Metabolic Dysfunction Associated Fatty Liver Disease (MASLD): An Approach

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Woodlands Health
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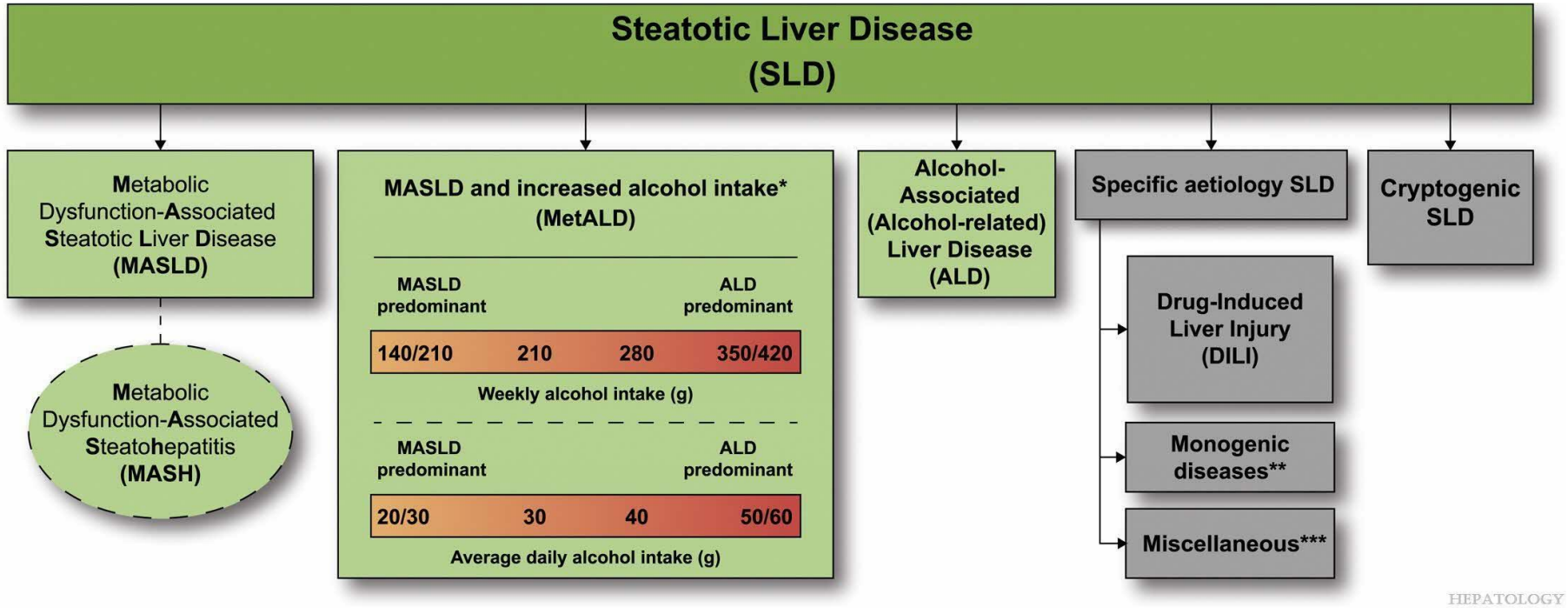
Agenda

Definition and diagnosis
Prevalence
Burden
Pathogenesis
Screening
Management
When to consider a referral
Summary

Definition of MASLD

- MASLD is a **multisystemic disease** defined by the presence of **hepatic steatosis in ≥5% of hepatocytes**, in addition to at least **≥1 of 5 cardiometabolic risk factors** and **absence of other causes of steatosis**

Steatotic Liver Disease



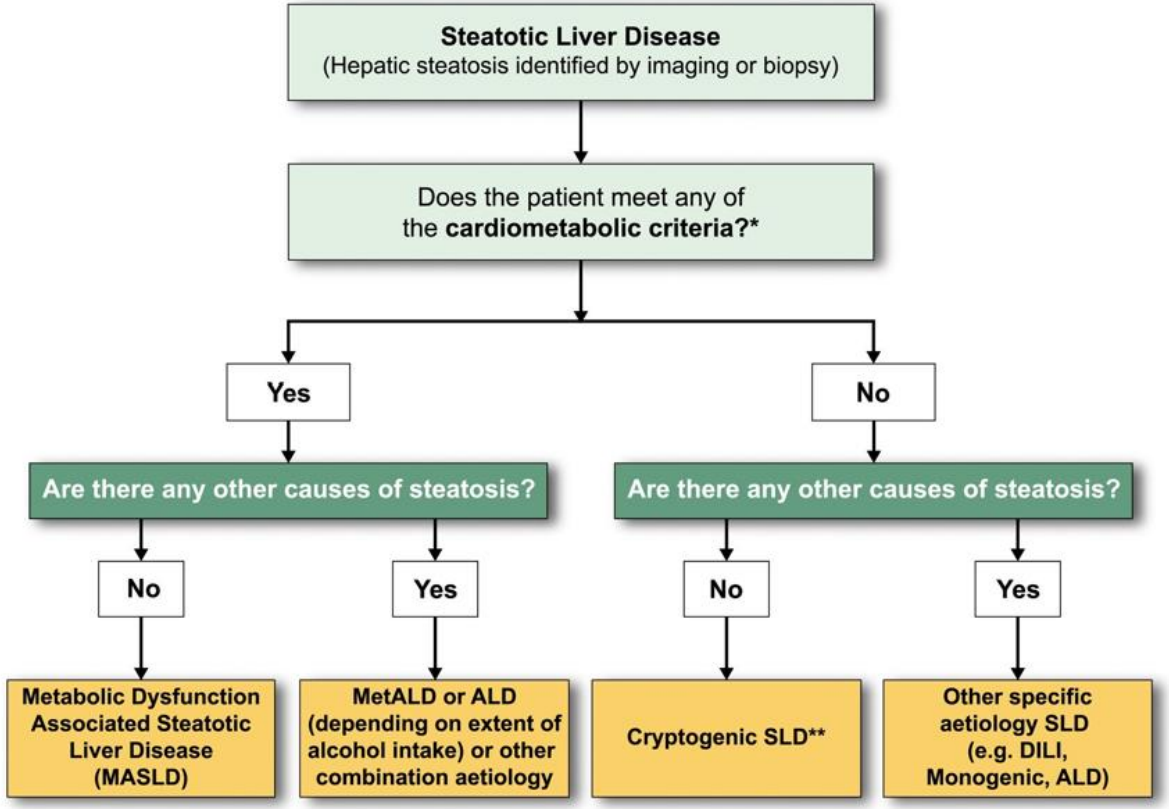
One Standard Drink
= 14 grams of pure alcohol

1 can of regular beer
330ml
5% alc.

1 glass of wine
120 ml
12% alc.

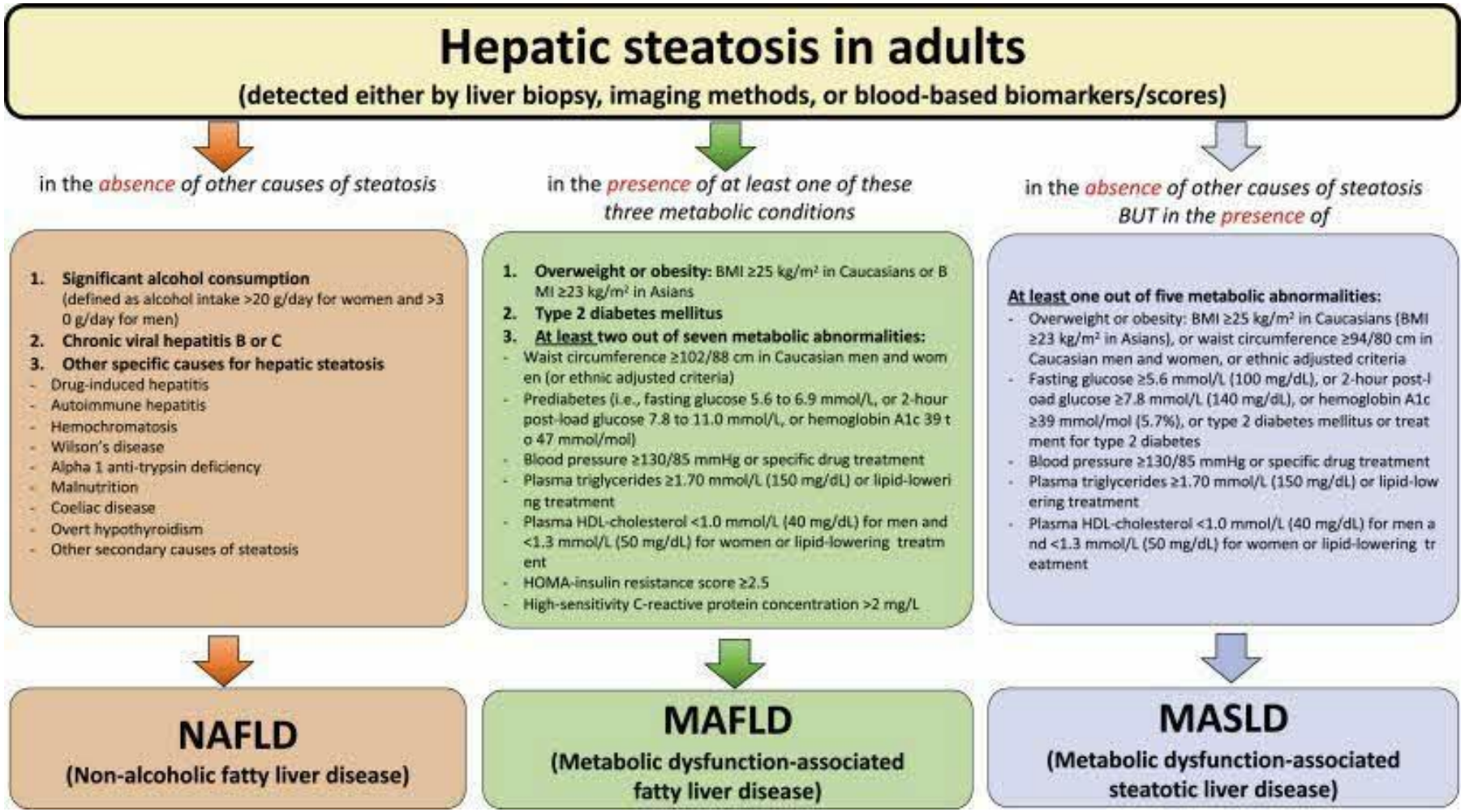
1 shotglass of spirit
30 ml
40% alc.

