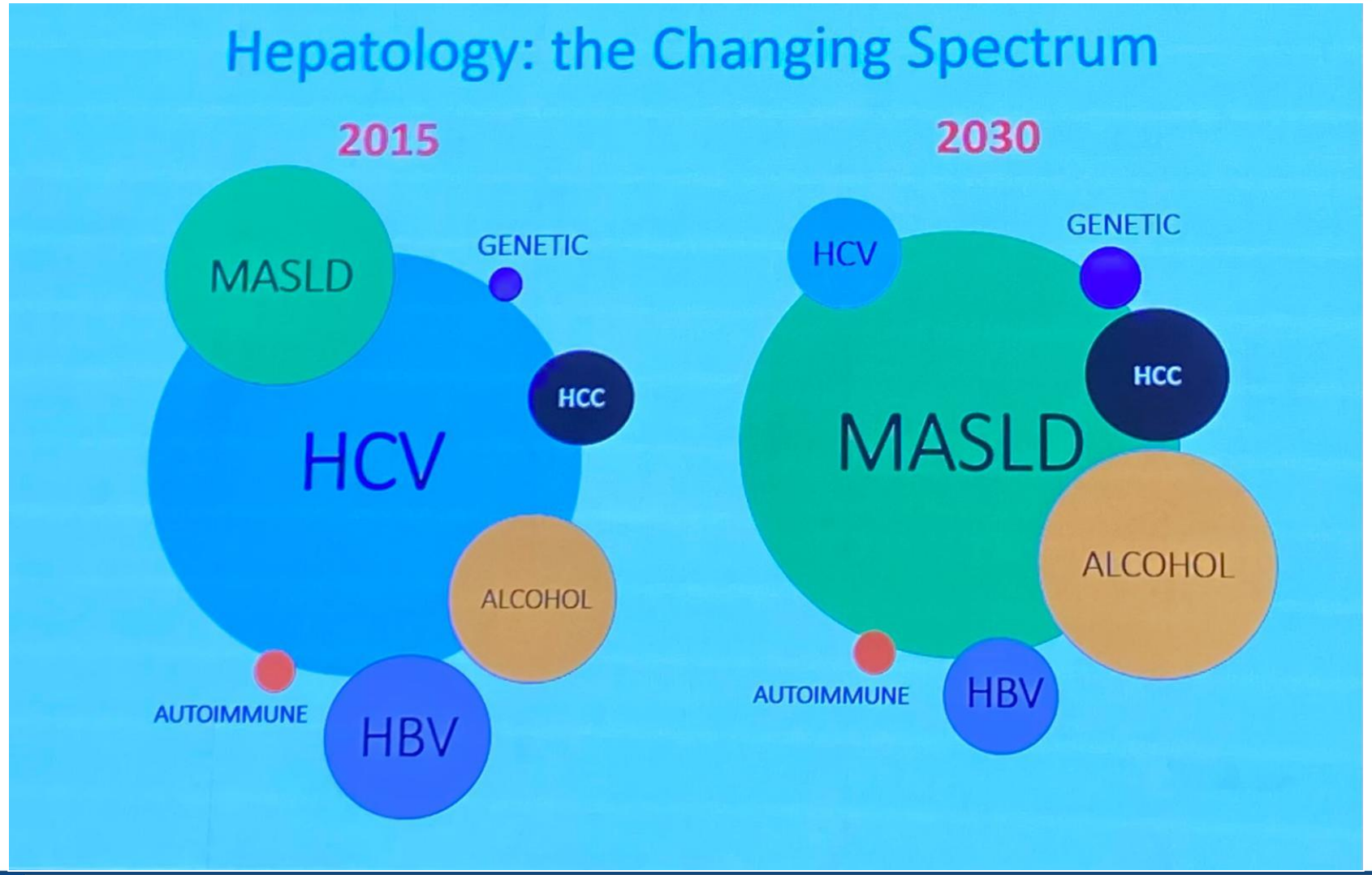
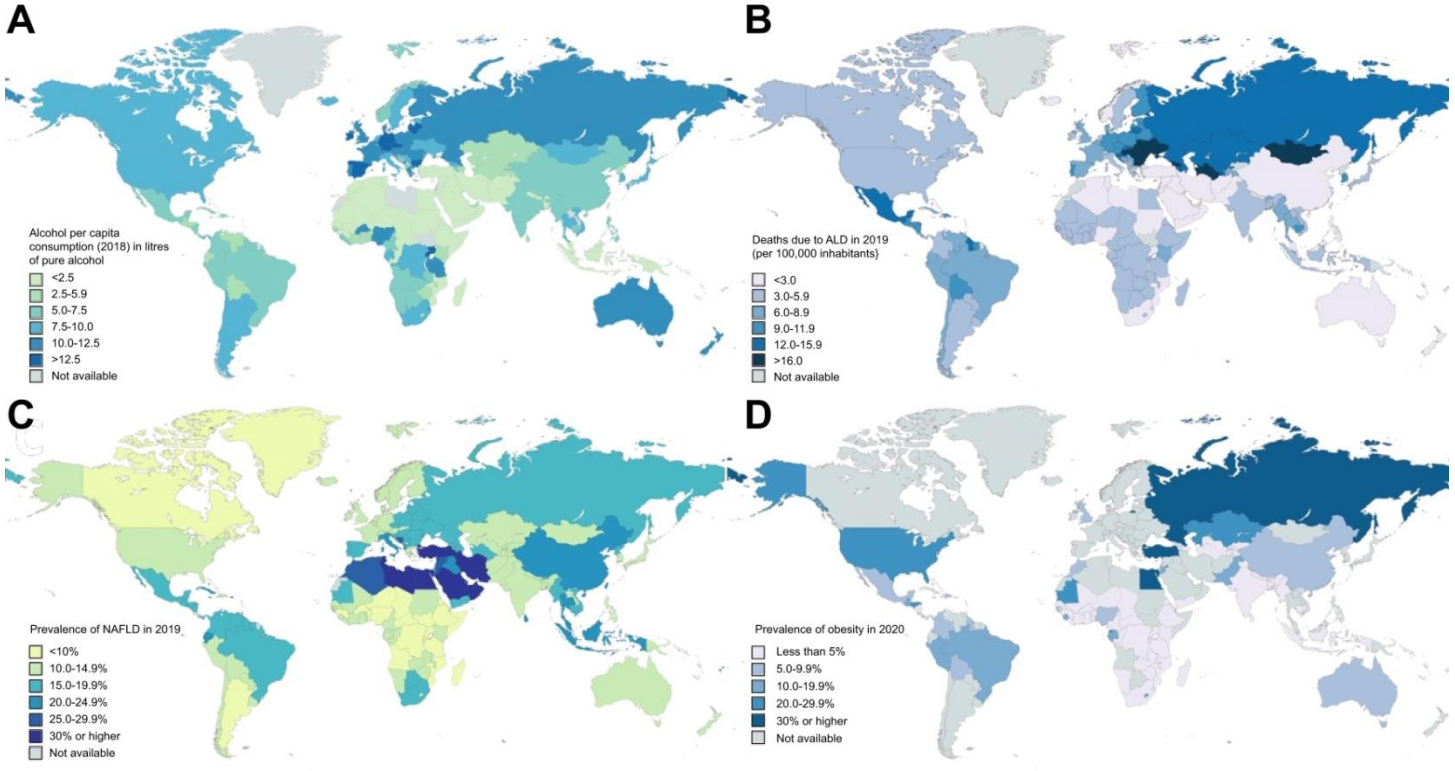
Il fegato e la sindrome metabolica: call to action

Dr Marco Rossi
Direttore UOC Gastroenterologia ed
Endoscopia Digestiva
Arezzo-Bibbiena-La Fratta-Sansepolcro
USL Toscana Sudest

Why we need the gastroenterologist?

Why we have to work as a team?


Hepatology: the Changing Spectrum
2015
MASLD
GENETIC
HCC
HCV
ALCOHOL
AUTOIMMUNE
HBV
2030
HCV
GENETIC
HCC
MASLD
ALCOHOL
AUTOIMMUNE
HBV



- Prevalenza Globale NAFLD: 32.4%
- In progressivo aumento (parallelo a quello dei disturbi metabolici associati)
- Prima eziologia di trapianto epatico
- Alto impatto economico (destinato a crescita esponenziale)
- Incremento stimato dell'incidenza della NAFLD e delle sue complicanze (cirrosi scompensata, HCC, mortalità): x2-x3 nel 2030

J Hepatol 2023: Global Burden of liver disease: 2023 update

(Estes C et al. 2018)

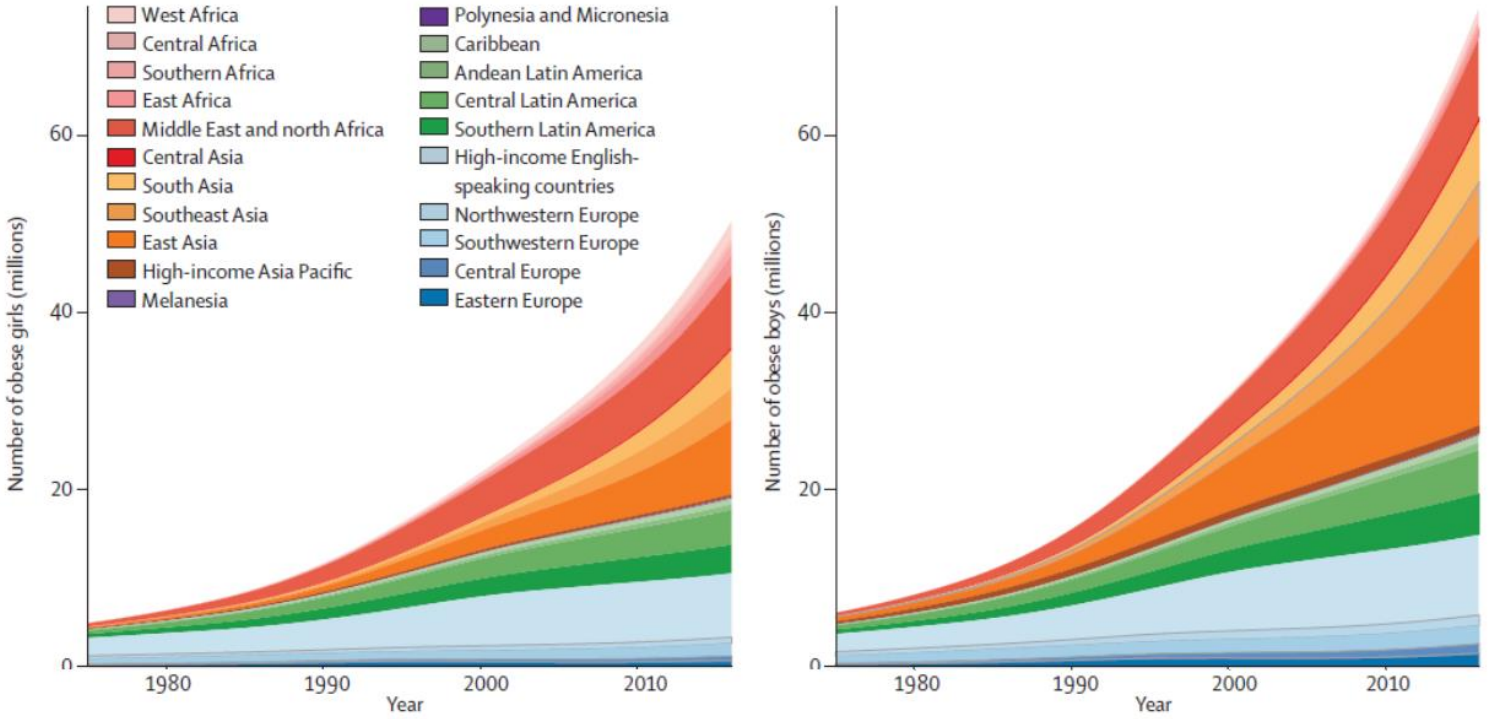
La principale minaccia per la salute globale dei prossimi decenni

Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults

NCD Risk Factor Collaboration (NCD-RisC)*

Articles

Lancet 2017; 390: 2627–42



Trends in the number of children and adolescents (5-19 y.o.) with obesity by region

US obesity rate:
an unstoppable rise

- 1968: 15%
- 2008: 30%
- 2030: 50%
- 2102: 100%

American Journal of TRANSPLANTATION
AST AMERICAN SOCIETY OF TRANSPLANTATION ASTS

Volume 20, Issue s1
Special Issue: OPTN/SRTR Annual Data Report 2018
Pages: 1-568
January 2020

SRTR SCIENTIFIC REGISTRY OF TRANSPLANT RECIPIENTS

OPTN/SRTR 2018 Annual Data Report: Liver

A. Kwong[1], W. R. Kim[1,2], J. R. Lake[1,3], J. M. Smith[1,4], D. P. Schladt[2], M. A. Skeans[2], S. M. Noreen[5], J. Foutz[5], E. Miller[5], J. J. Snyder[2,6], A. K. Israni[2,6,7], B. L. Kasiske[2,7]

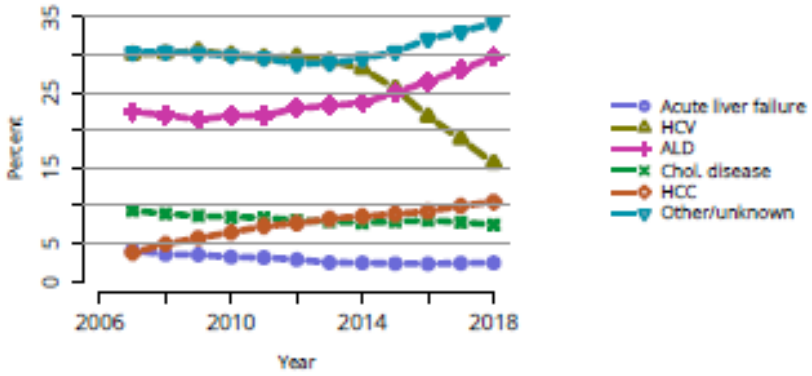


Figure LI 6. Distribution of adults waiting for liver transplant by diagnosis. Candidates waiting for transplant at any time in the given year. Candidates listed concurrently at multiple centers are counted once. Active and inactive patients are included. HCV, hepatitis C virus; ALD, alcoholic liver disease; Chol. disease, cholestatic disease; HCC, Hepatocellular carcinoma.

NAFLD (Non-Alcoholic Fatty Liver Disease)

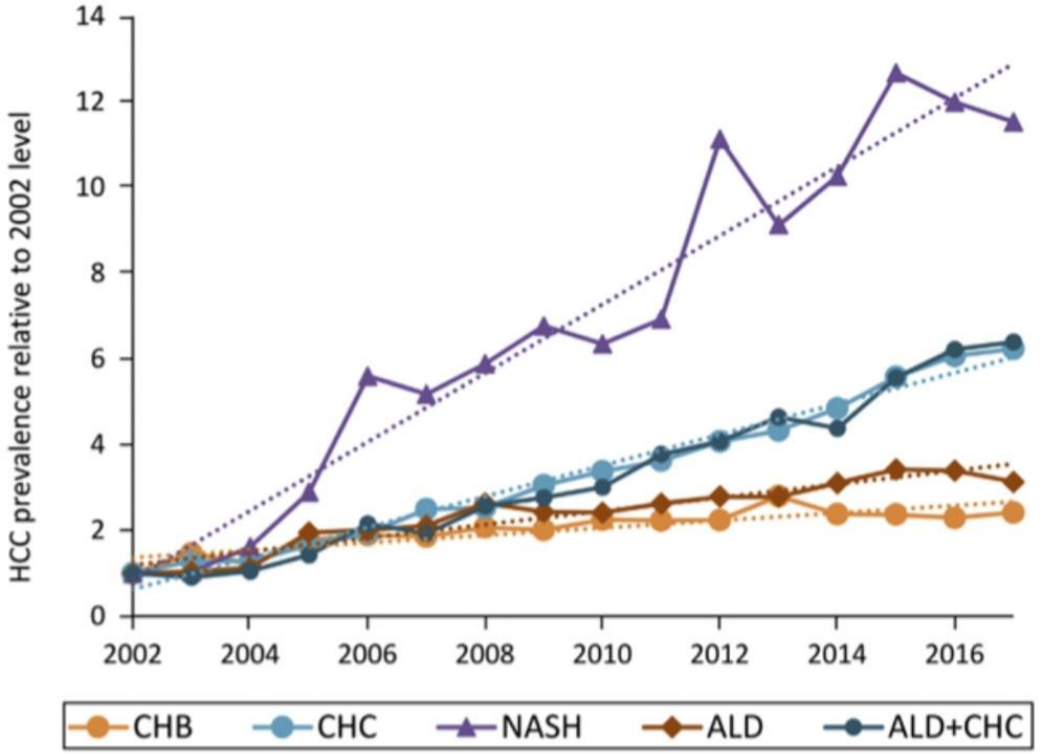
- *principale causa di epatopatia cronica nel mondo occidentale*
- *Principale indicazione a trapianto di fegato (USA)*
- *manifestazione epatica della sindrome metabolica*

Aumento del Rischio CV

Clinical Gastroenterology and Hepatology 2019;17:748–755

Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates

Zobair Younossi,[*,‡] Maria Stepanova,[§] Janus P. Ong,[‖] Ira M. Jacobson,[¶] Elisabetta Bugianesi,[#] Ajay Duseja,[**] Yuichiro Eguchi,[‡‡] Vincent W. Wong,[§§] Francesco Negro,[‖‖] Yusuf Yilmaz,[¶¶] Manuel Romero-Gomez,[##] Jacob George,[***] Aijaz Ahmed,[‡‡‡] Robert Wong,[§§§] Issah Younossi,[§] Mariam Ziayee,[§] and Arian Afendy,[§] on Behalf of the Global Nonalcoholic Steatohepatitis Council

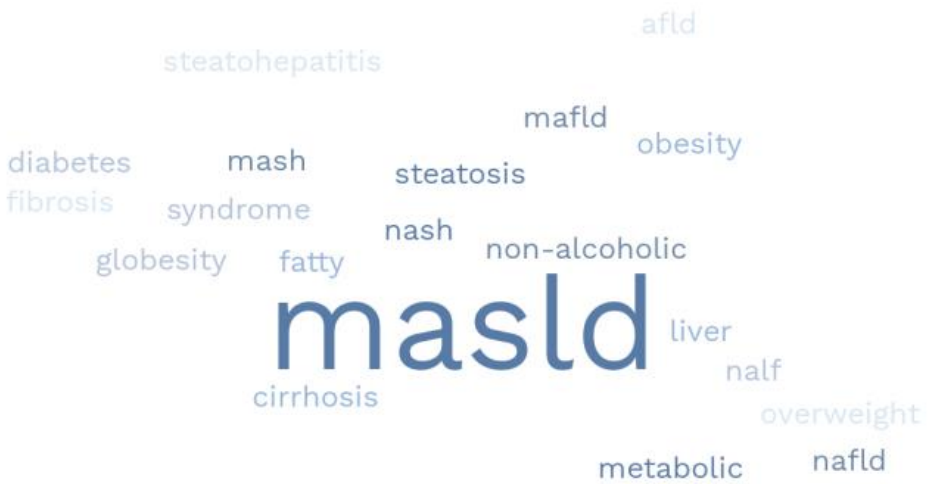


Nonalcoholic steatohepatitis is the most rapidly growing cause of HCC among US patients listed for liver transplantation.

Fig. 1 **Steatosi epatica negli adulti**

Rilevata mediante biopsia, imaging o biomarcatori/score ematici

In assenza di altre cause di steatosi	*In presenza di almeno 1 dei 3 seguenti disturbi metabolici*	*In assenza di altre cause di steatosi MA in presenza di*
1. **Significativo consumo alcolico** (definito come assunzione >20 g/die per le donne o >30 mg/die per gli uomini) 2. **Epatite cronica B o C** 3. **Altre cause specifiche di steatosi epatica** • Epatite indotta da farmaci • Epatite autoimmune • Emocromatosi • Malattia di Wilson • Deficit di alfa1 anti-tripsina • Malnutrizione • Malattia celiaca • Ipotiroidismo franco • Altre cause secondarie di steatosi	1. **Sovrappeso o obesità:** BMI ≥25 kg/m^2 in uomini e donne caucasici (BMI ≥23 kg/m^2 negli asiatici) 2. **Diabete mellito di tipo 2** 3. **Almeno 2 delle 7 anomalie metaboliche:** • Circonferenza vita ≥120/88 cm in uomini e donne caucasici (o criteri aggiustati per i diversi gruppi etnici) • Prediabete (es. glicemia a digiuno 5.6-6.9 mmol/L o glicemia 7.8-11.0 mmol/L a 2 ore da carico orale di glucosio o HbA1c 39-47 mmol/mol) • Pressione arteriosa ≥130/85 mmHg o terapia antipertensiva • Trigliceridi ≥1.70 mmol/L (150 mg/dL) o terapia ipolipemizzante • Colesterolo HDL uomini <1.0 mmol/L (40 mg/dL), donne <1.3 mmol/L (50 mg/dL) o terapia ipolipemizzante • Sensibilità all'insulina all'HOMA test ≥2.5 • Valori di PCR ad alta sensibilità >2 mg/L	**Almeno 1 delle 5 anomalie metaboliche:** • Sovrappeso o obesità: BMI ≥25 kg/m^2 nei caucasici (BMI ≥23 kg/m^2 negli asiatici), o circonferenza vita ≥94/80 cm in uomini e nelle donne caucasici, o criteri aggiustati per i diversi gruppi etnici • Glicemia a digiuno ≥5.6 mmol/L (100 mg/dL), o glicemia ≥7.8 mmol/L (140 mg/dL) a 2 ore da carico orale di glucosio, o HbA1c ≥ 39 mmol/mol (5.7%), o diabete mellito di tipo 2 o terapia per diabete di tipo 2 • Pressione arteriosa ≥130/85 mmHg o terapia antipertensiva • Trigliceridi ≥1.70 mmol/L (150 mg/dL) o terapia ipolipemizzante • Colesterolo HDL uomini <1.0 mmol/L (40 mg/dL), donne <1.3 mmol/L (50 mg/dL) o terapia ipolipemizzante
NAFLD (steatosi epatica non alcolica)	**MAFLD** (fegato grasso associato a disfunzione metabolica)	**MASLD** (steatosi epatica associata a disfunzione metabolica)

