Epidemiologia e diagnosi della MASLD

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Conflitti di interesse

Il dr. Mario Luca Morieri dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

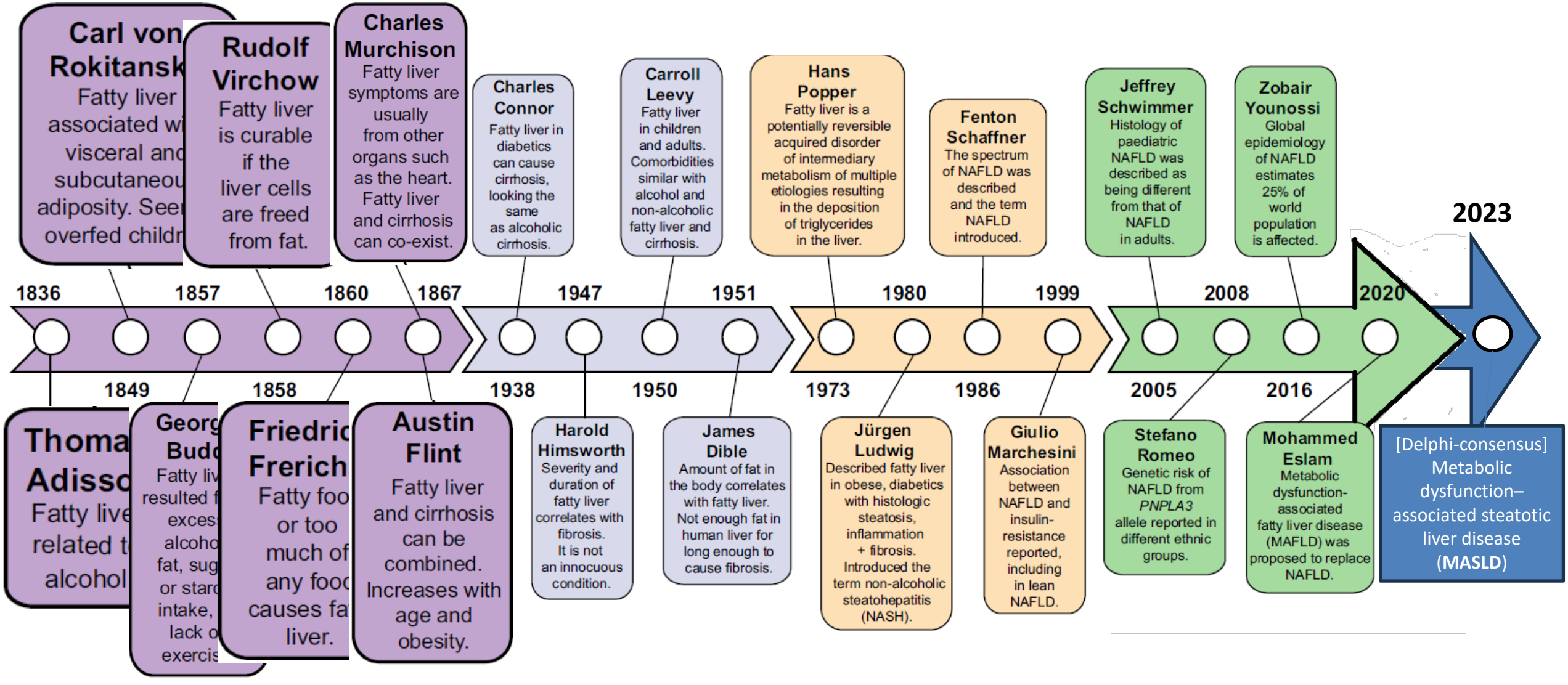
Amarin, Amgen, Astrazeneca, Eli Lilly, Merck Sharp & Dohme, Mylan, Novartis, Novo Nordisk, Sanofi, and Servier

Nessuna in relazione agli argomenti trattati in questa relazione

Epidemiologia e diagnosi della MASLD - Agenda

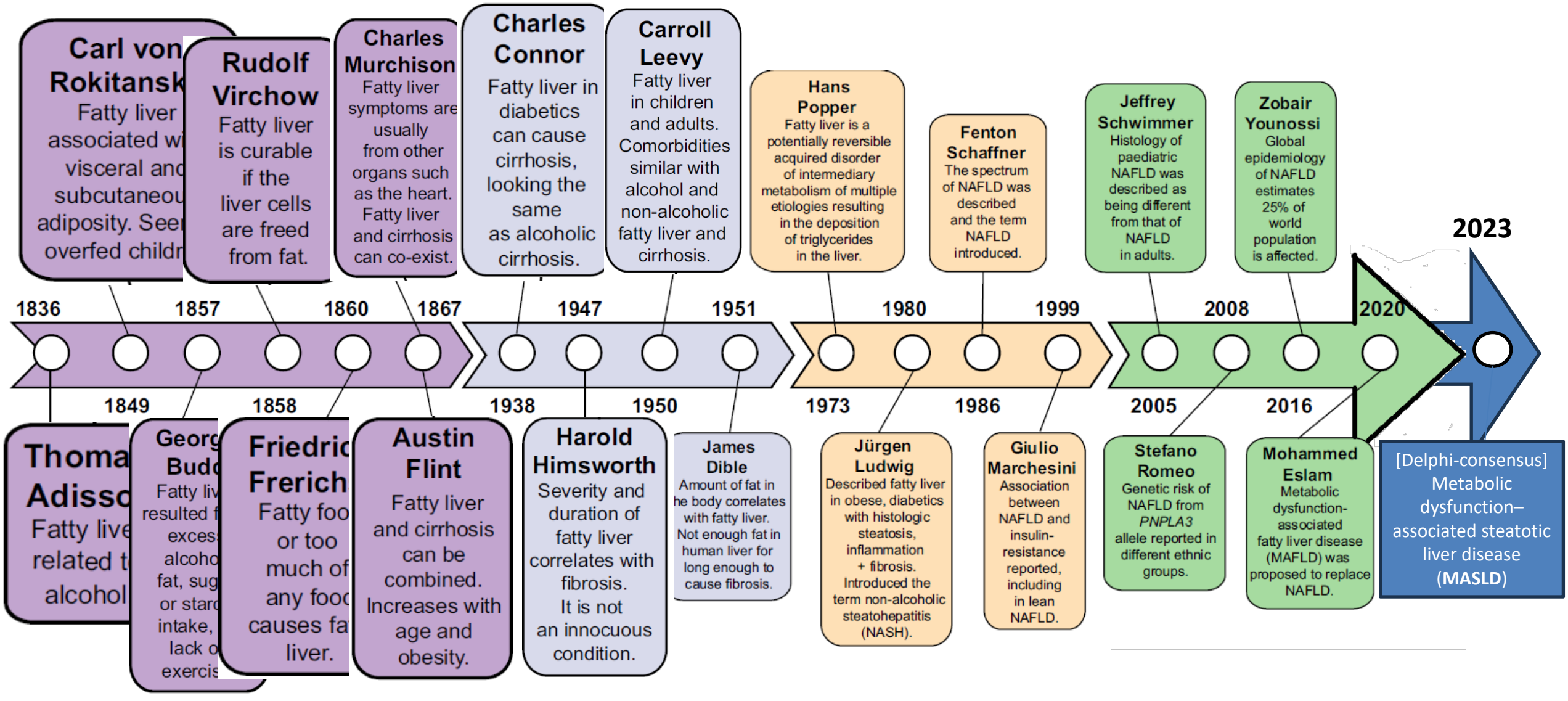
- Contesto Storico, Definizioni, e Diagnosi
- Epidemiologia
- Strategie di screening non invasivi e loro performance

Timeline evolution of Fatty Liver Disease



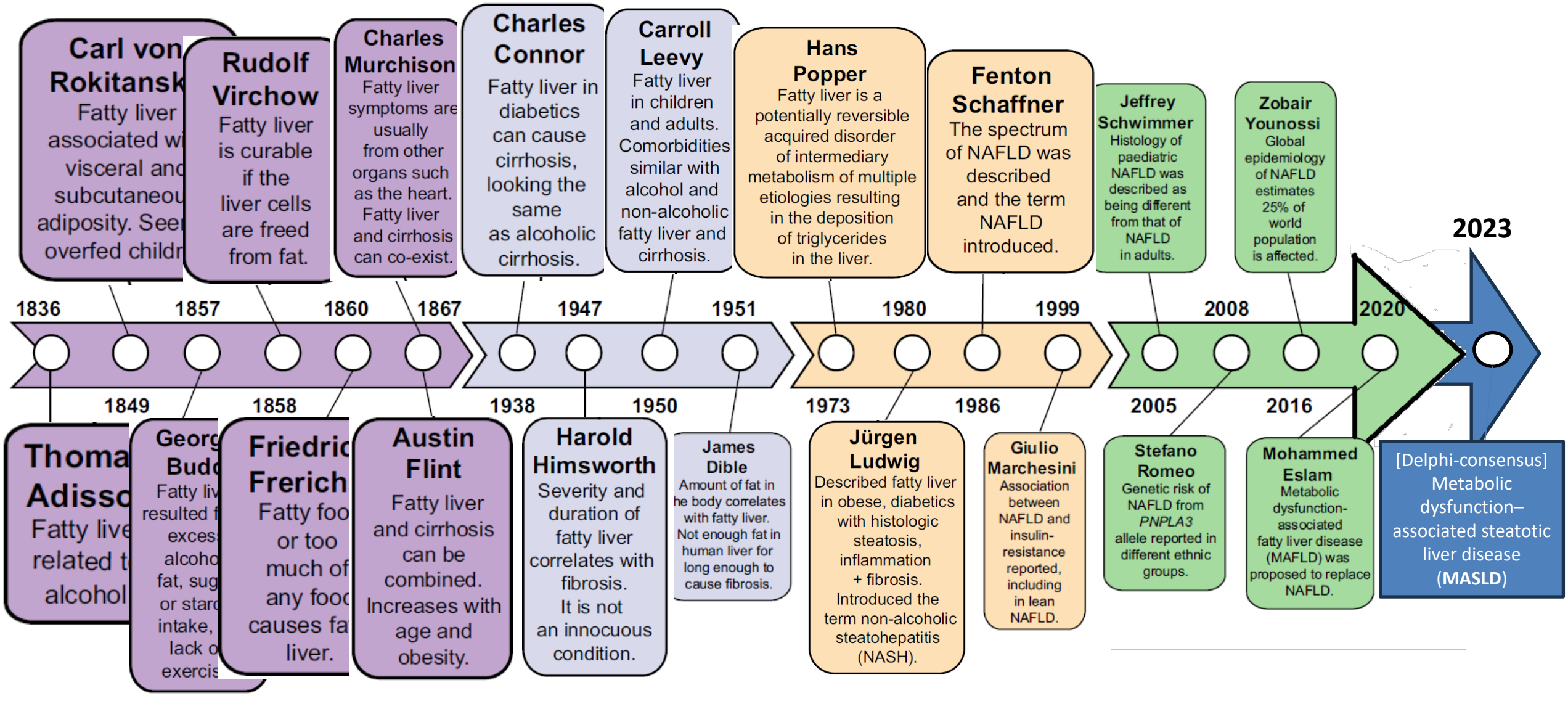
Adapted from Ayonrinde, JHEP 2021

Timeline evolution of Fatty Liver Disease



Adapted from Ayonrinde, JHEP 2021

Timeline evolution of Fatty Liver Disease



Adapted from Ayonrinde, JHEP 2021

NAFLD: non-alcoholic fatty liver disease

Definizione:

Presenza di steatosis epatica (almeno in 5% degli epatociti),
Identificata con imagin o biopsia

IN ASSENZA DI

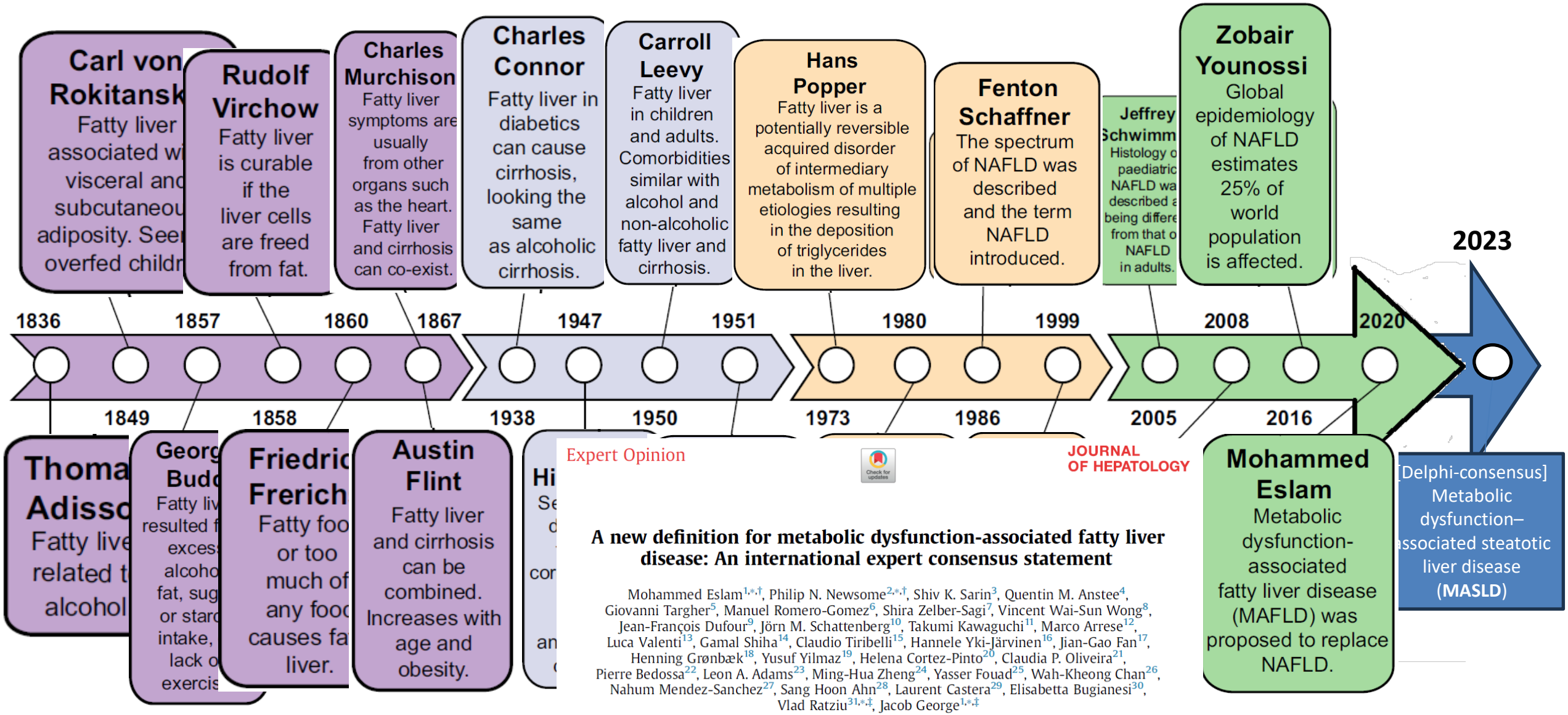
Significativo cosnumo alcolico attuali o pregresso (<limiti di sciurezza o zero alcohol)

E

altre cause di epatopatia

(e.g. epatiti virali, auto-immune, lipodistrofia)

Timeline evolution of Fatty Liver Disease

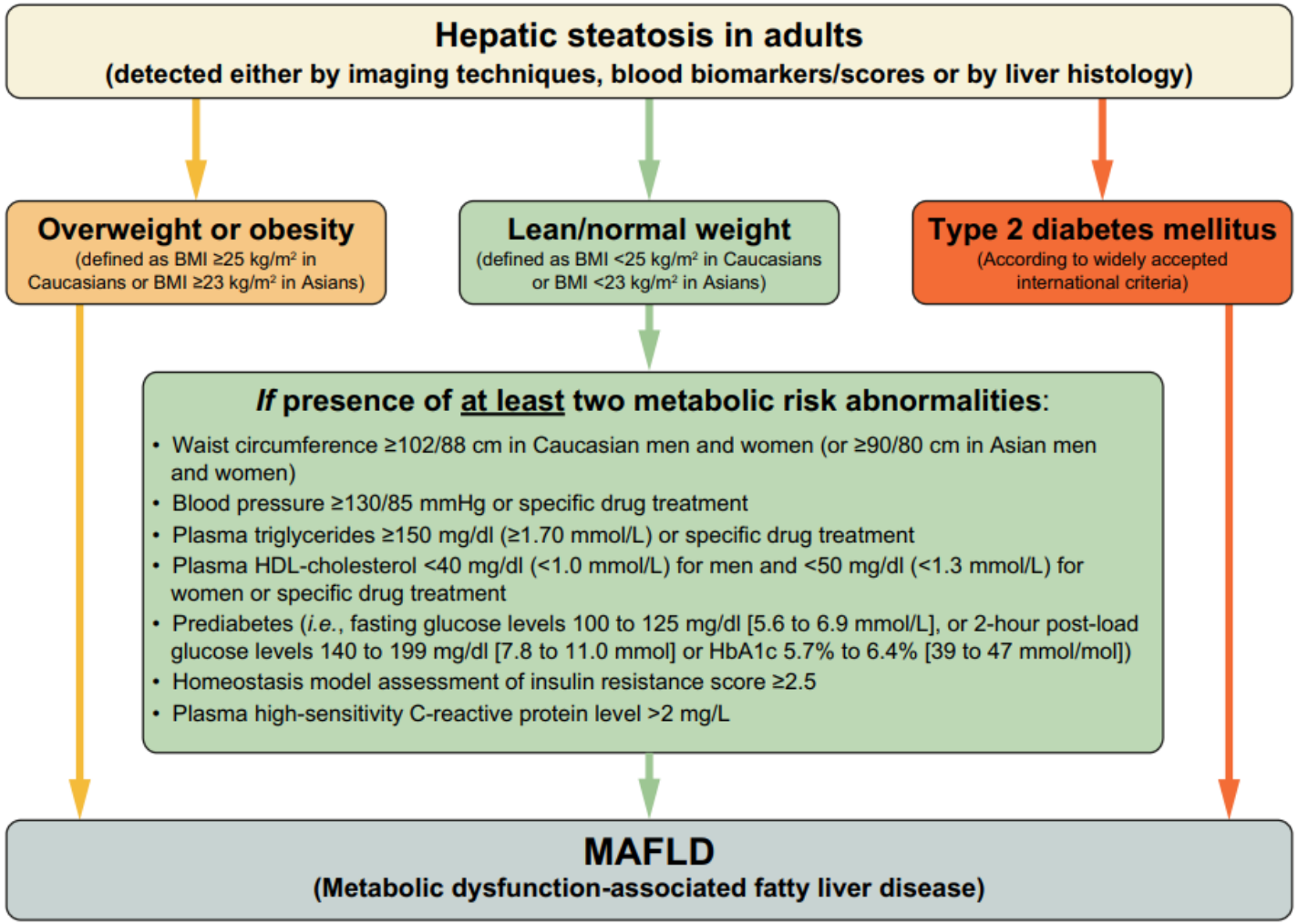


Adapted from Ayonrinde, JHEP 2021

Metabolic dysfunction and MAFLD definition

FROM ***exclusion of*** other etiology (e.g. alchool, virus,..)