2.5 shotglasses of sake
75 ml
18% alc.

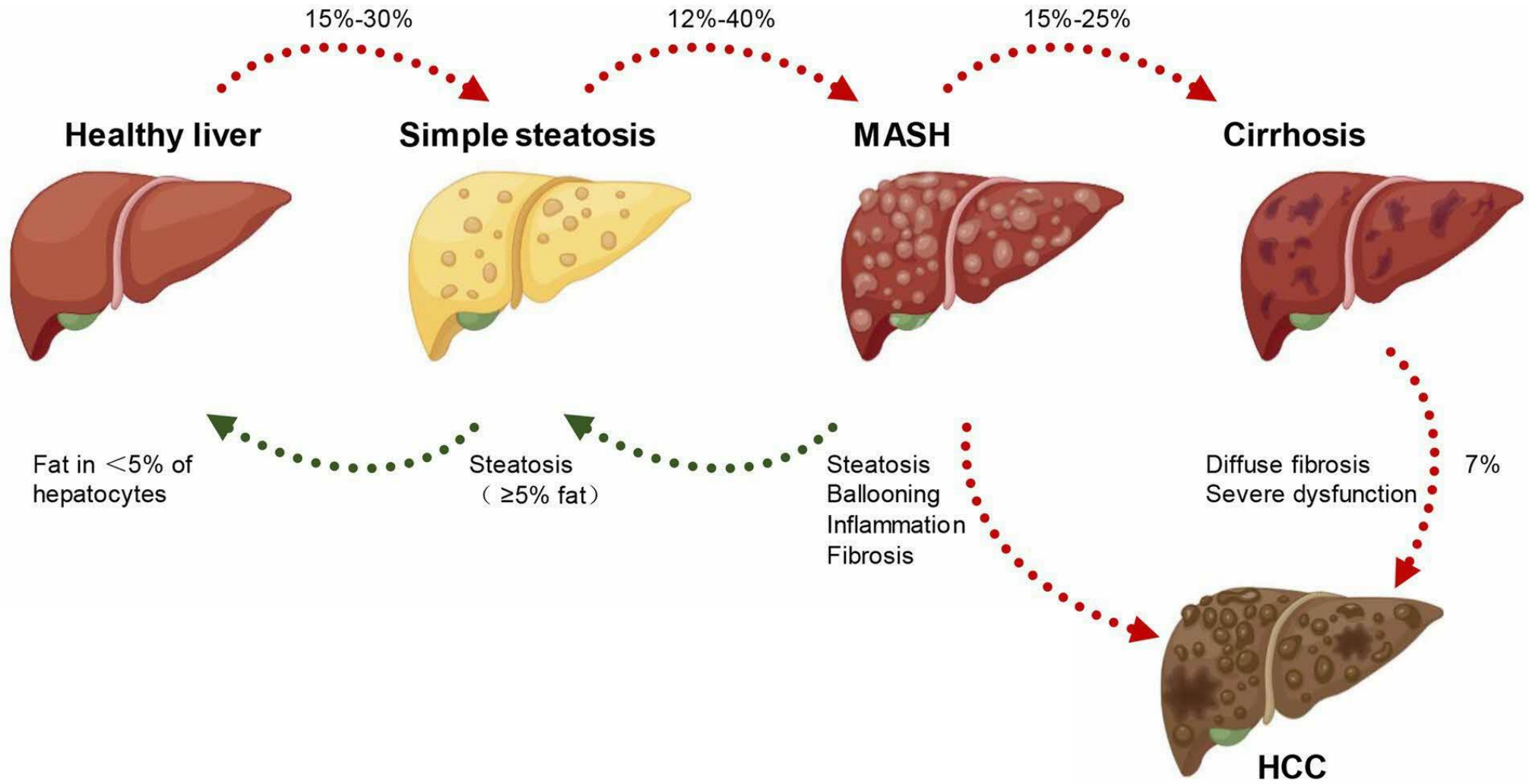


***Cardiometabolic criteria**

Adult Criteria	Paediatric Criteria
At least 1 out of 5:	**At least 1 out of 5:**
☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent	☐ 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** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes	☐ 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 ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment	☐ 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 ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering 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] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment	☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] **OR** lipid lowering treatment


Hepatic steatosis in adults
(detected either by liver biopsy, imaging methods, or blood-based biomarkers/scores)
in the absence of other causes of steatosis
in the presence of at least one of these three metabolic conditions
in the absence of other causes of steatosis BUT in the presence of
1. Significant alcohol consumption (defined as alcohol intake >20 g/day for women and >30 g/day for men)
2. Chronic viral hepatitis B or C
3. Other specific causes for hepatic steatosis
- Drug-induced hepatitis
- Autoimmune hepatitis
- Hemochromatosis
- Wilson's disease
- Alpha 1 anti-trypsin deficiency
- Malnutrition
- Coeliac disease
- Overt hypothyroidism
- Other secondary causes of steatosis
1. Overweight or obesity: BMI ≥25 kg/m² in Caucasians or BMI ≥23 kg/m² in Asians
2. Type 2 diabetes mellitus
3. At least two out of seven metabolic abnormalities:
- Waist circumference ≥102/88 cm in Caucasian men and women (or ethnic adjusted criteria)
- Prediabetes (i.e., fasting glucose 5.6 to 6.9 mmol/L, or 2-hour post-load glucose 7.8 to 11.0 mmol/L, or hemoglobin A1c 39 to 47 mmol/mol)
- Blood pressure ≥130/85 mmHg or specific drug treatment
- Plasma triglycerides ≥1.70 mmol/L (150 mg/dL) or lipid-lowering treatment
- Plasma HDL-cholesterol <1.0 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women or lipid-lowering treatment
- HOMA-insulin resistance score ≥2.5
- High-sensitivity C-reactive protein concentration >2 mg/L
At least one out of five metabolic abnormalities:
- Overweight or obesity: BMI ≥25 kg/m² in Caucasians (BMI ≥23 kg/m² in Asians), or waist circumference ≥94/80 cm in Caucasian men and women, or ethnic adjusted criteria
- Fasting glucose ≥5.6 mmol/L (100 mg/dL), or 2-hour post-load glucose ≥7.8 mmol/L (140 mg/dL), or hemoglobin A1c ≥39 mmol/mol (5.7%), or type 2 diabetes mellitus or treatment for type 2 diabetes
- Blood pressure ≥130/85 mmHg or specific drug treatment
- Plasma triglycerides ≥1.70 mmol/L (150 mg/dL) or lipid-lowering treatment
- Plasma HDL-cholesterol <1.0 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women or lipid-lowering treatment
NAFLD
(Non-alcoholic fatty liver disease)
MAFLD
(Metabolic dysfunction-associated fatty liver disease)
MASLD
(Metabolic dysfunction-associated steatotic liver disease)

