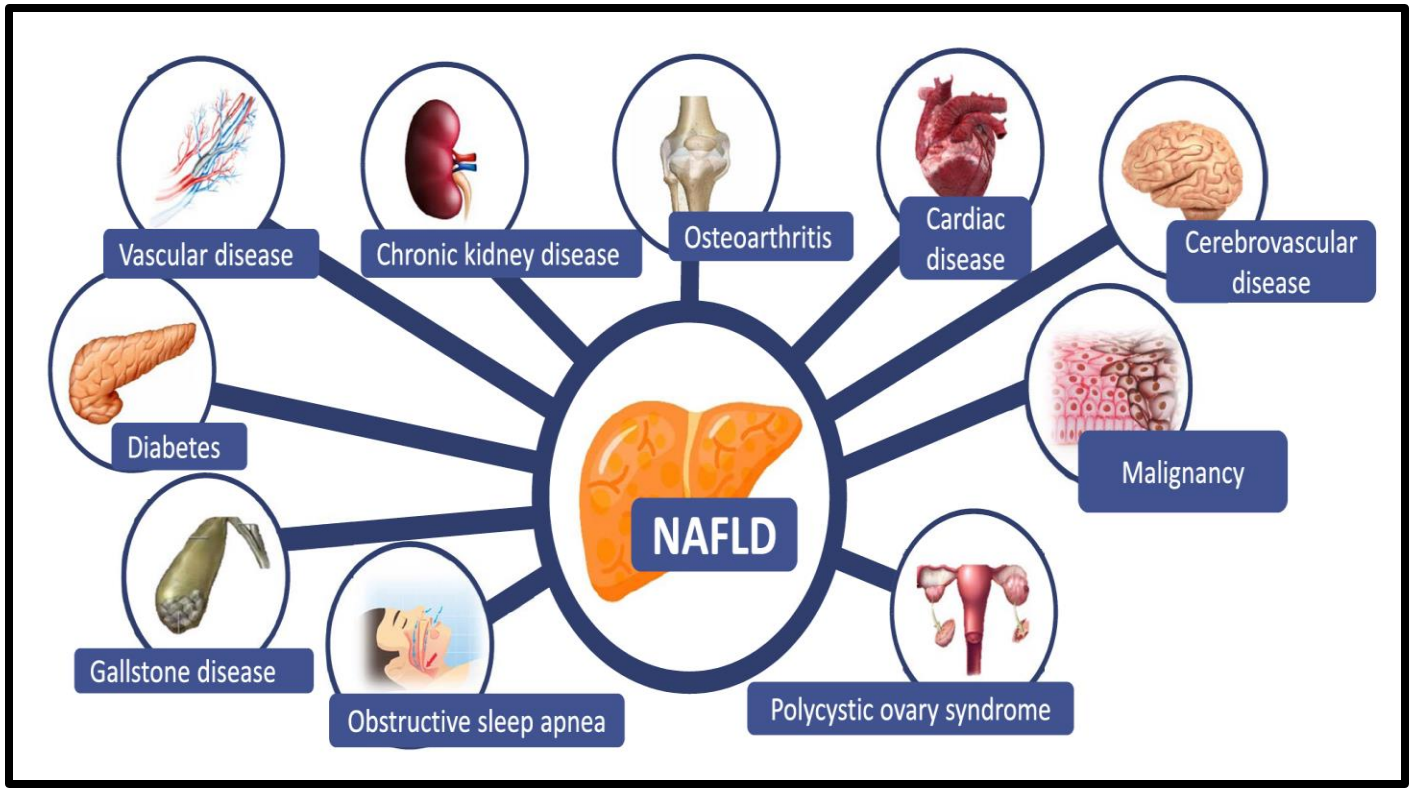
- **Increases our awareness and ability to diagnose MASLD**
- **Recent Studies: 95% overlap between NAFLD and the new MASLD diagnostic criteria**

Importance of diagnosing MASLD

- High all-cause and liver-related morbidity and mortality associated with MASLD
- Important to risk stratify individuals with at-risk MASLD
- Develop diagnosis strategies and pathways of referral for at-risk MASLD
- Diagnosis and management of extra-hepatic manifestations of MASLD
- Active management of associated non-communicable diseases