TO ***regardless of*** **other etiology**



Eslam et al.
Journal of Hepatology 2020

Eziologia duale o multipla: MAFLD + alter epatopatie

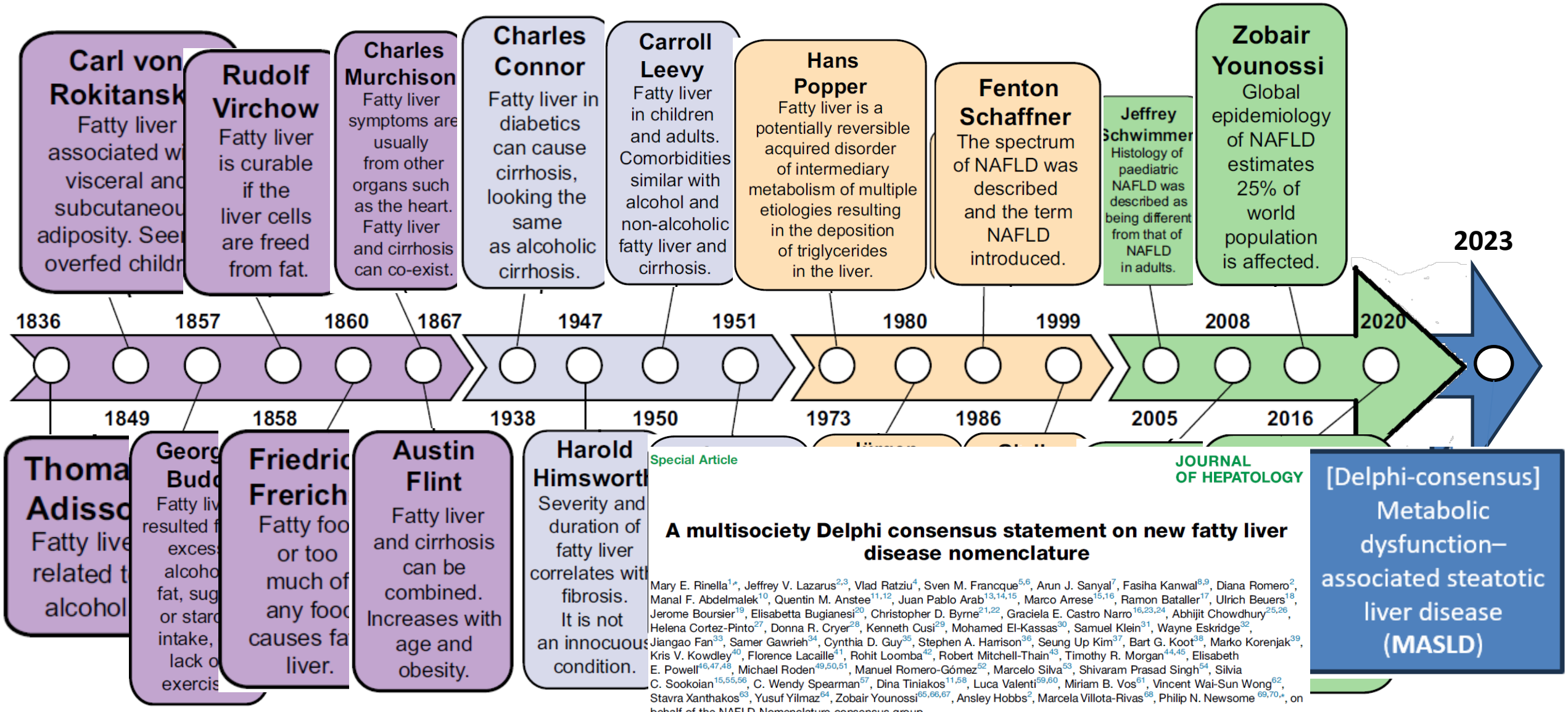
Meeting the criteria for a diagnosis of MAFLD

Plus

Any other cause of liver disease *e.g.*, alcohol-use disorder defined as consumption of >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)*, as defined by the National Institute of Alcoholism and Alcohol Abuse[47,82], viral infection (HIV, HBV and HCV), autoimmune hepatitis, inherited liver disorders, drug-induced liver injury or other known liver disease

Eslam et al.
Journal of Hepatology 2020

Timeline evolution of Fatty Liver Disease



Adapted from Ayonrinde, JHEP 2021

Metabolic dysfunction–Associated Steatotic Liver Disease - MASLD

Delphi consensus:

-

-

Table 1. Delphi panel characteristics (N = 225).

Professional characteristics	N (%)
Primary sector of employment	
EASL (70)	66 (29)
GI and endocrinological societies (21)	15 (7)
Pathology societies (4)	3 (1)
Patient organisation (29)	24 (11)

74% → consider a name change

(current nomenclature was flawed)

c”

t

d

steatotic liver disease (MASLD) →

revision of criteria

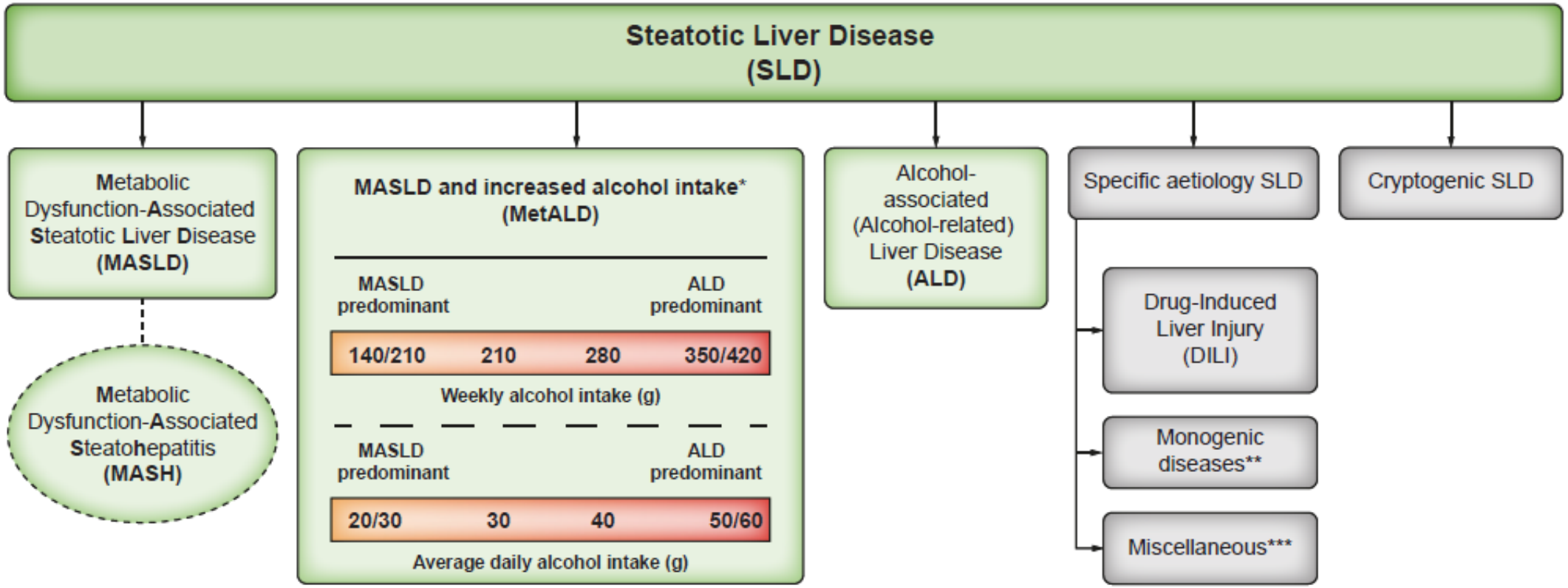
Nuove denominazioni: MASLD e MASH…

1. Per sottolineare il ruolo patogenetico della **resistenza insulinica** e della **disfunzione metabolica**

2. Per eliminare lo **stigma** associato ai termini *non alcolica* e *grasso*

3. Per offrire un **supporto diagnostico pragmatico**, includendo almeno un fattore di rischio cardiometabolico nella definizione

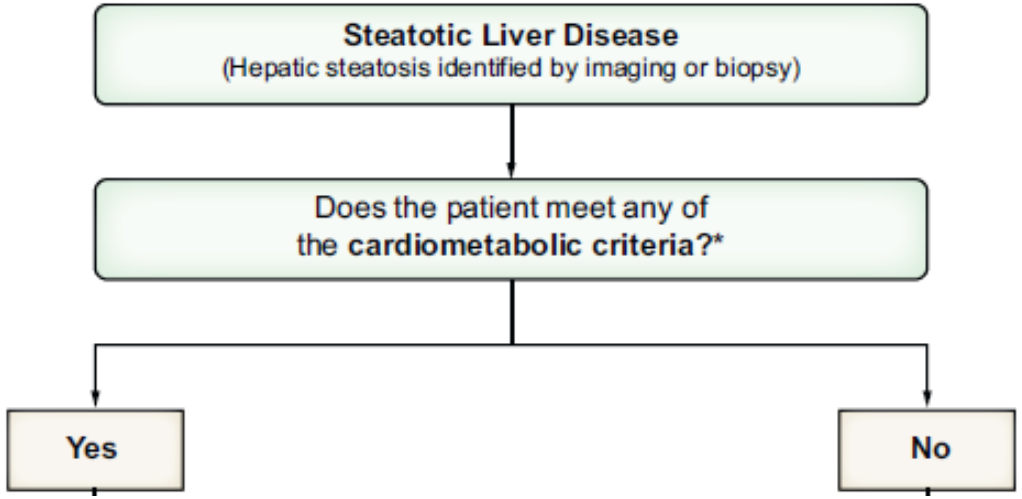
MASLD



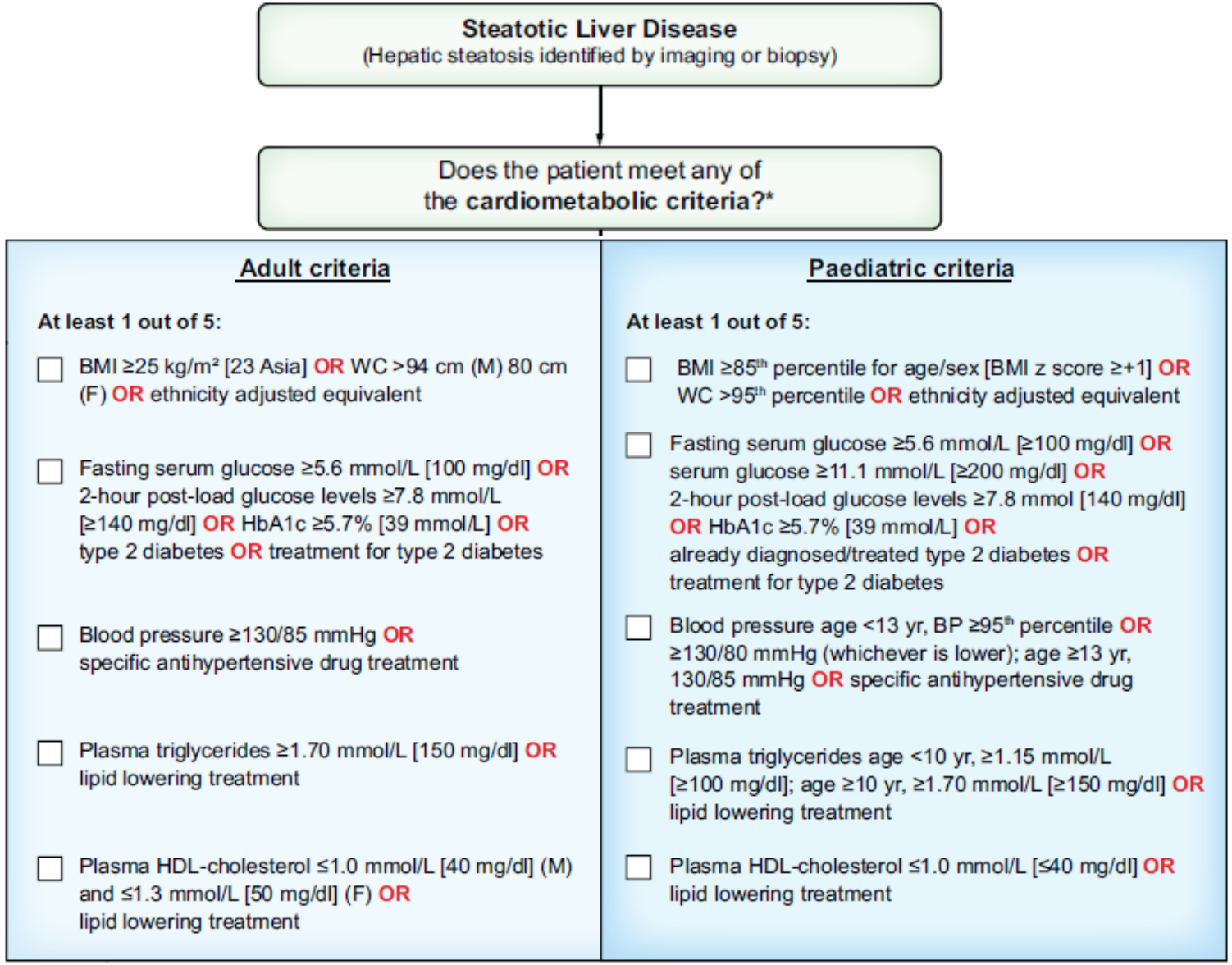
**e.g. Lysosomal acid lipase deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism

***e.g., HCV, malnutrition, celiac disease, HIV

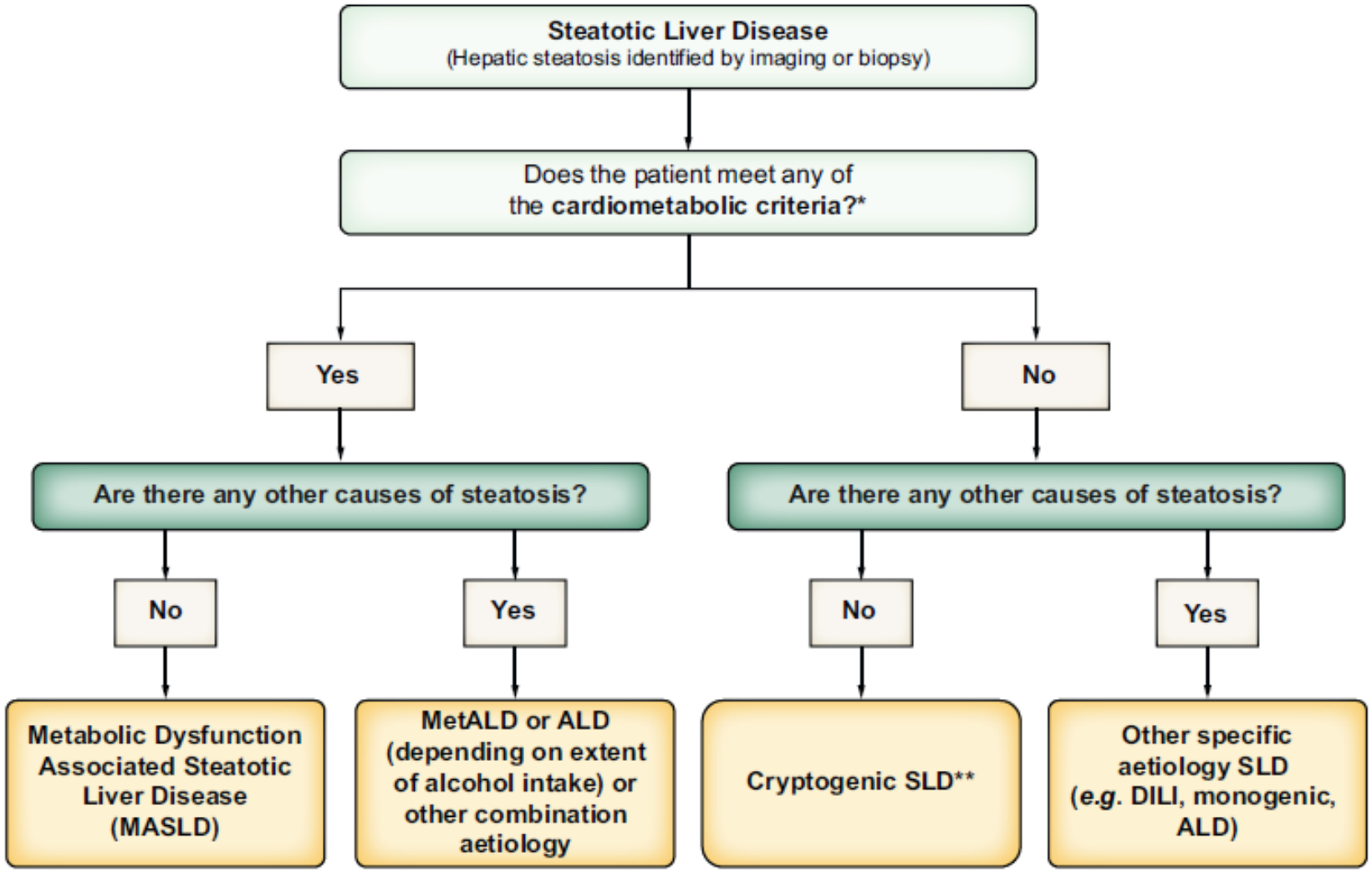
MASLD


Steatotic Liver Disease
(Hepatic steatosis identified by imaging or biopsy)
Does the patient meet any of
the cardiometabolic criteria?*
Yes
No