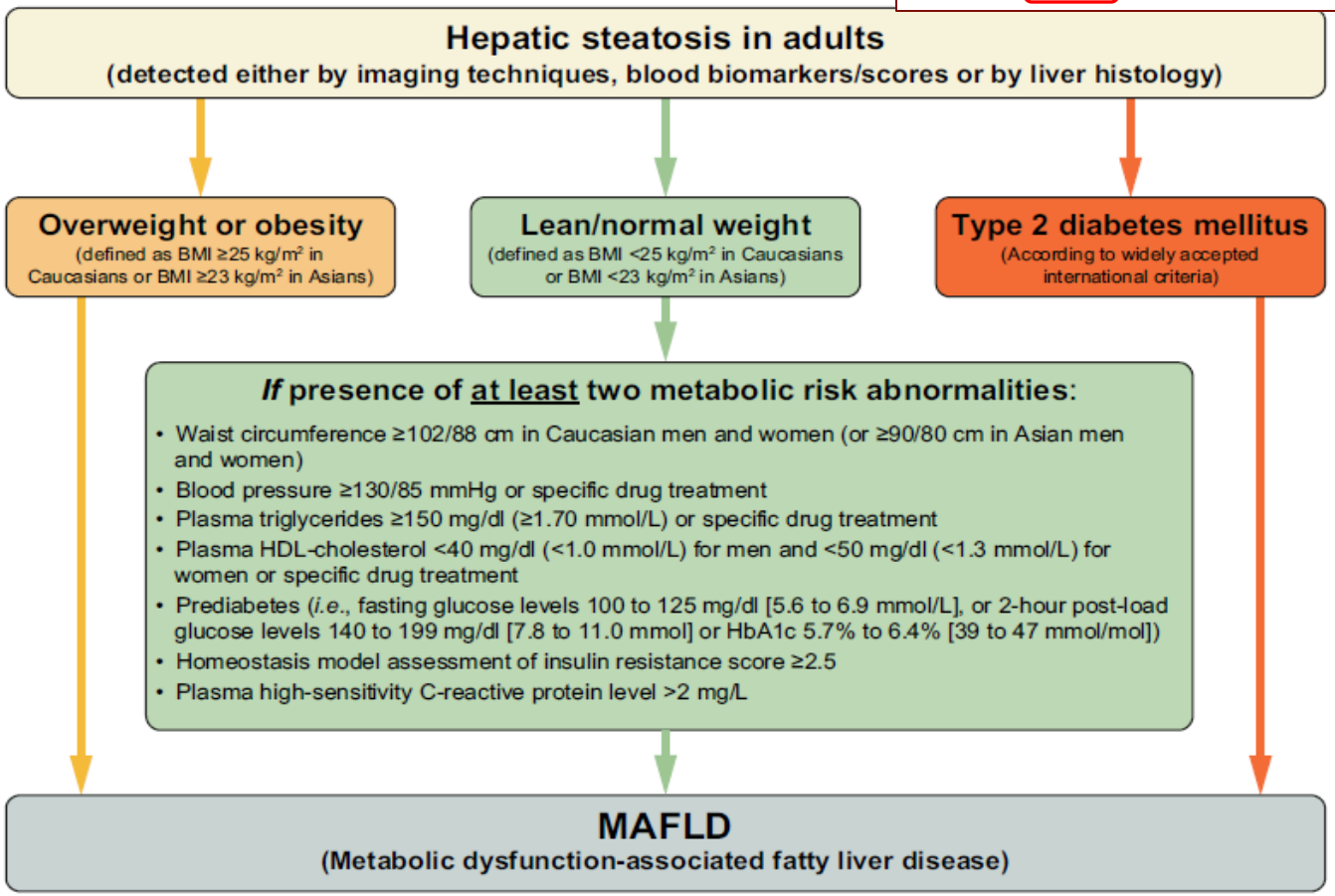


+ other etiologies
(MASLD+AFLD)
(MASLD+HCV) …

A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement

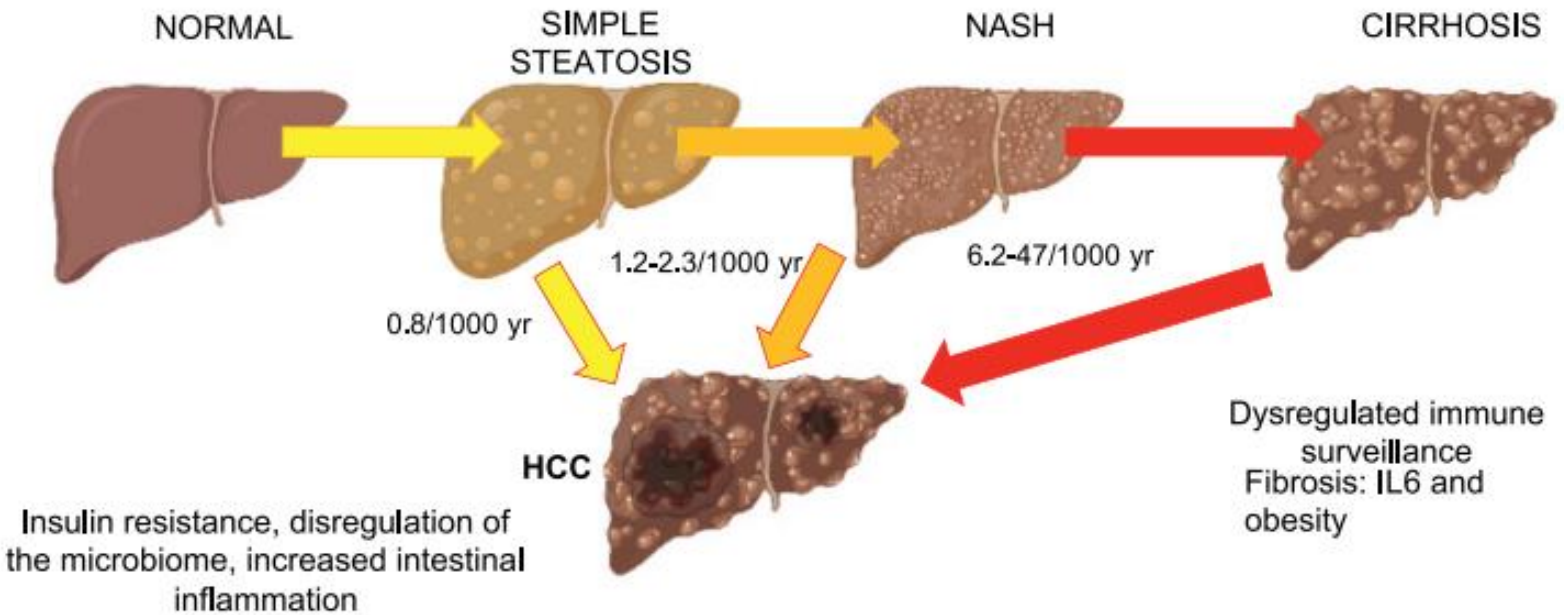
EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)



+ other etiologies

(MAFLD+AFLD)(MAFLD+HCV) …



Digestive and Liver Disease 54 (2022) 154–163

Table 2. MASLD and MASH Prevalence, Incidence, and Mortality Values

Group	Value
Global NAFLD prevalence (2016–2019)	38%
Highest global NAFLD prevalence	Middle East and North Africa (42.6%)
Prevalence of lean MASLD in general population	5%-7%
Prevalence of lean NAFLD within the NAFLD population	20% in the western and eastern hemispheres ~ 40% (nonobese) in eastern hemisphere
F1–F2 prevalence in general population	7%–8%
F3–F4 prevalence in general population	1%–2%
Incidence of NAFLD	48.89–50.09 per 1000 person-years
All-cause mortality	12.61–7.1 per 1000 person-years
Cardiac-specific mortality	4.2–5.5 per 1000 person-years
Extrahepatic cancer mortality	2.8–4.2 per 1000 person-years
Liver-specific mortality	0.92–1.75 per 1000 person-years

NOTE. Data are based on NAFLD.
F1, F2, F3, F4, fibrosis stages 1, 2, 3, and 4.

Gastroenterology 2025;169:1017–1032

Global Consensus Recommendations for Metabolic Dysfunction-Associated Steatotic Liver Disease and Steatohepatitis

Gastroenterology 2025;169:1017–1032

Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

When to Use | Pearls/Pitfalls | Why Use

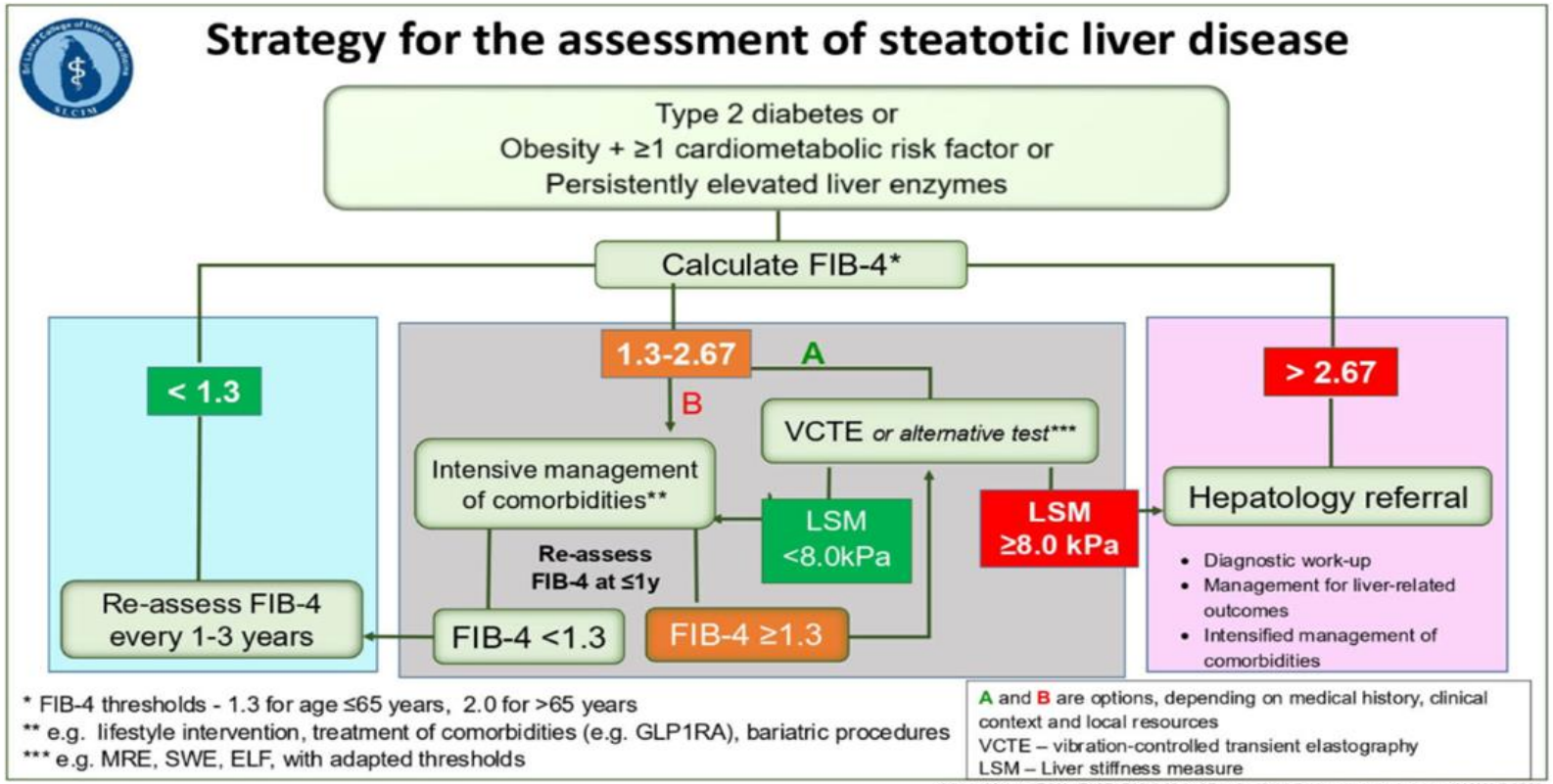
Age Use with caution in patients <35 or >65 years old, as the score has been shown to be less reliable in these patients		years
AST Aspartate aminotransferase	Norm: 15 - 41	U/L
ALT Alanine aminotransferase	Norm: 1 - 35	U/L
Platelet count	Norm: 150 - 350	x 10^3/µL

Result:

Please fill out required fields.