Hepatology 2023 1;78(6):1966; Ann Hepatol 2024;29(1):101133; J Hepatol 2023;79(6):1542

Extrahepatic Manifestations of MASLD



Pooled mortality rates per 1000 PY for NAFLD: US or FLI

- **12.60: All-cause mortality**
- **4.20: Cardiac-specific mortality**
- 2.83: Extrahepatic cancer-specific mortality
- 0.92: Liver-specific mortality

- Although liver-related mortality is increased**, cardiovascular disease remains the leading cause of death** in patients with MASLD and liver fibrosis stages F3 or F4
- **HCC can occur in the absence of cirrhosis**

Lancet Gastroenterol Hepatol 2021; 6: 578; Hepatology 2023;77:1335

SSA: MASLD and Non-communicable Diseases

2017 GBD study, all-age total DALYs due to NCDs increased by 67% in SSA

- **1990: 90.6 million** (95% UI 81.0–101.9) **2017: 151.3 million** (133.4–171.8)

NCD	Prevalence in SSA
Metabolic syndrome	11.1- 23.9%
Hypertension	30% (95% CI 27–34)
Dyslipidaemia	25.5% (95% CI 20·0–31·4)
Diabetes MASLD	8.5% (6·5–10·8) in men and 8.9% (6·9–11·2) in women 30.4% (95% CI 11.6–67.1)
Chronic kidney disease	15.8% (95% CI 12·1–19·9)

Increasing number of metabolic diseases are associated with increased risk of progressive liver disease and reduced survival:

Odds ratios for development of moderate-to-severe fibrosis for metabolic risk factors:

- **1.72 (1.13–2.31; p=0.0205) for type 2 diabetes, hypertension, and visceral obesity**

Int J Epidemiol 2017; 46: 1421; J Hepatol 2019; 71: 793; Clin Gastroenterol Hepatol 2009; 7: 1224

Who must we screen for at-risk MASLD?

Incidental finding of steatosis: Prompt assessment of potential aetiology of SLD, alongside tests for presence of advanced fibrosis as this determines risk of liver-related and/or cardiovascular outcomes and appropriate care

Need to identify individuals at increased risk of progressive fibrosis and the development of cirrhosis and its complications

- **MASH: Liver-related mortality is as high as 25.6/1,000 PY** (range, 6.3–103.8) with fibrosis stage being strongest predictor for liver-related mortality and HCC risk in biopsy-proven MASLD

Type 2 diabetes and obesity (particularly abdominal obesity)