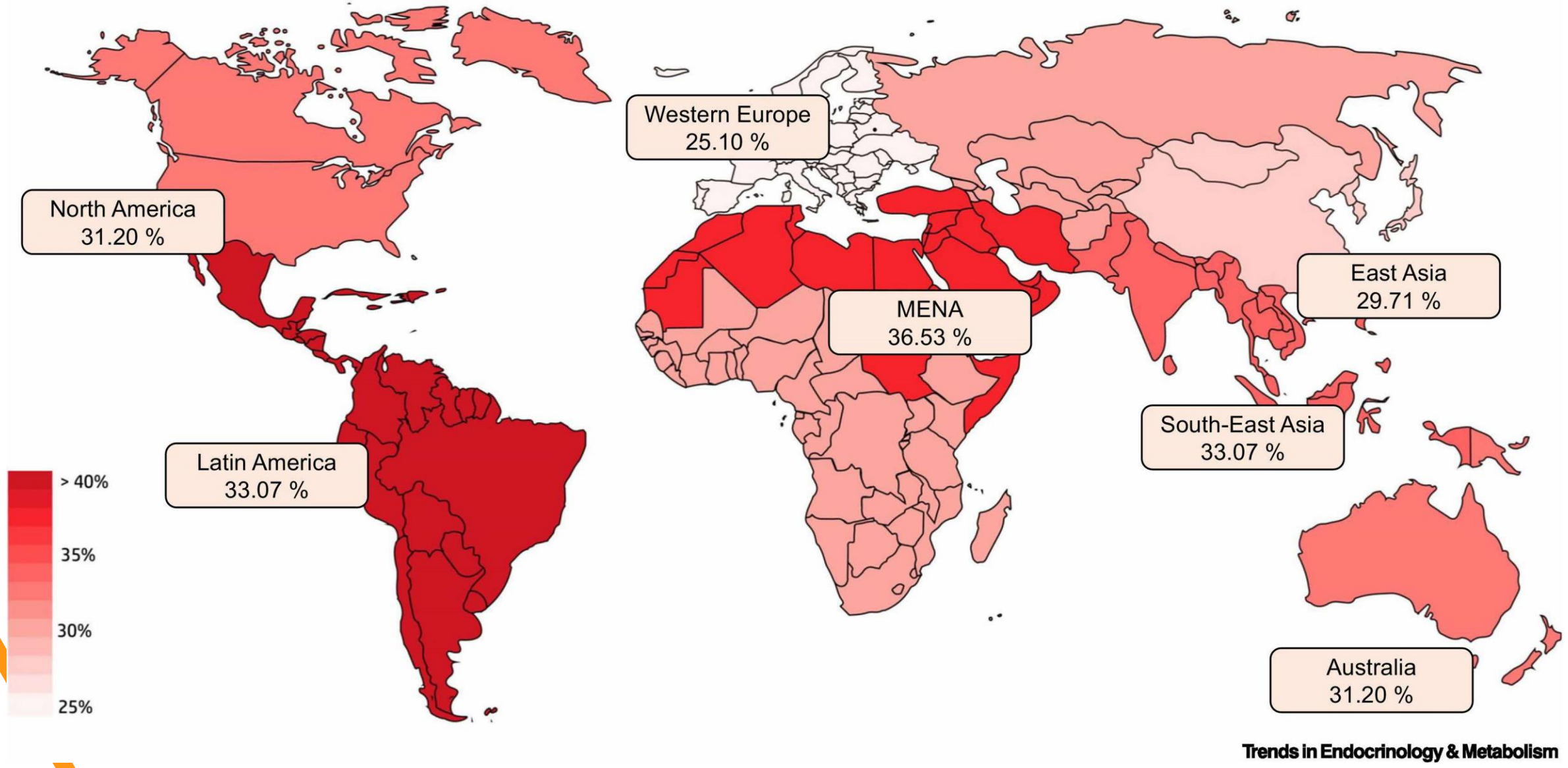
MASLD exists as a spectrum

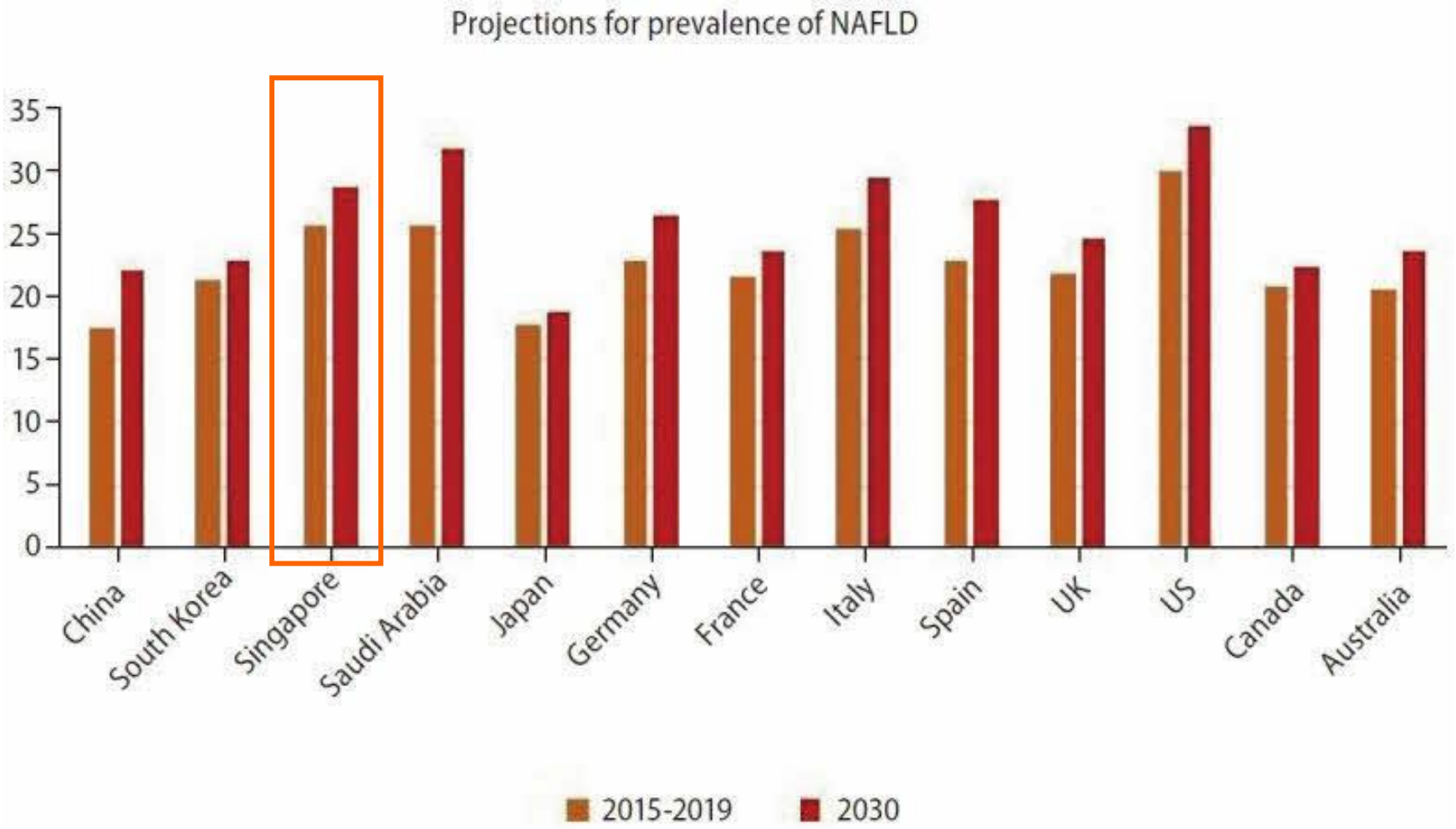


Prevalence of MASLD and MASH

MASLD is a growing problem

- The burden of MASLD has dramatically increased worldwide, becoming the most common cause of chronic liver disease
  - Parallels the escalating rates of obesity, type 2 diabetes and metabolic syndrome globally
- The global prevalence of MASLD has risen from 25.3% (1990–2006) to 38.2% (2016–2019)

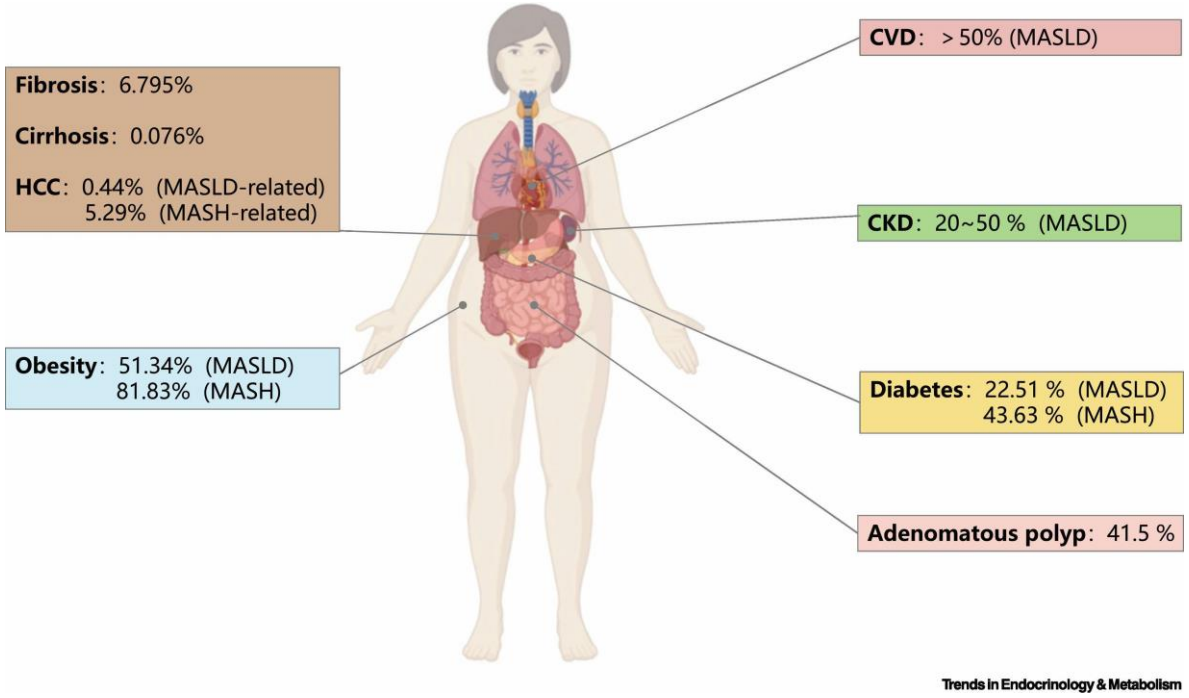

Western Europe
25.10 %
North America
31.20 %
MENA
36.53 %
East Asia
29.71 %
South-East Asia
33.07 %
Latin America
33.07 %
Australia
31.20 %
> 40%
35%
30%
25%
Trends in Endocrinology & Metabolism


Projections for prevalence of NAFLD
35
30
25
20
15
10
5
0
China
South Korea
Singapore
Saudi Arabia
Japan
Germany
France
Italy
Spain
UK
US
Canada
Australia
2015-2019
2030

Burden of MASLD

The Global Burden of MASLD

- Expected economic burden of MASLD could reach an estimated $1.005 trillion in the USA and €334 billion in the Europe in the next 10 years
- MASH has become a leading cause of liver-related complications (such as cirrhosis and HCC) and liver transplantation
- MASLD is also significantly associated with increased long-term risk of cardiovascular disease



