NAFLD – MASLD

YAĞLI KARACİĞER HASTALIĞINA YAKLAŞIM

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Adana Şehir Eğitim ve Araştırma Hastanesi
İç Hastalıkları Anabilim Dalı

- Nonalcoholic fatty liver disease (NAFLD) tüm dünyada kronik karaciğer hastalığının en önemli nedenidir.
- NAFLD metabolik sendromun **karaciğer tutulumu** olarak değerlendirilmektedir ve sıklıkla obezite, dislipidemi, hipertansiyon ve diyabet gibi metabolik risk faktörleri ile ilişkilidir.
- Tüm dünyada artan obezite ve T2 DM oranları global olarak artan NAFLD prevalansı ile paralel seyretmektedir.

Nat. Rev. Gastroenterol. Hepatol. 2013; 10: 686-690; Nat. Rev. Gastroenterol. Hepatol. 2018; 15: 11-20; Cell 2021 184; 2537-2564
Younossi Z, Golabi P, Paik J et al. Hepatology. 2023;77:1335–1347

Alkolik olmayan yağlı karaciğer Spektrumu

YAĞLI KARACİĞER

Yağ karaciğerde depolanır

Karaciğerde en az %5 yağ depolanması/hepatoselüler zedelenme bulgusu olmaması (hepatosit balonlaşması)

Nonalkolik Steatohepatit

Yağ ve beraberinde inflamasyon ile skatris(nedbe) dokusu oluşması

Karaciğerde en az %5 yağ depolanması/inflamasyon var ve hepatoselüler zedelenme bulgusu var (hepatosit balonlaşması)
Fibrozis var veya yok. (az-orta-çok)

Siroz

Karaciğer hücrelerinin yerini skar dokusu kaplar

Nedbe, yıkıma uğramış dokuya benzer yeni bir doku yaratma olanağı bulunmadığında vücudun, doku yitimlerini onardığı sürecin son evresidir

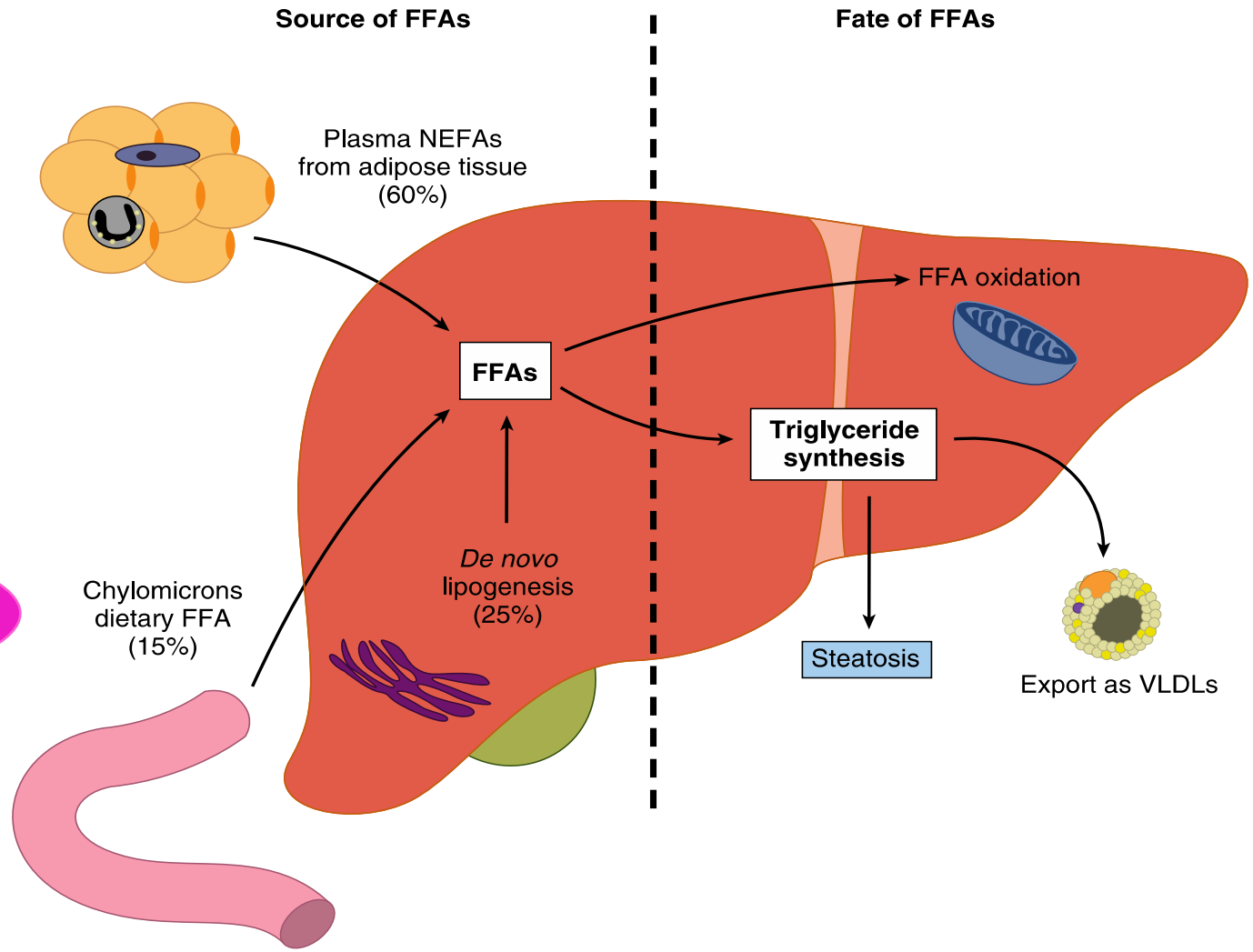
Liver International. 2007;27(4):423-433.

Karaciğer'in yağ kaynakları nelerdir?

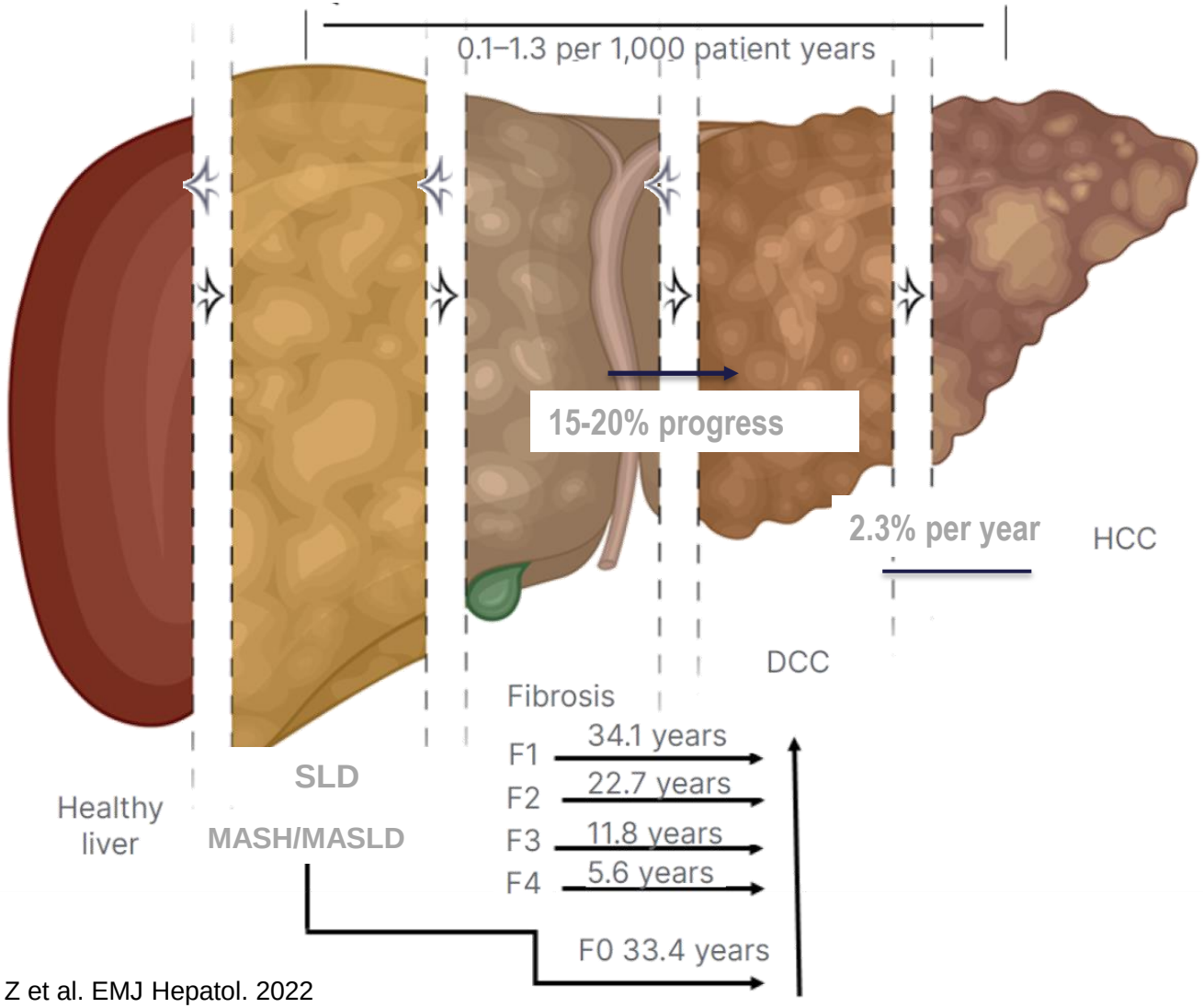
Diyetteki SYA leri

IR nin şiddetine bağlı..adiposit kaynaklı SYA

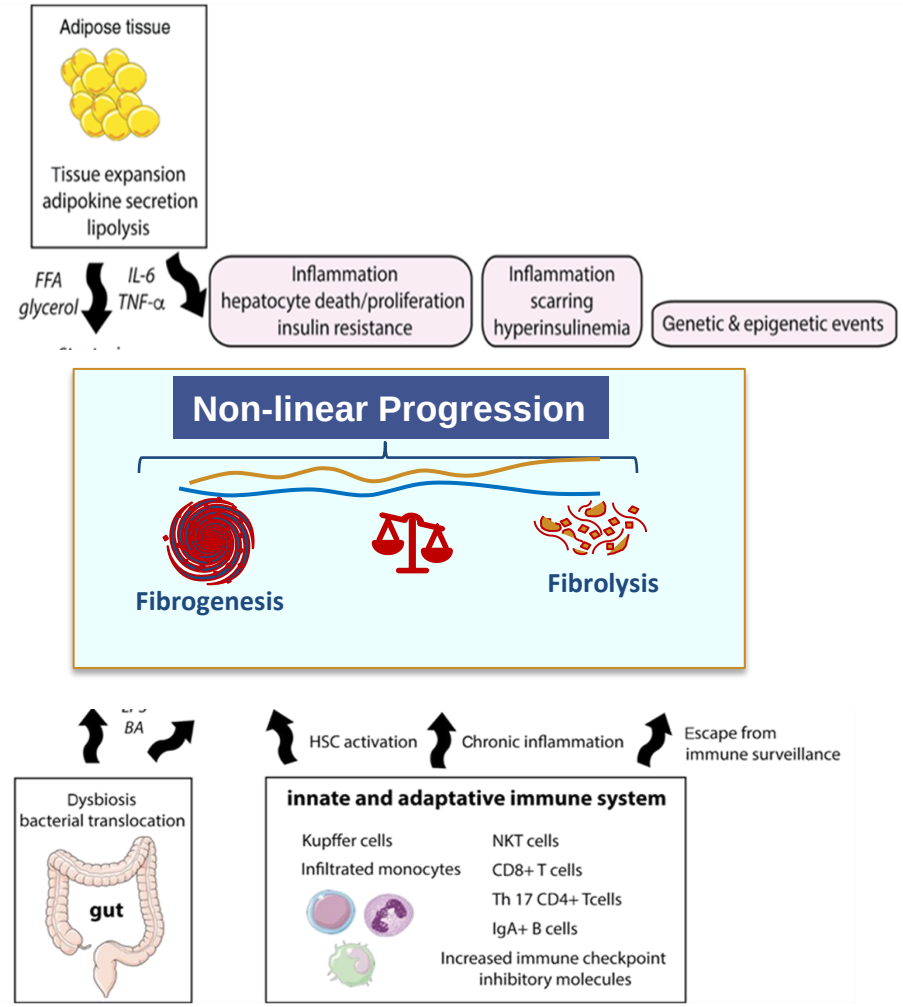
Hepatosit denovo lipogenez
NAFLD de normalde '<%5 iken.%26kadar çıkar