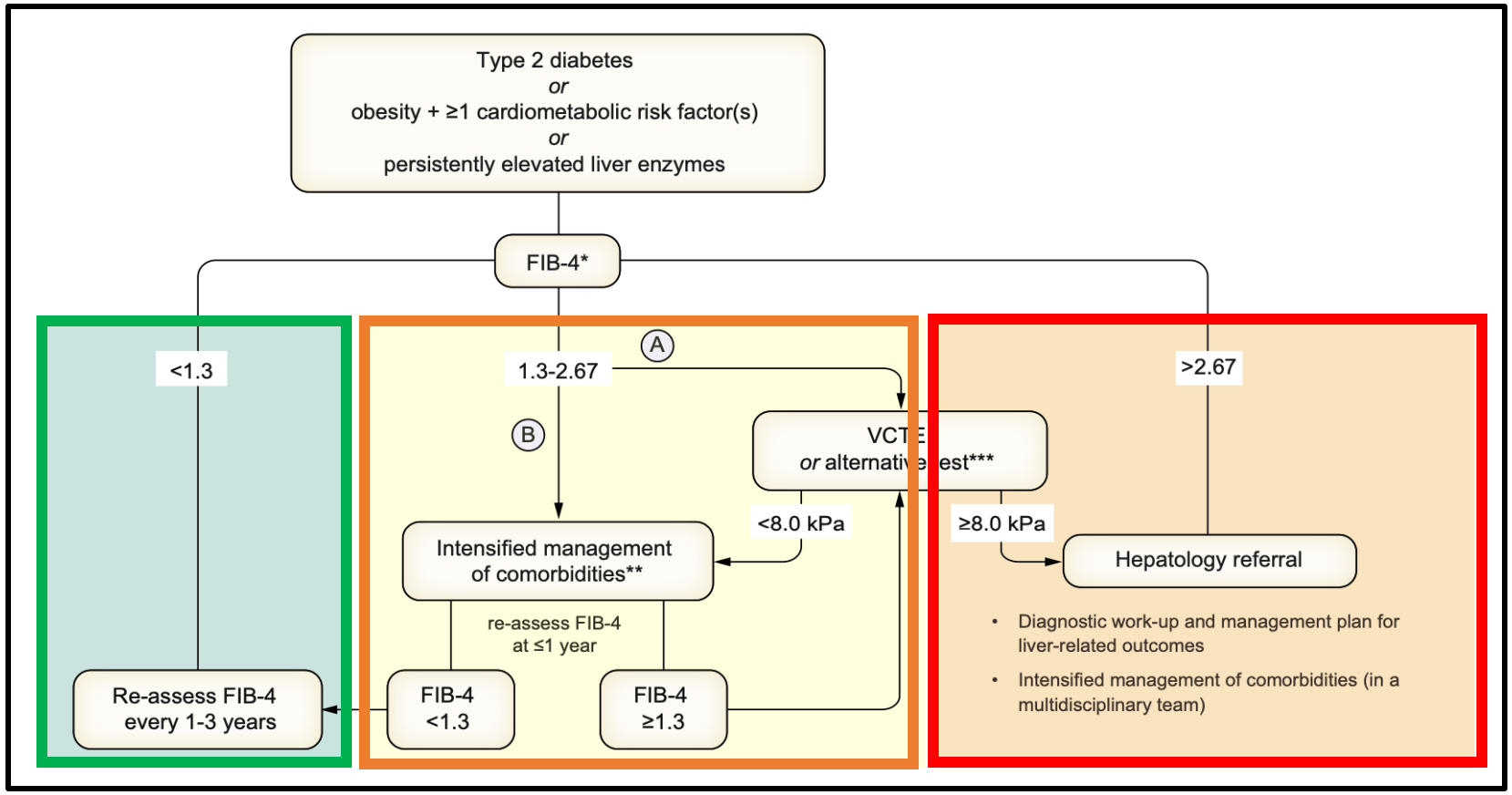
- Metabolic diseases with strongest impact on the natural history of MASLD
  - Progression to MASLD/MASH-related advanced fibrosis, cirrhosis & HCC

Individuals at increased risk of progressive fibrosis and the development of cirrhosis and its complications

- Males aged >50 years
- Postmenopausal women
- Individuals with multiple cardiometabolic risk factors