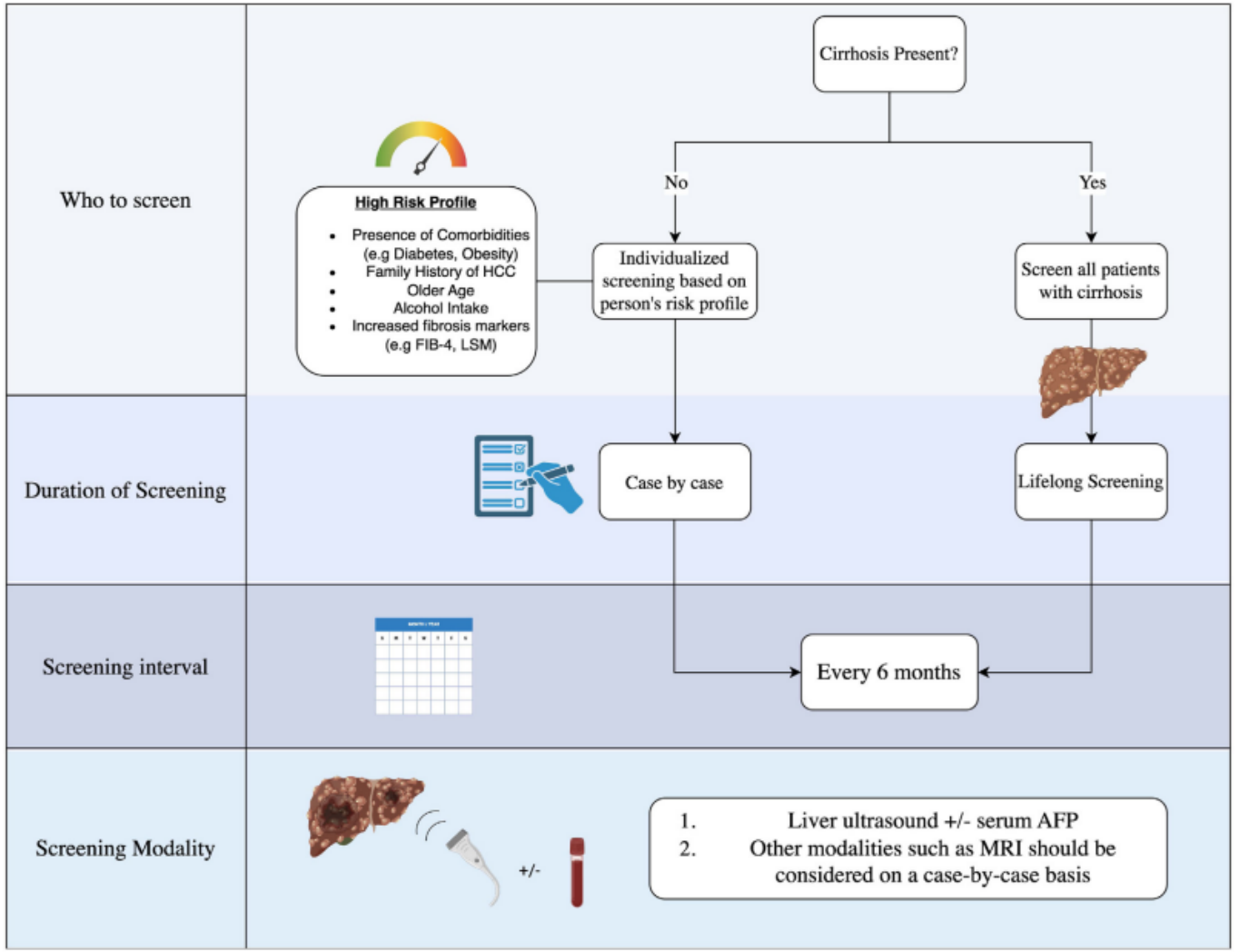
» Next Steps | Evidence | Creator Insights

Global Consensus Recommendations for Metabolic Dysfunction-Associated Steatotic Liver Disease and Steatohepatitis



Adopted from – 'EASL–EASD–EASO Clinical Practice Guidelines on the management of MASLD 2024

Screening for MASLD-Associated HCC



- Il più grave pericolo per la salute pubblica nel mondo moderno (problema globale)
- Costi totali (diretti ed indiretti): trillions
- «Present trend is not susteinable **unless a magic cure is found (unlikely)** or concerted global governmental/societal effort are made to **change the lifestyle** that is promoting it (high calorie-low fiber diet - fast food – and decrease in physical activity)»

(Saklayen MG 2018)

MISSION:IMPOSSIBLE ?

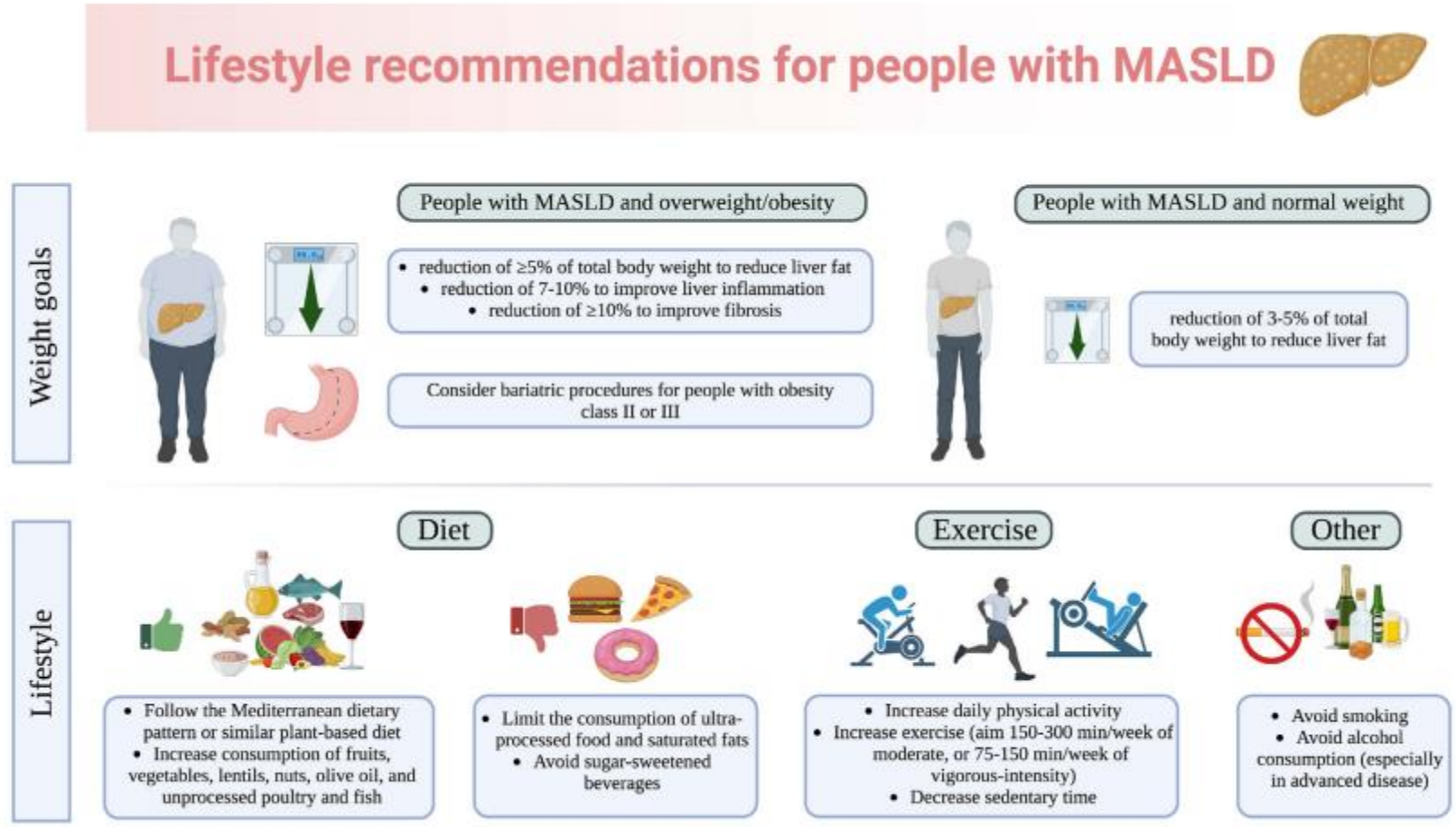
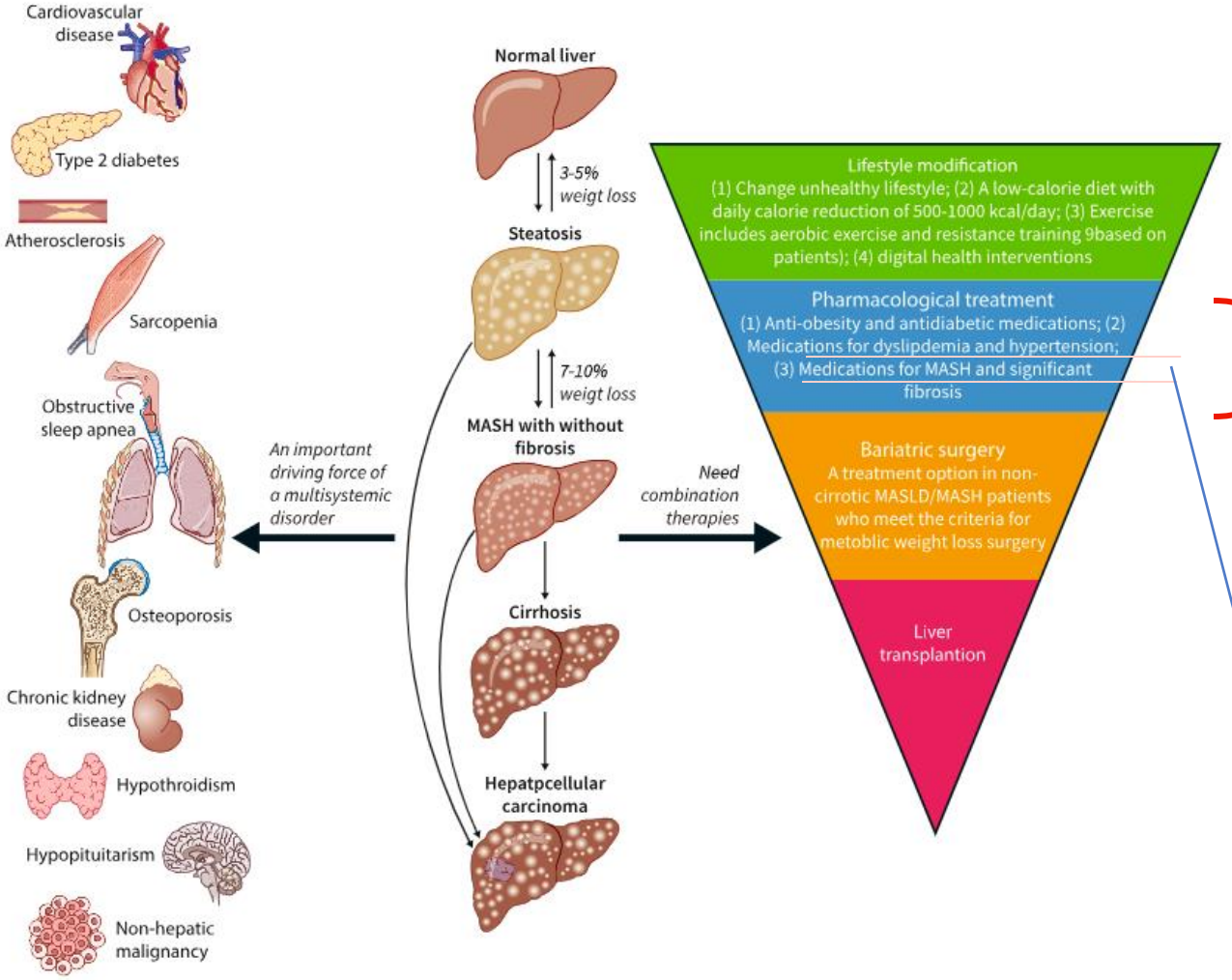