Natural History of MASLD and MASH



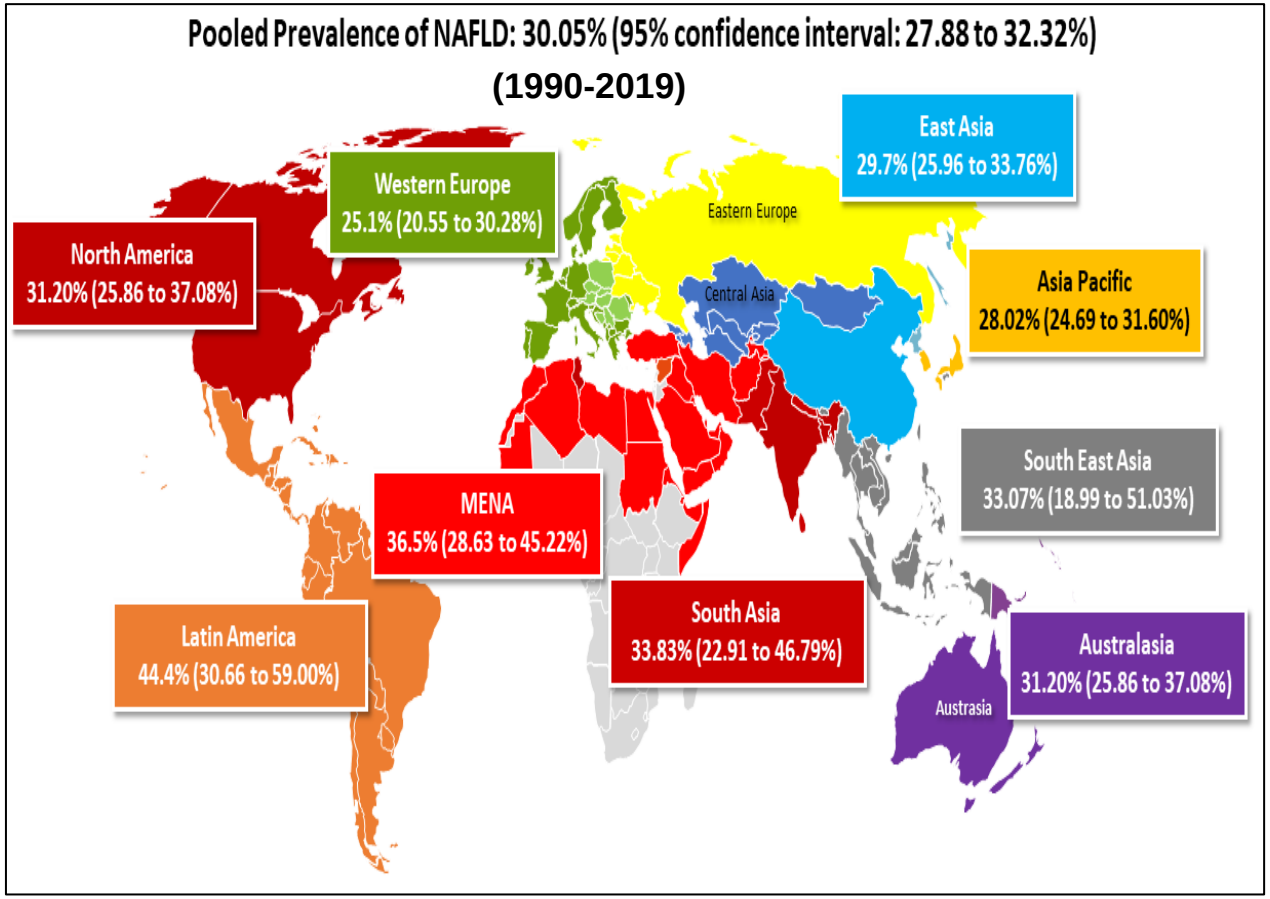
Younossi Z et al. EMJ Hepatol. 2022



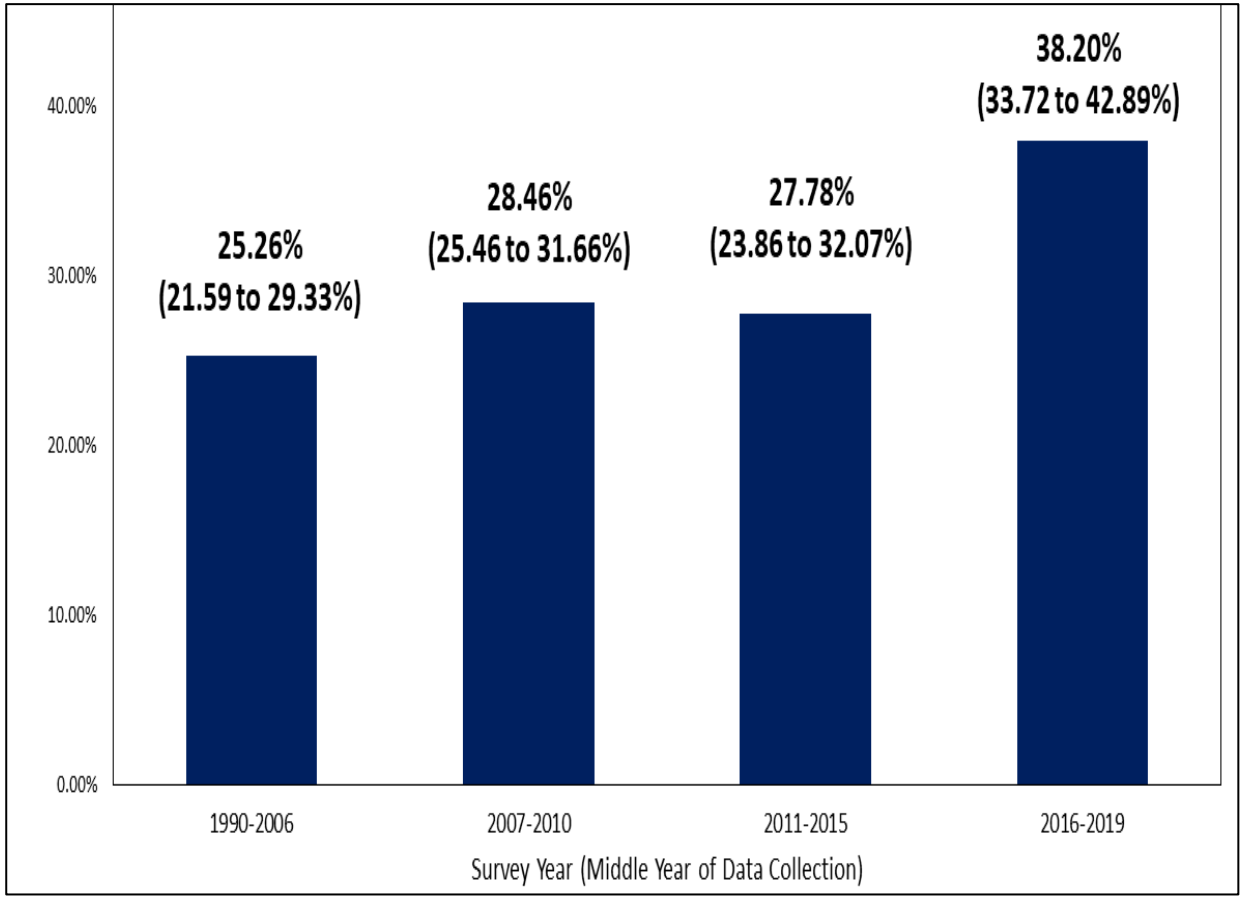
Sayiner M, et al. *Clin Liver Dis*. 2016;20(2):205-214; Younossi ZM, et al. *Hepatology*. 2016; 64(5):1577-1586. Lequoy M, et al. Horm Mol Biol Clin Investig. 2020, 29;41(1), Younossi Z et al. Hepatology 2018, Younossi Z J Hepatology 2019

Global Prevalence of NAFLD/MASLD

The Global Prevalence of MASLD



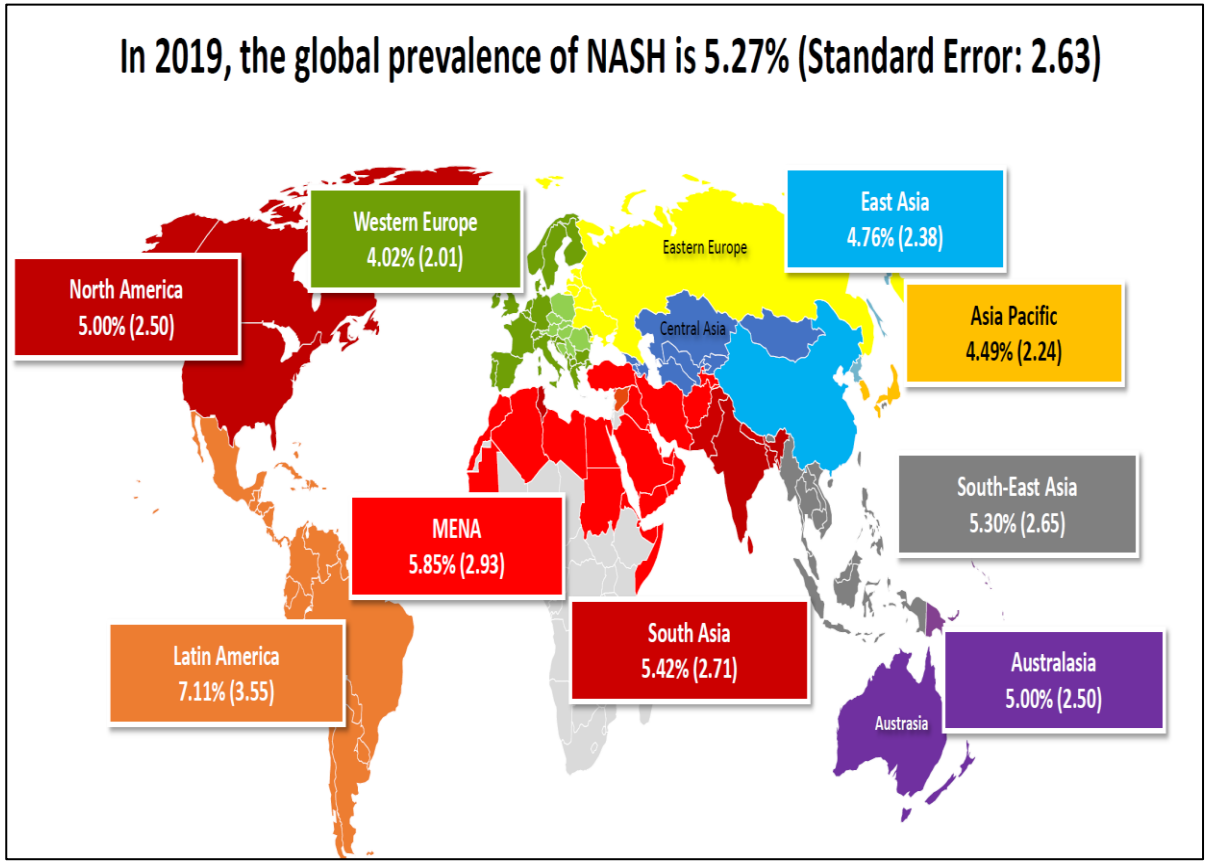
The Global Prevalence of MASLD over Time



Younossi ZM et al, Hepatology. 2023 Apr 1;77(4):1335-1347.