MASLD increases the risk of extrahepatic cancers

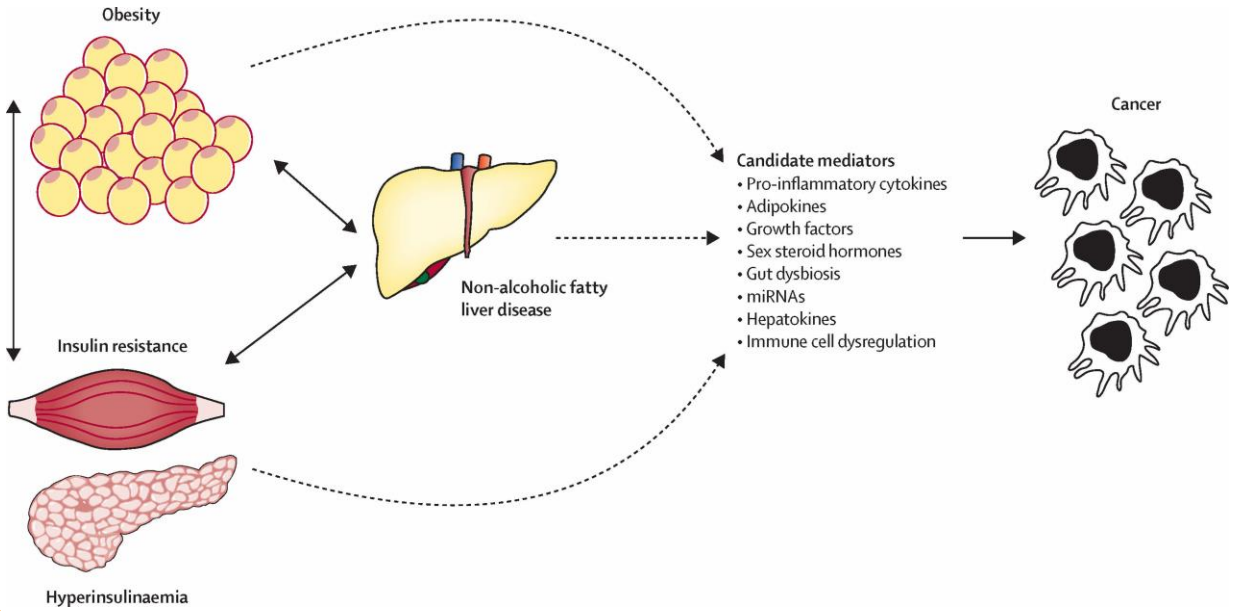


Table 1. Extrahepatic cancers significantly associated with non-alcoholic fatty liver disease

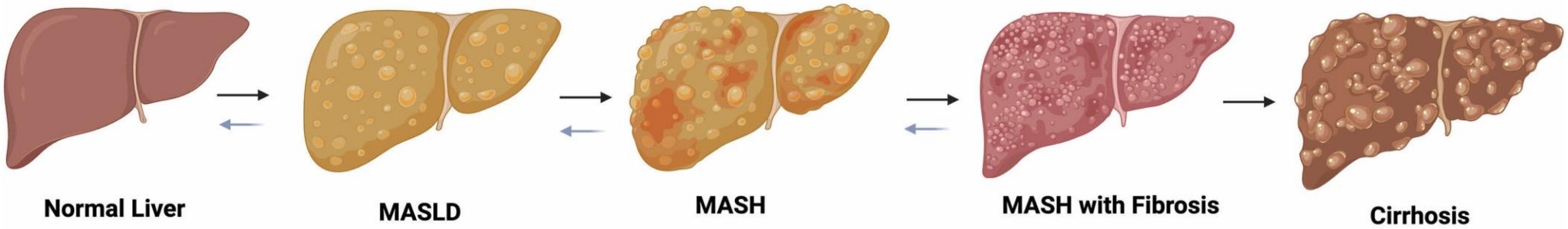
	Metric of association (95% CI)	Number of studies	Evidence grade
Thyroid cancer	HR 2·63 (1·27–5·45)	2	Moderate
Cholangiocarcinoma *	OR 2·05 (1·53–2·75)	9	Low
Pancreatic cancer	HR 1·98 (1·47–2·65)	4	Low
Oesophageal cancer	HR 1·92 (1·19–3·12)	5	Low
Urinary tract cancer	HR 1·36 (1·14–1·62)	5	Low
Breast cancer	HR 1·28 (1·00–1·63)	5	Low
Lung cancer	HR 1·25 (1·11–1·40)	6	Low
Gastric cancer	HR 1·81 (1·19–2·75)	6	Very low
Colorectal cancer	OR 1·45 (1·29–1·62)	13	Very low

Pathogenesis

Pathogenesis of Metabolic Dysfunction-Associated Liver Disease

Risk Factors for MASLD/MASH

Lifestyle Factors	**Altered Microbiome**	**Genetic Factors**
(Sedentary Behavior, Low Physical Activity, High Fat High Sugar Diet)	(Increased firmicutes, decreased diversity, increased lipopolysaccharides)	(PNPLA3, TM6SF2, HSD17B13 and others)



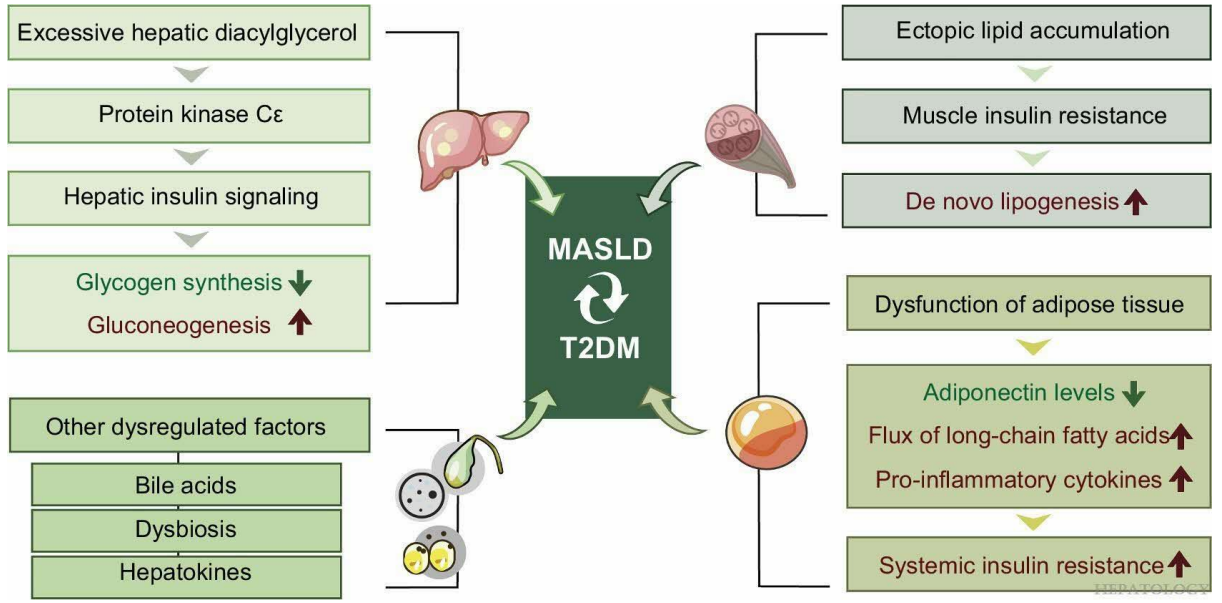
Normal Liver → MASLD → MASH → MASH with Fibrosis → Cirrhosis

Molecular Mechanisms for Progression from Steatosis to Cirrhosis

Insulin Resistant Adipose Tissue	Mitochondrial dysfunction Inflammatory Pathway Activation	ER Stress
↓Adiponectin ↑Lipolysis→↑FFA flux to liver ↑Pro-inflammatory cytokines ↑Pro-phagocytic macrophages		↑C-reactive protein ↑ROS ↑TNF-α

Type 2 Diabetes Mellitus (T2DM) as an important factor driving the progression of MASLD

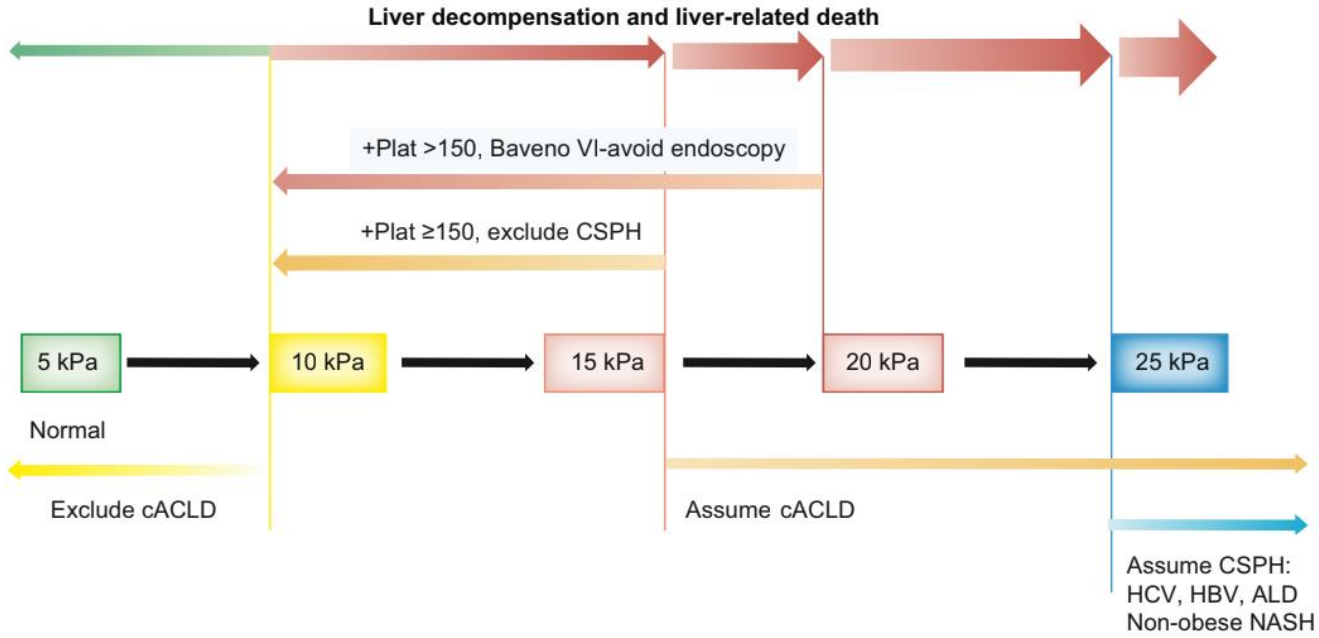
- In individuals with T2DM
  - 35.54% demonstrated clinically significant fibrosis (F2-F4)
  - 14.95% had advanced fibrosis (F3-F4)
- MASLD is closely related to the development of T2DM
- **<u>Insulin resistance</u>** is key in the development of both diseases