MASLD

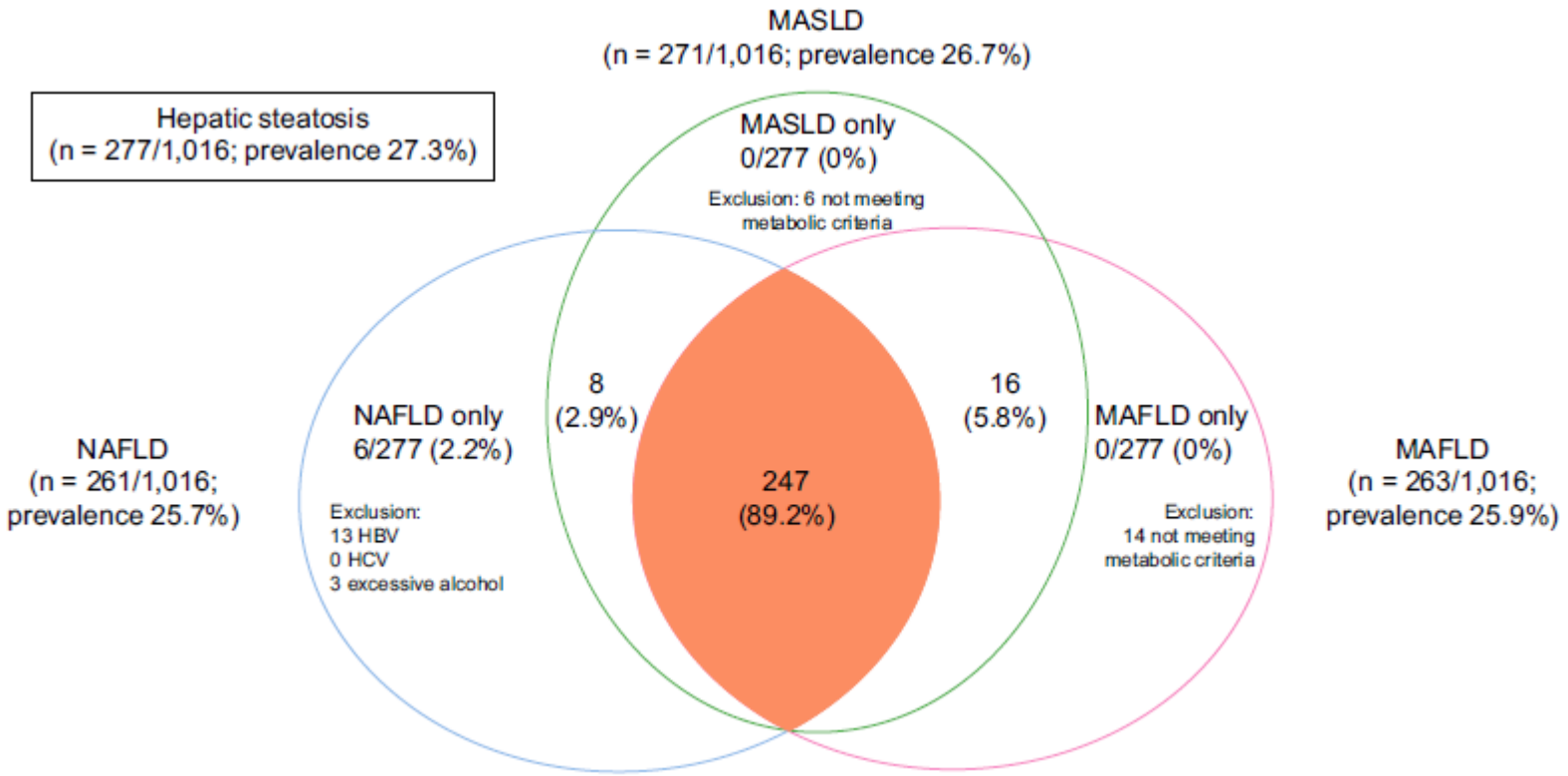

Steatotic Liver Disease
(Hepatic steatosis identified by imaging or biopsy)
Does the patient meet any of the cardiometabolic criteria?*
Adult criteria
At least 1 out of 5:
BMI ≥25 kg/m² [23 Asia] OR WC >94 cm (M) 80 cm (F) OR ethnicity adjusted equivalent
Fasting serum glucose ≥5.6 mmol/L [100 mg/dl] 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
Blood pressure ≥130/85 mmHg OR specific antihypertensive 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] (M) and ≤1.3 mmol/L [50 mg/dl] (F) OR lipid lowering treatment
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 <13 yr, BP ≥95th percentile OR ≥130/80 mmHg (whichever is lower); age ≥13 yr, 130/85 mmHg OR specific antihypertensive drug treatment
Plasma triglycerides age <10 yr, ≥1.15 mmol/L [≥100 mg/dl]; age ≥10 yr, ≥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

MASLD


Steatotic Liver Disease
(Hepatic steatosis identified by imaging or biopsy)
Does the patient meet any of the cardiometabolic criteria?*
Yes
No
Are there any other causes of steatosis?
Are there any other causes of steatosis?
No
Yes
No
Yes
Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)
MetALD or ALD (depending on extent of alcohol intake) or other combination aetiology
Cryptogenic SLD**
Other specific aetiology SLD (e.g. DILI, monogenic, ALD)

NAFLD, MAFLD and MASLD in general population (Hong Kong)

1,016 random individuals from the community [**Hong Kong 2008-2010**]
→ proton-magnetic resonance spectroscopy (mean age 48±10 years; 57.3% women; BMI 22.8±3.5 kg/m2).



565 (out of 739) without SLD at baseline underwent a second MR examination ≈4 years later
78 (14%) → incident SLD → 24% not fulfilling MAFLD vs 10% non fulfilling MASLD criteria

Song – Journal oh Hepatology 2023

NAFLD, MAFLD and MASLD in general population (Brazil)

Multicentric cohort

15,105 public servants from Brazil (age 35-74 yrs; 46% male; 30% with obesity) [2008 to 2010]

			34.7%		34.9%		33.4%
	All (N = 10,651)	No-NAFLD (n = 6,954)	NAFLD (n = 3,697)	No-MAFLD (n = 6,933)	MAFLD (n = 3,718)	No-MASLD (n = 7,082)	MASLD (n = 3,569)
Male sex at birth[a]	4,687 (44.0)	2,889 (41.5)	1,798 (48.6)	2,751 (39.7)	1,936 (52.1)	2,940 (41.5)	1,747 (48.9)
Age, yr[b]	51 (45-58)	50 (45-58)	52 (46-59)	50 (44-58)	53 (46-59)	50 (44-58)	52 (46-59)
Excessive alcohol intake[a]	726 (6.8)	726 (10.4)	0 (0.0)	412 (5.9)	314 (8.4)	726 (10.3)	0 (0.0)
Metabolic features							
BMI, kg/m^2[b]	26.5 (23.9-29.6)	25.5 (23.1-28.2)	28.7 (25.9-31.9)	25.1 (22.9-27.8)	29.1 (26.6-32.3)	25.4 (23.1-28.1)	28.9 (26.2-32.2)
WC, cm[b]	89.9 (81.7-98.5)	87 (79-95)	96 (89-104)	86 (79-93)	98 (91-105)	86 (79-94)	97 (90-105)
Systolic BP, mmHg[b]	119 (109-130)	116 (107-128)	122 (113-133)	116 (107-127)	123 (114-135)	117 (107-128)	123 (113-134)
Diastolic BP, mmHg[b]	75 (69-83)	74 (67-81)	78 (71-85)	73 (67-80)	79 (72-86)	74 (67-81)	78 (72-85)
Type 2 diabetes[a]	1,631 (15.3)	756 (10.9)	875 (23.7)	667 (9.6)	964 (25.9)	757 (10.6)	874 (24.8)
Hypertension[a]	4,620 (43.4)	2,603 (37.4)	2,017 (54.6)	2,416 (34.8)	2,204 (59.3)	2,603 (36.8)	2,017 (56.5)
Metabolic syndrome[a]	3,266 (30.8)	1,482 (21.4)	1,784 (48.3)	1,303 (18.9)	1,963 (52.9)	1,482 (21.0)	1,784 (50.1)

Hugo Perazzo et al – Journal oh Hepatology 2023

NAFLD, MAFLD and MASLD concordance/discordance

Cryptogenic SLD

NAFLD	MASLD		Total
	No	Yes	
No	6,954 (100.0%)	0 (0.0%)	6,954
Yes	128 (3.5%)	3,569 (96.5%)	3,697
Total	7,127 (66.5%)	3,524 (33.5%)	10,651 (100.0%)

Agreement and kappa values between different criteria:
NAFLD and MASLD: agreement=98.8%; k=0.973

e.g. Lean individual with NAFLD not reaching MAFLD criteria (30-70%)*

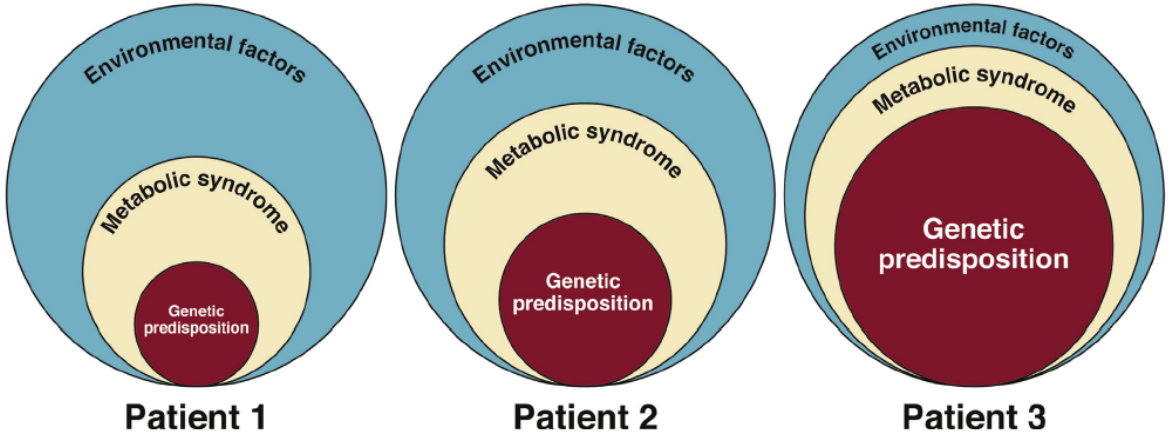
98.1% (n=314) MetALD
1.9% (n=6) MASLD+other

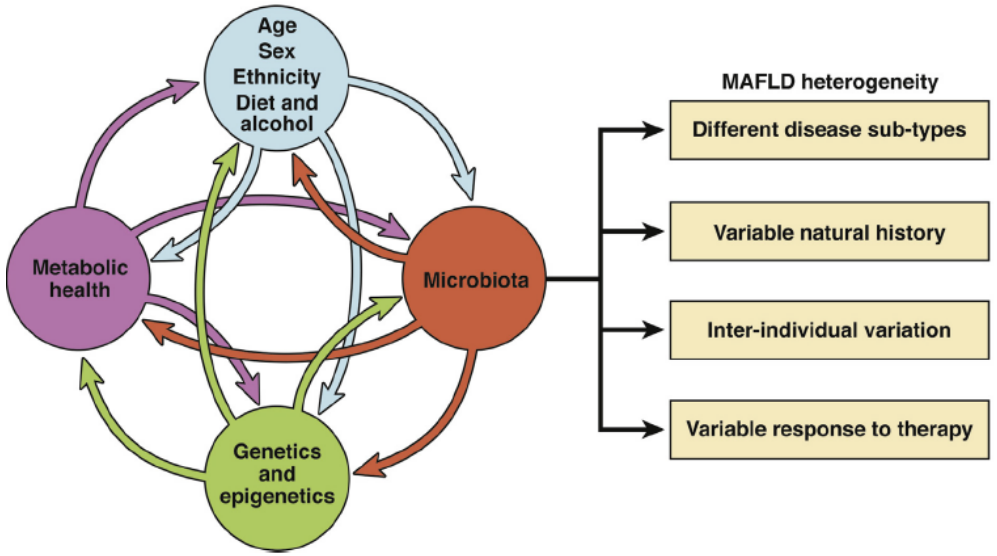
MAFLD	MASLD		Total
	No	Yes	
No	6,762 (97.5%)	171 (2.5%)	6,933
Yes	320 (8.6%)	3,398 (91.4%)	3,718
Total	7,082 (66.5%)	3,569 (33.5%)	10,561

Agreement and kappa values between different criteria:
MAFLD and MASLD: agreement=95.4%; k=0.900

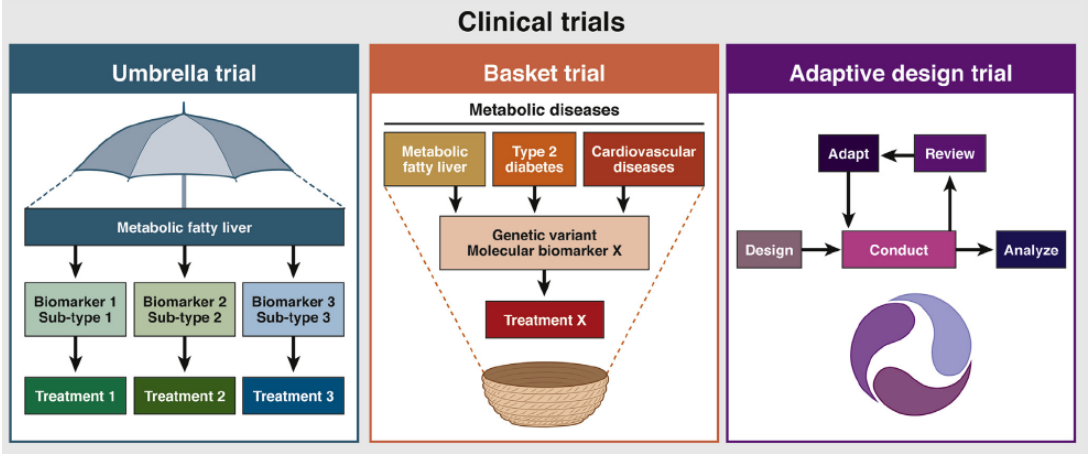
Hugo Perazzo et al – Journal oh Hepatology 2023

Steatotic Liver Disease: un background eterogeneo





→Criteri diagnostici ≠ Criteri di inclusione



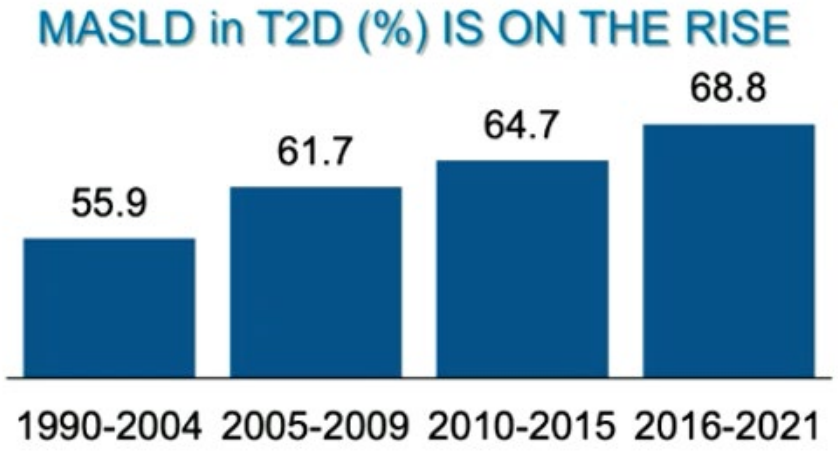
Eslam, Gastroenterology 2020

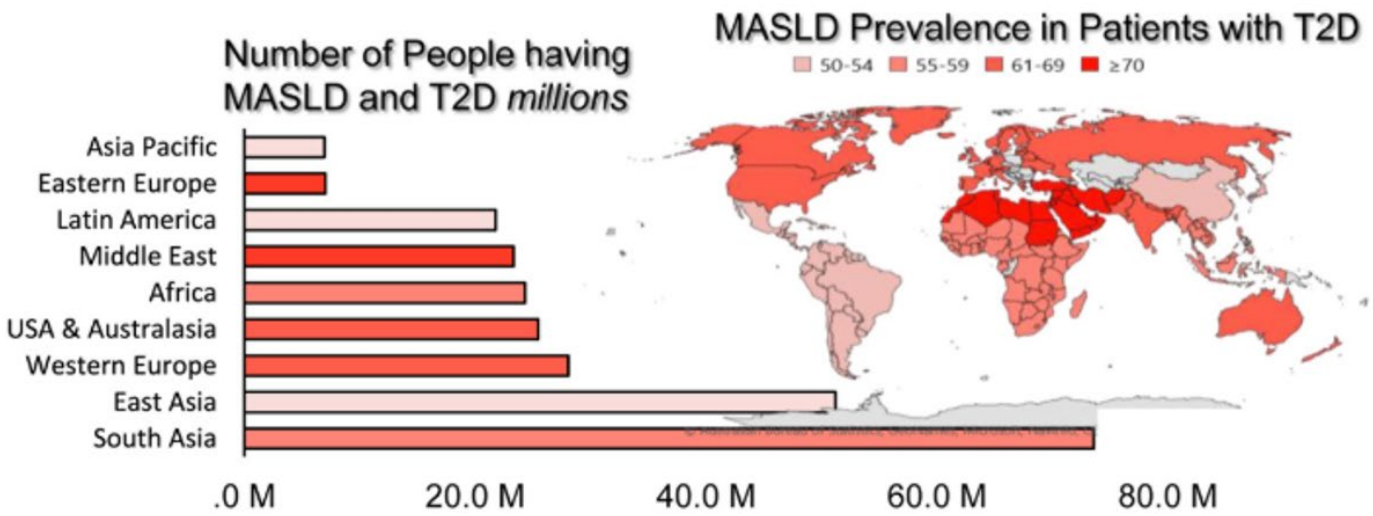
Epidemiologia della MASLD

Globally

436 Million Adults with T2D

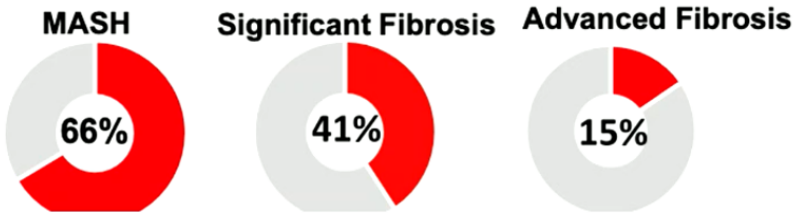
65% of T2D with MASLD





Meta-analysis:

- 123 studies (N = 2,224,144 patients with T2D)
- 12 studies (N =2733 T2D patients with LB)



Younossi Z et al. CGH 2024; 22: 1999–2010

Elevata prevalenza di statosi, steato-epatite e fibrosi avanzata

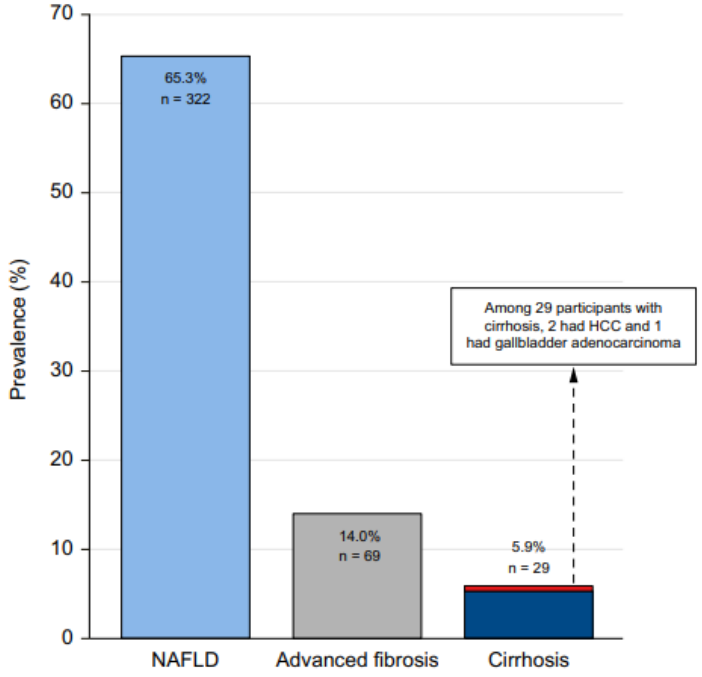
Research Article
NAFLD and Alcohol-Related Liver Diseases