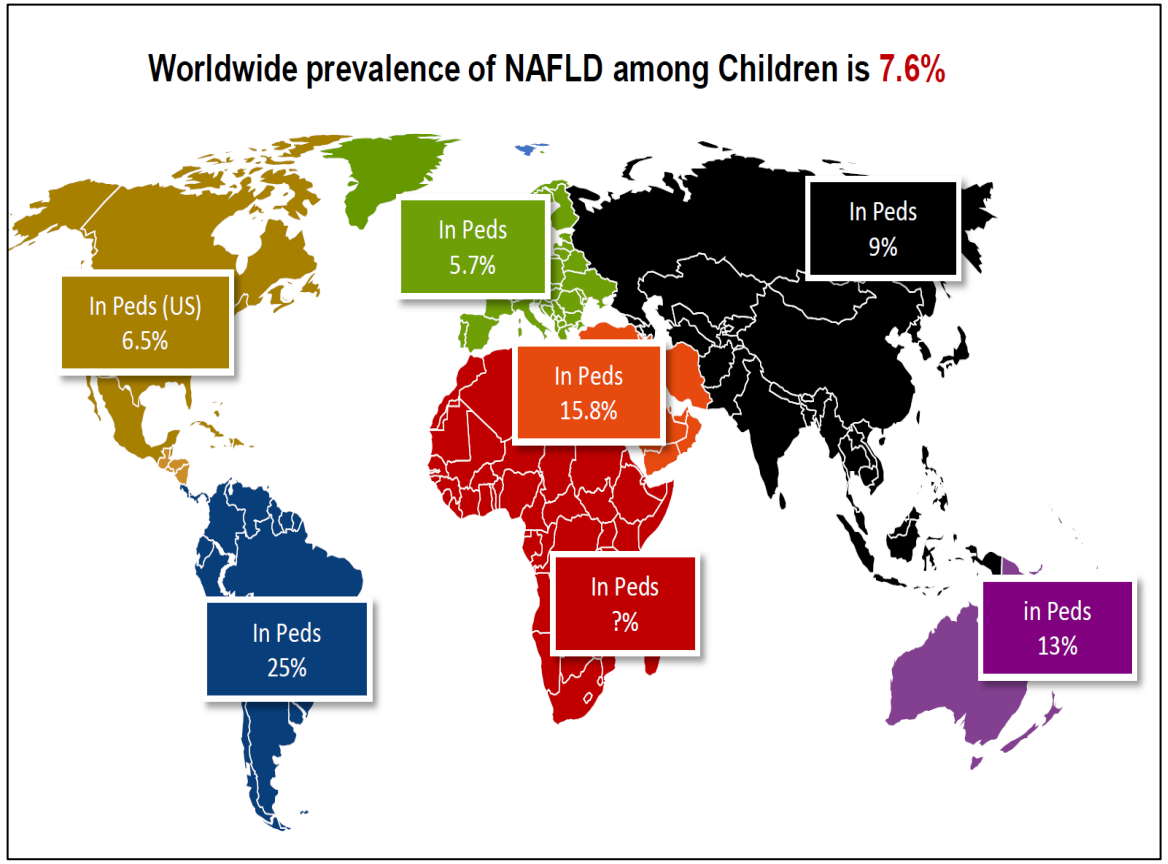
Global Prevalence of NAFLD/MASLD

The Global Prevalence of MASH



Younossi ZM et al, Hepatology. 2023 Apr 1;77(4):1335-1347.

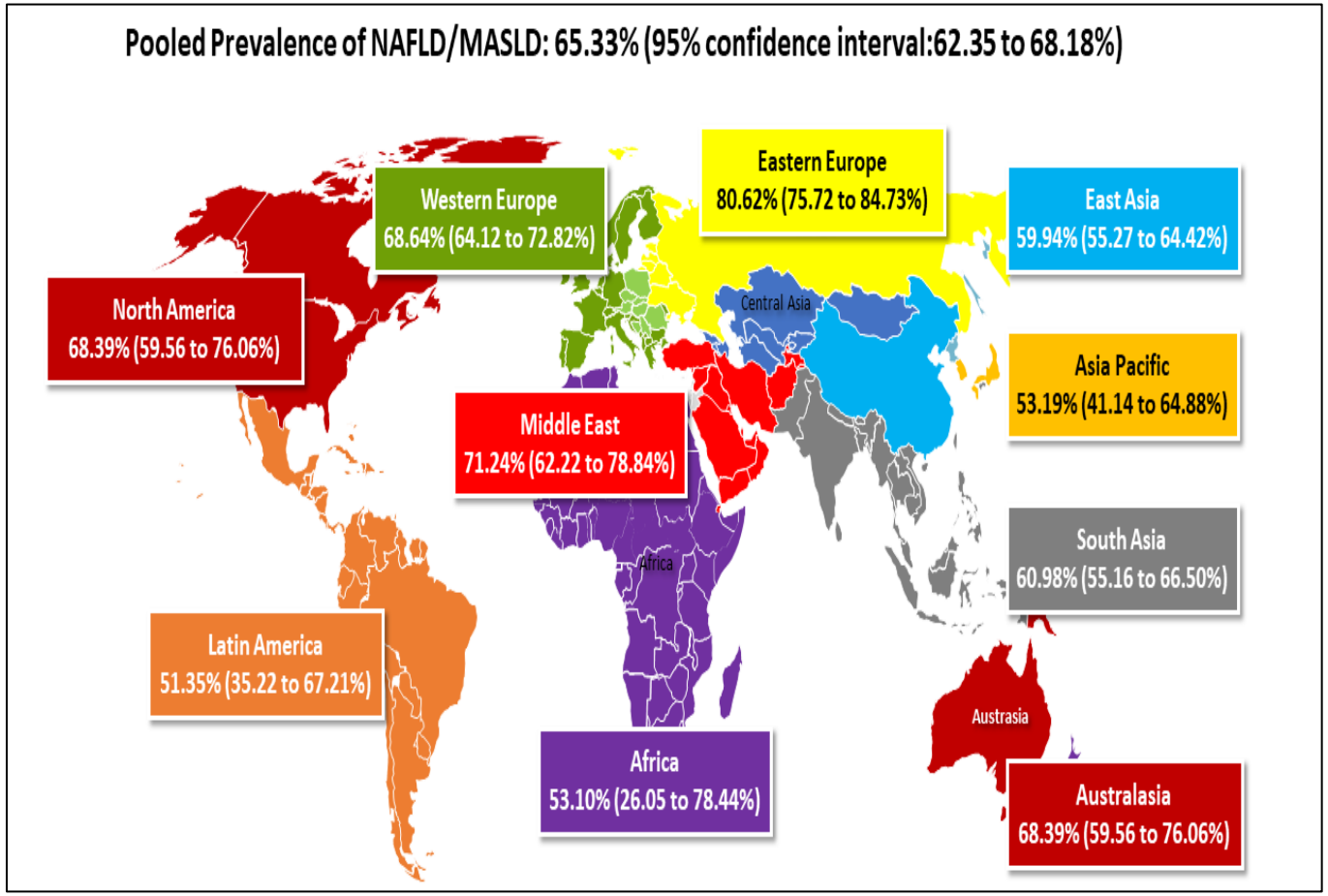
The Global Prevalence of MASLD: Pediatrics



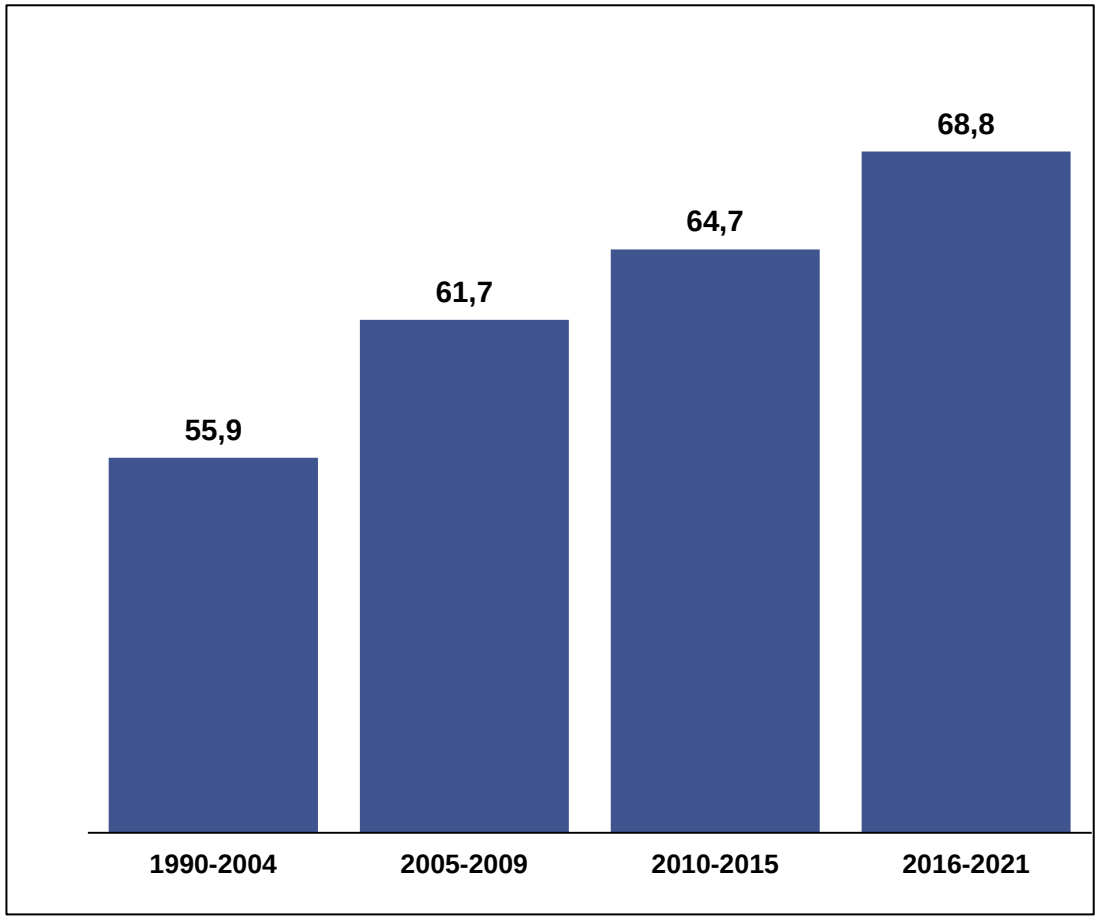
Schwimmer JB, et al. *Pediatrics*. 2006, Vos M et al. J Pediatr Gastroenterol Nutr. 2017