Screening for MASLD

Fibrosis Assessment

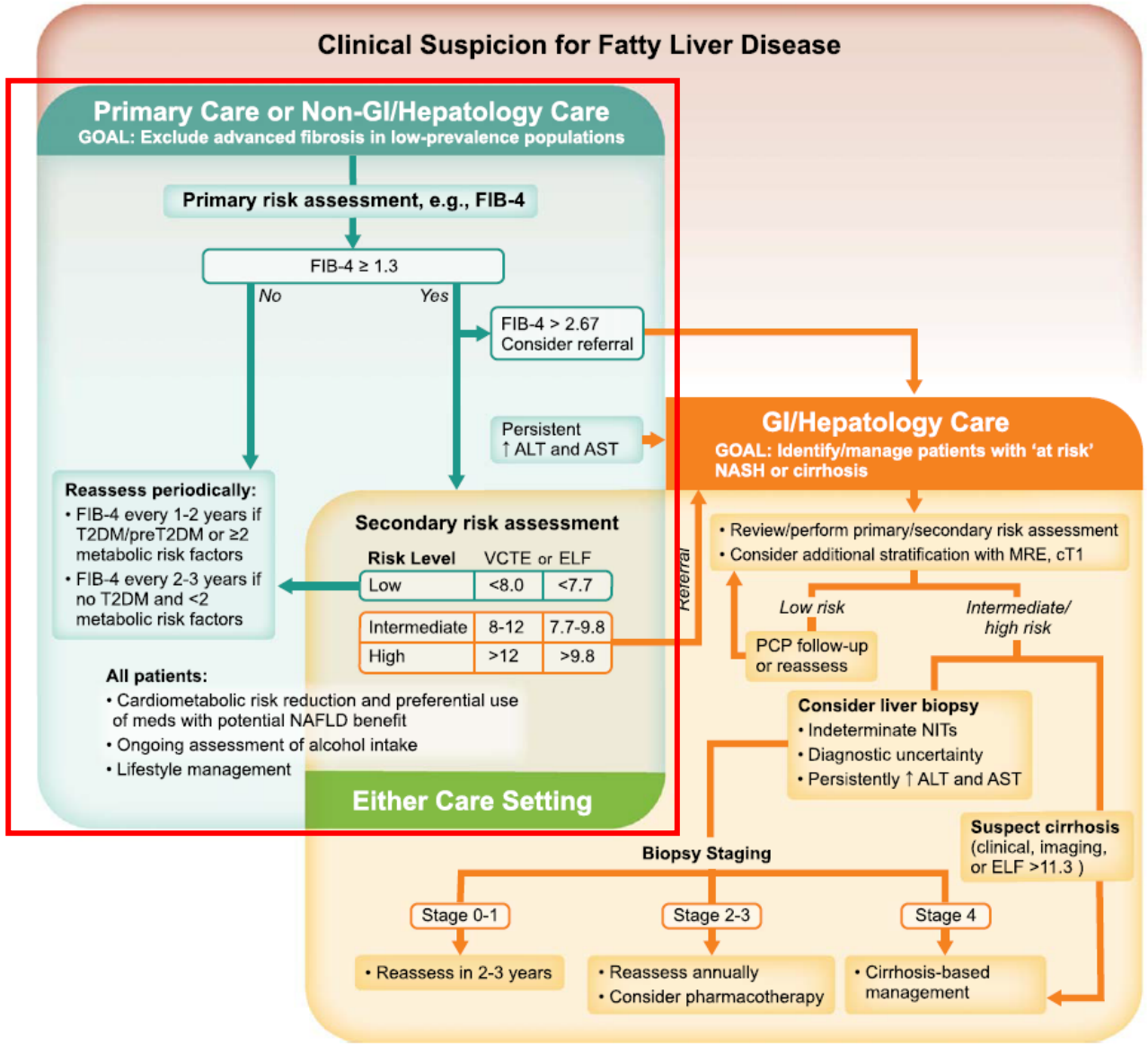
- Gold standard: Liver biopsy
  - Invasive, risks
- Non invasive methods
  - Blood based: FIB4, NAFLD fibrosis score, APRI
  - Imaging based: Shear wave elastography, transient elastography, magnetic resonance elastography



Which patients should be screened?

- Screening in high risk populations help to identify individuals with asymptomatic but clinically significant fibrosis

Screening recommended[a]	Prevalence of advanced fibrosis, %
T2DM	6–19
Medically complicated obesity	4–33
NAFLD in context of moderate alcohol use	17
First-degree relative of a patient with cirrhosis due to NAFLD/NASH	18



- In patients older than age 65, a FIB-4 cutoff of >2.0 should be used
- FIB-4 has low accuracy in those under age 35
  - Secondary assessment should be considered in those <35 with increased metabolic risk or elevated liver chemistries.

Management

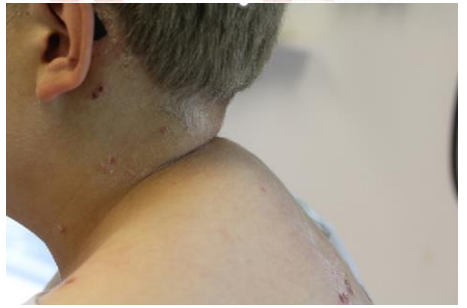
Initial Evaluation of a patient with MASLD

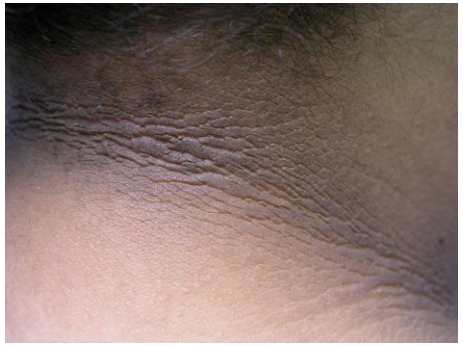
History

- Weight history, medical comorbidities, recent and current medications, family history of T2DM/MASLD/cirrhosis, screening for OSA, alcohol use (amount, pattern of use, duration)

Physical examination

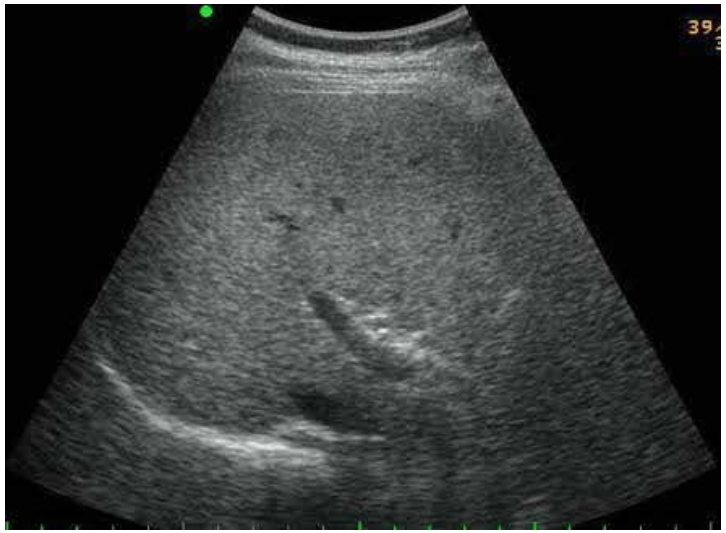
- Body mass index, body fat distribution (android vs gynoid), features of insulin resistance (e.g. dorsal-cervical fat pad, acanthosis nigricans), features of advanced liver disease (e.g. firm liver, splenomegaly, prominent abdominal veins, ascites, gynaecomastia, spider naevi, palmar erythema)





Initial Evaluation of a patient with MASLD

- Full blood count
- Renal Panel
- Liver panel
- Viral hepatitis B and C screen: HBs antigen, anti HBs, anti HCV
- Lipid panel
- Diabetes screen (fasting glucose/OGTT/HbA1c)
- Thyroid function test
- Ultrasound of the hepatobiliary system

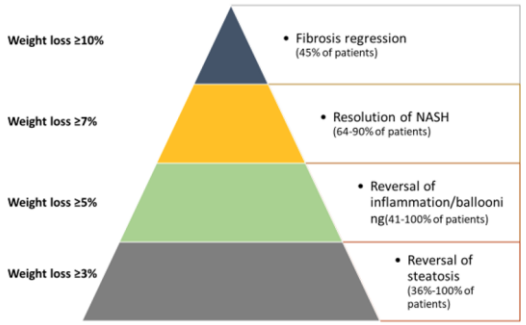


Lifestyle intervention is the cornerstone in the management of MASLD

Developing liver healthy behaviours

Weight loss

- Weight loss of 3-5% improves steatosis
- Weight loss of >7-10% improves MASH and liver fibrosis