JOURNAL
OF HEPATOLOGY

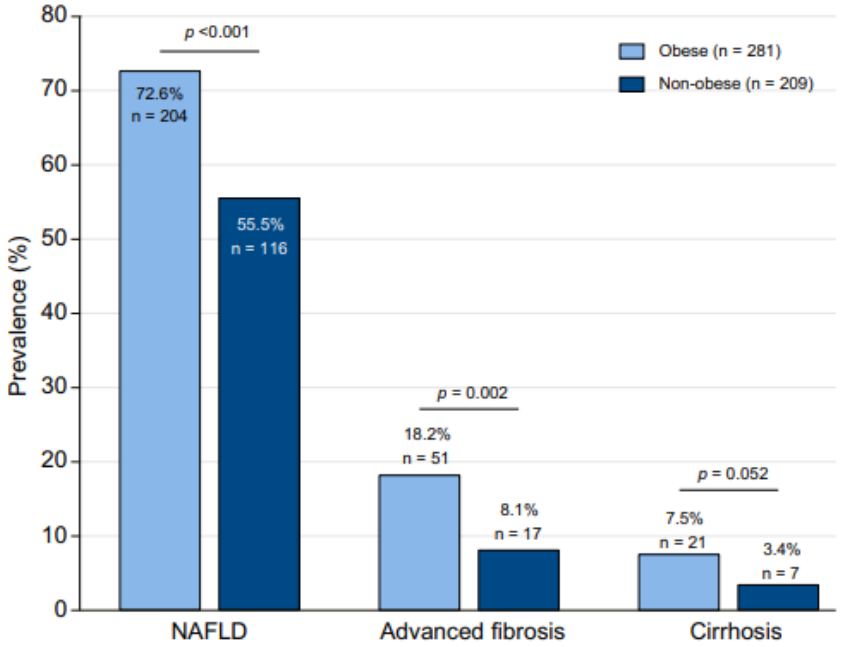
A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes

Veeral Ajmera[1,2], Sandra Cepin[1], Kaleb Tesfai[1], Heather Hofflich[3], Karen Cadman[4], Scarlett Lopez[1], Egbert Madamba[1], Ricki Bettencourt[1], Lisa Richards[1], Cynthia Behling[5], Claude B. Sirlin[6], Rohit Loomba[1,2,7,*]

Ajmera J of Hepatology 2023



- ***Prospective, cross sectional study***
- ***PCP and Endocrinologist San Diego – USA (2016-2022)***
- ***493 T2D patients > 50 years old → MRI and Fibroscan/VCTE***
- ***Excluded patients with excessive alchol consuption or other causes of liver disease***



NAFLD: MRI-PDFF ≥ 5% (or CAP ≥ 288 dB/m)
Advance fibrosis: MRE ≥3.63 kPa (or VCTE ≥ 8.8 kPa)
Cirrhosis: MRE ≥ 4.67 kPa (or VCTE ≥ 15 kPa)

Elevated ALT, liver fat (MRI-PDFF >10%) or ↑ liver stiffness
→ offered biopsy → 134/303 with biopsy
→ NASH= 61%, Advance fibrosis= 30%.

Elevata prevalenza di MASH e fibrosi avanzata, da biopsie, in pazienti con transaminasi lievemente aumentate

The QUID-NASH program

QUantitative Imaging in Diabetes and NASH

Investigator-initiated, prospective, cross-sectional, multicenter study

- 713 T2D outpatients systematically screened for MASLD (US and LFT) in 4 Diabetes clinics (Oct 2018-March 2021) were referred to an hepatologist for further work-up:

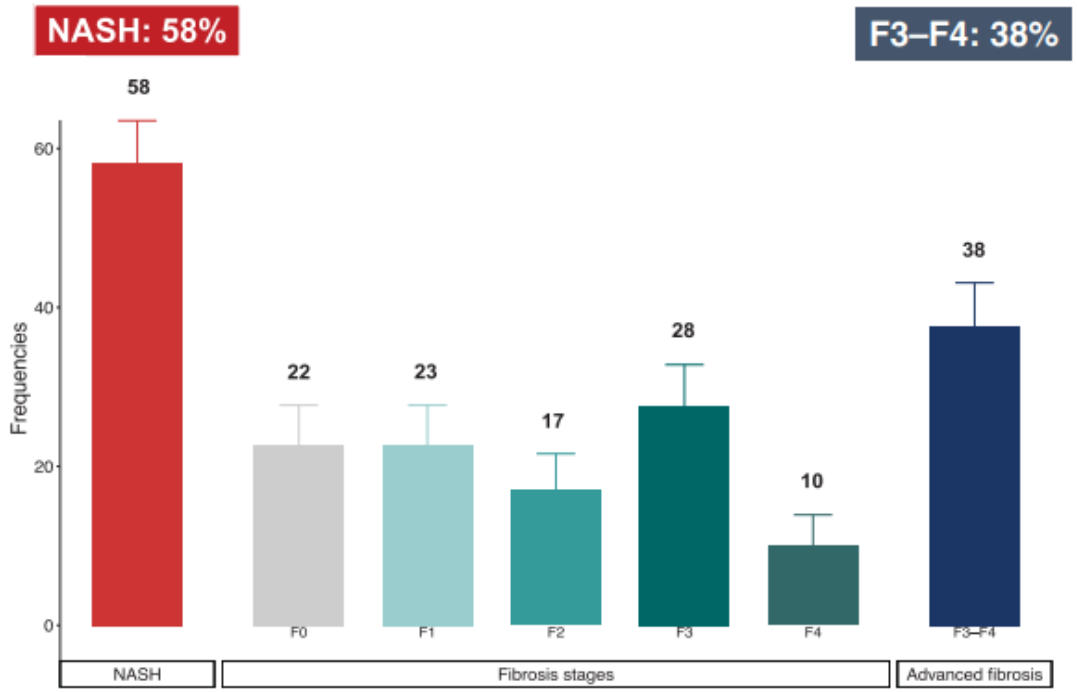
- A liver biopsy was indicated:

  - in case of persistent elevated ALT:
    > 20 IU/L in ♀
    > 30 IU/L in ♂ ← **Low AST/ALT threshold for biopsy**

  and
  - In the absence of other cause of liver disease

ClinicalTrials.gov number, NCT03634098

High prevalence of Nonalcoholic Steatohepatitis (NASH) and Advanced Fibrosis (F3–F4) in Type 2 Diabetes *N* = 330 liver biopsy specimens (ALT >20 IU/L in women or >30 IU/L in men)



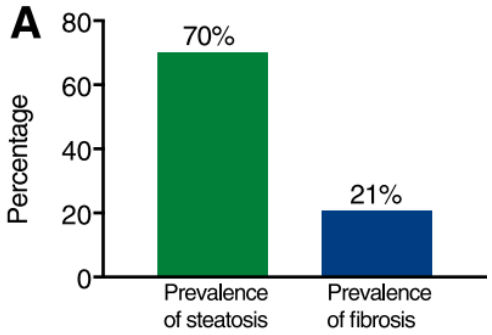
La fibrosi epatica avanzata è frequente nel diabete tipo 2, anche con AST e ALT normali

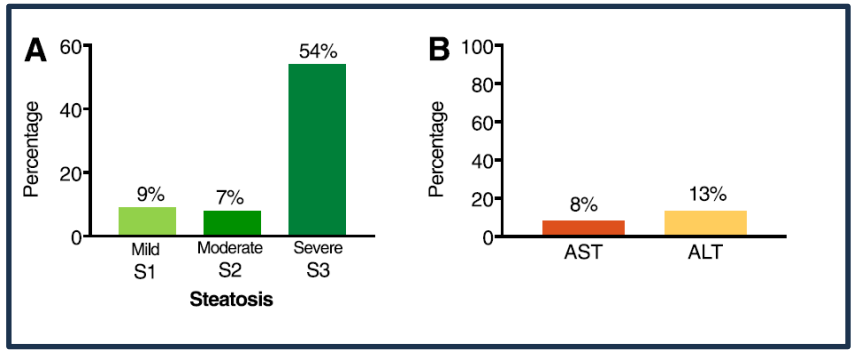
Advanced Liver Fibrosis Is Common in Patients With Type 2 Diabetes Followed in the Outpatient Setting: The Need for Systematic Screening

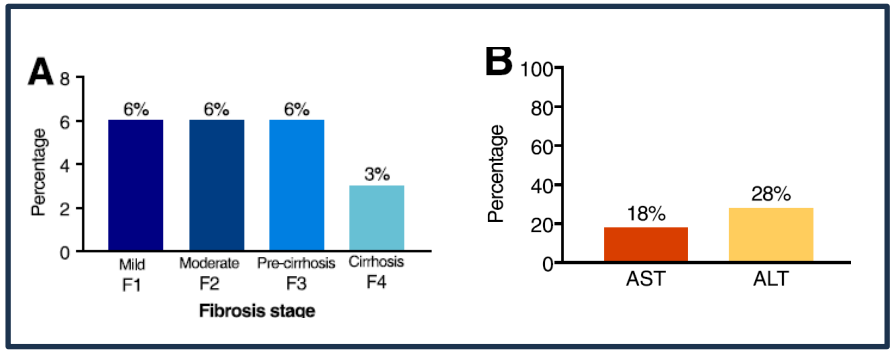
Romina Lomonaco,[1] Eddison Godinez Leiva,[1] Fernando Bril,[1] Sulav Shrestha,[1] Lydia Mansour,[1] Jeff Budd,[2] Jessica Portillo Romero,[2] Siegfried Schmidt,[3] Ku-Lang Chang,[3] George Samraj,[3] John Malaty,[3] Katherine Huber,[2] Pierre Bedossa,[4] Srilaxmi Kalavalapalli,[1] Jonathan Marte,[1] Diana Barb,[1] Danielle Poulton,[1] Nada Fanous,[1] and Kenneth Cusi[1,5]

Diabetes Care 2021;44:399–406 | https://doi.org/10.2337/dc20-1997

- 561 patients with T2DM (age: 60 yrs; BMI: 33.4 Kg/m2 ; HbA1c: 7.5)
- Primary care or endocrinology outpatient clinics
- **Unaware of having NAFLD**
- Screened by VCTE for steatosis (CAP > 274 dB/m) and fibrosis (LSM; >7.0 kPa).
- Invited to biopsy if moderate-to-severe risk of fibrosis.





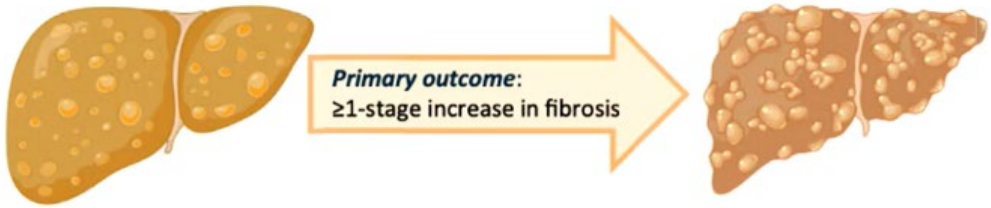


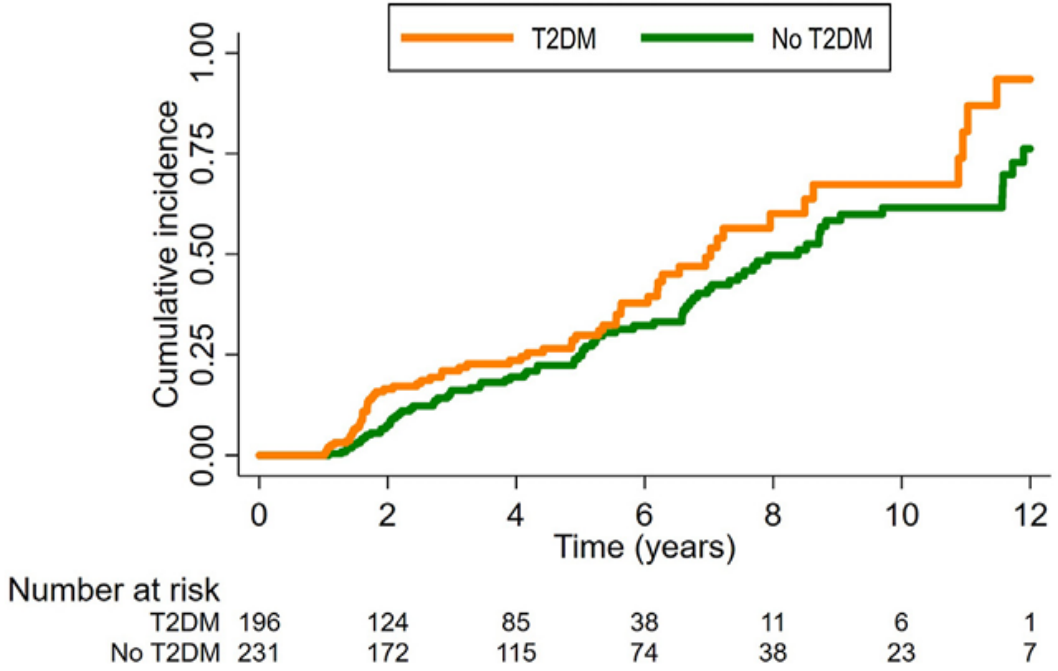
Moderate-to-advanced fibrosis (F2 or higher), an established risk factor for cirrhosis and overall mortality, affects at least one out of six (15%) patients with T2DM.

→ AST/ALT alone are insufficient as initial screening

Progressione di MASLD e MASH – Biopsy proven!

Multicenter (n=447)
Biopsy-proven NAFLD
Prospective data collection
Central pathology review
Liver biopsy at two time points





In 8 years 60% of subjects with T2D had fibrosis progression
And in 12 years 93% of subjects with T2D had fibrosis progression

Huang D et al. Gastroenterology 2023; 65:463–472

Steatosi epatica: risultati dal DARWIN T2D (Italia)

Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-021-01501-y

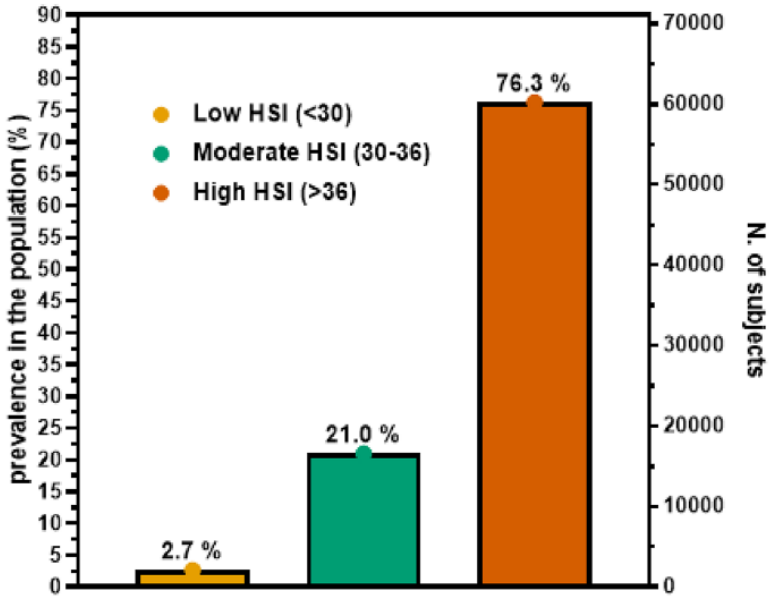
ORIGINAL ARTICLE

Prevalence of hepatic steatosis in patients with type 2 diabetes and response to glucose-lowering treatments. A multicenter retrospective study in Italian specialist care

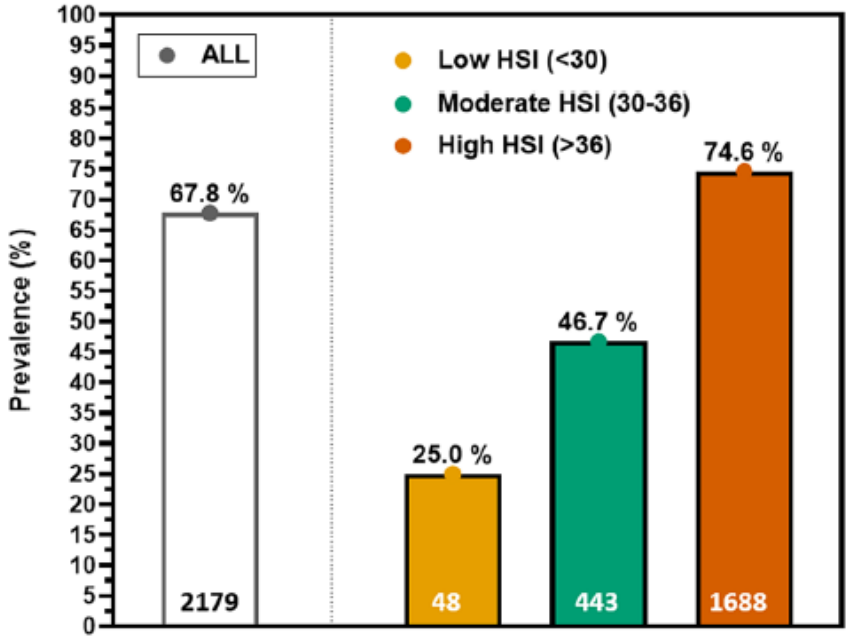
M. L. Morieri[1] · N. Vitturi[1] · A. Avogaro[1] · G. Targher[2] · G. P. Fadini[1] · DARWIN-T2D Network of the Italian Diabetes Society

N=78,895 T2D

MAFLD



US-detected steatosis [n=2179 T2D]



MASLD → n=1478 (67,8%)
+Viral → 69 (3,1%)
Excess alcohol → 13 (0,5%)
Excess or moderate alcohol→ 142 (6,5%)
Missing data on alcohol=65%

Modified from Morieri et al – JEI 2021

Score per Steatosi e Fibrosi Epatica: Risultati GLP1- Real Word Evidence (Veneto)

Nutrition, Metabolism & Cardiovascular Diseases (2021) 31, 3474–3483

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

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Changes in markers of hepatic steatosis and fibrosis in patients with type 2 diabetes during treatment with glucagon-like peptide-1 receptor agonists. A multicenter retrospective longitudinal study

Mario Luca Morieri [a], Giovanni Targher [b], Annunziata Lapolla [a,c], Michele D'Ambrosio [d], Federica Tadiotto [d], Mauro Rigato [e], Vera Frison [f], Agostino Paccagnella [e], Natalino Simioni [f], Angelo Avogaro [a], Gian Paolo Fadini [b,*]

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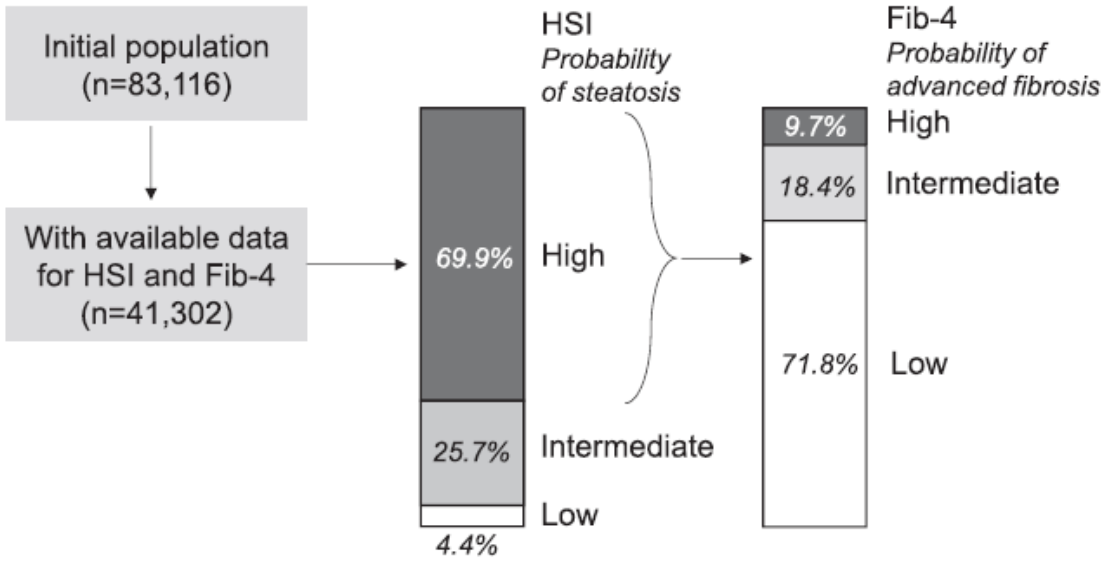


Figure 1 Flowchart of T2D patients included in the study. HSI, hepatic steatosis index. Fib-4 fibrosis index.