Figure 2. Lifestyle management.



Baveno VII

4.1 The use of **STATINS** should be encouraged in pts with cirrhosis and an approved indication for statins since these agents **may decrease portal pressure (A1) and improve overall survival (B.1)** - Changed

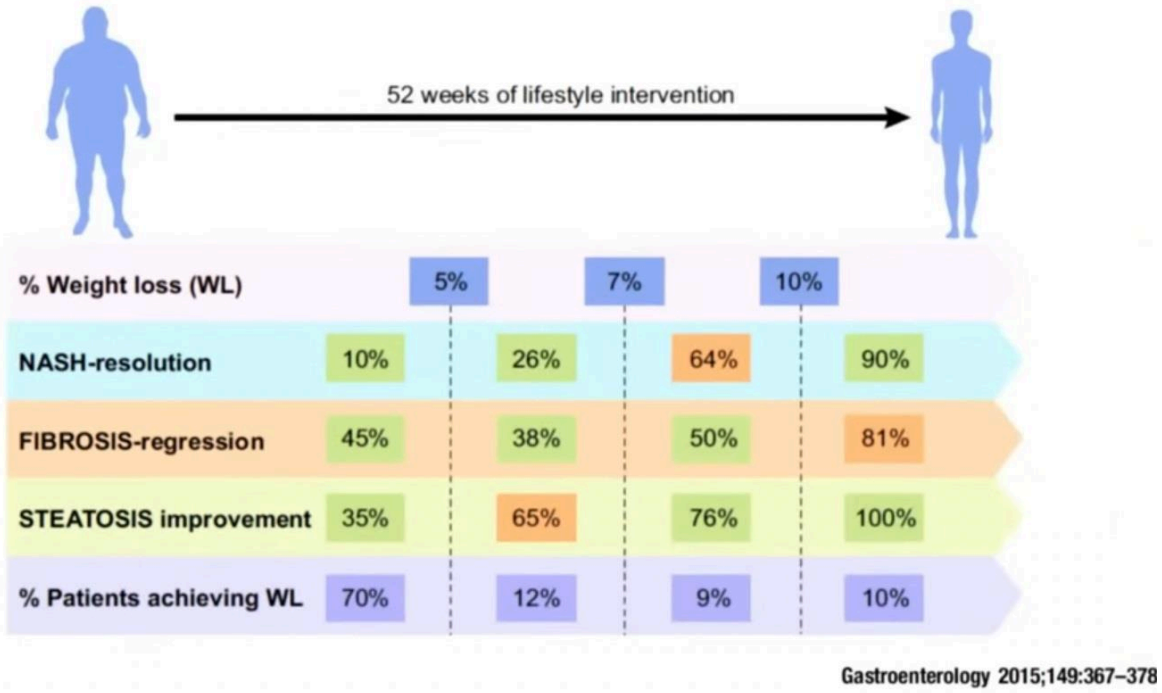
4.3 The use of **ASPIRIN** should not be discouraged in pts with cirrhosis and an approved indication for aspirin, since it **may reduce the risk of HCC, liver-related complications, and death** (B2) – New

… anti-obesity / antidiabetic medications?

DIETA e STILE DI VITA: COSA POSSIAMO FARE IN PREVENZIONE SECONDARIA?

Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis

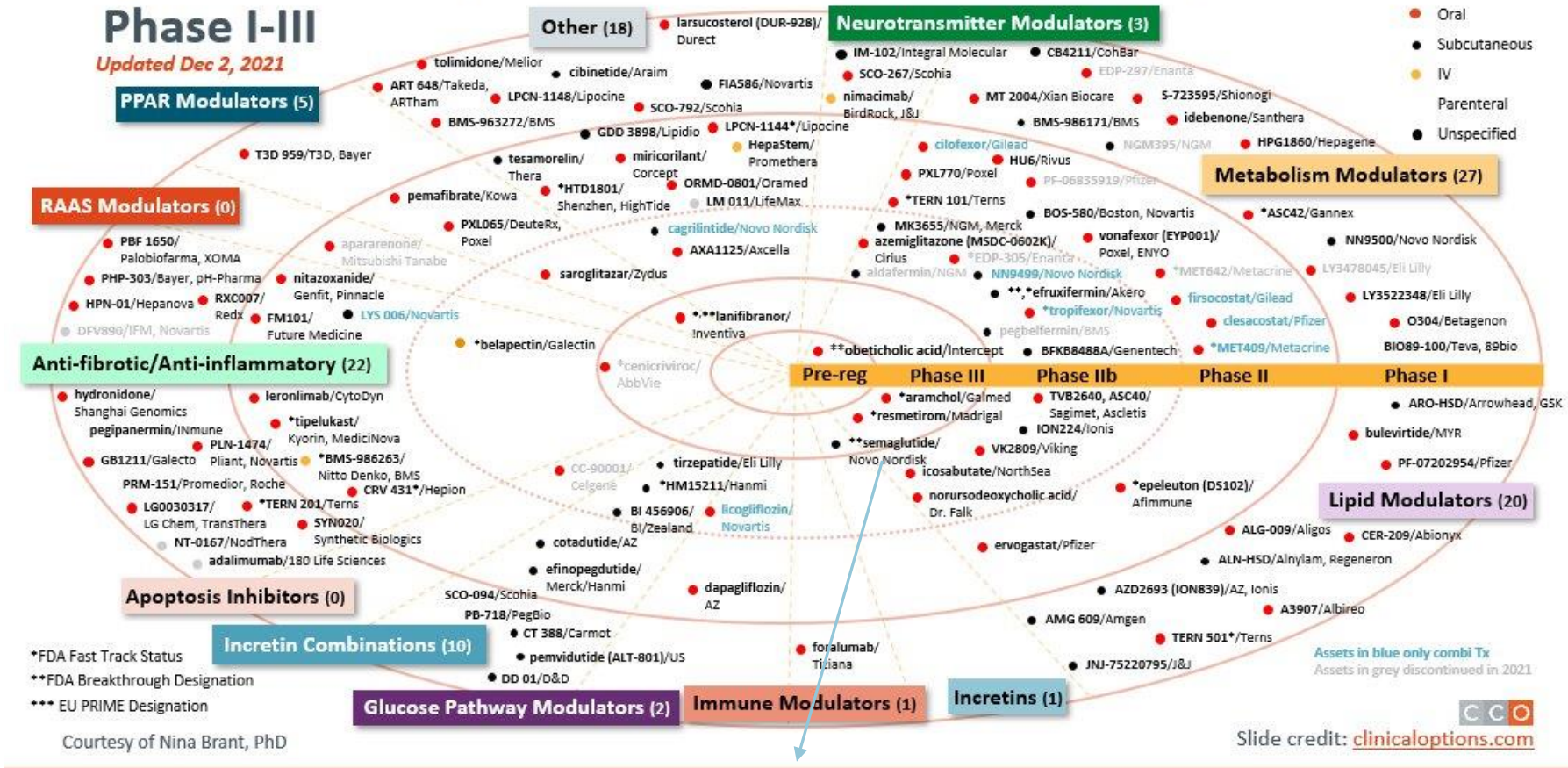
Eduardo Vilar-Gomez,[1,2] Yadina Martinez-Perez,[1] Luis Calzadilla-Bertot,[1] Ana Torres-Gonzalez,[1] Bienvenido Gra-Oramas,[3] Licet Gonzalez-Fabian,[3] Scott L. Friedman,[4] Moises Diago,[5] and Manuel Romero-Gomez[2]



Gastroenterology 2015;149:367–378

- 293 pazienti
- «Paired liver biopsies» in 261 pazienti

Agents in Development for NASH in US, EU, and Japan:



semaglutide

Consideration for selection of medications for treatment of comorbidities in those with MASH	
Pioglitazone	Pioglitazone can be considered as a treatment for T2D for individuals with or without MASH but not as a MASH-targeted therapy
GLP-1RAs	Until the FDA approves GLP-1RAs for MASH, these drugs should be considered the preferred treatments for T2D and/or obesity in individuals with MASH.
Sodium-glucose co- transporter-2 (SGLT-2) inhibitors	SGLT-2 inhibitors should be considered as treatments for T2D for individuals with or without MASH, but not as MASH-targeted therapies
Dipeptidyl peptidase-4 inhibitors	Dipeptidyl peptidase-4 inhibitors can be considered as treatments for T2D for individuals with or without MASH, but not as MASH-targeted therapies
Metformin, Insulin, and sulfonylureas	Metformin, insulin,[b] and sulfonylureas are used for treatment for T2D, but are not the preferred drugs for treatment of T2D in patients with MASLD or as MASH-targeted therapy[b]
Vitamin E	Due to a lack of sufficient evidence and balancing risks and benefits, vitamin E supplementation cannot be recommended as a MASH-targeted therapy, except in select individuals without T2D or cirrhosis
Ursodeoxycholic acid or Omega-3 fatty acids	Ursodeoxycholic acid or omega-3 fatty acids should not be considered as a treatment for people with MASH

MASH treatment with THR-β agonist (Resmetirom, approved in the United States)

Recommendation 1	If available and licensed, resmetirom should be considered as treatment in individuals who meet NIT criteria: MASH with F2-F3 fibrosis in the absence of cirrhosis

EASL The Home of Hepatology

Table 1. Glucose-lowering agents with some evidence to improve metabolic dysfunction-associated steatotic liver disease in histology-based studies.