Source: Hannah WN. Et al. Clin Liver Dis. 2016:20L229-350

Diet

- Hypocaloric diet (500 to 1000 kcal deficit)
- Cut back on foods containing excess saturated fats, refined carbohydrates, sugar-sweetened beverages
- Coffee consumption (3 or more cups a day) may be beneficial

Physical activity

- Regular moderate intensity exercise at least 5 times a week for a total of 150 minutes per week
- Optimal duration and intensity need to be individualised

Alcohol Cessation

- Alcohol consumption and metabolic risk factors have modifying effects on the onset and progression of chronic liver disease which are independent and can be synergistic

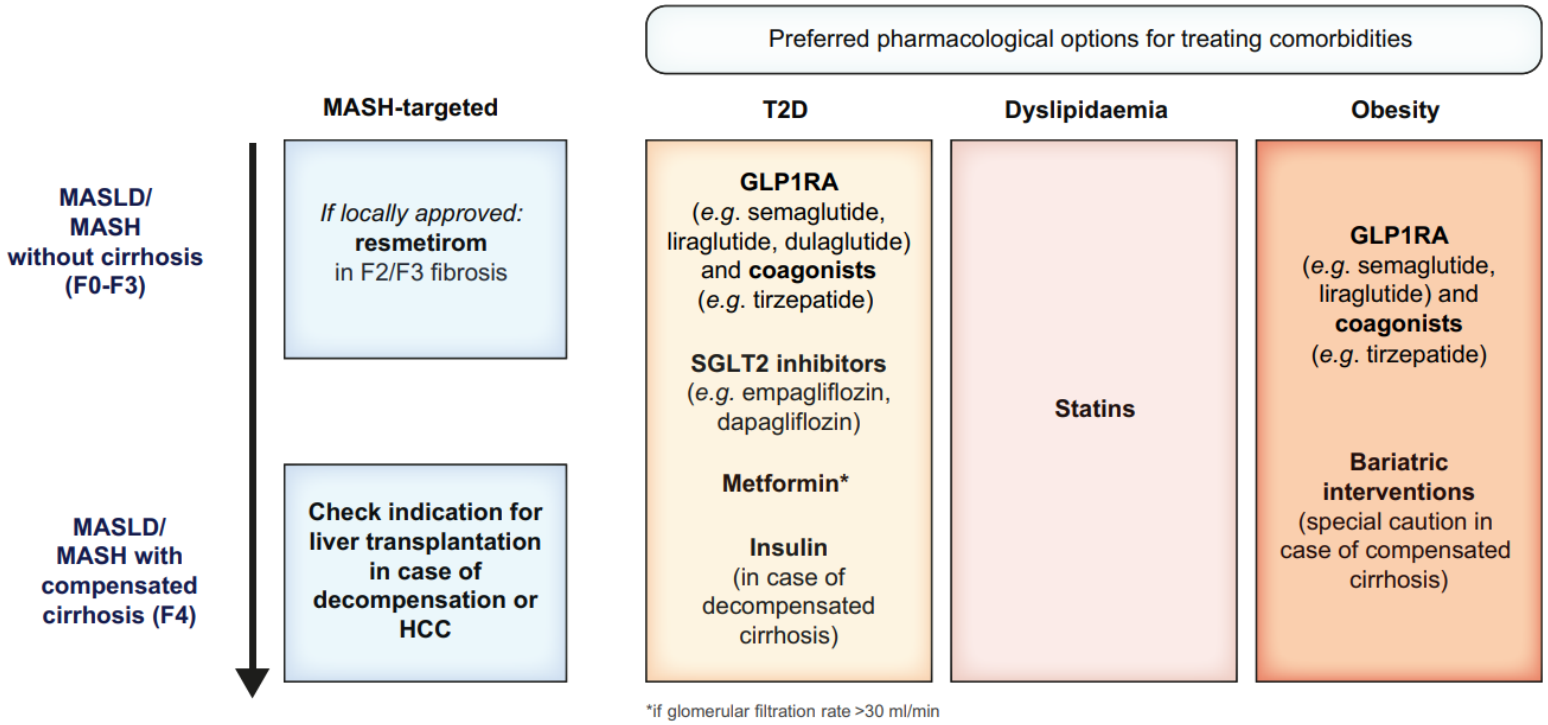
- Alcohol consumption in individuals with all steatotic liver disease is discouraged
  - The presumed beneficial health effects of moderate alcohol consumption are inconsistent across studies
  - Emerging evidence does not support a protective effect of light to moderate amounts of alcohol, particularly in individuals with cardiometabolic risk factors

Pharmacological therapy

- Resmetirom: Liver-directed thyroid hormone receptor agonist
  - Thyromimetic selective for ß subtype (liver expressed) of the thyroid hormone receptor
  - Reduces hepatic steatosis by stimulating hepatic lipophagy and mitochondrial biogenesis, and inhibits hepatic lipogenesis
  - considered for individuals with MASLD who are noncirrhotic and with documentation of either: (A) advanced fibrosis; (B) at-risk steatohepatitis with significant fibrosis (C) risk of adverse liver related outcomes

Resmetirom is not locally available

Optimising management of co-morbidities



Optimising management of co-morbidities

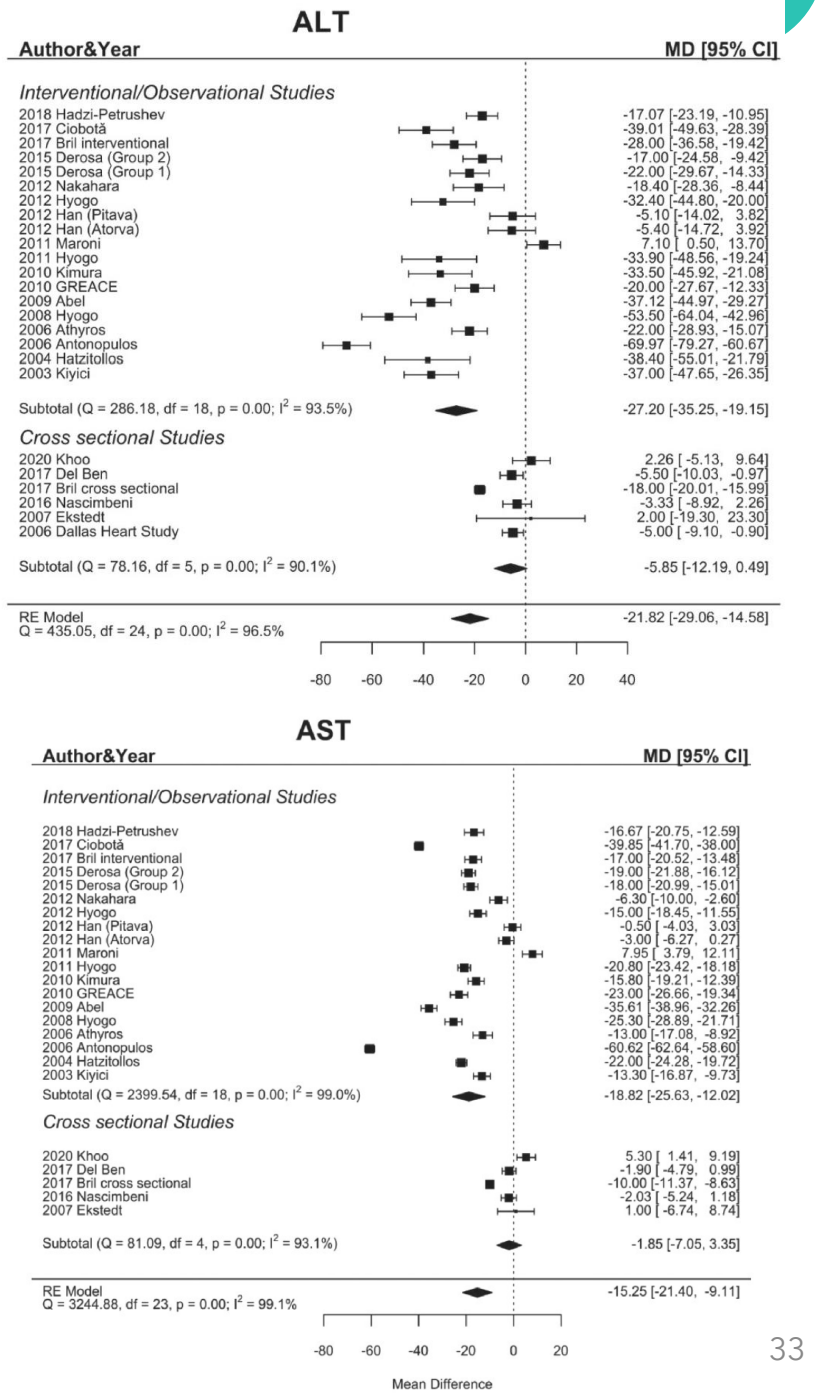
Table 3. Effects of anti-hyperglycemic drugs on metabolic dysfunction-associated steatotic liver disease[55,56,62]

	Liver parameters				Cardiorenal-metabolic parameters	
	Serum aminotransferase	Liver fat	Liver fibrosis	MASH resolution	Body weight	Cardiorenal benefits
Pioglitazone	↓	↓	↓	Yes	↑	↔
GLP1 RAs	↓	↓	↓	Yes	↓	Yes
GLP1/GIP RAs	↓	↓	Unknown	Unknown	↓	Unknown
SGLT2 inhibitors	↓	↓	Unknown	Unknown	↓	Yes
Insulin	↓	↓	Unknown	Unknown	↑	↔
Metformin	↔	↔	↔	↔	↔	↔
DPP-4 inhibitors	↔	↔	↔	↔	↔	↔

MASH, metabolic dysfunction-associated steatohepatitis; GLP1 RA, glucagon-like peptide-1 receptor agonist; GIP RA, glucose-dependent insulinotropic polypeptide receptor agonist; SGLT2, sodium glucose co-transporter-2; DPP-4, dipeptidyl peptidase-4.