Global Prevalence of NAFLD/MASLD

The Global Prevalence of MASLD: T2D



Global Prevalence of MASLD over Time: T2D

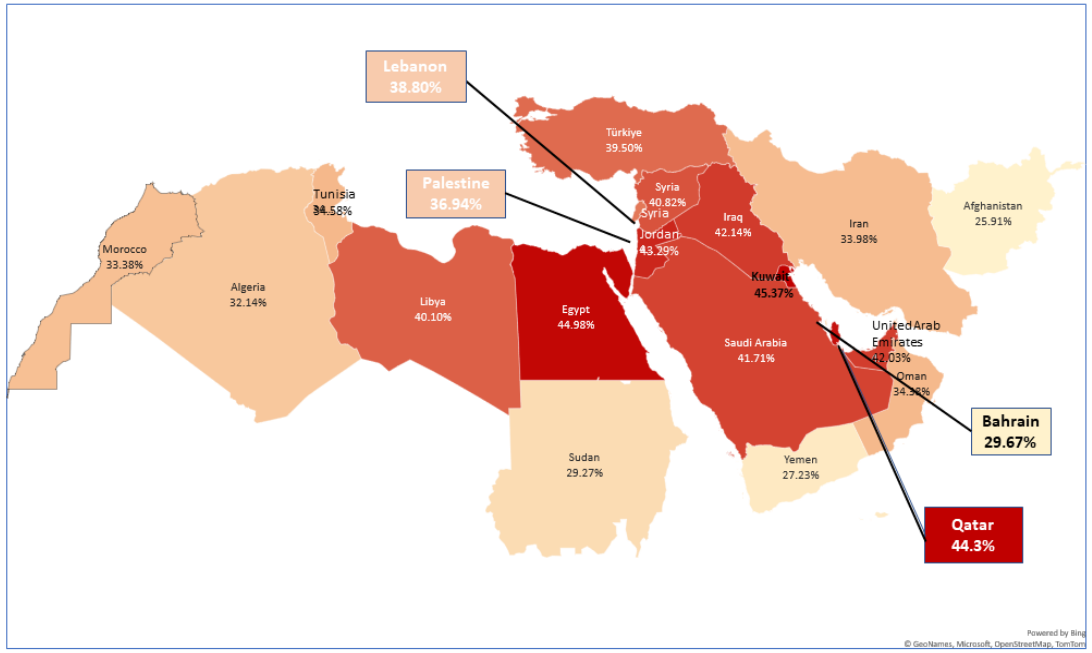


Younossi ZM,Clin Gastroenterol Hepatol. 2024 Mar 21:S1542-3565(24)00287-8

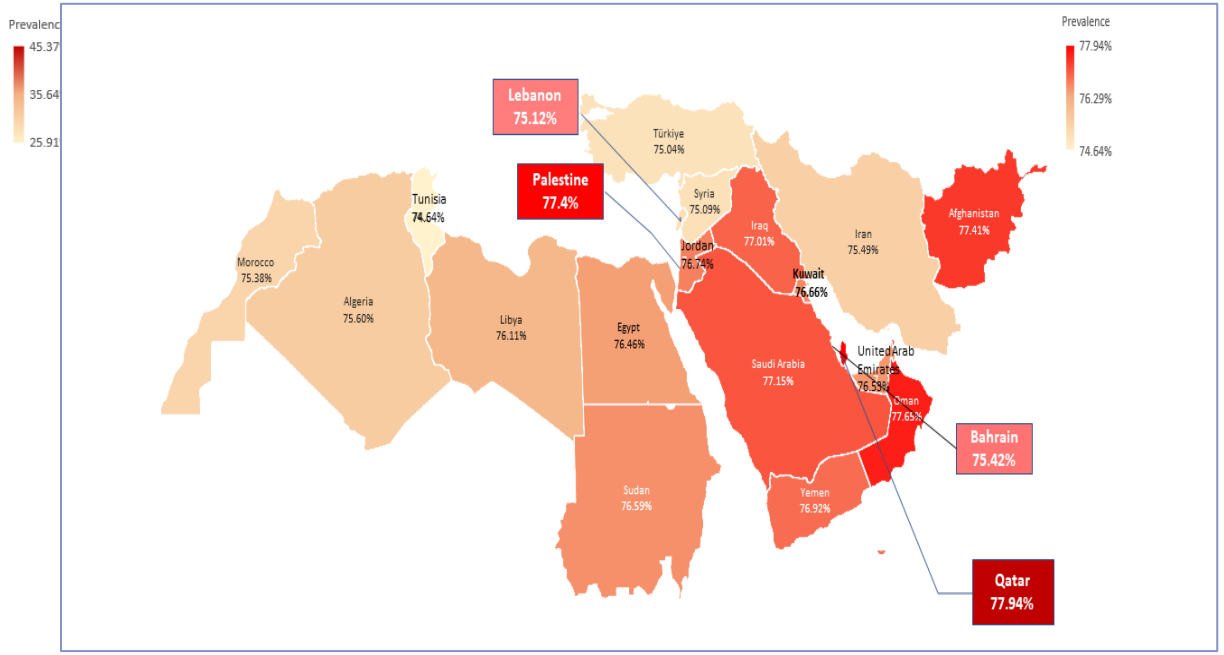
Prevalence Of Metabolic Dysfunction-associated Steatotic Liver Disease In MENA Region and Turkiye

- PubMED and Embase: articles published (1990-2023)
- Each country's prevalence rate was predicted by multivariable amnd 3 meta regression model using data from our systematic review, GBD and NCD Risk Factor Collaboration.
- Prevalence of NAFLD/MASLD in **MENA and Turkiye general population: 39.43% and 39.5%**
- General population prevalence has increased from 35.42% (2008-2016) to **46.20% (2017-2020**).
- Prevalence of MASLD among **T2D** in **MENA and Turkiye is 68.71% and 75%**

General Population



T2D



Younossi ZM, et al. Liver Int. 2024 Feb 2. doi:10.1111/liv.15852. Epub ahead of print.

The Disease Burden: NAFLD, MAFLD and MASLD

The Journey From NAFLD to MASLD: The Evolution of Nomenclature

1980 — **NASH**

Ludwig J, Viggiano TR, McGill DB, et al. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980;55:434–438.

1998 — **NAFLD**

› Mod Pathol. 1998 Jun;11(6):560-5.

Nonalcoholic fatty liver disease: assessment of variability in pathologic interpretations

2002 — **?NAFLD**

First AASLD STC on NAFLD:

2020 — **MAFLD**

MAFLD:

- Elimination of

2021 — **?MAFLD**

HEPATOLOGY AASLD

SPECIAL ARTICLE | HEPATOLOGY, VOL. 73, NO. 3, 2021

From NAFLD to MAFLD: Implications

2023 — **MASLD**

A multi-society Delphi consensus statement on new fatty liver disease nomenclature.

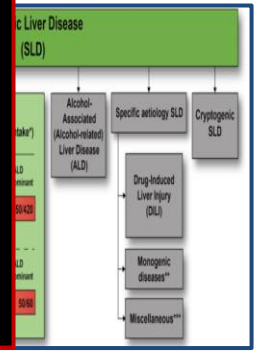
Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, Romero D, Abdelmalek MF, Anstee QM, Arab JP, Arrese M, Bataller R, Beuers U, Boursier J, Bugianesi E, Byne C, Castro Narro GE, Chowdhury

F, Loomba R, Mitchell-Thain R, Morgan TR, Powell E,

kokoian SC, Spearman CW, Tiniakos D, Valenti L, Vos

ossi Z, Hobbs A, Villota-Rivas M, Newsome PN; NAFLD

: 10.1016/j.jhep.2023.06.003. Online ahead of print.



Challenges:

- All terminologies are being used
- **Is MASLD the same disease as NAFLD?**
- **Is disease stigma related to NAFLD or obesity?**
- Does the new name reduce stigma?
- Does the new name help or harm awareness?

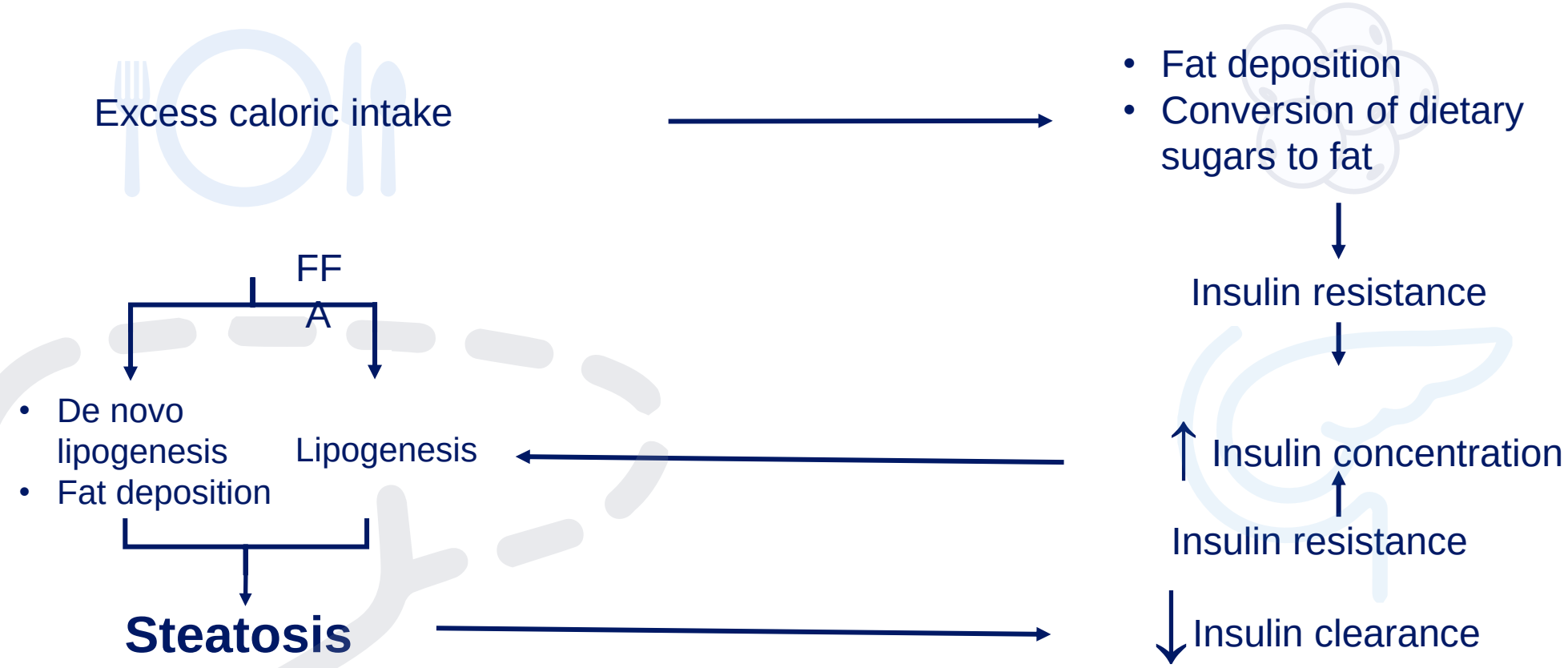
99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical

Table 1. Baseline characteristics and outcomes of patients with NAFLD and MASLD, respectively.

Parameter	NAFLD (n = 1,333)	MASLD (n = 1,329)
Age (years)	52 (40-61)	52 (40-61)
Sex (male)	780 (58.5)	777 (58.5)
Body mass index (kg/m^2)	29.3 (26.8-32.3)	29.3 (36.8-32.3)
FIB-4 score	1.04 (0.72-1.62)	1.04 (0.72-1.62)
Fibrosis stage[1]		
F0	223 (16.7)	223 (16.7)
F1	373 (27.9)	370 (27.8)
F2	211 (15.8)	211 (15.9)
F3	100 (7.5)	99 (7.5)
F4	55 (4.1)	55 (4.1)
NASH[1]	545 (40.9)	544 (40.9)
Cardiometabolic criteria		
Body mass index ≥25 kg/m^2	1,179 (88.5)	1,179 (88.7)
Insulin resistance*	809 (60.7)	809 (60.8)
Hypertension**	1,114 (83.6)	1,114 (83.8)
High triglycerides***	969 (72.7)	969 (72.1)
Dyslipidemia****	783 (58.7)	783 (58.7)
Outcomes		
Liver-related outcome	143 (10.7)	142 (10.7)
Overall mortality	402 (30.2)	401 (30.2)