Morieri et al – NMCD 2021

Epidemiologia e caratteristiche della MASLD impongono uno screening mirato!

- **Prevalenza MASLD nei pazienti con DT2 ≥60%**
  - **≈ ½ con MASH**
  - **≈ 20% (1 su 5) con fibrosi avanzata**

- **AST e ALT la maggiorparte delle volte sono nei limiti di norma**

MASLD Screening

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) in People With Diabetes: The Need for Screening and Early Intervention. A Consensus Report of the American Diabetes Association

Kenneth Cusi,[1] Manal F. Abdelmalek,[2] Caroline M. Apovian,[3] Kirthikaa Balapattabi,[4] Raveendhara R. Bannuru,[4] Diana Barb,[1] Joan K. Bardsley,[5] Elizabeth A. Beverly,[6,7] Karen D. Corbin,[8] Nuha A. ElSayed,[4,9] Scott Isaacs,[10] Fasiha Kanwal,[11] Elizabeth J. Pekas,[4] Caroline R. Richardson,[12] Michael Roden,[13,14,15] Arun J. Sanyal,[16] Jay H. Shubrook,[17] Zobair M. Younossi,[18,19] and Mandeep Bajaj[11]

Diabetes Care 2025;48:1057–1082 | https://doi.org/10.2337/dci24-0094

Razionale degli screening:

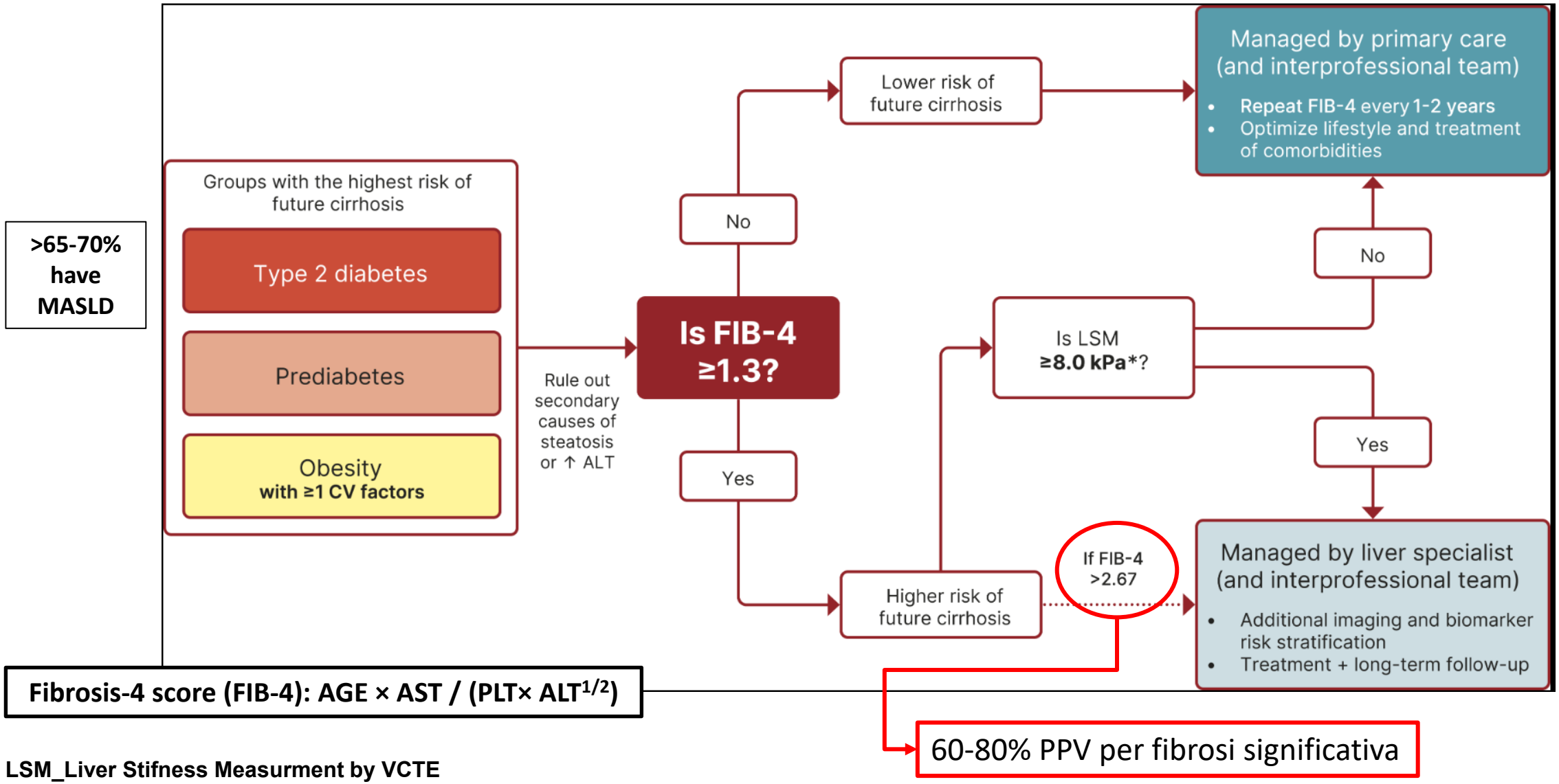
applicare le adeguate strategie diagnostiche al fine di

identificare e trattare una condizione

che potrebbe portare a gravi comorbidità e mortalità

Diabetes Care. 2025;48(7):1057-1082. doi:10.2337/dci24-0094

Algoritmo diagnostico per la stratificazione del rischio e prevenzione della cirrosi

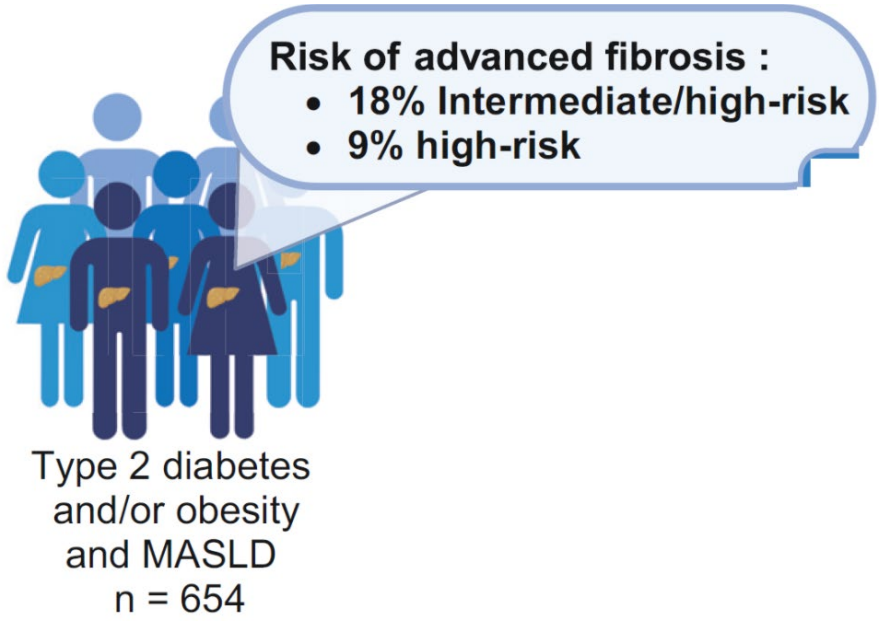


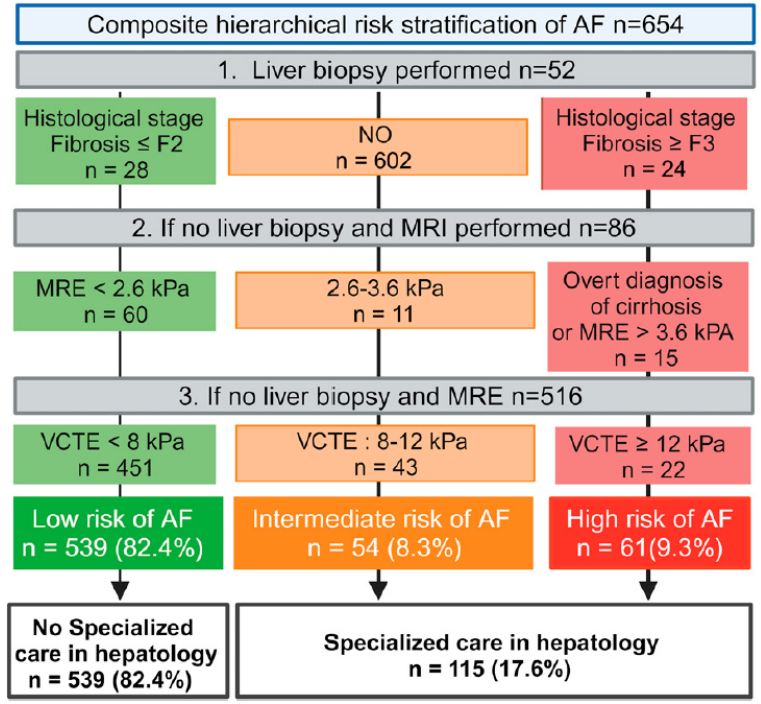
LSM_Liver Stifness Measurment by VCTE

Diabetes Care. 2025;48(7):1057-1082. doi:10.2337/dci24-0094

Efficacia dello two-steps screening non invasivo

Screening for MASLD-related advanced fibrosis in diabetology

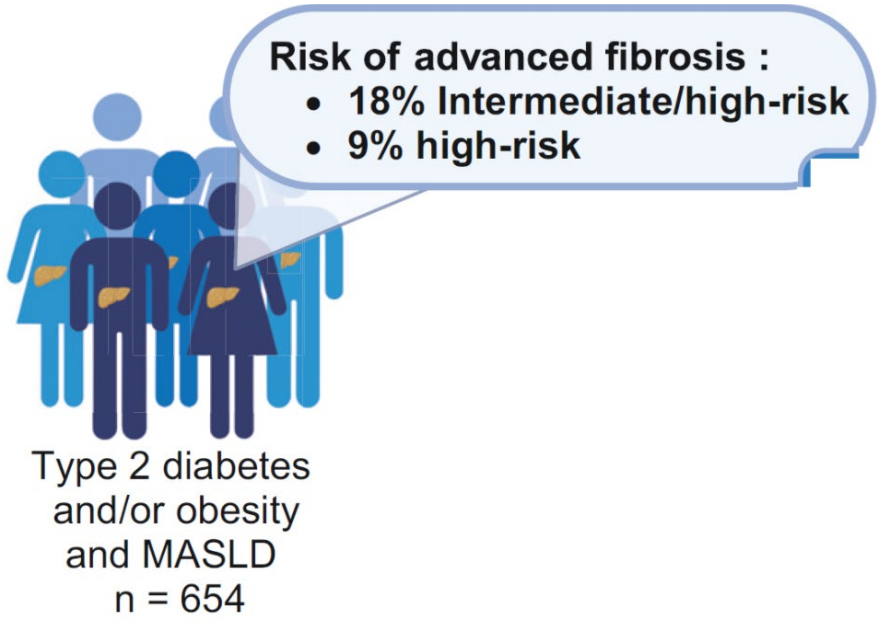




Caussy C - Diabetes Care 2025

Efficacia dello two-steps screening non invasivo

Screening for MASLD-related advanced fibrosis in diabetology



Among first-line tests, FIB-4 performed the best, classifying more than half the cohort (54%) as low risk, with a negative predictive value (NPV) of 97%.

Table 2—Diagnostic accuracy of NITs for detection of high risk of AF using literature-suggested threshold

	AUROC (95% CI)	Sensitivity	Specificity	PPV	NPV	Uncertainty area, %
NFS	0.71 (0.64–0.79)					63.04
<−1.455		89.8	23	10.7	95.1	
>0.676		35.6	87	22	92.9	
FIB-4 score	0.78 (0.72–0.84)					41.46
<1.30		84.7	58	17.1	97.2	
>2.67		16.9	96.9	35.7	91.9	
MAF-5	0.77 (0.71–0.84)					8.0
<0		100	2.8	9.5	95.1	
≥1		100	11.5	10.4	98.7	
FibroMeter						
≥F3*	0.74 (0.66–0.83)	46.8	89.9	31.9	94.2	NA
FibroTest						
≥F3	0.78 (0.72–0.85)	36.8	91	29.4	93.3	NA
ELF test	0.82 (0.76–0.87)					
<7.7		100	2.19	9.5	100	73.1
<9.8		65.6	79.1	24.2	95.6	23.15
≥11.3		11.5	99.3	61.8	91.6	23.15
Optimal cutoff 9.6		75.4	73.4	22.5	96.7	NA
Fixed 90% sensitivity <9.2		90.0	49.7	15.8	98.3	39.9
Fixed 90% specificity ≥10.2		52.5	90.0	35.2	94.8	39.9
2D-SWE-SSI	0.84 (0.78–0.89)					17.8
<8		76.3	80.3	28.5	97.1	
≥10.5		45.8	92.7	39.1	94.3	

*Participants with a FibroMeter report classified as F2–F3 were classified as ≥F3 in analysis (*n* = 3). NA, not applicable.

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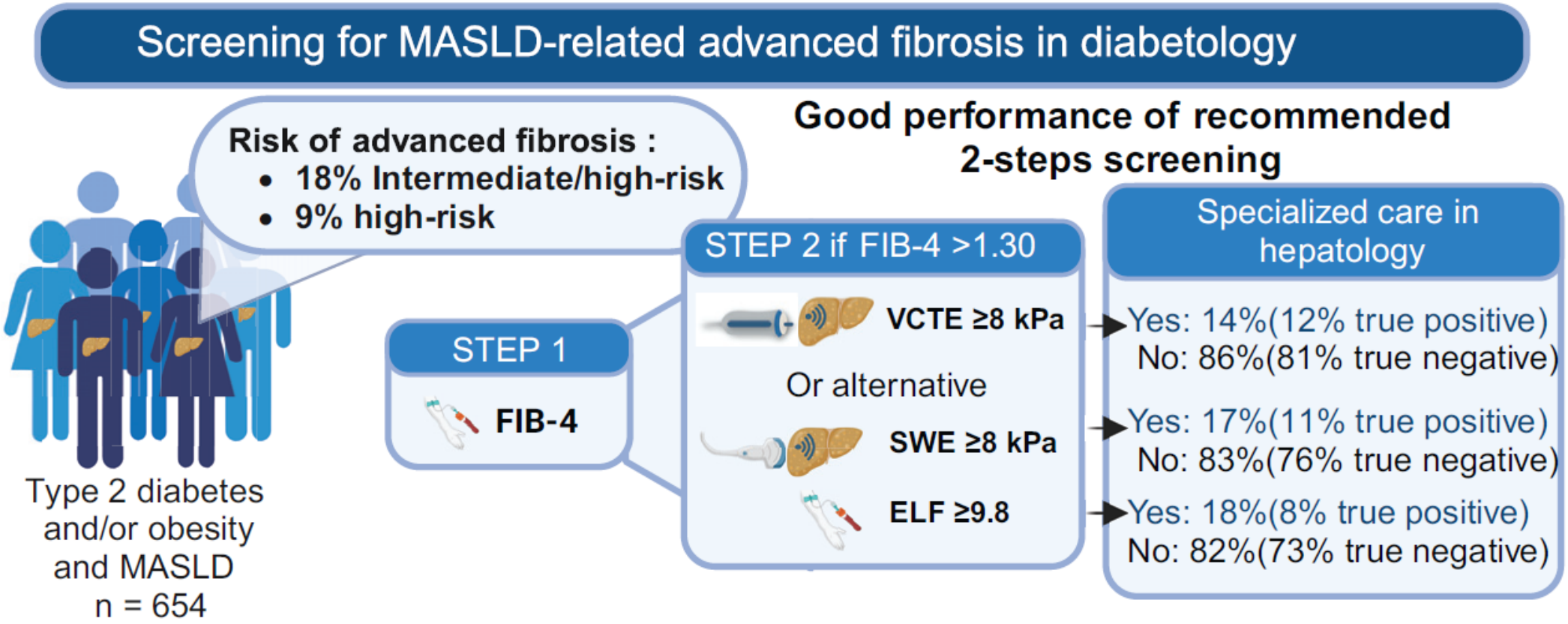
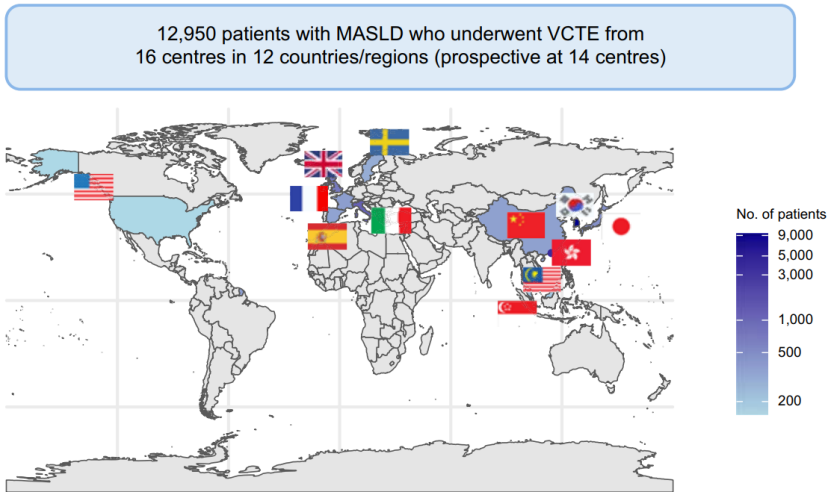
Efficacia dello two-steps screening non invasivo



Caussy C - Diabetes Care 2025

Performance dell'algoritmo a 2-step FIB-4 - VCTE

VCTE-Prognosis study was a longitudinal study of patients with MASLD who had undergone VCTE examinations at 16 centres from the US, Europe and Asia with subsequent follow-up for clinical events.