J Hepatology 2024;81:492

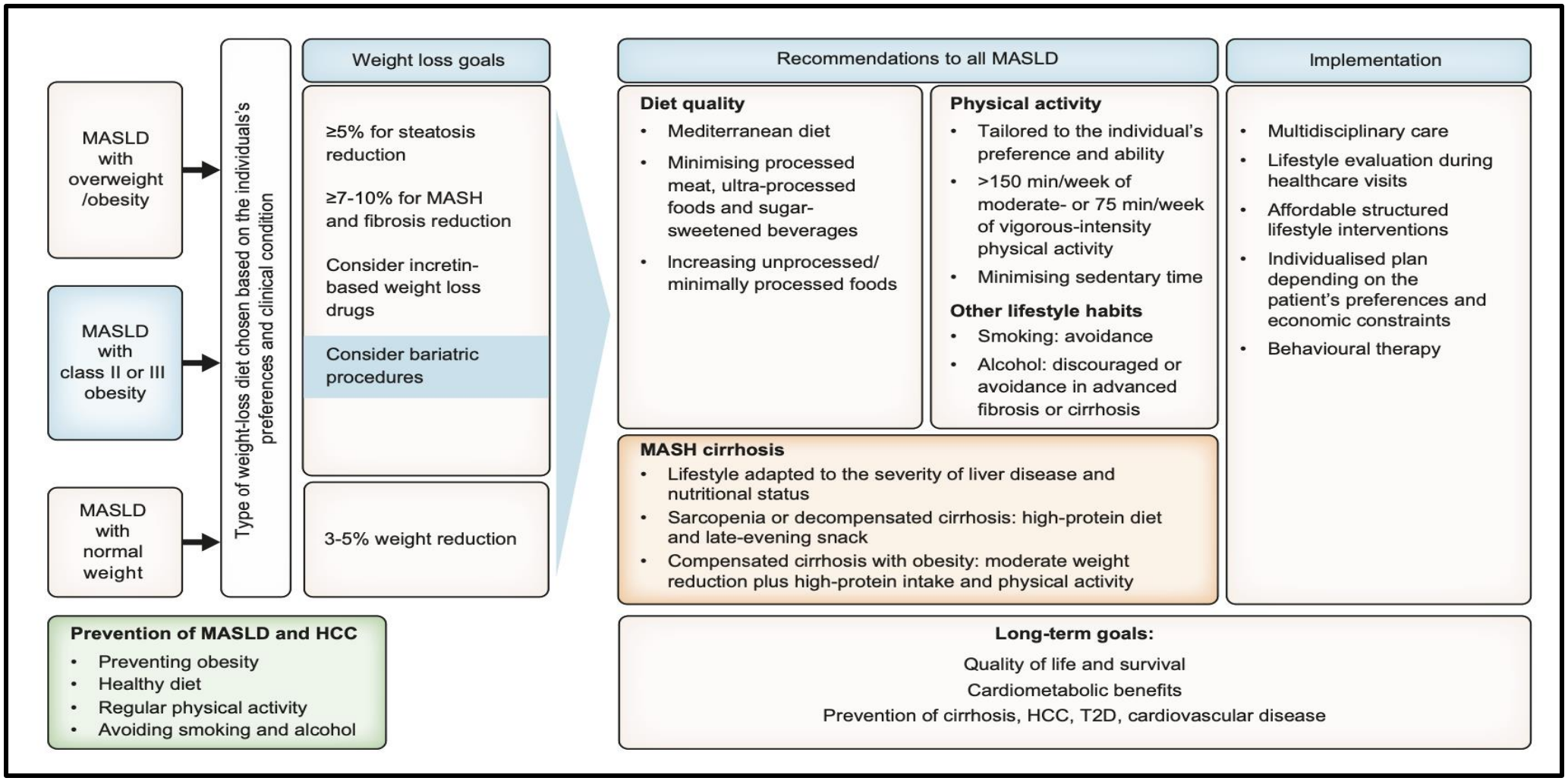
Strategy for non-invasive assessment of the risk for advanced fibrosis and liver-related outcomes in individuals with metabolic risk factors or signs of SLD



FIB-4 : Age ([yr] x AST [U/L]) / ((PLT [10(9)/L]) x (ALT [U/L])(1/2))