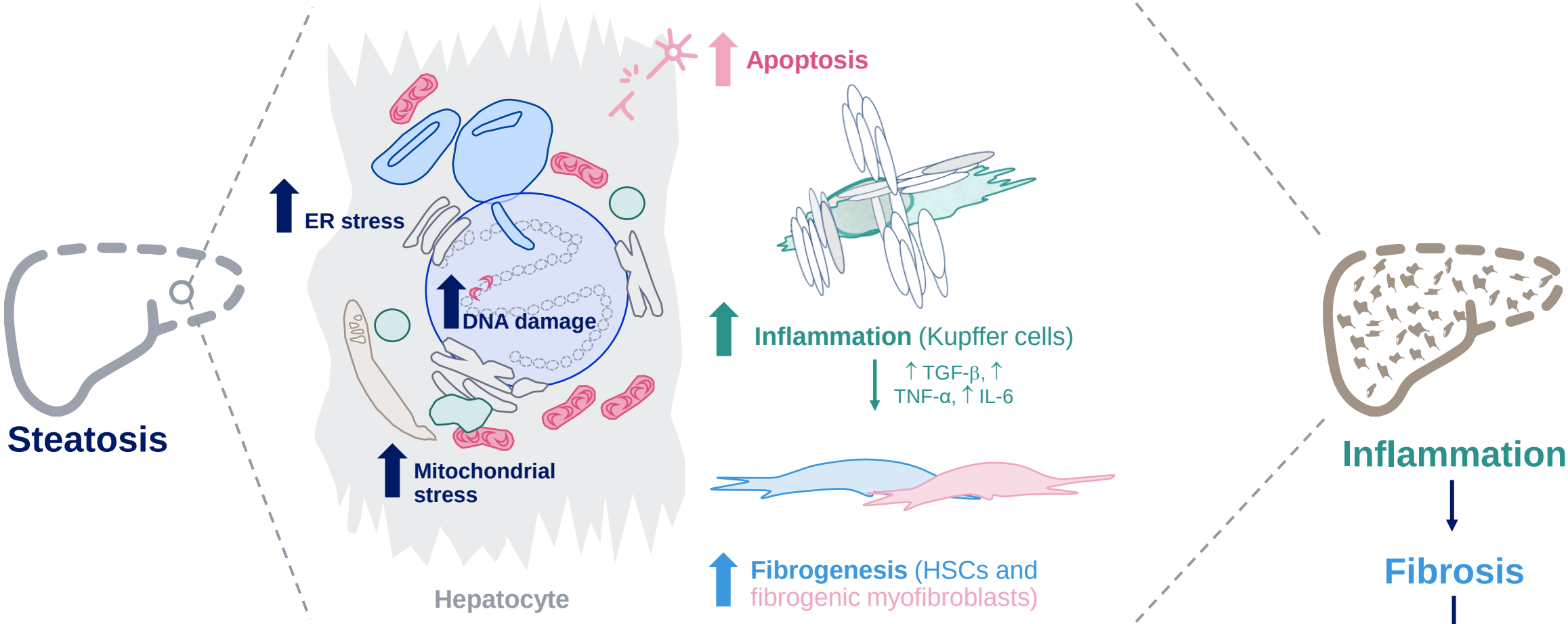
Hagström H et al. Journal of Hepatology, February 2024.

Pathophysiology of NAFLD



FFA, free fatty acid; NAFLD, non-alcoholic fatty liver disease.
Gaggini et al. Nutrients. 2013;5:1544–60.

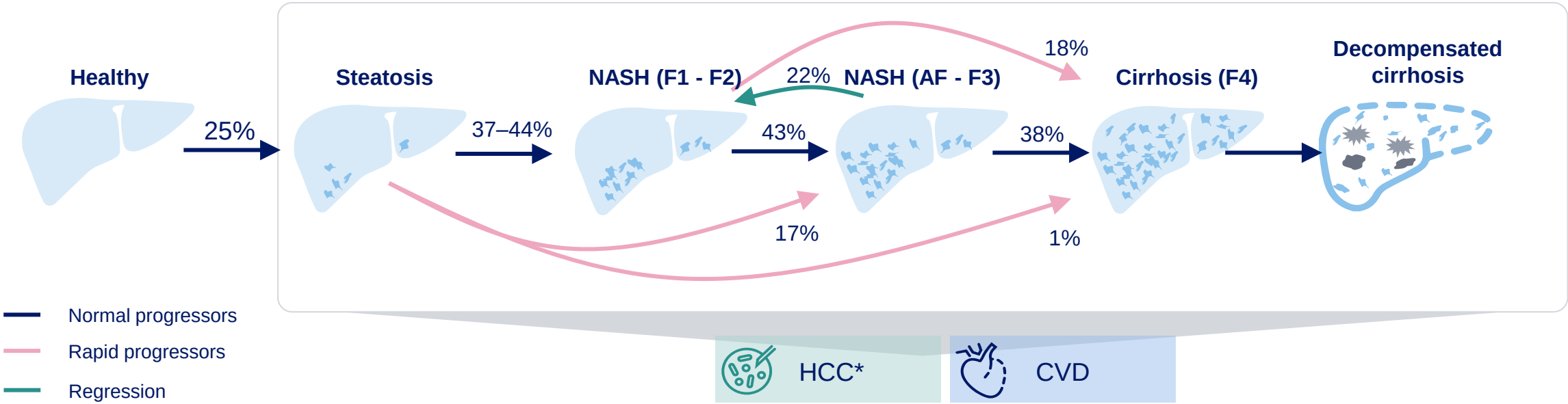
Progression of NAFLD to NASH



DNA, deoxyribonucleic acid; ER, endoplasmic reticulum; HSC, hepatic stellate cell; IL-6, interleukin-6; NASH, non-alcoholic steatohepatitis; TGF, transforming growth factor; TNF, tumor necrosis factor.
Adapted from Tillman EJ and Rolph T Front Endocrinol (Lausanne). 2020;11:601290.
1. Kim KH et al. Front Endocrinol (Lausanne). 2018;9:485; Konerman MA et al. J Hepatol. 2018;68:362–375.

NASH fibrosis evolves stepwise or rapidly

Leading to HCC and death if untreated

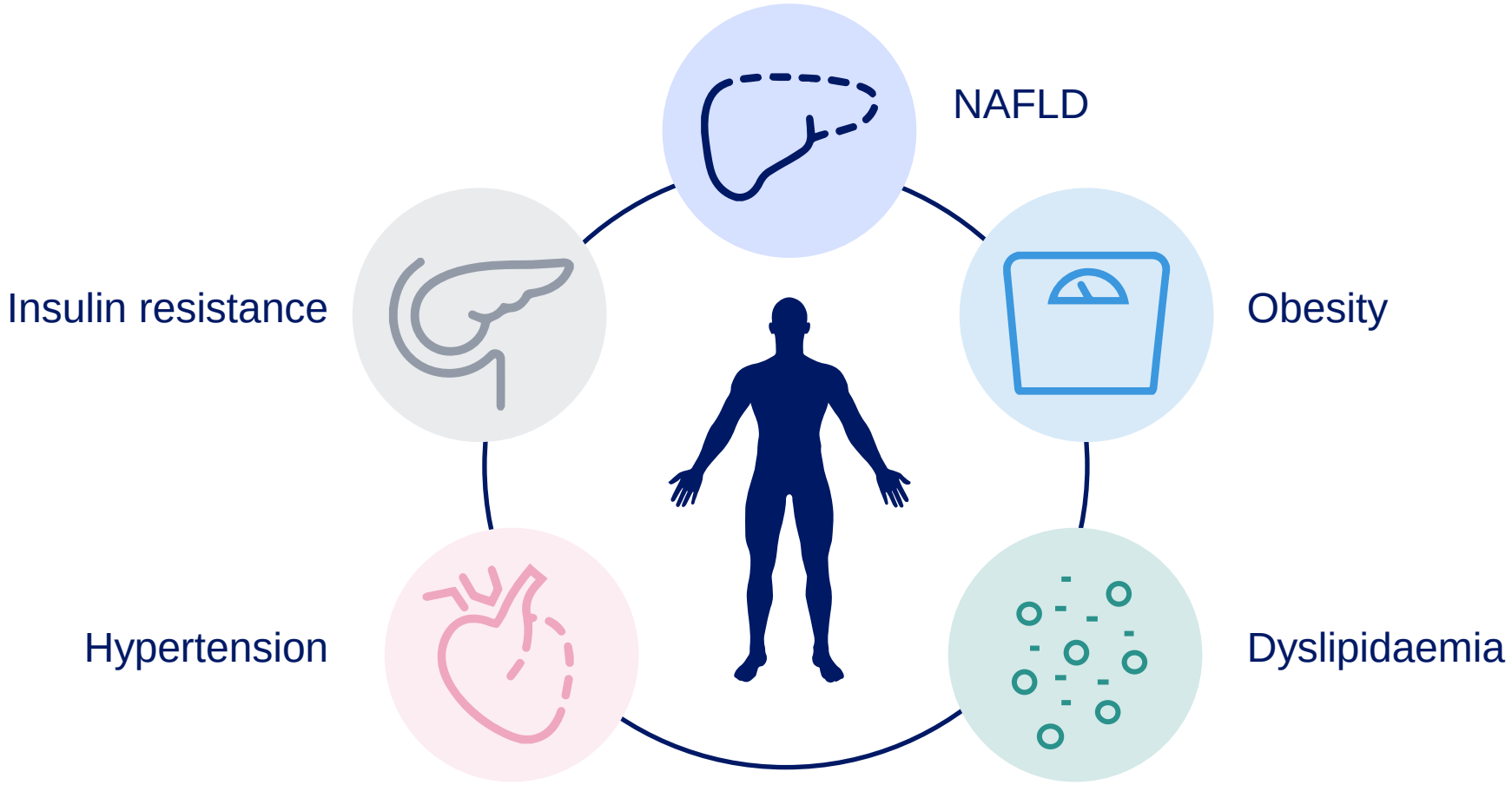


**NASH may involve varying stages of liver fibrosis, represented by stages F0 (non-cirrhotic) to F4 (cirrhotic), leading to HCC, liver transplant or liver-related death*

AF, advanced fibrosis; CV, cardiovascular; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

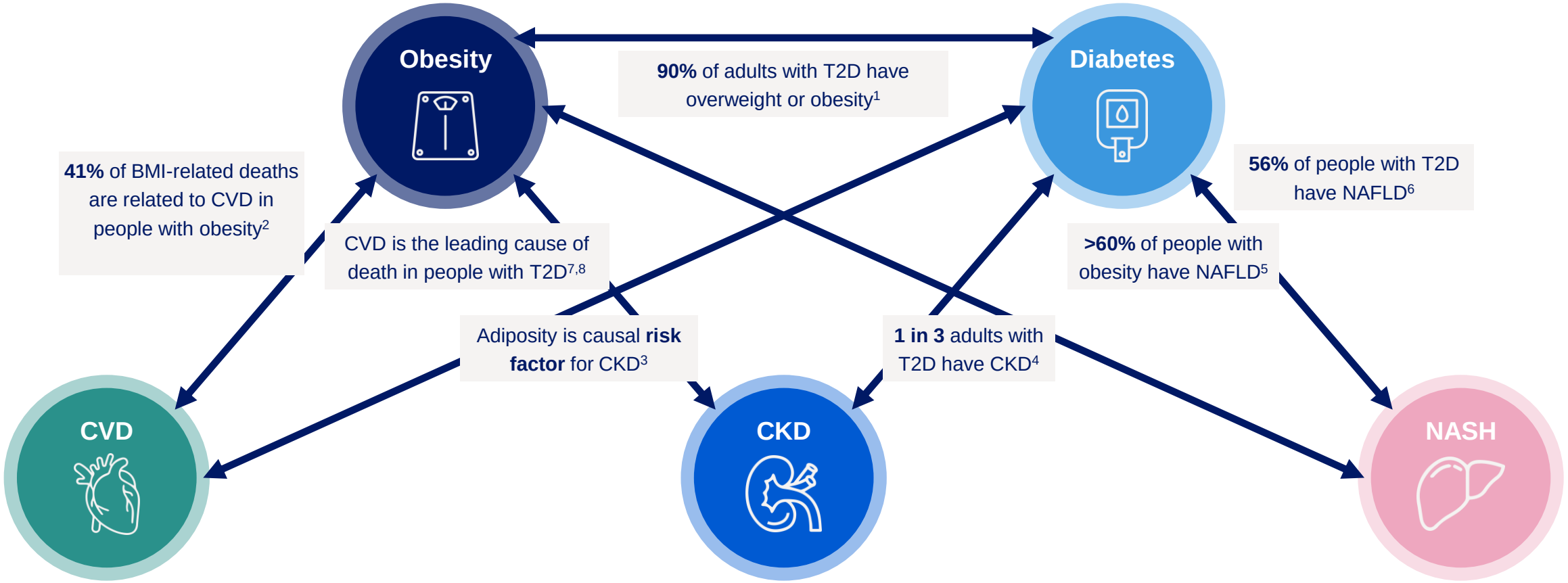
Marengo A et al. Clin Liver Dis 2016;20:313–24.