The primary outcome: HCC, hepatic decompensation, liver transplant, and liver-related death

At a median (IQR) follow-up of 47 (23-72) months, 248 (1.9%) patients developed LREs.

Characteristics	All patients N = 12,950
Age (years)	51.7 (13.9)
Female sex, n (%)	5,316 (41.1)
Male sex, n (%)	7,634 (58.9)
BMI (kg/m^2)	27.2 (24.7 to 30.4)
Diabetes, n (%)	4,429 (34.2)
Hypertension, n (%)	4,835 (37.3)
ALT (IU/L)	38 (24 to 64)
AST (IU/L)	31 (23 to 47)
GGT (IU/L)	44 (27 to 78)
Albumin (g/L)	44.8 (3.8)
Total bilirubin (µmol/L)	12.0 (8.6 to 16.0)
Platelet (×10^9/L)	239 (200 to 282)
Creatinine (µmol/L)	72 (60 to 83)

Caussy C - Diabetes Care 2025

Performance dell'algoritmo a 2-step FIB-4 - VCTE

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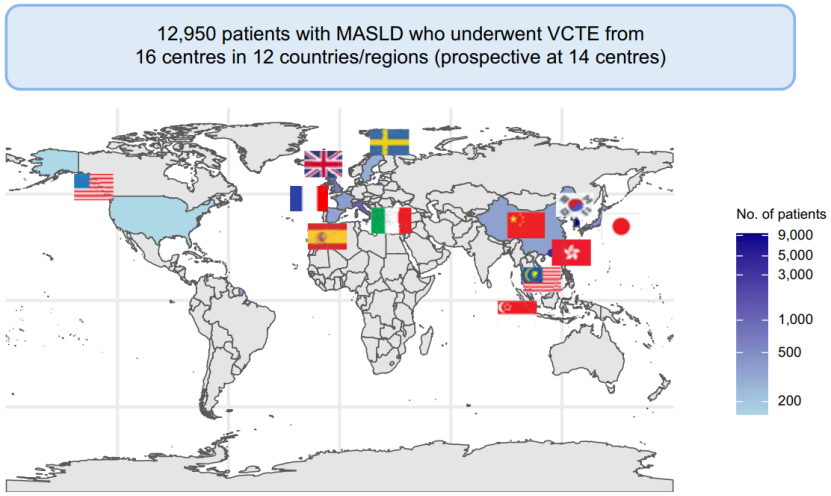

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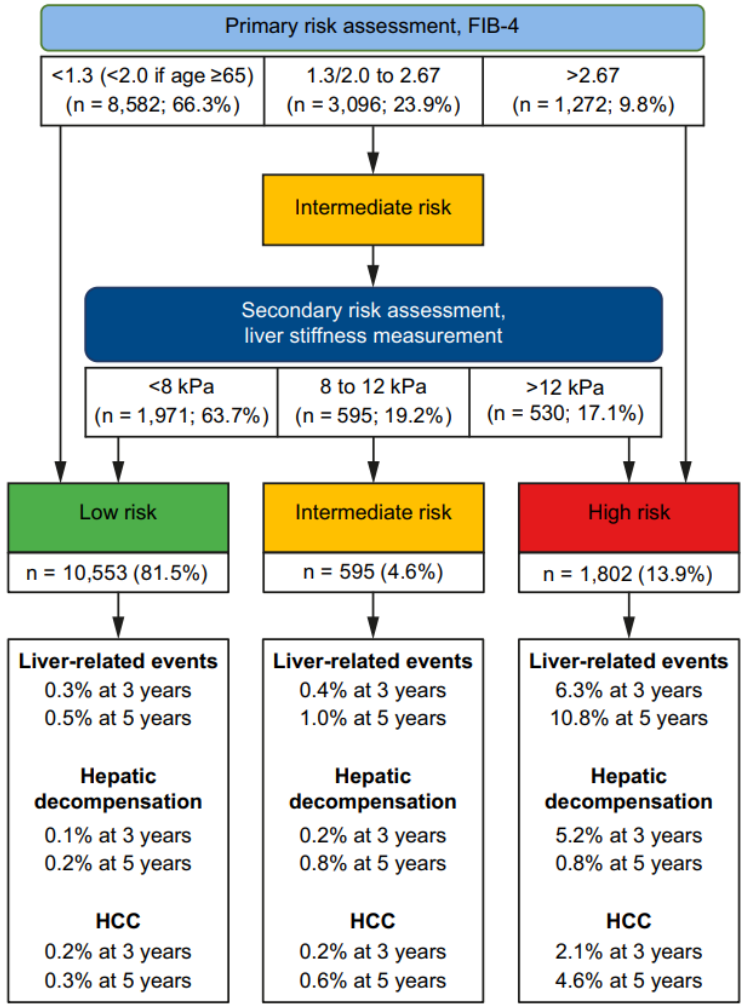

Caussy C - Diabetes Care 2025

Conclusioni

- **L'evoluzione semantica: riflette le maggiori conoscenze scientifiche e le necessità della società odierna**
  - **Criteri positivi metabolici (non solo di esclusione) e attenzione verso eziologie multiple/combinate (es. MetALD)**

- **Prevalenza elevata e in crescita di MASLD, e quota rilevante con steato-epatatite e fiborsi avanzata**

- **Screening non invasivo con FIB-4 ed elastometria (VCTE) stratifica efficacemente la popolazione da indirizzare a percorsi e trattamenti specifici**

- **Lo screening della MASLD va eseguito, al pari di quello delle complicanze micro e macrovascolari, in tutti i pazienti con diabete tipo 2**

GRAZIE!

Mario Luca Morieri MD PhD

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Dipartimento di Medicina, Università di Padova, Padova, Italia

BACK up

- ggg

The QUID-NASH program

QUantitative Imaging in Diabetes and NASH

Investigator-initiated, prospective, cross-sectional, multicenter study

- 713 T2D outpatients systematically screened for MASLD (US and LFT) in 4 Diabetes clinics (Oct 2018-March 2021) were referred to an hepatologist for further work-up:
- A liver biopsy was indicated:

- in case of persistent elevated ALT:
  > 20 IU/L in ♀
  > 30 IU/L in ♂

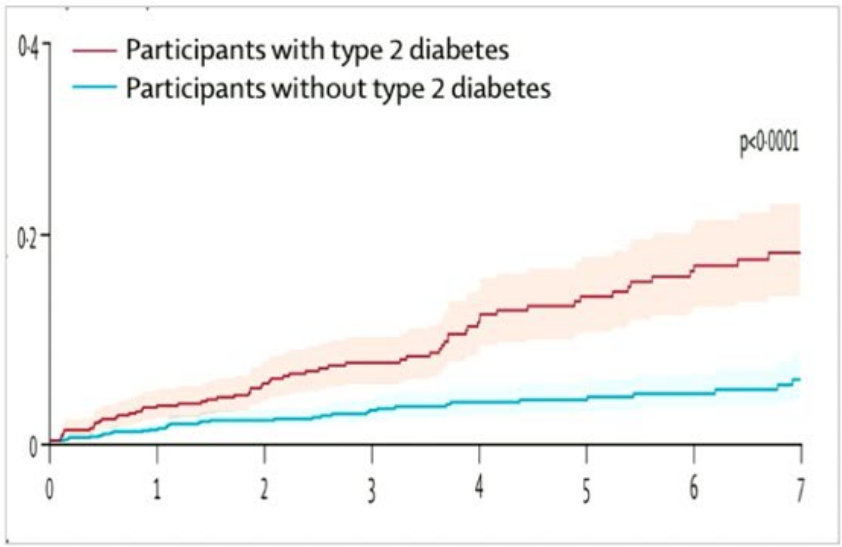
and

- In the absence of other cause of liver disease

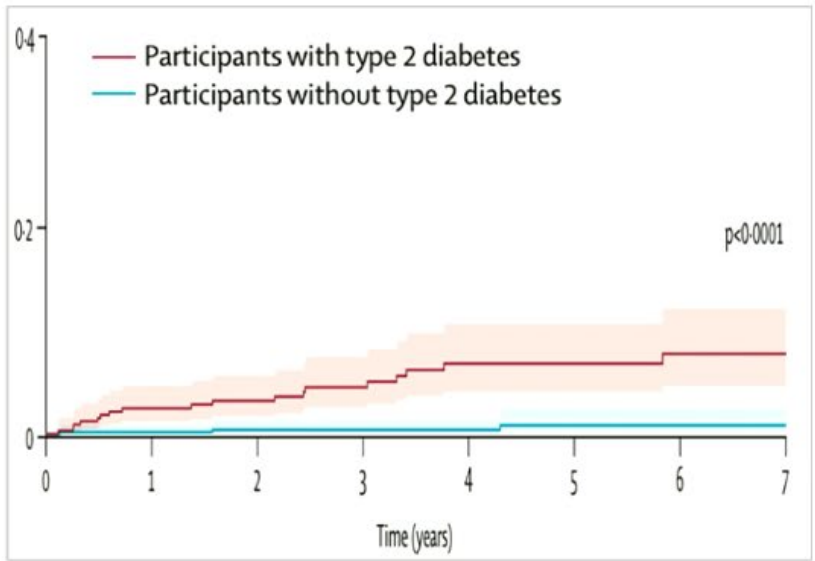
ClinicalTrials.gov number, NCT03634098

TD2 patients are at higher risk of complications

Decompensation

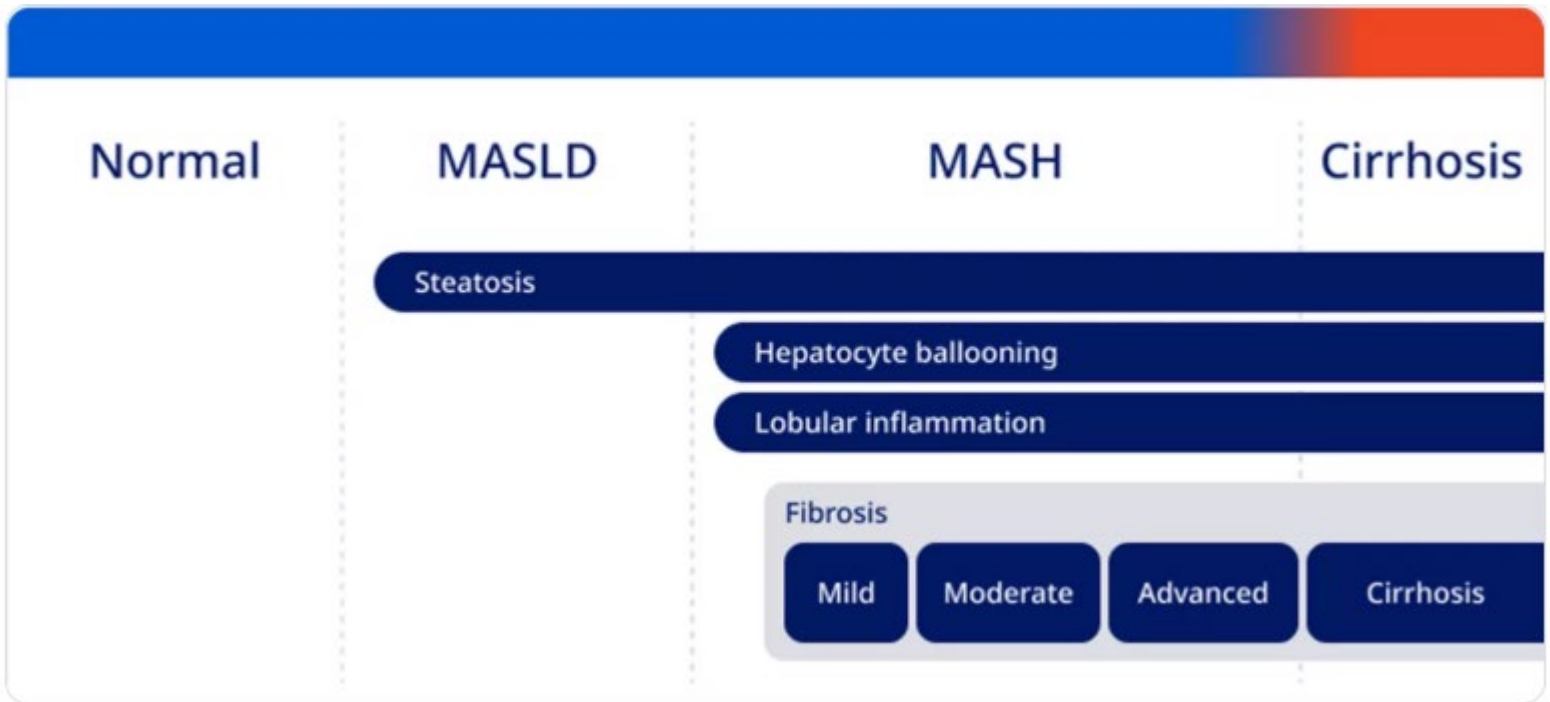


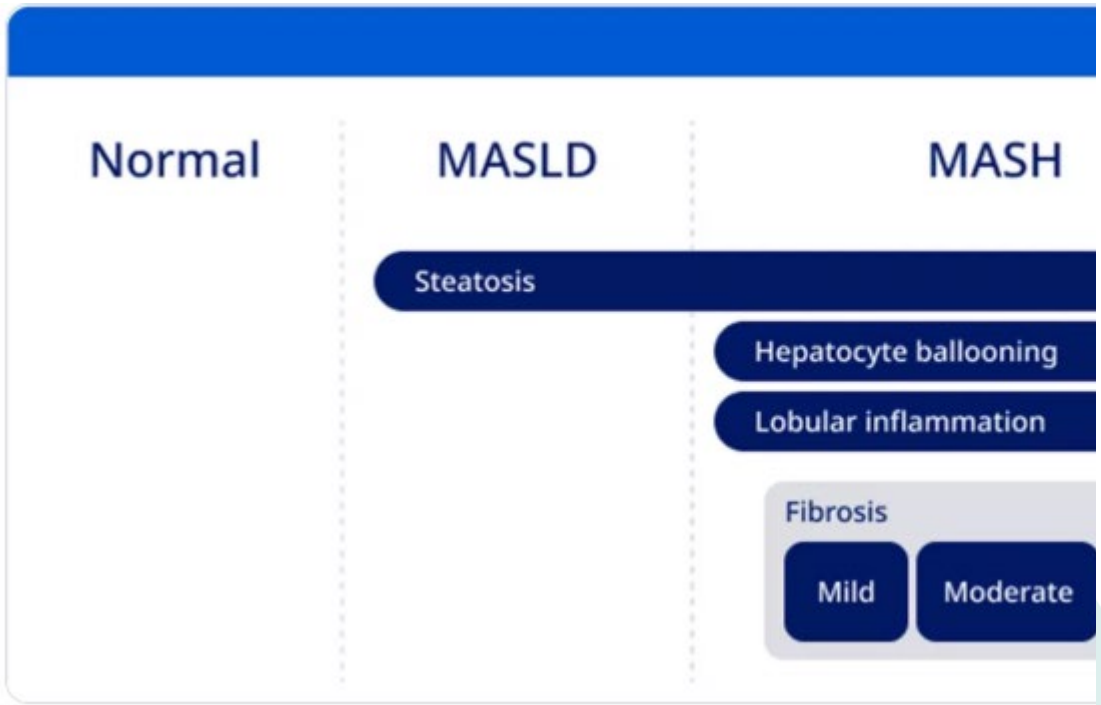
HCC



Meta-analysis; 6 studies N= 1,737 participants (602 TD2+ and 1135 TD2-); median f-up 2.8 yrs

Huang D et al. Lancet GH 2023; 8: 829–36


Normal
MASLD
MASH
Cirrhosis
Steatosis
Hepatocyte ballooning
Lobular inflammation
Fibrosis
Mild
Moderate
Advanced
Cirrhosis



AASLD's MASLD Decision Tree

Explanations At A Glance

START HERE

Does the patient have elevated liver enzymes?
ALT> 33 males
ALT> 25 females

No

Yes

Does the patient have hepatic steatosis?
As identified by ...
- Imaging
- Biopsy

No

Yes

The patient has steatotic liver disease.

Does the adult patient meet any one of the cardiometabolic criteria?

Have you ruled out Hepatitis B, C or other causes of chronic liver disease?

Yes

No

Does the patient have hepatitis steatosis?

Check Hepatitis C Ab with Reflex to PCR
Hepatitis BsAg, sAb, cAb
Ceruloplasmin
Immunoglobulins
ANA, ASMA, AMA
Iron Studies
Celiac Antibodies
Alpha-1-AT levels
OR
Rule out other underlying etiologies of liver diseases

Does the patient have features suggestive of cirrhosis?

No

No, it is likely not Metabolic Dysfunction Associated Steatotic Liver Disease.

Yes

Does the adult patient meet any one of the cardiometabolic criteria?

No

You should investigate for other underlying liver etiologies

Yes

Your patient may have Metabolic Dysfunction Associated Steatotic Liver Disease cirrhosis.

*We also encourage you check for other discernable causes.

Adult Criteria

At least 1 out of 5:

- BMI ≥ 25 kg/m² [23 Asia] **OR** WC> 94 cm (M) 80 cm (F) **OR** ethnicity adjusted
- 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
- Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive 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] (M) and ≤ 1-3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

Yes

No

Are there any other causes of steatosis, such as ALD, Drug-Induced Liver Injury (DILI), Monogenic diseases or Miscellaneous (see SLD Classifications)?

Yes

No

Your patient may have cryptogenic SLD or possible MASLD.

See Practice Guideline

Does your patient regularly drink >50 g/day for females or >60 g/day for males?

Your patient has primarily ALD.

Does your patient regularly drink alcohol (140-350 g/week (20-50 g/day) for females or 210-420 g/week (30-60 g/day) for males)?