	Pioglitazone[a]	GLP-1RAs	Tirzepatide	Survodutide[b]
Benefits in steatohepatitis	Yes	Yes	Yes	Yes
Benefits in liver fibrosis	Yes, based on phase II studies	Not demonstrated to date, based on phase II studies	Yes, based on a single phase II study	Yes, based on a single phase II study
Benefits in major cardiovascular outcomes	Yes	Yes	Not demonstrated to date	Not demonstrated to date
Cost	Low	High	High	Unknown
Adverse events	Heart failure, bone loss/fractures at the extremities, fluid retention, hemodilution, and weight gain	Gastrointestinal disorders (nausea, constipation, decreased appetite, vomiting, and abdominal pain) and gallbladder-related disorders Progression of retinopathy?	Gastrointestinal disorders, including nausea, diarrhea, and constipation	Gastrointestinal disorders, including nausea, diarrhea, and vomiting

[a]No longer available in many European countries.
[b]Not approved for the treatment of type 2 diabetes. GLP-1RAs, glucagon-like peptide 1 receptor agonists.

Journal of Hepatology, **January 2025**. vol. 82 | e21–e22

EASL
The Home of Hepatology

EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD): Executive Summary

European Association for the Study of the Liver[1] · European Association for the Study of Diabetes[2] · European Association for the Study of Obesity[3]

Published online: 13 June 2024

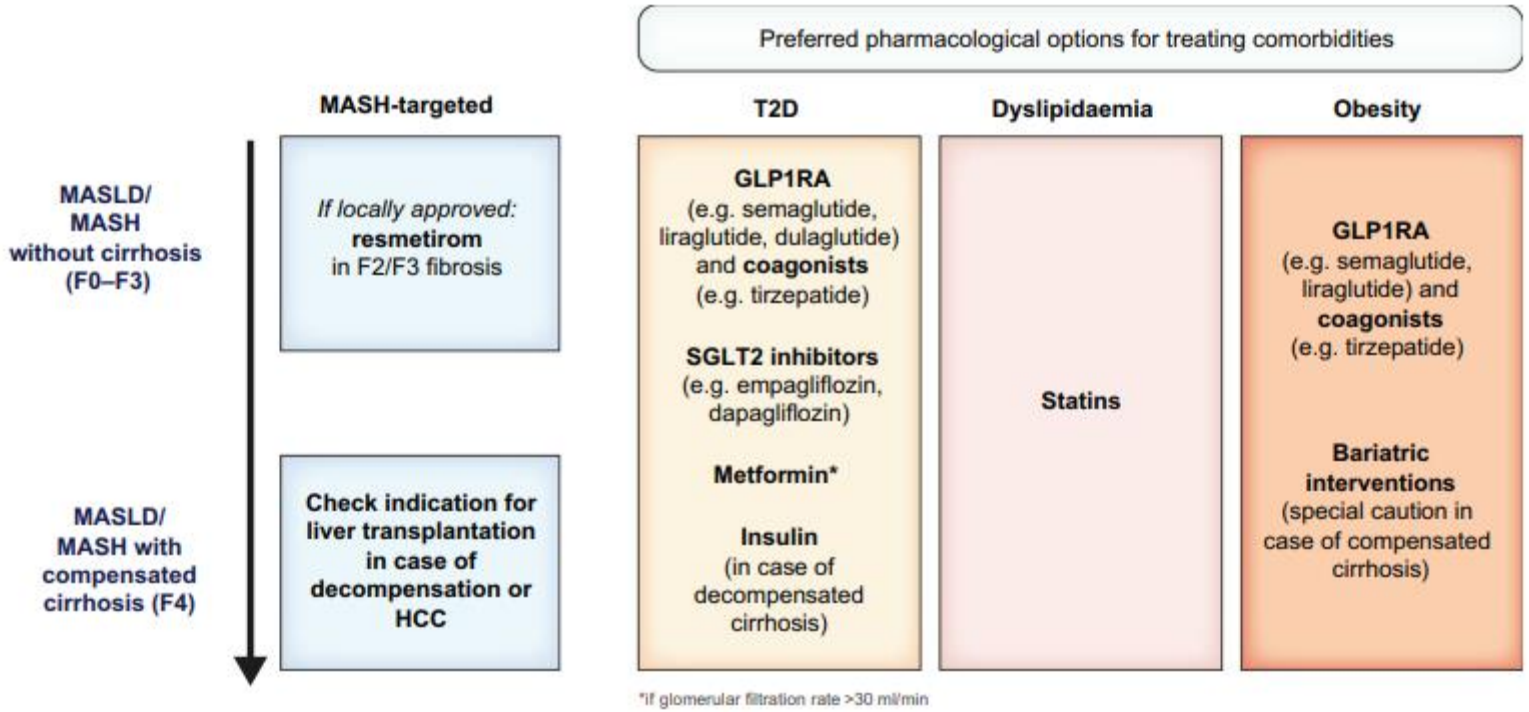


Fig. 4 Treatment recommendations beyond lifestyle modification in MASLD/MASH. The recommended choice of pharmacological treatment options in individuals with MASLD/MASH is dependent on comorbidities and stage of disease. T2D, type 2 diabetes

gastroenterologo

endocrinologo

radiologo

nutrizionista

pediatra

diabetologo

chirurgo

psicologo

patologo

Conclusions

It has been estimated that approximately one-third of adults worldwide have metabolic dysfunction associated steatotic liver disease (MASLD formally known as nonalcoholic fatty liver disease, NAFLD)

The progressive form of MASLD know as metabolic dysfunction associated steatohepatitis (MASH) is characterized by steatosis, hepatocite ballooning and associated liver inflammation

As MASH progresses, the liver becomes fibrotic, leading to cirrhosis, possible hepatocellular carcinoma (HCC), and the need for liver transplantation.

Furthermore, MASH is associated with impaired health related quality of life and a tremendous economic burden.

The global burden of MASH has been increasing in parallel with the increasing prevalence of obesity and additional metabolic disorders.

Conclusions

In patients with NAFLD diagnosed by imaging or histology over a median follow-up of 6.9 years , there was a 65% increased risk of developing both fatal and nonfatal cardiovascular events

Patients with NAFLD are twice as likely to die of cardiovascular disease than liver disease, which is largely related to shared risk factors including diabetes mellitus , HNT, and obesity

In fact liver disease is only the third leading cause of death in patients with NAFLD, following cardiovascular disease and malignancy


Grazie
Thank You
Merci
Obrigado
Kiitos
Spasibo
Danke
Maake
Mamana
Juspaxar
Mochchakkeram
Terma Kasih
Kia Ora
Asante
Salamat
Dyakuyu
Arigato
Multumesc
Cam on ban
Vinaka
Raibh Maith Agat
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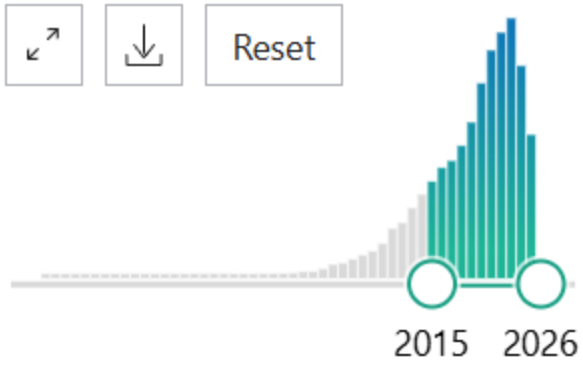
Ua Tsaug Rau Koj
Nirringrazzjak
Merci



Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis

Jingxuan Quek * • Kai En Chan * • Zhen Yu Wong, MBBS * • Caitlyn Tan • Bryan Tan • Wen Hui Lim • et al.

Show all authors • Show footnotes

Pooled analysis comprising 101 028 individuals:

NAFLD in overweight population 69-99%
NASH in overweight population 33-50%

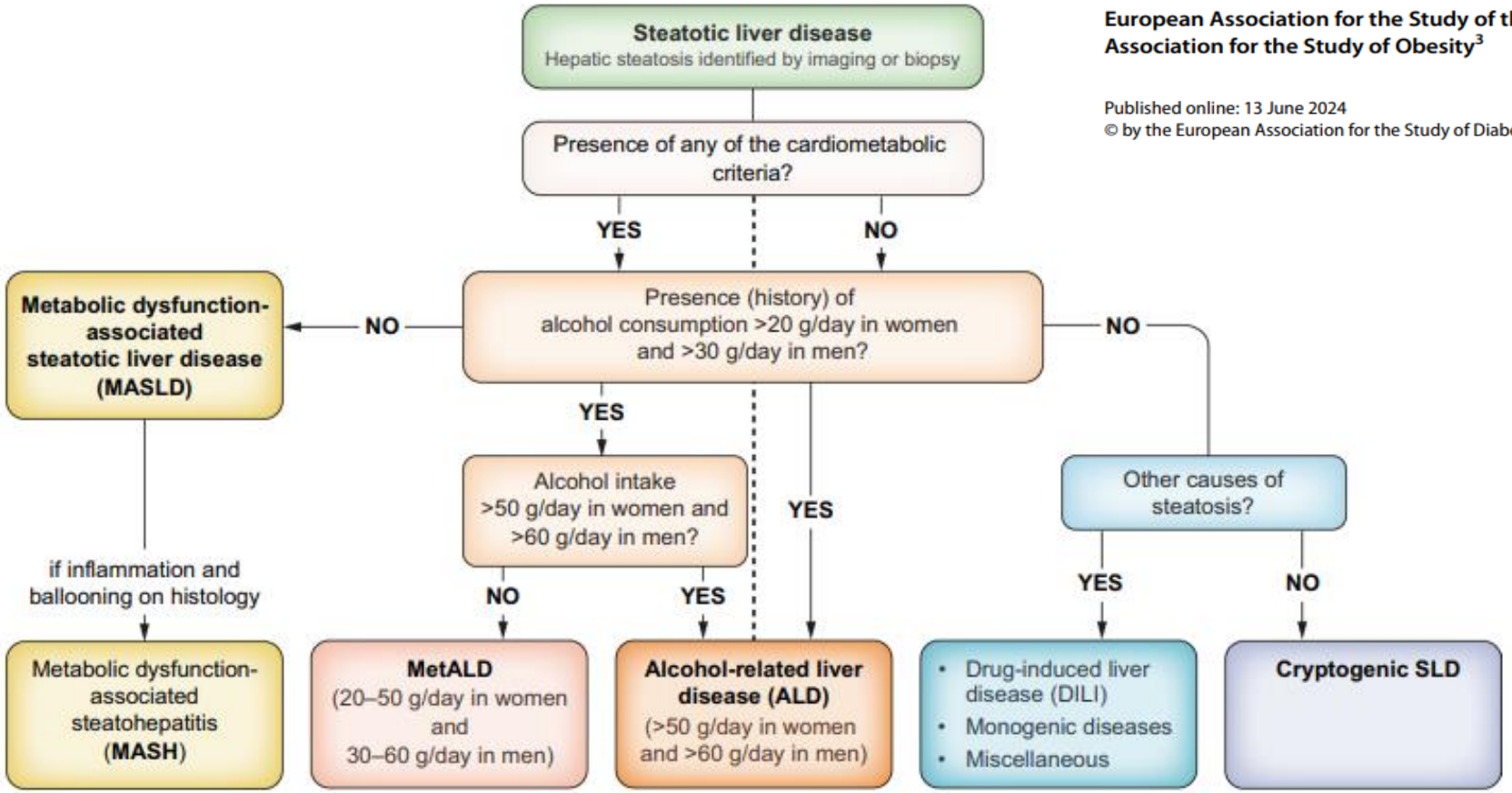
NAFLD in obese population 27-75%
NASH in obese poplulation 33-67%