NAFLD is associated with metabolic syndrome



NAFLD, non-alcoholic fatty liver disease.
Samson SL and Garber AJ. Endocrinol Metab Clin North Am 2014;43:1–23.

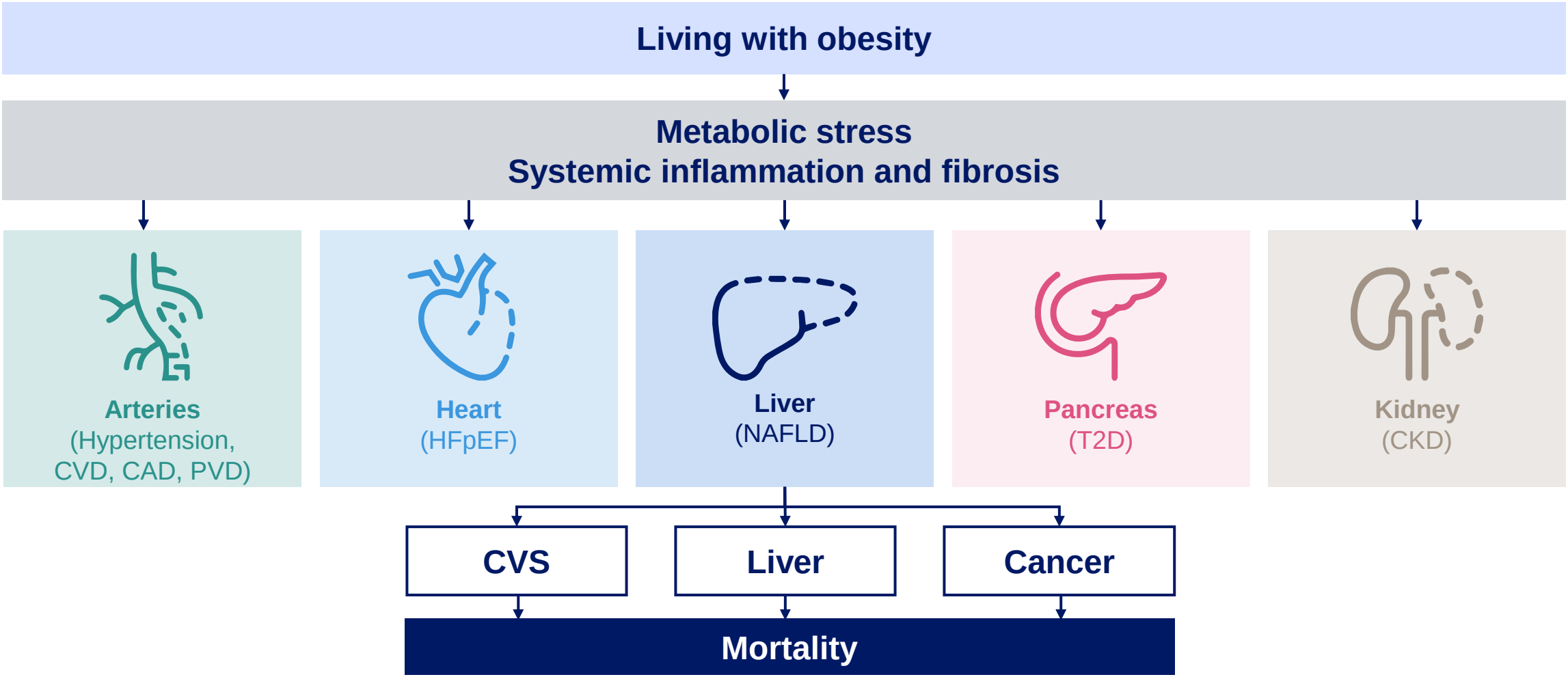
Obesity, diabetes, and other metabolic diseases are closely linked



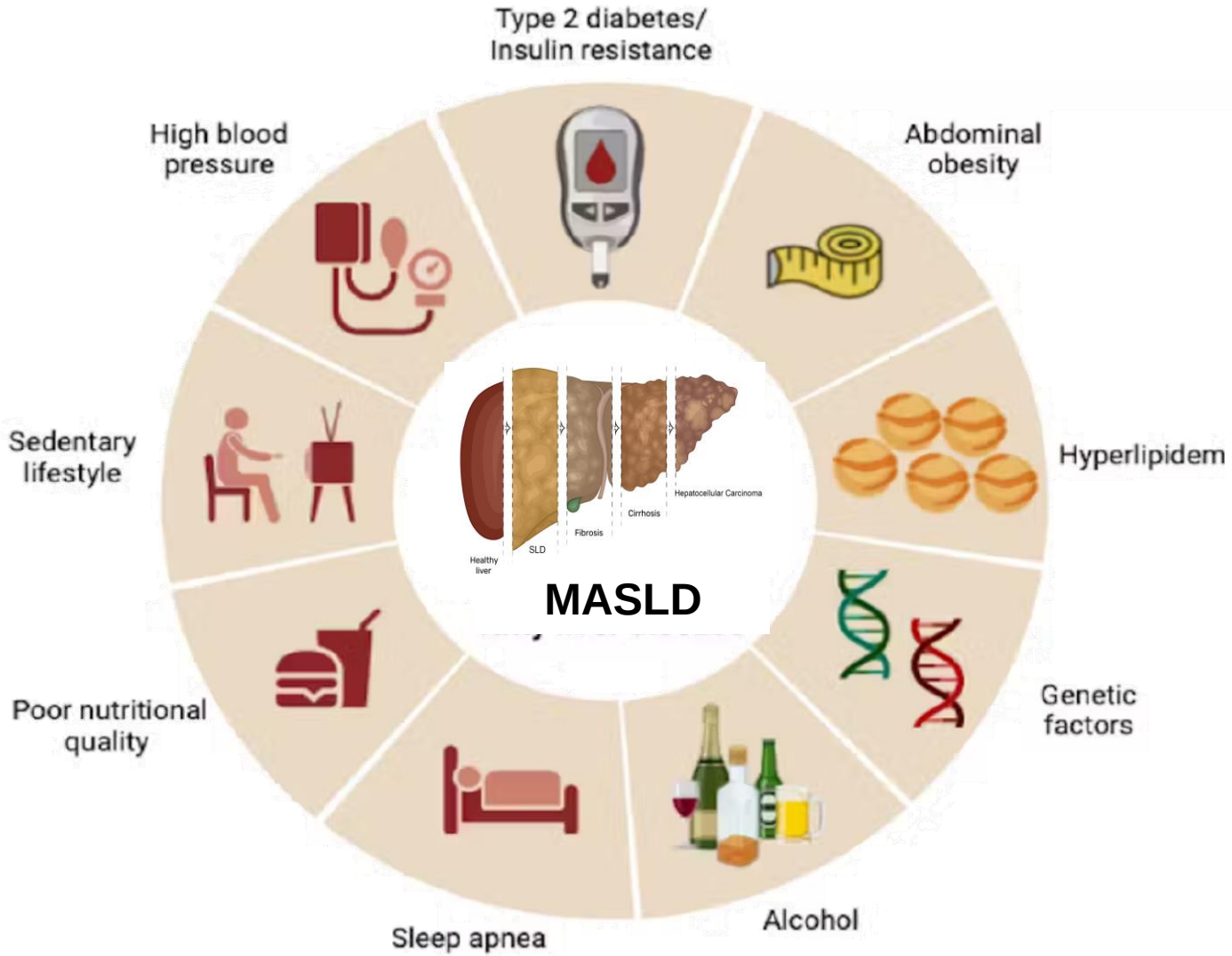
BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2D, type 2 diabetes

1. Public Health England. Adults Obesity and Type 2 Diabetes PHE 2014. Available at: Adult obesity and type 2 diabetes (publishing.service.gov.uk). Last accessed in January 2023; 2. GBD 2015 Obesity Collaborators; Afshin A, et al. N Engl J Med. 2017 Jul 6;377(1):13-27; 3. Zhu P, et al. J Am Soc Nephrol. 2021 Jan;32(1):127-137; 4. CDC. Diabetes and Chronic Kidney Disease; Available in; Diabetes and Chronic Kidney Disease | CDC Last accessed in January 2023; 5. Petta S, Di et al. Liver Int. 2018 Nov;38(11):2060-2068; 6. Younossi ZM, et al. J Hepatol. 2019 Oct;71(4):793-801; 7. Stamler J, et al. Diabetes Care. 1993 Feb;16(2):434-44; 8. An Y, et al. Diabetes Care. 2015 Jul;38(7):1365-71.

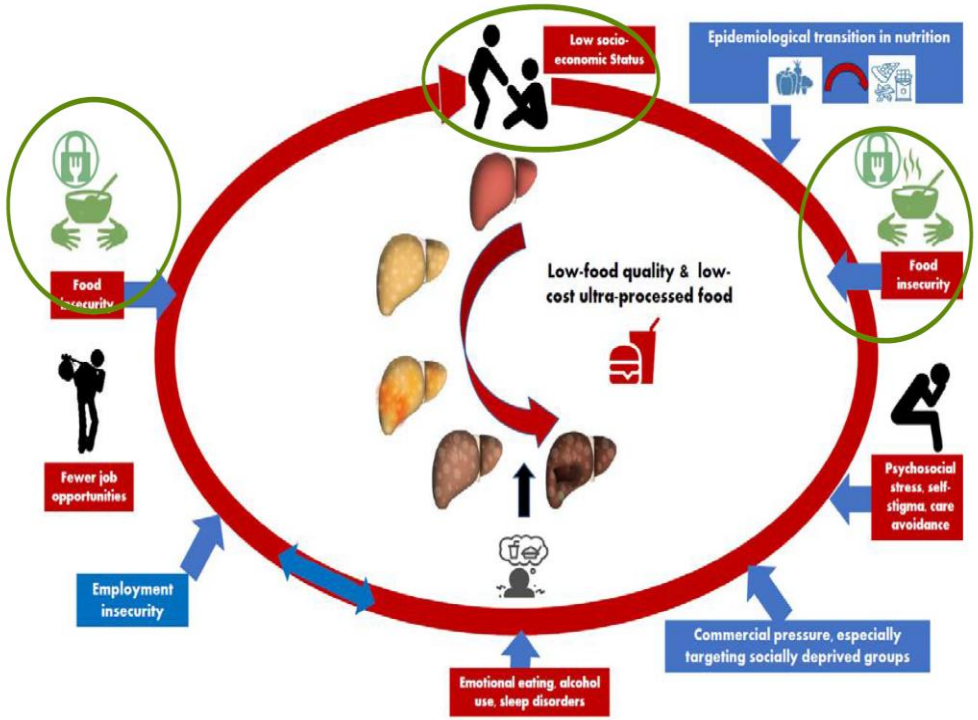
Obesity is a key driver of NAFLD



CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; CVS, cardiovascular system; HFpEF, heart failure with preserved ejection fraction; PVD, peripheral vascular disease; T2D, type 2 diabetes.
Yao L et al. J Immunol Res 2014;181450; Sanyal AJ. Nat Rev Gastro Hepatol 2019;16:377–86.