Yes

No

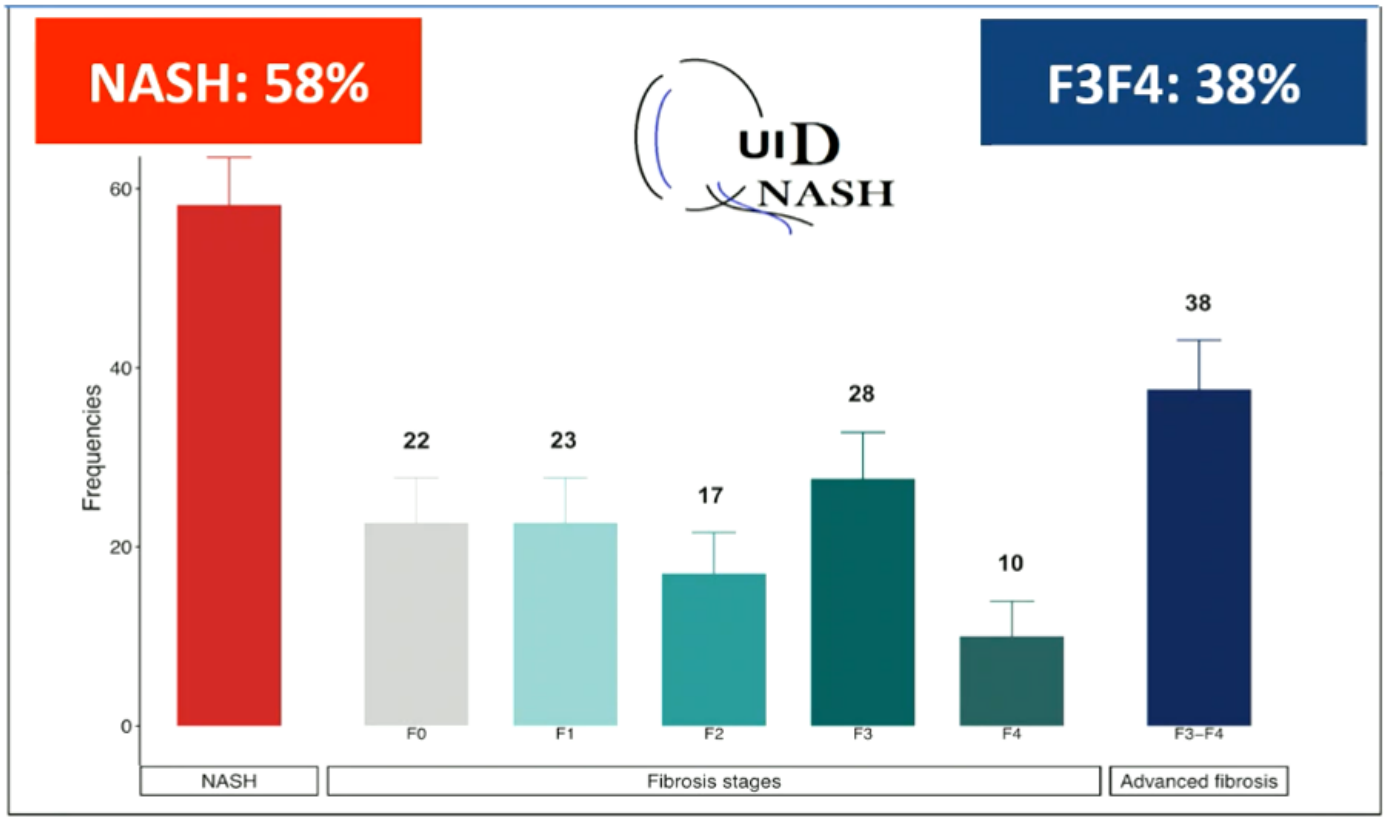
Your patient has Met-ALD.

*Multiple etiologies may coexist in a patient, thus exclude other causes of liver disease as appropriate.

Your patient has MASLD.

*Multiple etiologies may coexist in a patient, thus exclude other causes of liver disease as appropriate.

High prevalence of MASH and F3F4 in T2D



N= 330 patients DT2 avec suspicion de NAFLD et PBH

Castera L et al. Diabetes Care 2023; 46: 1354-1362

Screening

Table 4—Preferred tests for the initial (FIB-4) and secondary (VCTE, ELF) liver fibrosis risk stratification of people at high risk for MASLD*

FIB-4	Calculated with the following inputs: age, AST and ALT levels, and platelet count. First-line screening test for clinically significant fibrosis (stage ≥F2). If FIB-4 score is >1.3, additional risk stratification is needed. Calculator: https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis
VCTE	Imaging technique for LSM, extensively validated with liver histology as a surrogate of liver fibrosis stage. Second-line screening test for clinically significant fibrosis (stage ≥F2). Diagnostic cutoffs:* • LSM score >8 kPa = stage ≥F2 (clinically significant fibrosis) • LSM score >10 kPa = stage F3 or F4 (advanced fibrosis) • LSM score >15 kPa = stage F4 (cirrhosis)
ELF	A blood test that helps identify individuals with advanced fibrosis and at risk of developing cirrhosis or liver-related outcomes. A score obtained from three proteins linked to liver fibrosis (hyaluronic acid, amino-terminal propeptide of type III procollagen [PIIINP], and tissue inhibitor of metalloproteinase-1 [TIMP-1]). Second-line screening test for clinically significant fibrosis (stage >F2). Diagnostic cutoffs:* • ELF score >9.8 = stage F3 or F4 (advanced fibrosis) • ELF score >11.2 = stage F4 (cirrhosis)

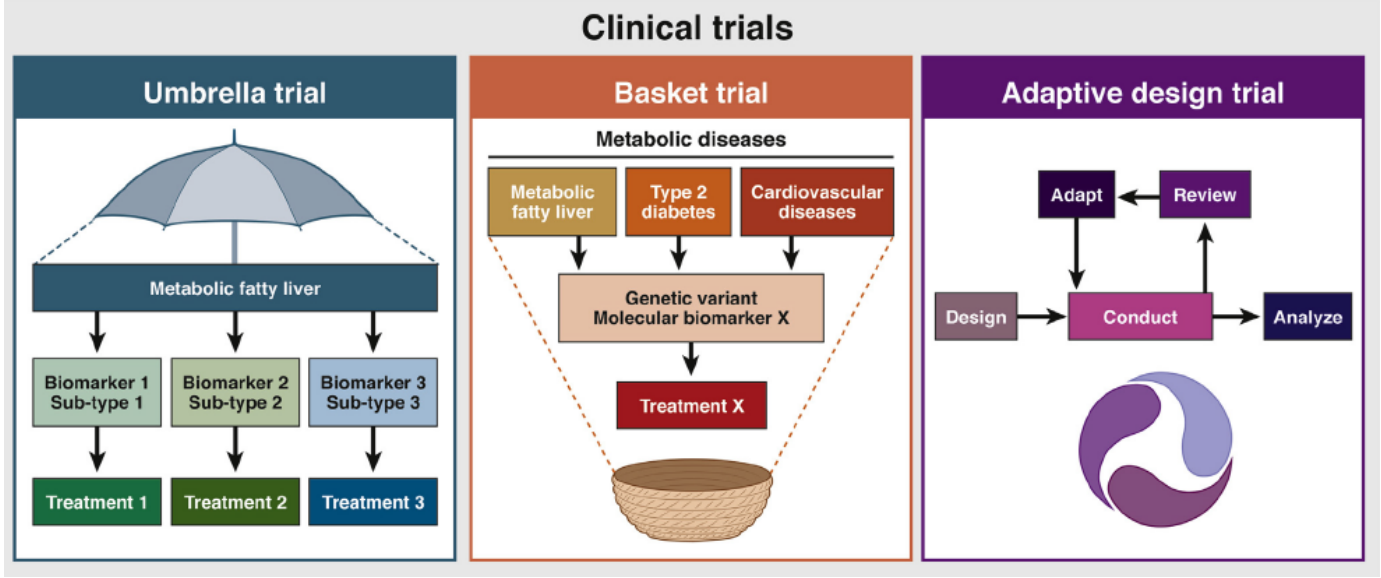
*Since NITs have significant interindividual variability and overlapping CIs across fibrosis stages, it is best to consider results in the context of having a "probability" of a given liver disease stage rather than the certainty that only a liver biopsy can provide.

Eslam, Gastroenterology 2020

Implicazioni/rischi

- Quali effetti sugli studi in corso per validazione diagnostica o terapeutica?

→Criteri diagnostici ≠ Criteri di inclusione



- Eccessiva medicalizzazione del lessico “steatosi”, ma possibilità di comunicare e parlare della malattia liberi da parole ricche di pregiudizi “grasso”.

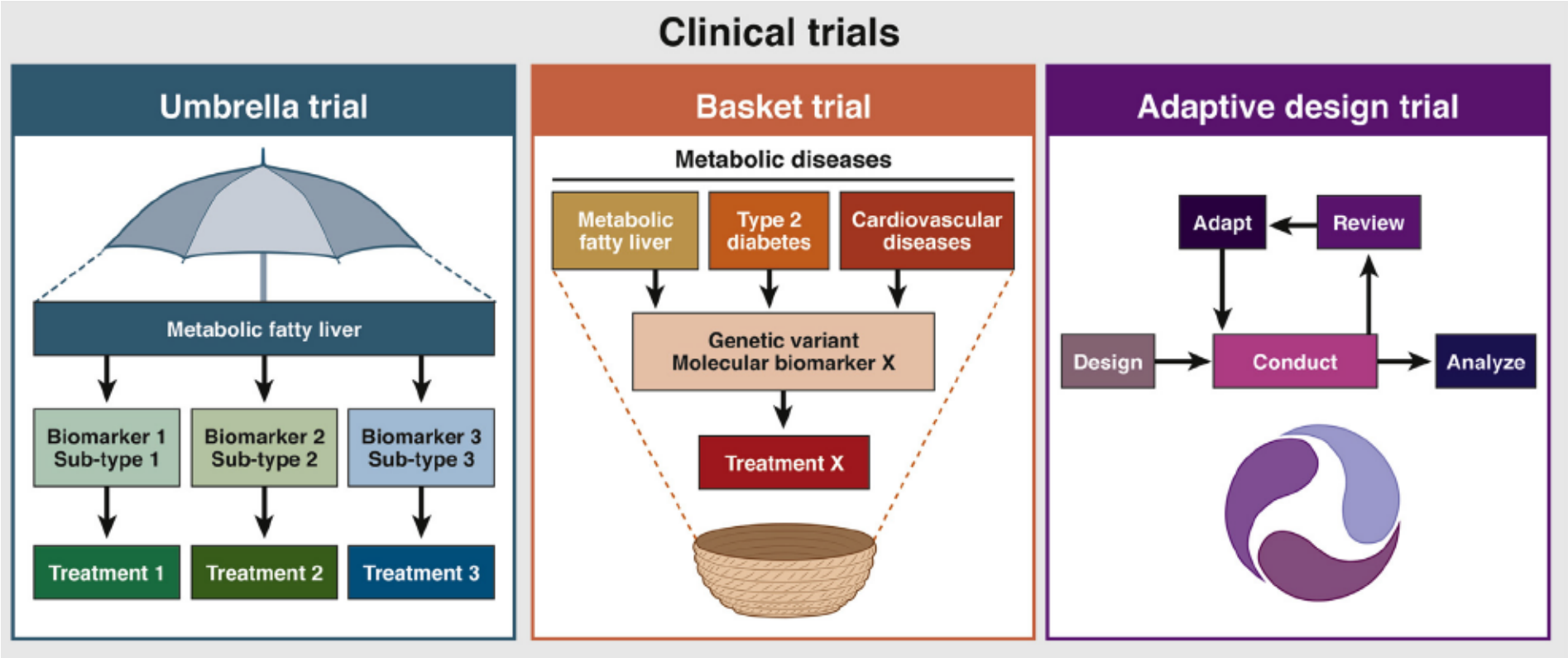
Alcohol related liver disease assessment.

Supplementary Table 3. Alcohol related liver disease assessment.

Steps	Assessment	Interpretation
Step 1:	Single question: how many times have you had 5 or more drinks in a day (for men) or 4 or more drinks/day (for women)	If answer is ≥ 1, proceed to step 2.
Step 2	Alcohol Use Disorders Inventory Test (AUDIT) (10 questions), AUDIT-C is a short form with 3 questions around alcohol consumption	A score > 7 is considered consumption of alcohol in amounts likely to lead to harmful outcomes - consider brief intervention. Score > 20 alcohol dependence (moderate to severe alcohol use disorder), consider drug therapy* AUDIT-C score > 4 may indicate AUD.
Monitoring	Peth (phosphatidylethanol)	>80 ng/ml levels seen with 4+ standard drinks daily in last 2-3 weeks. > 20 ng/ml seen with any alcohol use in last 2-3 weeks.

† AUD: Alcohol Use Disorders.
*Drugs approved for alcohol use disorder include acamprosate (for those in recovery who are no longer drinking alcohol), naltrexone (blocks drinking related euphoria and reduces relapses), disulfiram (for those who have stopped drinking, consumption of alcohol leads to flushing and unpleasant side effects). These are best prescribed by a professional with experience in AUD management.

Implications



Interindividual variation

Table 1. Statements of the Consensus Panel

Nomenclature and definition of metabolic associated fatty liver disease (MAFLD)

- We suggest that the nomenclature of NAFLD should be updated to MAFLD.
- The diagnosis of MAFLD should be based on the presence of metabolic dysfunction not the absence of other conditions.
- MAFLD can coexist with other liver diseases.
- A reference to alcohol should not be included in the MAFLD acronym.
- Patients with both MAFLD and a contribution from alcohol to their liver disease represent a large and important group that requires further investigation and characterization.

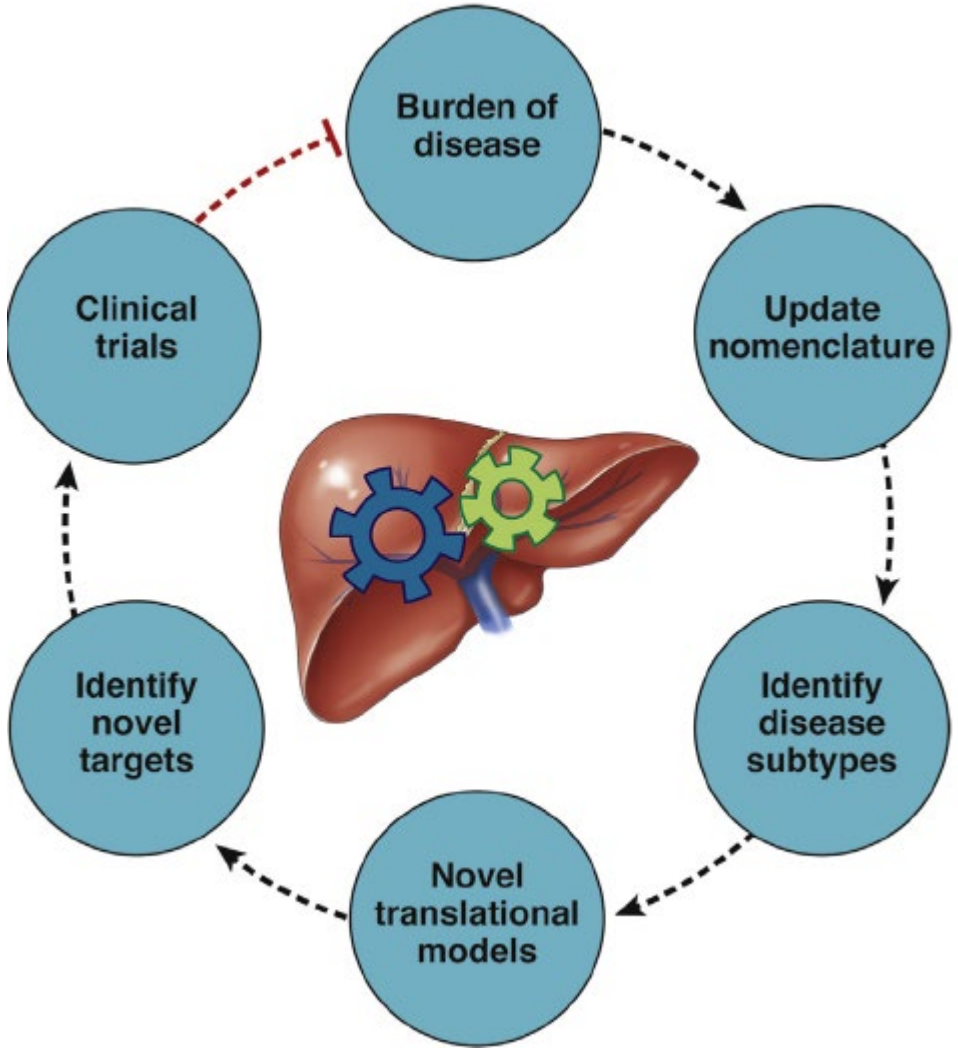
MAFLD heterogeneity

- MAFLD is a heterogeneous entity.
- Appropriate patient stratification must be considered when noninvasive fibrosis scores are developed and in clinical trial design.
- Studies are required to map the landscape of MAFLD and to precisely define subtypes of the disease.

Clinical trials for MAFLD

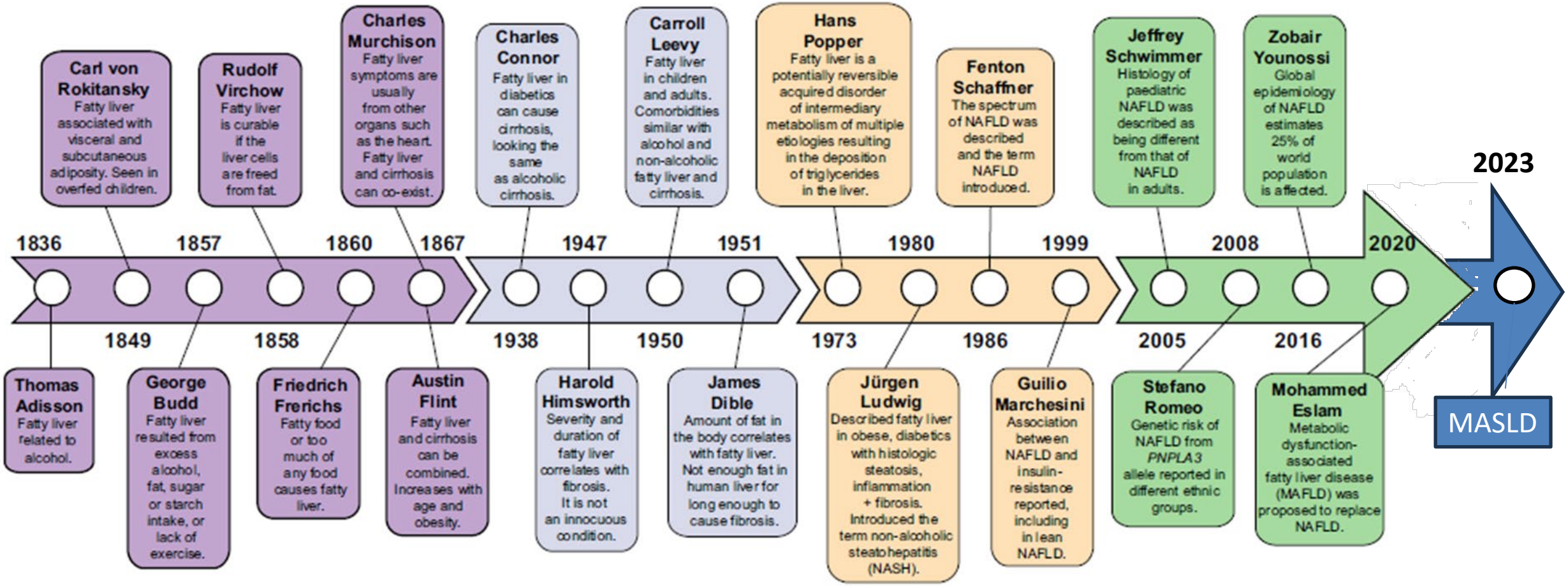
- Detailed patient stratification and tailoring clinical trial inclusion criteria based on drivers of disease will likely yield more informative and meaningful results.
- Innovative designs for clinical trials and personalized combination therapy approaches will likely be required to overcome the challenges of disease heterogeneity and for optimal clinical efficacy.