«The global burden of NAFLD parallels the increase in obesity rate across the world»

EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD): Executive Summary

European Association for the Study of the Liver[1] · European Association for the Study of Diabetes[2] · European Association for the Study of Obesity[3]

Published online: 13 June 2024



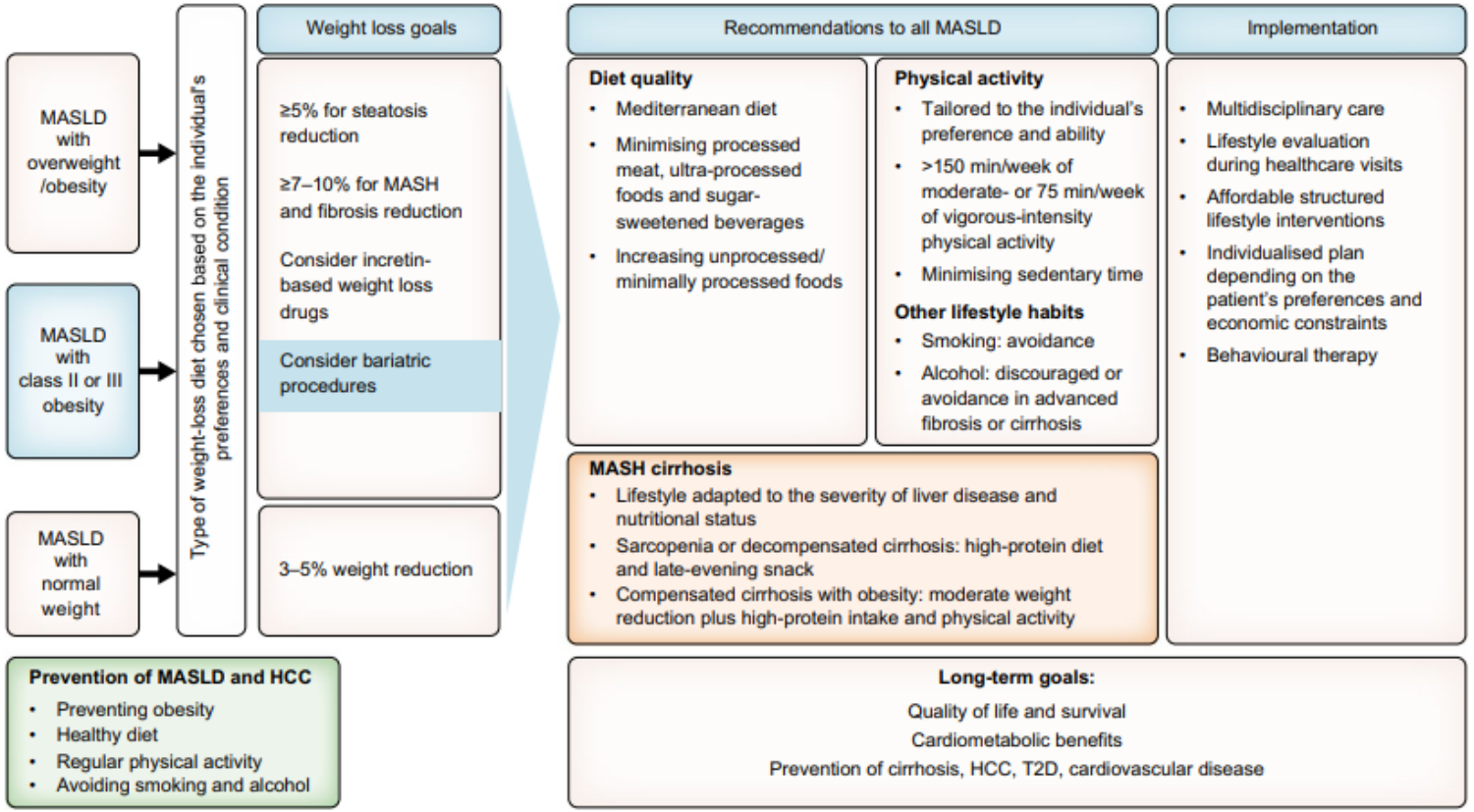


Fig. 3 Lifestyle management algorithm for MASLD. Behavioural therapy includes: self-monitoring, clinicians providing affected individuals with self-efficacy and motivation, setting realistic negotiable goals and overcoming barriers. Examples of unprocessed/minimally processed foods: vegetables, fruits (not juice), low-fat dairy, nuts, olive oil, legumes, unprocessed fish and poultry. Overweight/obesity: Overweight: BMI of 25–29.9 kg/m^2 (non-Asian) or 23–24.9 (Asian), Obesity: ≥30 kg/m^2 (non-Asian) ≥25 kg/m^2 (Asian). Class II obesity: BMI ≥35 kg/m^2 (non-Asian) or BMI ≥30 kg/m^2 (Asian). Normal weight: BMI<25 kg/m^2 (non-Asian) or <23 kg/m^2 (Asian). T2D, type 2 diabetes

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

Journal of Hepatology 2016 vol. 64 | 1388–1402

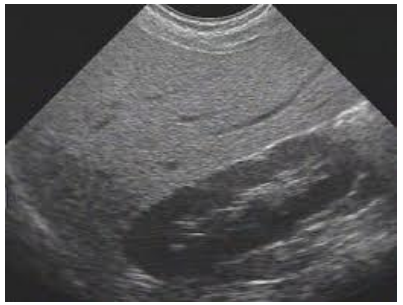
EASL | JOURNAL OF HEPATOLOGY

NAFLD

- *Excessive hepatic fat accumulation with IR*
- *Steatosis in >5% hepatocytes*
- *Exclusion of secondary causes and AFLD*

NAFL

- *Pure steatosis*
- *Steatosis and mild lobular inflammation*



NASH

HCC

EARLY

F0/F1 Fibrosis

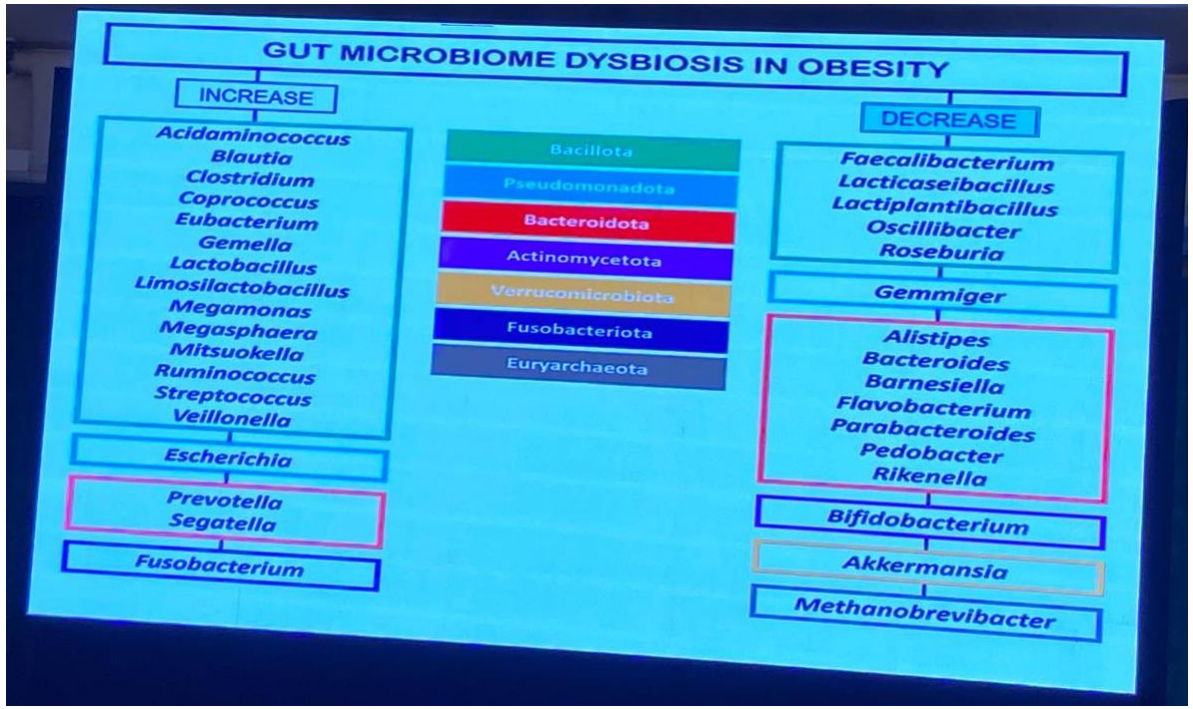
FIBROTIC

F2/F3 Fibrosis

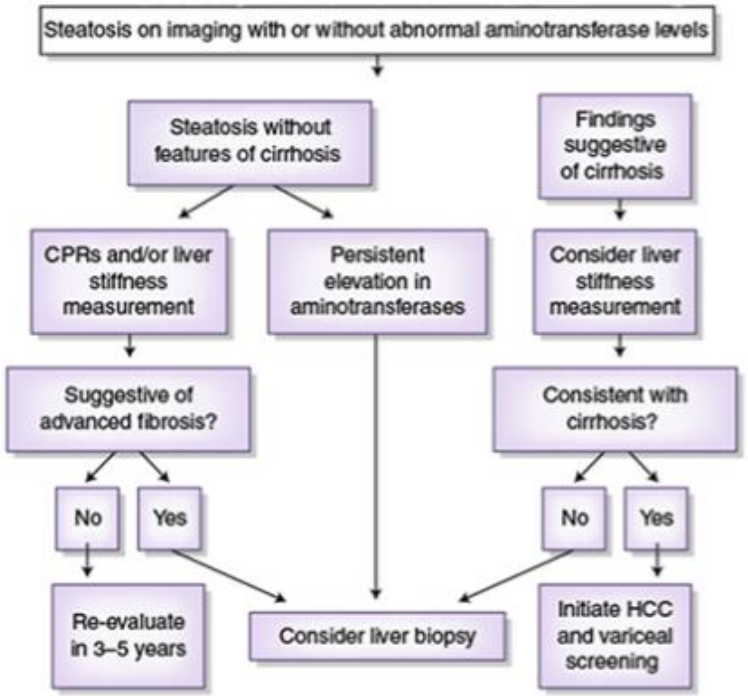
CIRRHOTIC

F4 Fibrosis

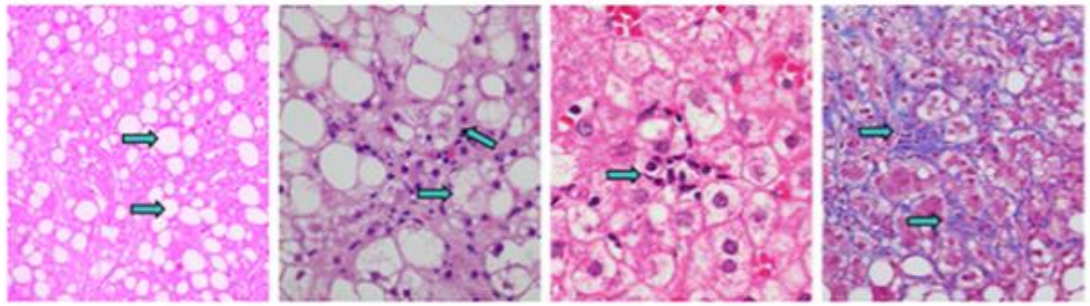
Definitive diagnosis of NASH requires a liver biopsy