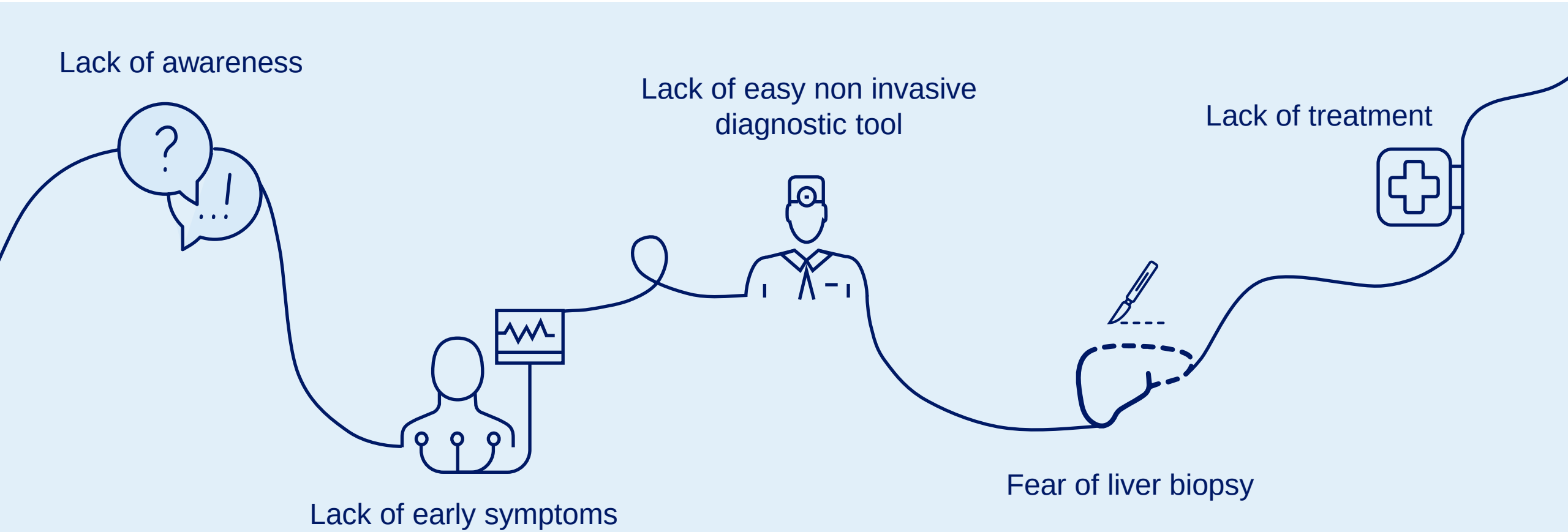


Food insecurity Contributing to Obesity, T2D and MASLD



Arsenault B et al. The Conversation Feb 27, 2022, https://theconversation.com/uncovering-the-genetic-causes-of-fatty-liver-disease-a-growing-health-concern-176641**,** Stefan N, Cusi K. Lancet Diabetes Endocrinol. 2022 Apr;10(4):284-296, Younossi ZM et al. *Hepatology.* 2016;64:73–84; Younossi ZM. *J Hepatol*. 2019;70:531–544., Younossi ZM, et al. Gut. 2020 Mar;69(3):564-568, Arshad T, Paik J, Biswas R, Alqahtani S, Henry L, Younossi ZM. *Hepatology Communications*. 2021, Younossi, Z.,. *et al. Nat Rev Gastroenterol Hepatol* **15,** 11–20 (2018). , AISF_SIO_SID CPG NAFLD Dig Liv Dis. 2021; Manolio TA. Nat Rev Genet. 2013;14(8):549-558., Zelber-Sagi S, Carrieri P, Pericàs J, Ivancovsky Wajcman D, Younossi ZM, Lazarus JV. NRGH 2024 (In Press

NASH is often undiagnosed

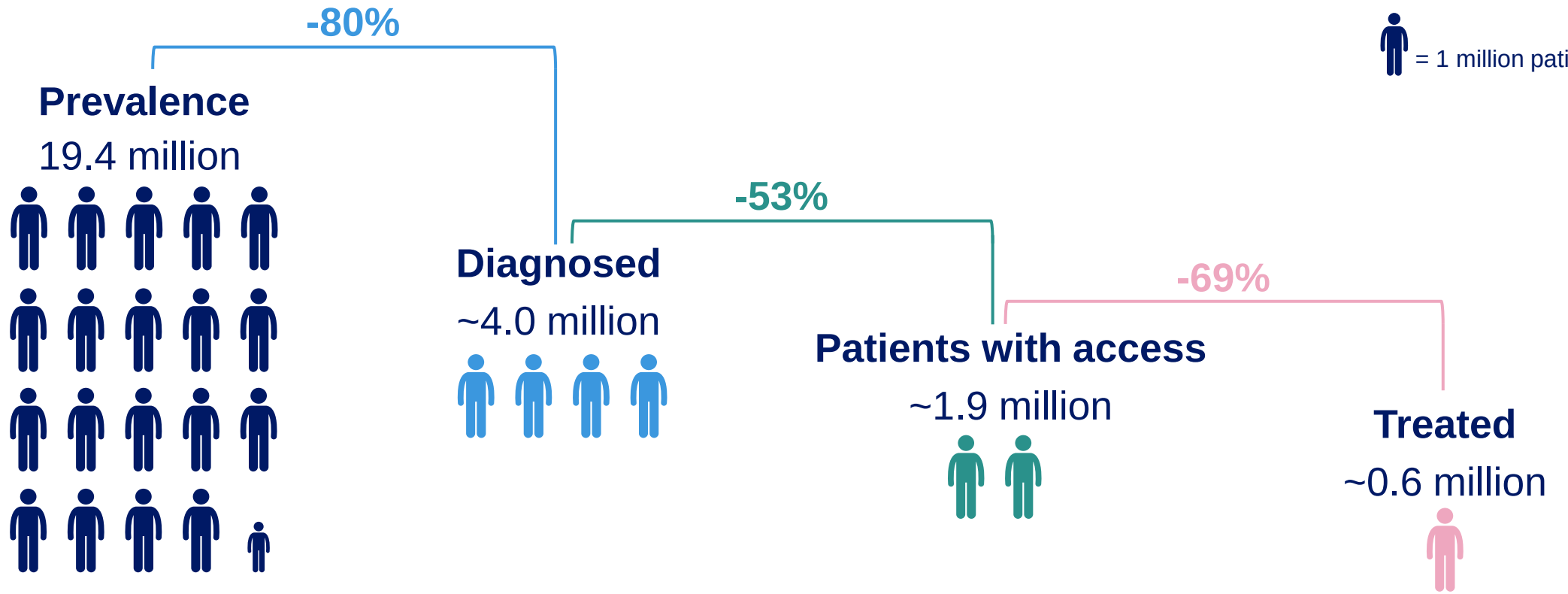


NASH, non-alcoholic steatohepatitis.

Ratziu V et al. J Hepatol. 2015;62:S65–S75; Rinella ME et al. Therap Adv Gastroenterol. 2016;9:4–12; Polanco-Briceno S et al. BMC Res Notes. 2016;9:157; Zelber-Sagi S et al. Therap Adv Gastroenterol. 2016;9:392–407; Ofosu A et al. Ann Gastroenterol 2018;31:288–95.

Diagnosis of NASH is identified as the largest barrier

NASH market barriers identified through ’25 patient waterfall if no/limited intervention (G7, million patients)*



Patients treated by pharmacological, approved drugs (not just treated by semaglutide); US/CA/JP/EU5 patient forecast (F2-F4c only).
**LTF21.*
CA, Canada; EU5, France, Germany, Italy, Spain and the United Kingdom; F2-F4C, fibrosis stage 2 to fibrosis stage 4 with cirrhosis; G7, Group of Seven countries; JP, Japan; NASH, non-alcoholic steatohepatitis; US, United States.
Novo Nordisk. Data on file.

Why we need biomarkers

Liver biopsy is essential for the diagnosis of NASH

Clinical, biochemical or imaging measures cannot distinguish NASH from steatosis

Limitations of biopsy

- Liver biopsy is expensive, invasive, and carries the risk of complications
- Potential sampling errors due to heterogeneity in fibrosis distribution
- Inter- and intra-observer variability of pathologic interpretation
- Biopsy is a cross-sectional interpretation of a dynamic process
- Liver biopsy is a diagnostic tool rather than a staging tool for liver fibrosis

NASH, non-alcoholic steatohepatitis.

1. Rockey D et al. Hepatology 2009;49:1017–44; 2. Golabi P et al. Expert Rev Gastroenterol Hepatol. 2016;10:63–71; 3. Ratziu V et al. Gastroenterol. 2005;128;1898–906; 4. Regev A et al. Am J Gastroenterol 2002;97:2614–8; 5. Patel K and Sebastiani G. JHEP Rep. 2020; 2:100067.

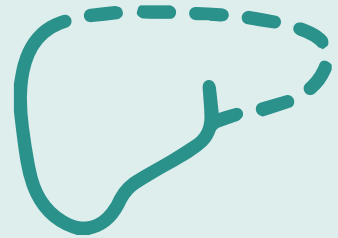
NASH diagnosis is complex

Few symptoms

- Often asymptomatic
- Nonspecific symptoms (eg, right upper quadrant discomfort or fatigue)

Liver enzymes and ultrasound

- Mildly elevated with ALT predominance in most patients
- Steatosis on ultrasound

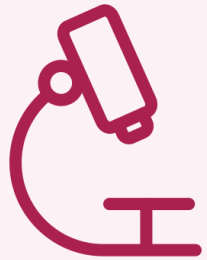


Exclusion of other aetiologies

- No significant alcohol consumption
- No competing aetiologies for hepatosteatosis
- No coexisting causes of chronic liver disease

Requires a liver biopsy

- Diagnosis of NASH requires the **joint presence of steatosis, ballooning and lobular inflammation**
- Diagnostic gold standard



ALT, alanine aminotransferase; NASH, non-alcoholic steatohepatitis.

European Association for the Study of the Liver et al. J Hepatol. 2016;64:1388–1402;
Stengel JZ and Harrison SA. Gasteroenterol Hepatol 2006;2:440–9; Chalasani N et al. Hepatology 2018;67:328–57.

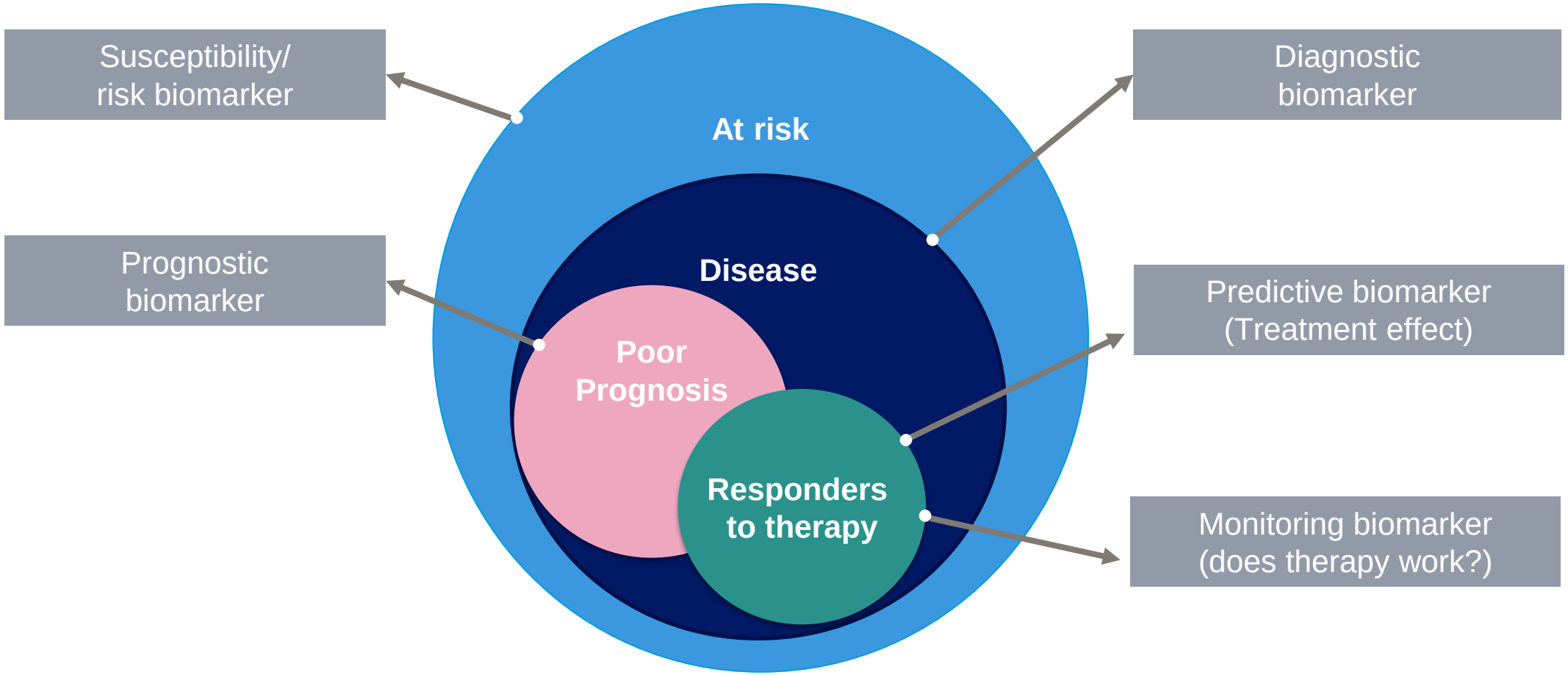
Ideal characteristics for a biomarker in NASH

- Widely available and affordable
- Accurate and reproducible
- Able to show minimal variation across populations (age, gender, ethnicity)
- Sensitive and specific in identifying NASH and fibrosis staging
- Able to identify fibrosis and fibrosis staging in NASH patients
- Able to follow longitudinal change in fibrosis progression/regression

NASH, non-alcoholic steatohepatitis.