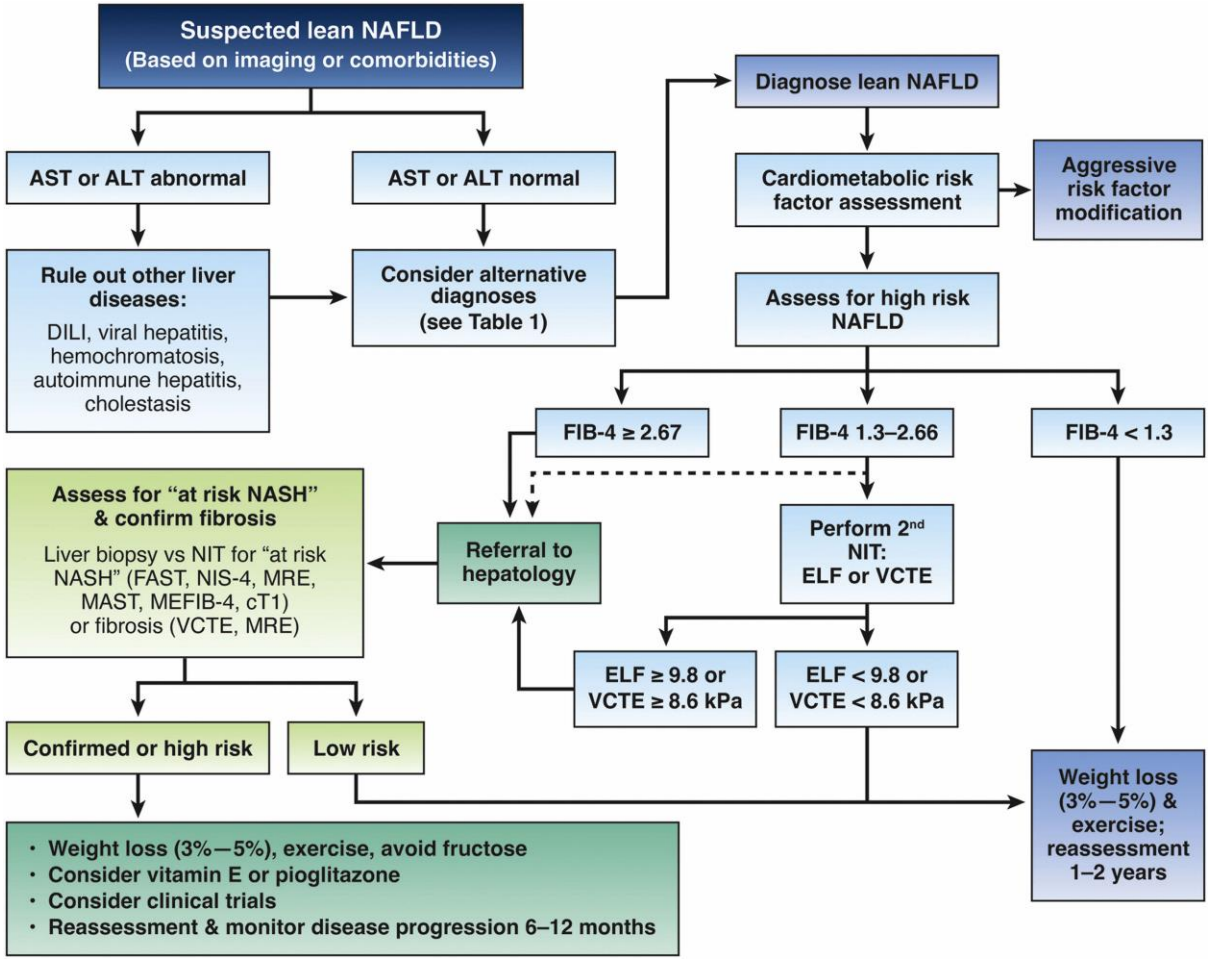
Statin use in MASLD is safe

- Transient asymptomatic elevations in aminotransferases could occur in 0.1–3% of patients, while fulminant hepatic failure is an extremely rare event (2 in 1 million of treated patients)
- Statins can be prescribed in patients with MASLD, even when elevation of serum liver enzymes is present



Management of MASLD in lean individuals

- Individuals with MASLD and body mass index (BMI) <25 kg/m^2 (non-Asian race) or a BMI <23 kg/m^2 (Asian race)
- Should be considered in lean individuals with metabolic diseases (such as T2DM, dyslipidemia, and hypertension), elevated liver biochemical tests, or incidentally noted hepatic steatosis.
- Likely the result of interactions between many factors, including the interplay between genetic variants and environmental factors
- Evaluate for comorbid conditions



When to consider a referral to Gastroenterology

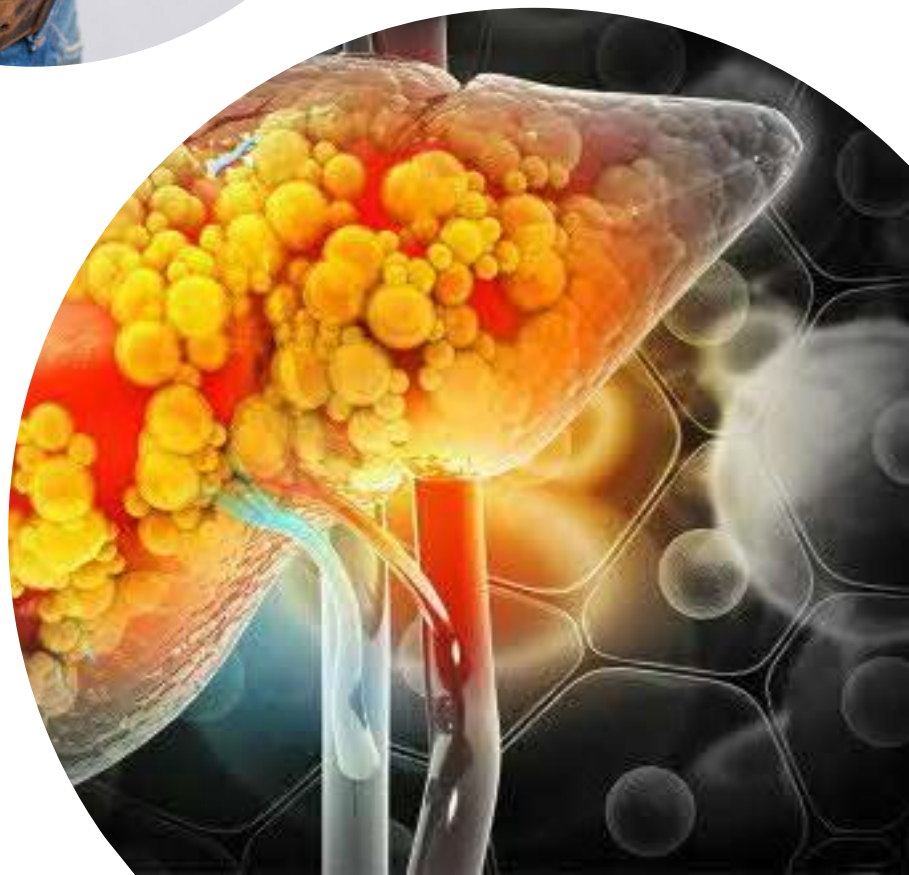
Consider a referral to Gastroenterology when

- FIB4 ≥ 1.3 (≤65 years old)
- FIB 4 ≥ 2.0 (>65 years old)
- MASLD with persistently raised ALT ≥ 120 IU/ml over 3 months