GUT MICROBIOME DYSBIOSIS IN OBESITY
INCREASE
Acidaminococcus
Blautia
Clostridium
Coprococcus
Eubacterium
Gemella
Lactobacillus
Limosilactobacillus
Megamonas
Megasphaera
Mitsuokella
Ruminococcus
Streptococcus
Veillonella
Escherichia
Prevotella
Segatella
Fusobacterium
Bacillota
Pseudomonadota
Bacteroidota
Actinomycetota
Verruconicrobiota
Fusobacteriota
Euryarchaeota
DECREASE
Faecalibacterium
Lacticaseibacillus
Lactiplantibacillus
Oscillibacter
Roseburia
Gemmiger
Alistipes
Bacteroides
Barnesiella
Flavobacterium
Parabacteroides
Pedobacter
Rikenella
Bifidobacterium
Akkermansia
Methanobrevibacter

a


Steatosis on imaging with or without abnormal aminotransferase levels
Steatosis without features of cirrhosis
Findings suggestive of cirrhosis
CPRs and/or liver stiffness measurement
Persistent elevation in aminotransferases
Consider liver stiffness measurement
Suggestive of advanced fibrosis?
Consistent with cirrhosis?
No
Yes
No
Yes
Re-evaluate in 3–5 years
Consider liver biopsy
Initiate HCC and variceal screening

b



INSULINO-RESISTENZA: substrato comune di molte patologie croniche

NAFLD/MAFLD

Rischio CV

DM tipo 2

INSULINO-RESISTENZA
IPERINSULINISMO

Neuropatie

Neoplasie

...

invecchiamento

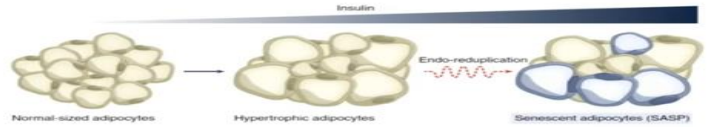
nature medicine

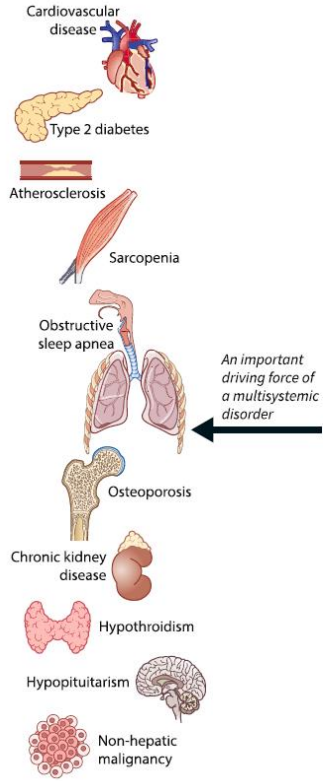
Article | Published: 04 October 2021

Obesity and hyperinsulinemia drive adipocytes to activate a cell cycle program and senesce

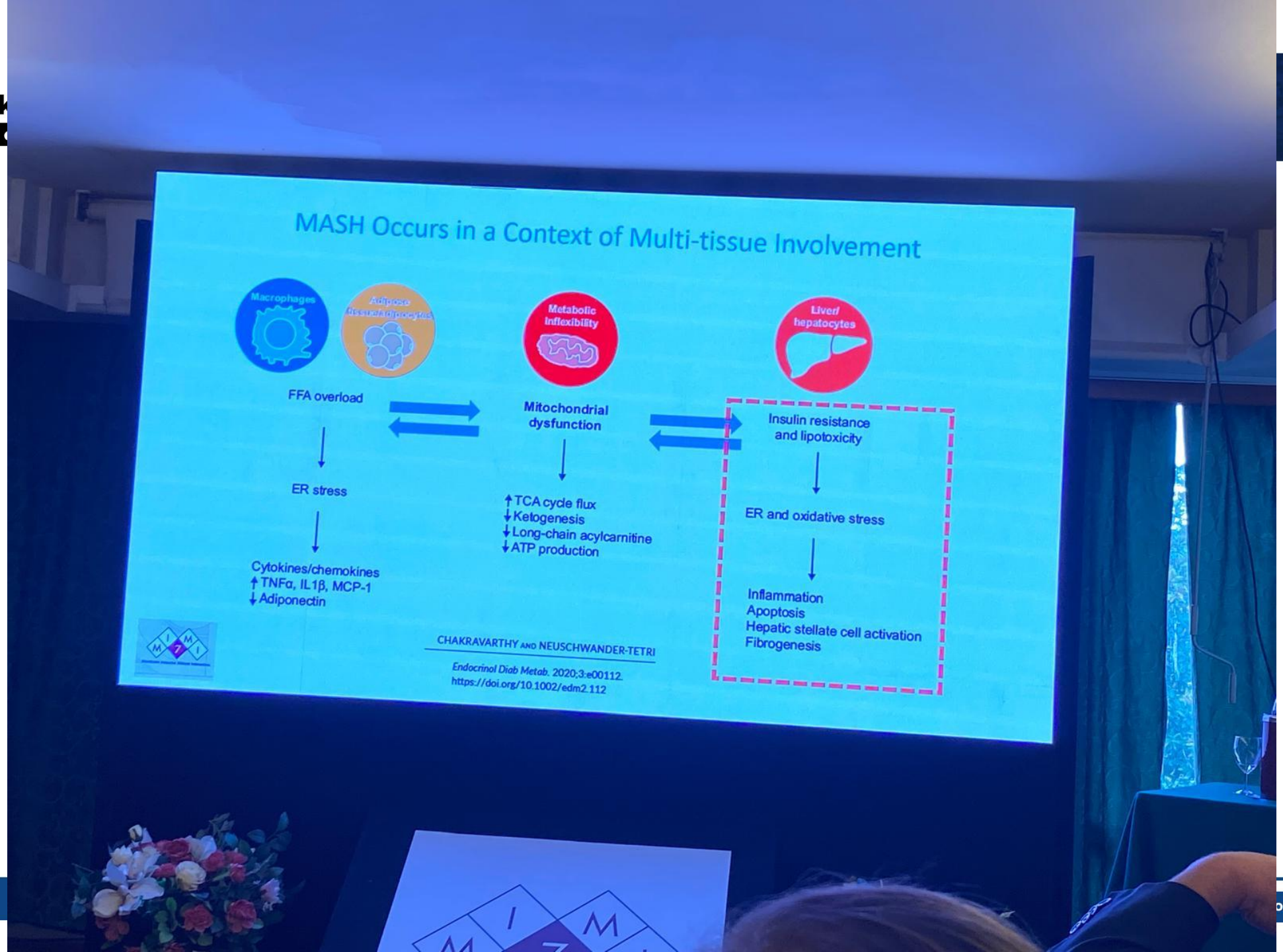
Qian Li, Carolina E. Hagberg, Helena Silva Cascales, Shuai Lang, Mervi T. Hyvönen, Firoozeh Salehzadeh, Ping Chen, Ida Alexandersson, Eleni Terezaki, Matthew J. Harms, Maria Kutschke, Nahida Arifen, Niels Krämer, Myriam Aouadi, Carole Knibbe, Jeremie Boucher, Anders Thorell & Kirsty L. Spalding

Nature Medicine 27, 1941–1953 (2021) | Cite this article





Adipocyte cell cycle progression associates with obesity and hyperinsulinemia, with a concomitant increase in cell size, nuclear size and nuclear DNA content. Chronic hyperinsulinemia in vitro or in humans, however, is associated with subsequent cell cycle exit, leading to a premature senescent transcriptomic and secretory profile in adipocytes


MASH Occurs in a Context of Multi-tissue Involvement
Macrophages
Adipose tissue/adipocytes
Metabolic inflexibility
Liver/ hepatocytes
FFA overload
ER stress
Cytokines/chemokines
↑TNFα, IL1β, MCP-1
↓Adiponectin
Mitochondrial dysfunction
↑TCA cycle flux
↓Ketogenesis
↓Long-chain acylcarnitine
↓ATP production
Insulin resistance and lipotoxicity
ER and oxidative stress
Inflammation
Apoptosis
Hepatic stellate cell activation
Fibrogenesis
CHAKRAVARTHY AND NEUSCHWANDER-TETRI
Endocrinol Diab Metab. 2020;3:e00112.
https://doi.org/10.1002/edm2.112

EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD): Executive Summary

European Association for the Study of the Liver[1] · European Association for the Study of Diabetes[2] · European Association for the Study of Obesity[3]

Published online: 13 June 2024

Statements

- Type 2 diabetes and obesity (particularly abdominal obesity) are the metabolic diseases with the strongest impact on the natural history of MASLD, including progression to MASLD/MASH-related advanced fibrosis, cirrhosis and hepatocellular carcinoma (**LoE 2, strong consensus**).
- Men aged >50 years, postmenopausal women and individuals with multiple cardiometabolic risk factors are at increased risk of progressive fibrosis and the development of cirrhosis and its complications (**LoE 2, strong consensus**).

There has been an explosive interest in NAFLD and its more advanced stage, NASH, because of their growing impact on world health. In the United States, the number of NAFLD cases is projected to expand from 83.1 million in 2015 (~25% of the population) to 100.9 million in 2030. An increased proportion of these cases will be NASH, rising from 20% to 27% of adults with NAFLD during this interval[1]. This rising disease prevalence will exact a growing economic burden[2] and will be accompanied by both an increasing number of patients with cirrhosis and end-stage liver disease necessitating liver transplantation[3,4] and an alarming increase in hepatocellular carcinoma[5]. Compared to incidence in other liver diseases, a larger percentage (~35–50%) of HCCs that arise in NASH occur before patients are cirrhotic and routine screening for cancer is conducted[5,6]. As a result, these tumors tend to be larger and less amenable to curative therapies than those with other etiologies[7].

Globally, the prevalence of NAFLD is estimated at ~25% and is highest in the Middle East and South America and lowest in Africa[8]. Whereas NAFLD typically is accompanied by

Box 2 |

Comorbidities of NAFLD

Patients with NAFLD are twice as likely to die of cardiovascular disease than liver disease, which is largely related to shared risk factors including diabetes mellitus, HTN and obesity12. In fact, liver disease is only the third leading cause of death in patients with NAFLD, following cardiovascular disease and malignancy[36,175]. Both increased age and metabolic comorbidities increase the occurrence and severity of NASH[176,177]. NAFLD and especially NASH also confer an independent risk of adverse cardiovascular events in affected individuals beyond that conferred by the shared risk factors, likely related to abnormalities including systemic vascular endothelial dysfunction, atherogenic dyslipidemia and the systemic and hepatic proinflammatory state associated with NAFLD and NASH; the magnitude of this risk has not yet been quantified, however. NAFLD and NASH are also associated with abnormalities of cardiac structure and function, which further contribute to its impact on CVD mortality[28,178]. In a recent meta-analysis of 34,000 patients with NAFLD diagnosed by imaging or histology over a median follow-up of 6.9 years, there was a 65% increased risk of developing both fatal and nonfatal cardiovascular events[179].