Implications



Eslam, Gastroenterology 2020

Timeline evolution of Fatty Liver Disease



Adapted from Ayonrinde, JHEP 2021

NAFLD: non-alcoholic fatty liver disease

Definition:

presence of hepatic steatosis (affecting at least 5% of hepatocytes), detected on imaging or histology,

in the absence of

ongoing or significant alcohol consumption (safe limits or no alcohol)

AND

other secondary causes of liver disease (e.g. viral hepatitis, auto-immune hepatitis, lipodystrophy)

Established ultrasound criteria: 2 out of the following 3 criteria

- increased echogenicity of the liver compared to kidney and spleen
- obliteration of the vascular architecture of the liver
- deep attenuation of the ultrasonic signal

Safe alcohol consumption (group-ethnic specific (<1/day or <7/wee in women and <2/day or <14/week in men)

MAFLD

Shift towards MAFLD

Metabolic dysfunction (the presence of obesity or diabetes or the presence of multiple other components of the metabolic syndrome or any combination of these) is also commonly seen in patients with fatty liver regardless of alcohol use [13], and the acronym NAFLD does not accurately reflect this association. Therefore, the more inclusive term metabolic (dysfunction) associated fatty liver disease (MAFLD) has been suggested as being more appropriate [14,15].

Exclusion of excessive alcoholic consumption is not mandatory

MAFLD-related cirrhosis vs cryptogenic cirrhosis

Box 2. Criteria for a diagnosis of MAFLD-related cirrhosis.

Patients with cirrhosis in the absence of typical histology who meet at least one of the following criteria:

Past or present evidence of metabolic risk factors that meet the criteria to diagnose MAFLD, as described in Box 1, with at least one of the following:

i) Documentation of MAFLD on a previous liver biopsy*.

ii) Historical documentation of steatosis by hepatic imaging*.

Eslam et al.
Journal of Hepatology 2020

Subphenotyping and Alternative causes

Subclassification for example may encompass the role of genetic variants such as patatin-like phospholipase domain-containing protein 3 (PNPLA3), transmembrane 6 superfamily 2 (TM6SF2), membrane bound O-acyltransferase domain-containing 7 (MBOA7) and hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13), and epigenetic or other modifiers of disease.

Alternative causes of fatty liver disease

We suggest that the terms “primary” and “secondary” hepatic steatosis are avoided because all pathological processes are secondary.

Instead, we propose use of “alternative causes” of fatty liver disease to describe the latter that includes conditions such as:

medications (corticosteroids, valproic acid, tamoxifen, methotrexate, and amiodarone), coeliac disease, starvation, total parenteral nutrition, severe surgical weight loss or disorders of lipid metabolism (abetalipoproteinemia, hypobetalipoproteinemia, lysosomal acid lipase deficiency, familial combined hyperlipidaemia, lipodystrophy, Weber–Christian syndrome, glycogen storage disease, Wilson disease). These may be associated with metabolic dysfunction (MAFLD) or be present with other triggers of less frequent forms of fatty liver disease.

Eslam et al.
Journal of Hepatology 2020

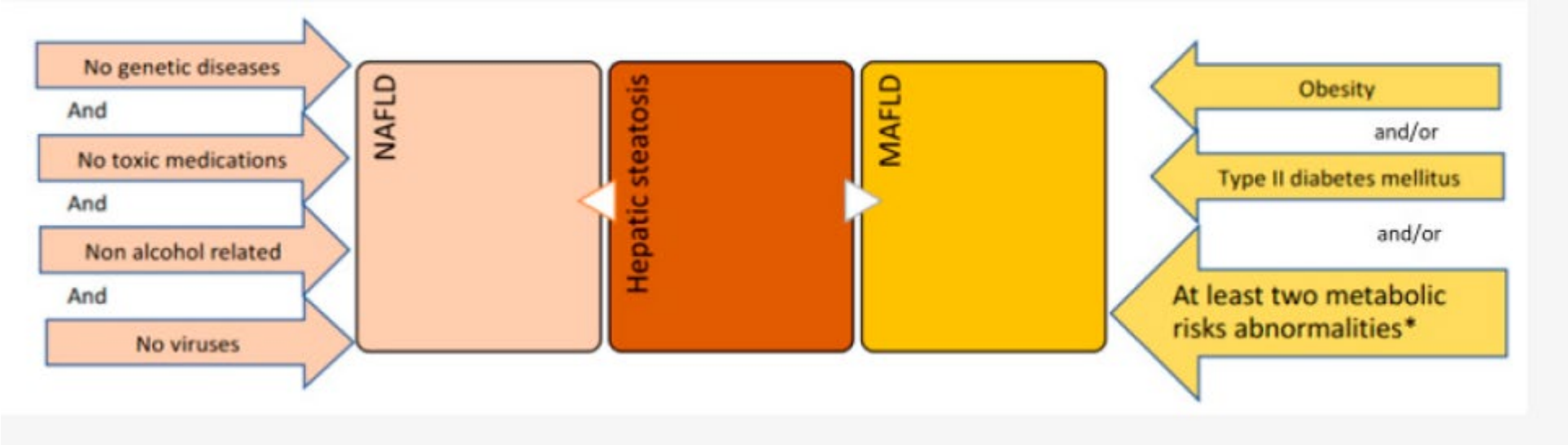


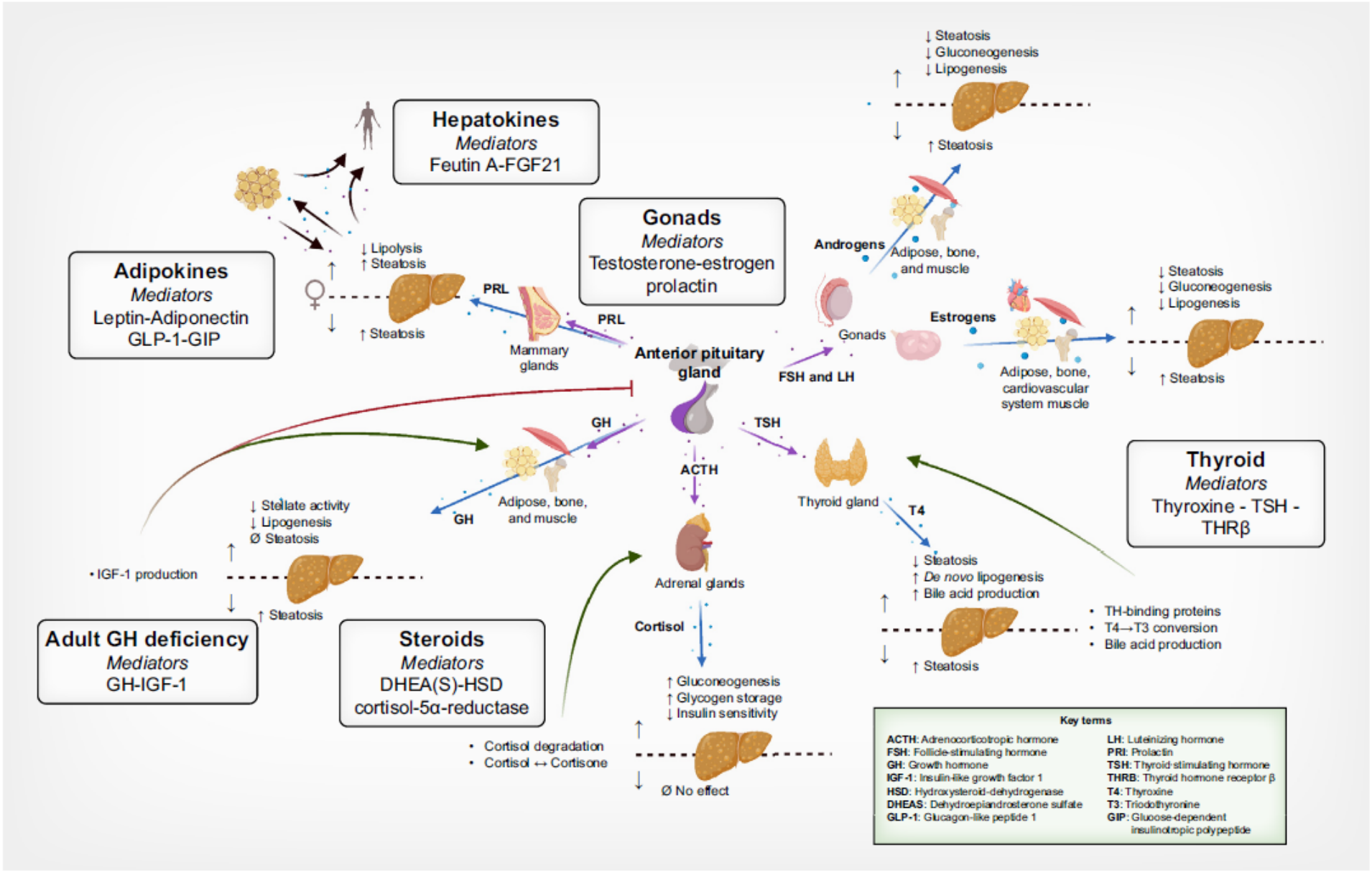
Figure 1. MAFLD vs. NAFLD diagnostic criteria. * Metabolic risk abnormalities: (1) Waist circumference > 102/88 cm in caucasian men/women or > 90/80 cm in Asian men/women; (2) Blood pressure ≥ 130/85 mmHg or antihypertensive medication; (3) Plasma Triglycerides > 150 mg/dl or triglycerides lowering drugs; (4) Plasma HDL-C < 40 mg/dl for men and < 50 mg/dl for women or specific lipid lowering drugs; (5) Prediabetes or HbA1c between 5.7–6.4%; (6) Plasma high-sensitivity C-reactive protein level > 2 mg/L.

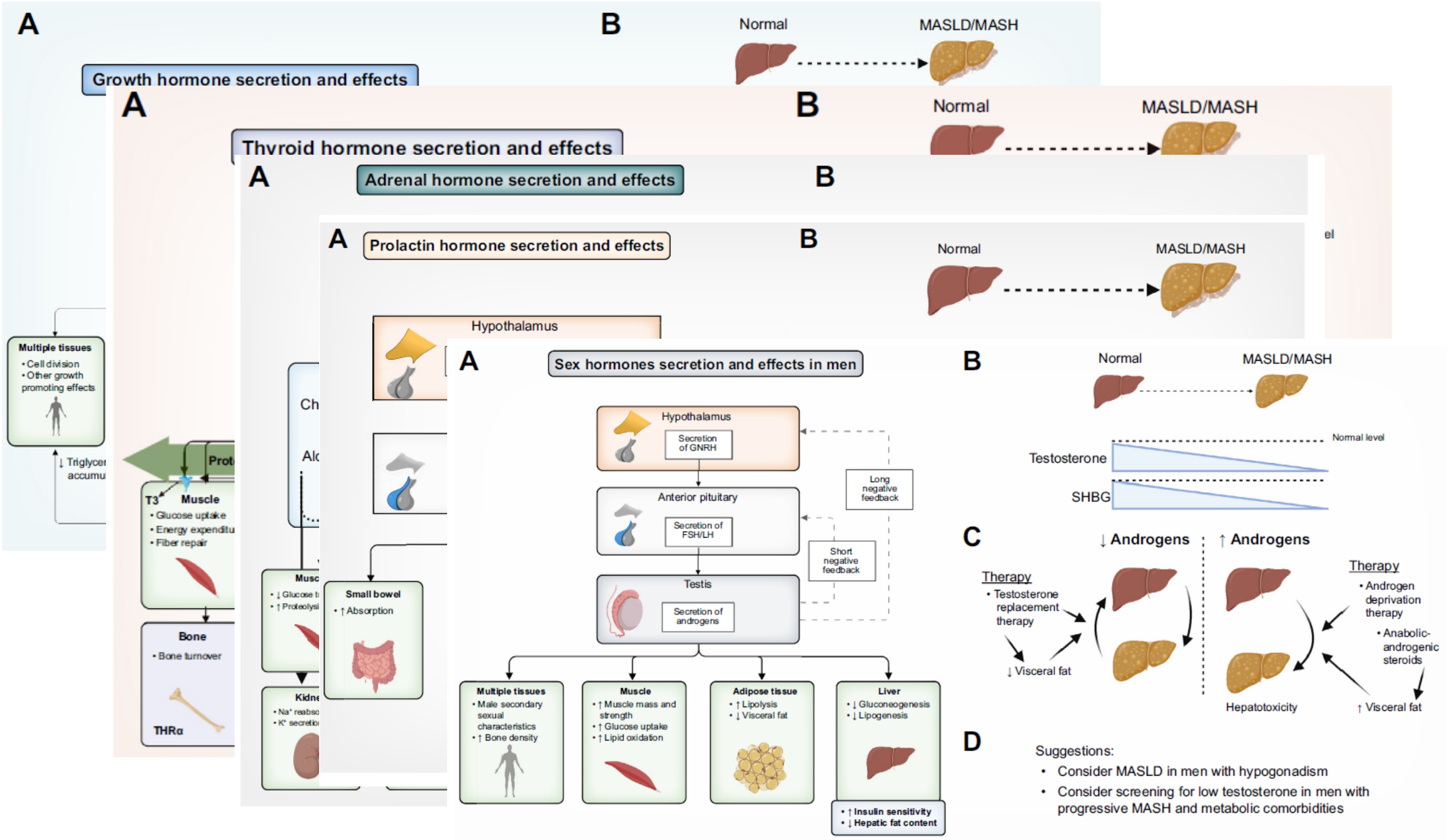
MAFLD

Exclusion of excessive alcoholic consumption is not mandatory

MAFLD was diagnosed on the proposed, consensus recommendation [14,15]: ultrasound criteria for fatty liver with (i) a body mass index
(BMI)> = 23 kg/m2 or diabetes (fasting blood sugar (FBS)>125 mg/dL or HbA1c >6.4% or
on treatment), or (ii) if BMI <23 kg/m2 and not diabetic, with at least two other features of
metabolic dysregulation, namely, waist circumference (WC) > = 90cm for men, WC > =
80cm for women; blood pressure (BP)> = 130/85 mmHg or on treatment; triglycerides (TG)>
150mg/dL or on treatment; high density lipoproteins (HDL)<40mg/dL for men and <50 mg/
dL for women or on treatment; and FBS between 100–125 mg/dL or HbA1c 5.7–6.4%.

Ddd


Hepatokines
Mediators
Feutin A-FGF21
Adipokines
Mediators
Leptin-Adiponectin
GLP-1-GIP
Gonads
Mediators
Testosterone-estrogen
prolactin
Thyroid
Mediators
Thyroxine - TSH -
THRβ
Steroids
Mediators
DHEA(S)-HSD
cortisol-5α-reductase
Adult GH deficiency
Mediators
GH-IGF-1
↓ Steatosis
↓ Gluconeogenesis
↓ Lipogenesis
↑ Steatosis
Androgens
Adipose, bone, and muscle
↓ Lipolysis
↑ Steatosis
PRL
Mammary glands
Anterior pituitary gland
FSH and LH
Gonads
Estrogens
Adipose, bone, cardiovascular system muscle
GH
TSH
ACTH
Adipose, bone, and muscle
Thyroid gland
T4
↓ Stellate activity
↓ Lipogenesis
Ø Steatosis
• IGF-1 production
↑ Steatosis
Adrenal glands
Cortisol
↓ Steatosis
↑ De novo lipogenesis
↑ Bile acid production
• TH-binding proteins
• T4→T3 conversion
• Bile acid production
↑ Gluconeogenesis
↑ Glycogen storage
↓ Insulin sensitivity
• Cortisol degradation
• Cortisol ↔ Cortisone
Ø No effect
Key terms
ACTH: Adrenocorticotropic hormone
FSH: Follicle-stimulating hormone
GH: Growth hormone
IGF-1: Insulin-like growth factor 1
HSD: Hydroxysteroid-dehydrogenase
DHEAS: Dehydroepiandrosterone sulfate
GLP-1: Glucagon-like peptide 1
LH: Luteinizing hormone
PRI: Prolactin
TSH: Thyroid-stimulating hormone
THRB: Thyroid hormone receptor β
T4: Thyroxine
T3: Triiodothyronine
GIP: Glucose-dependent insulinotropic polypeptide


A
Growth hormone secretion and effects
Multiple tissues
• Cell division
• Other growth promoting effects
↓ Triglycer
accumu
Prot
T3
Muscle
• Glucose uptake
• Energy expenditu
• Fiber repair
Bone
• Bone turnover
THRα
B
Normal
MASLD/MASH
A
Thyroid hormone secretion and effects
B
Normal
MASLD/MASH
A
Adrenal hormone secretion and effects
B
A
Prolactin hormone secretion and effects
B
Normal
MASLD/MASH
Hypothalamus
Ch
Ald
Musc
• ↓ Glucose t
• ↑ Proteolysi
Kidne
• Na+ reabso
• K+ secretio
Small bowel
• ↑ Absorption
A
Sex hormones secretion and effects in men
Hypothalamus
Secretion of GNRH
Anterior pituitary
Secretion of FSH/LH
Testis
Secretion of androgens
Long negative feedback
Short negative feedback
Multiple tissues
• Male secondary sexual characteristics
• ↑ Bone density
Muscle
• ↑ Muscle mass and strength
• ↑ Glucose uptake
• ↑ Lipid oxidation
Adipose tissue
• ↑ Lipolysis
• ↓ Visceral fat
Liver
• ↓ Gluconeogenesis
• ↓ Lipogenesis
• ↑ Insulin sensitivity
• ↓ Hepatic fat content
B
Normal
MASLD/MASH
Normal level
Testosterone
SHBG
C
↓ Androgens
↑ Androgens
Therapy
• Testosterone replacement therapy
↓ Visceral fat
Therapy
• Androgen deprivation therapy
• Anabolic-androgenic steroids
Hepatotoxicity
↑ Visceral fat
D
Suggestions:
• Consider MASLD in men with hypogonadism
• Consider screening for low testosterone in men with progressive MASH and metabolic comorbidities