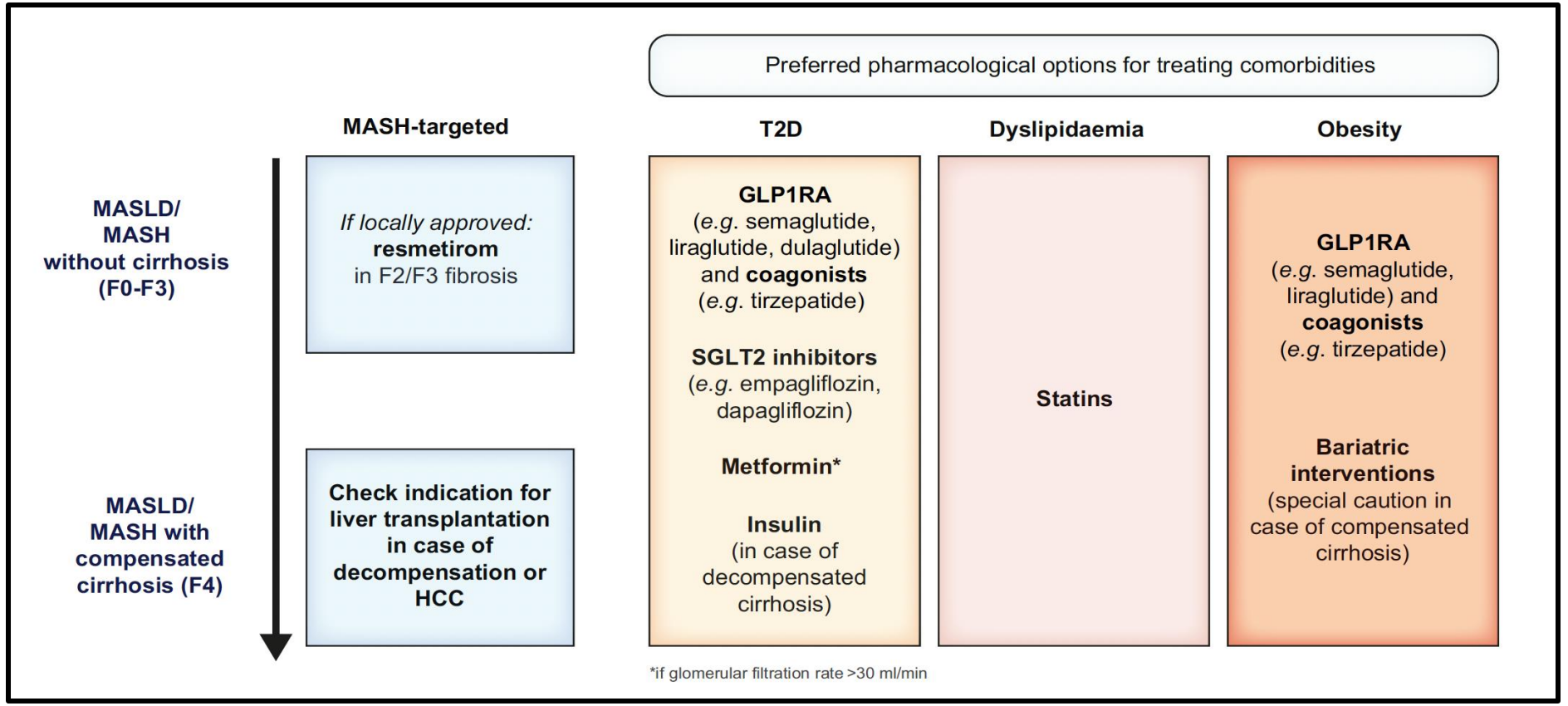
J Hepatology 2024;81:492

Lifestyle management algorithm for MASLD



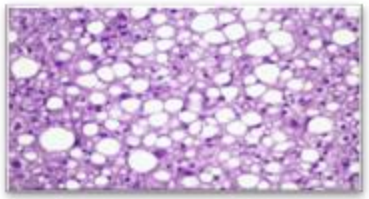
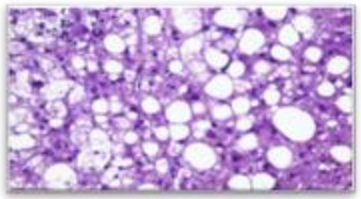
J Hepatology 2024;81:492

Treatment recommendations beyond lifestyle modifications: MASLD/MASH

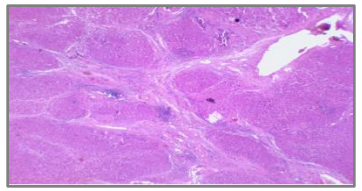
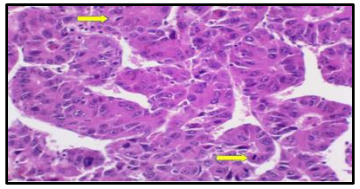


The recommended choice of pharmacological treatment options in individuals with MASLD/MASH is dependent on comorbidities and stage of disease

J Hepatology 2024;81:492

MASLD in 2024

Steatotic liver disease is overarching term to encompass the various aetiologies of steatosis: MASLD nomenclature endorsed by >75 societies

- **5 subgroups:** MASLD, MetALD, ALD, Specific aetiology SLA, Cryptogenic SLD
- **Enables the co-existence of other liver diseases:** MASLD and viral hepatitis, AIH

MASLD is the leading global cause of chronic liver disease

- Defined as presence of hepatic steatosis (histology or imaging) in conjunction with one of 5 cardiometabolic risk factors and no other discernible cause
- Nomenclature is non-stigmatising and can improve awareness and patient identification
- Not a diagnosis of exclusion - has specific diagnostic criteria
- MetALD: Allows for increased alcohol intake: 20-50 g/day (women) and 30-60 g/day (men)
- Important to recognise individuals with MASH who are at-risk of progressive fibrosis and complications of cirrhosis and HCC
- Encourage and educate HCW on the use of NITs: FIB-4 and Transient elastography to identify individuals at risk of advanced fibrosis with increased all-cause and liver related mortality