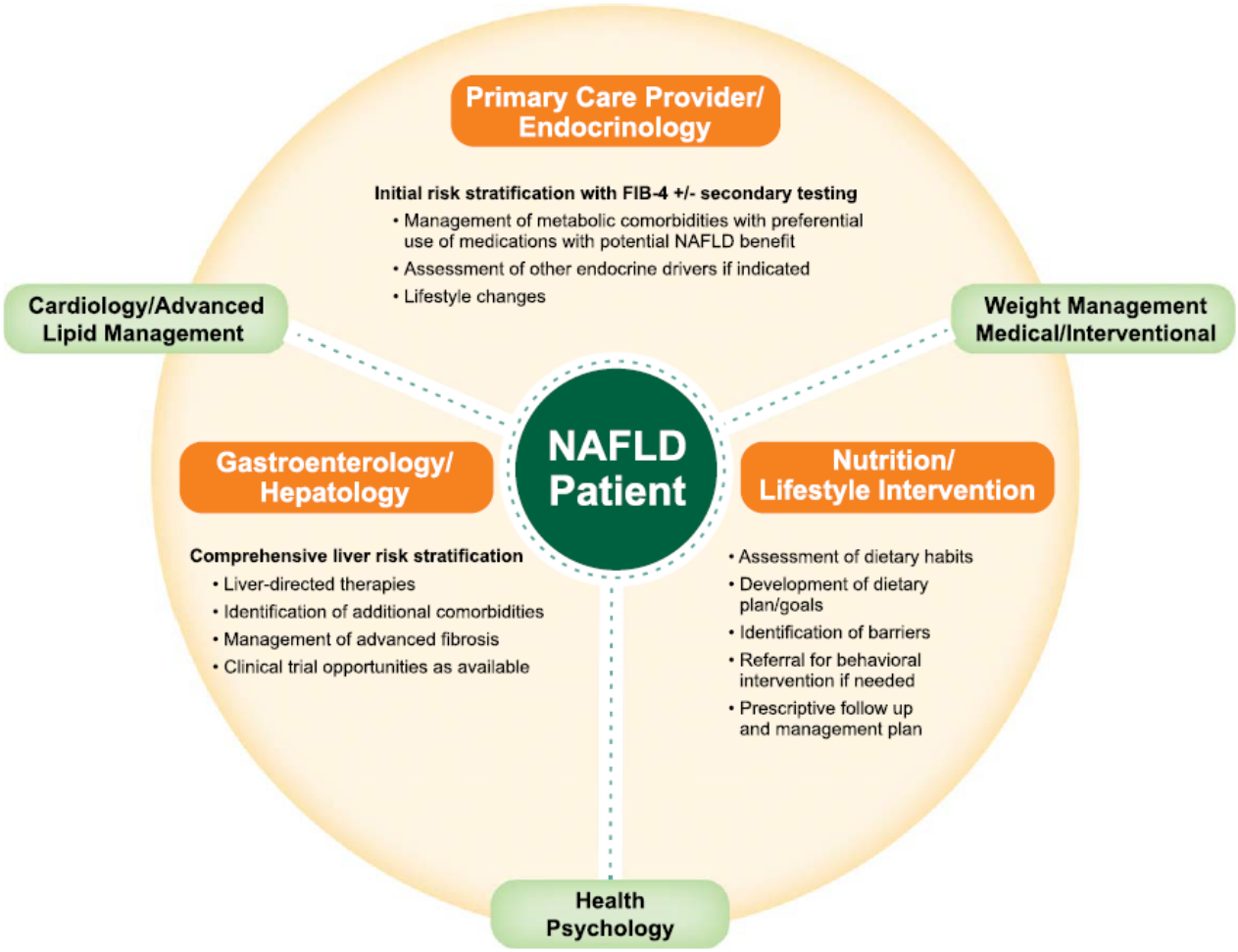
Summary

Summary

- Increasing burden of MASLD in Singapore and worldwide
- T2DM is the most impactful risk factor for the development of MASLD, fibrosis progression and HCC
- Screening at risk individuals with FIB4 and transient elastography
- Lifestyle management is key
- Optimising control of comorbidities



PCPs are crucial in the management of patients with MASLD



Thank you

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Dr Edric Hee
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Dr Shann Long
Hepatology

Dr Deborah Tan
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Scope of Services

- Dyspepsia, Gastro-oesophageal Reflux Disease (GERD), Peptic ulcer disease and Helicobacter pylori
- Functional Gut Disorder (Irritable bowel syndrome, Functional Bloating)
- Inflammatory Bowel Disease (Crohn's Disease, Ulcerative Colitis)
- Disease of Pancreas and Biliary System (Biliary stone, Biliary Stricture, Pancreatic Cyst / Mass, Pancreatitis)
- Cancer (Oesophagus, Stomach, Colon, Liver, Pancreas, Bile Duct)
- Various liver conditions include:
    - Liver Tumour / Hepatocellular Carcinoma (HCC)
    - Liver Diseases such as Viral Hepatitis, Fatty Liver, Alcohol-induced Liver Disease, Autoimmune Hepatitis, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis and Wilson's Disease.
    - Liver Fibrosis and Cirrhosis

References

Rao G, Peng X, Li X, An K, He H, Fu X, Li S, An Z. Unmasking the enigma of lipid metabolism in metabolic dysfunction-associated steatotic liver disease: from mechanism to the clinic. Front Med (Lausanne). 2023 Nov 27;10:1294267

Miao L, Targher G, Byrne CD, Cao YY, Zheng MH. Current status and future trends of the global burden of MASLD. Trends Endocrinol Metab. 2024 Feb 29:S1043-2760(24)00036-5.

Teng ML, Ng CH, Huang DQ, Chan KE, Tan DJ, Lim WH, Yang JD, Tan E, Muthiah MD. Global incidence and prevalence of nonalcoholic fatty liver disease. Clin Mol Hepatol. 2023 Feb;29(Suppl):S32-S42.

Qi X, Li J, Caussy C, Teng GJ, Loomba R. Epidemiology, screening, and co-management of type 2 diabetes mellitus and metabolic dysfunction-associated steatotic liver disease. Hepatology. 2024 May 8.

de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol. 2022 Apr;76(4):959-974. doi: 10.1016/j.jhep.2021.12.022. Epub 2021 Dec 30. Erratum in: J Hepatol. 2022 Jul;77(1):271.

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, Kleiner DE, Loomba R. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023 May 1;77(5):1797-1835.

Miao L, Targher G, Byrne CD, Cao YY, Zheng MH. Current status and future trends of the global burden of MASLD. Trends Endocrinol Metab. 2024 Aug;35(8):697-707.

Thomas JA, Kendall BJ, El-Serag HB, Thrift AP, Macdonald GA. Hepatocellular and extrahepatic cancer risk in people with non-alcoholic fatty liver disease. Lancet Gastroenterol Hepatol. 2024 Feb;9(2):159-169.

Long MT, Noureddin M, Lim JK. AGA Clinical Practice Update: Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Lean Individuals: Expert Review. Gastroenterology. 2022 Sep;163(3):764-774.e1.

Pastori D, Pani A, Di Rocco A, Menichelli D, Gazzaniga G, Farcomeni A, D'Erasmo L, Angelico F, Del Ben M, Baratta F. Statin liver safety in non-alcoholic fatty liver disease: A systematic review and metanalysis. Br J Clin Pharmacol. 2022 Feb;88(2):441-451.

Table 4. SLD due to aetiologies other than MASLD, MetALD or ALD.

Condition	Clinical/lab/histological findings	Diagnostic criteria
Hepatitis C virus-associated steatotic liver (genotype 3)	Low triglycerides, HCV genotype 3	HCV antibody with reflex testing HCV RNA and HCV genotype
Drug-induced liver disease (DILI)	Mostly microvescicular SLD	Investigate for drug intake: • Corticosteroids • Tamoxifen • Amiodarone • Irinotecan • Methotrexate • Lomitapide • Valproate • 5-Fluorouracil Liver biopsy for confirmation
Hypobetalipoproteinaemia	Low triglycerides and cholesterol, fat malabsorption, vitamin A deficiency	ApoB level, genetic testing (*APOB, MTTP, PCSK-9*, targeted panel sequencing)
Lipodystrophy	Accumulation of fat in the visceral area and in the muscle (generically inherited or induced by HAART therapy)	CT scan or MRI, targeted panel sequencing for congenital lipodystrophies, MRI
LAL deficiency (Wolman disease, cholesteryl ester storage disease-CESD)	Elevated LDL-C and triglycerides, low HDL-C, hypersplenism, advanced fibrosis in young age, predominately microvesicular steatosis	Enzyme assay, genetic testing (LIPA)
Pregnancy associated	HELLP syndrome Acute onset	Elevated liver enzymes and low platelets, haemolysis, SLD at abdominal ultrasound
Wilson disease	Younger age, neuropsychiatric symptoms, low ceruloplasmin	24-h urine copper excretion; quantitative copper on liver biopsy, genetic testing (*ATP7B*)
Nutrient deficiency/malnutrition	Parenteral nutrition, bypass surgeries, bariatric surgery, anorexia	Nutrient levels
Celiac disease	Diarrhoea, iron deficiency, vitamins deficiency	Tissue transglutaminase IgA, duodenal biopsy
Endocrine diseases	Hypothyroidism, PCOS, growth hormone (GH) deficiency, panhypopituitarism (primary or secondary)	TSH, fT4, fT3, endocrine testing
Other inherited metabolic conditions	Early age and severe onset, absence of triggering factors, systemic involvement, positive history of advanced disease in first degree relatives	Targeted panel sequencing, whole exome sequencing (WES)

ALD, alcohol-related liver disease; ApoB, apolipoprotein B; fT3, free triiodothyronine; fT4, free thyroxine; HCV, hepatitis C virus; HAART, highly active antiretroviral therapy; HELLP, haemolysis, elevated liver enzymes and low platelets; LAL, lysosomal acid lipase; MASLD, metabolic dysfunction-associated steatotic liver disease; PCOS, polycystic ovary syndrome; SLD, steatotic liver disease; TSH, thyroid-stimulating hormone.

Genetic testing

- PNPLA3 p.I148M and TM6SF2 p.E167K variants are major risk factors for progressive MASLD
  - Accuracy is suboptimal for prediction of liver disease severity and progression at the individual level
- Additional variants, including common risk variants in MBOAT7, GCKR, GPAM, protective variants in HSD17B13, APOE and MTARC1, and rare variants (e.g. in APOB, MTTP, CIDEB and ATG7), have been robustly associated with the risk of progressive MASLD
- Individuals with a) strong family history, b) early disease onset, or c) lack of accruing factors may benefit from a comprehensive genetic evaluation

GLP-1 receptor agonists

- Wegovy – semaglutide 2.4 mg weekly for weight loss
- Saxeda – liraglutide 3 mg weekly for weight loss
- Rybelsus – oral

FDA-approved GLP-1 receptor agonists for glycemic control include:

- Dulaglutide (subcutaneous-SC)
- Exenatide injectable solution subcutaneous
- Exenatide injectable suspension SC
- Liraglutide SC
- Liraglutide/insulin degludec
- Lixisenatide/insulin glargine
- Semaglutide (oral, SC)
- Tirzepatide (dual GIP/GLP-1 receptor agonist)

FDA-approved GLP-1 agonists for weight loss include:

- Semaglutide SC
- Liraglutide SC [1]