1. Arulanandan A and Loomba R. Curr Hepatol Rep 2015;14:109–18; 2. Long MT et al. Metabolism 2020;111S:154259; Patel K and Sebastiani G. JHEP Rep 2020;2:100067.

Overview of the different functions of biomarkers



1. Arulanandan A and Loomba R. Curr Hepatol Rep 2015;14:109–18; 2. Long MT et al. Metabolism 2020;111S:154259; Patel K and Sebastiani G. JHEP Rep 2020;2:100067.

Fibrozis Teşhisi İçin En Sık Kullanılan Noninvasif Testler

Vibration-controlled transient elastography) (FibroScan)

Serologic Markers

- **Simple**
  - FIB-4
  - NFS
- **Complex**
  - ELF
  - Pro-C3

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

AASLD

Imaging

- **Elastography**
  - VCTE
  - MRE
  - Multiparametric
  - ARFI

Liver stiffness

- Obtained through a VCTE measurement
- Correlated to extent of fibrosis

CAP

- Quantification of ultrasound attenuation obtained in VCTE measurement
- Correlated to liver steatosis

Sık kullanılan noninvazif testler

Klinik veya Laboratuar Skorlar

Basit

- Fibrosis-4 (FIB-4) index
- NAFLD fibrosis score (NFS)
- AST/platelet ratio index

Proprietary

- Enhanced liver fibrosis panel (not available in US)
- NIS4
- ADAPT/Pro-C3 (not available in US)
- *FibroSure*
- Hepascore

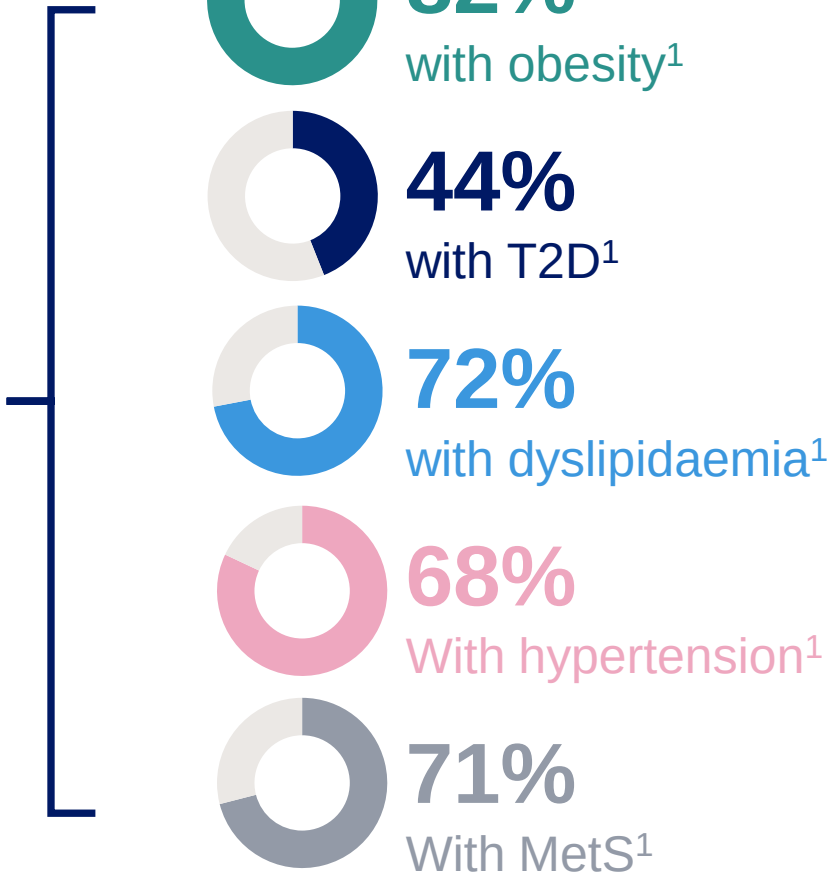
Görüntüleme

Elastography

- Transient elastography (eg, *FibroScan*)
- 2D shear wave elastography
- Magnetic resonance elastography
- Corrected T1 (*Liver MultiScan*)
- MRI-PDFF
- FAST score

Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. Daniels. Hepatology. 2019;69:1075. EASL. J Hepatol. 2015;63:237. Idilman. Radiology. 2013;267:767. Jayaswal. AASLD 2018. Abstr 1042. Jayaswal. Liver Int. 2020;40:3071. Newsome. Lancet Gastroenterol Hepatol. 2020;5:362. Sigrist. Theranostics 2017;7:1303. Harrison. Lancet Gastroenterol Hepatol. 2020;5:970.

Association between NASH and comorbidities



82%
with obesity[1]

44%
with T2D[1]

72%
with dyslipidaemia[1]

68%
With hypertension[1]

71%
With MetS[1]

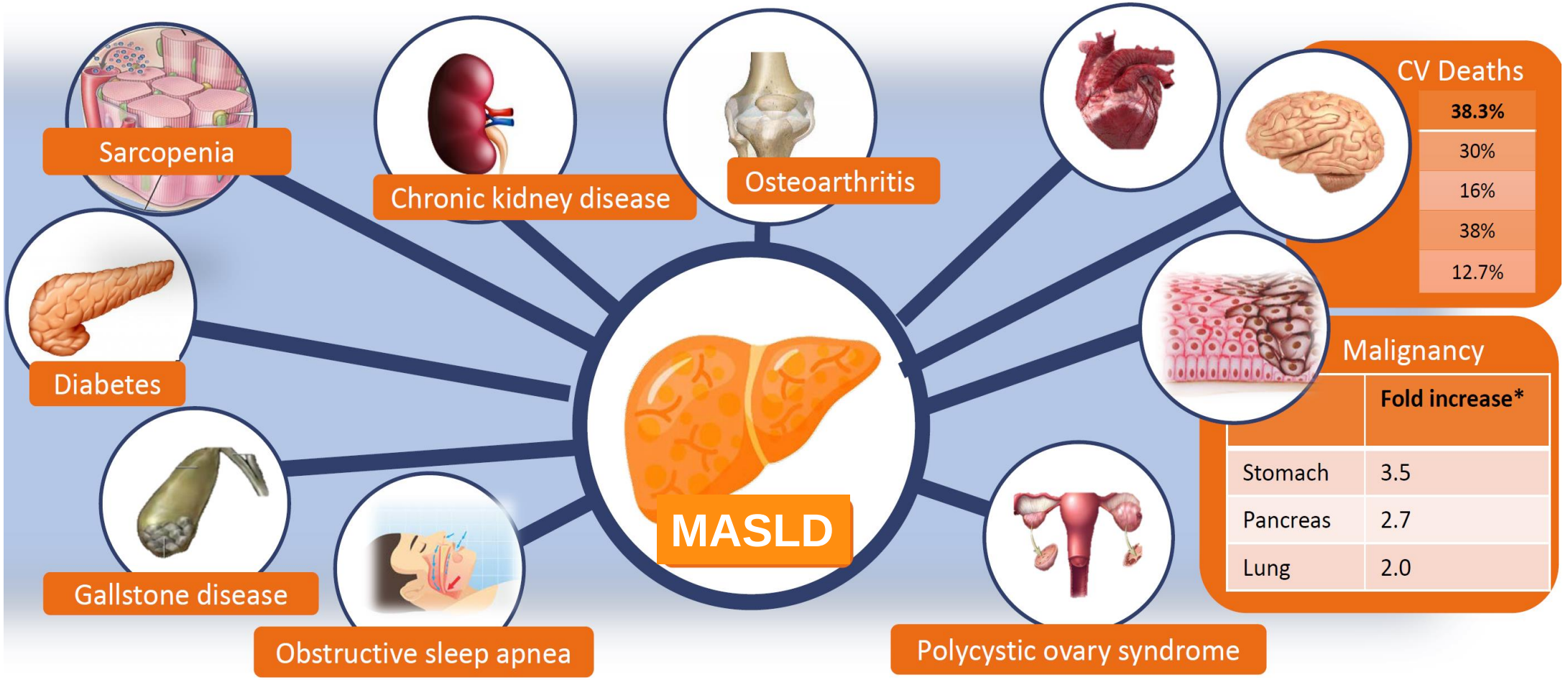
Prevalence of NASH in at-risk populations

37.3%
in people with T2D[3]

37%
in people with obesity[2]

MetS, metabolic syndrome; NASH, non-alcoholic steatohepatitis; T2D, type 2 diabetes.
1. Younossi ZM et al. Hepatology 2016;64:73–84; 2. Machado M et al. J Hepatol 2006;45:600–6; 3. Younossi ZM et al. J Hepatol 2019;71:793–801.

Other Important Associations: Extraheaptic Diseases



Younossi Z et al 2020

How to translate NAFLD to MASLD?

NAFLD is now Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) to better reflect the cardiometabolic disease drivers

Non-Alcoholic Fatty Liver Disease **(NAFLD)**

Non-Alcoholic Steatohepatitis **(NASH)**

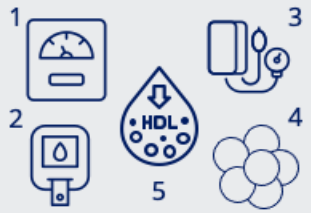
→

Metabolic Dysfunction-Associated Steatotic Liver Disease **(MASLD)**

Metabolic Dysfunction-Associated Steatohepatitis **(MASH)**

MASLD is defined by presence of*

Hepatic steatosis + ≥1 cardiometabolic risk factor



Reflects disease aetiology

Non-stigmatising

MASLD/MASH

Improves disease awareness

Improves patient identification

**Following exclusion of other causes or specific-aetiologies of steatosis. [1]BMI ≥ 25 kg/m or waist circumference > 94 cm (male) or 80 cm (female) or ethnicity adjusted; [2]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% or type 2 diabetes or on treatment for type 2 diabetes; [3]BP ≥ 130/85 mmHg or on anti-hypertensive treatment; [4]Plasma triglycerides ≥ 1.70 mmol/L or lipid lowering treatment; [5]Plasma HDL-cholesterol ≤ 1.0 mmol/L (40 mg/dL for males) and ≤ 1.3 mmol/L (50 mg/dL for females) or lipid lowering treatment. Rinella, ME et al. Hepatology. 2023. doi: 10.1097/HEP.0000000000000520*

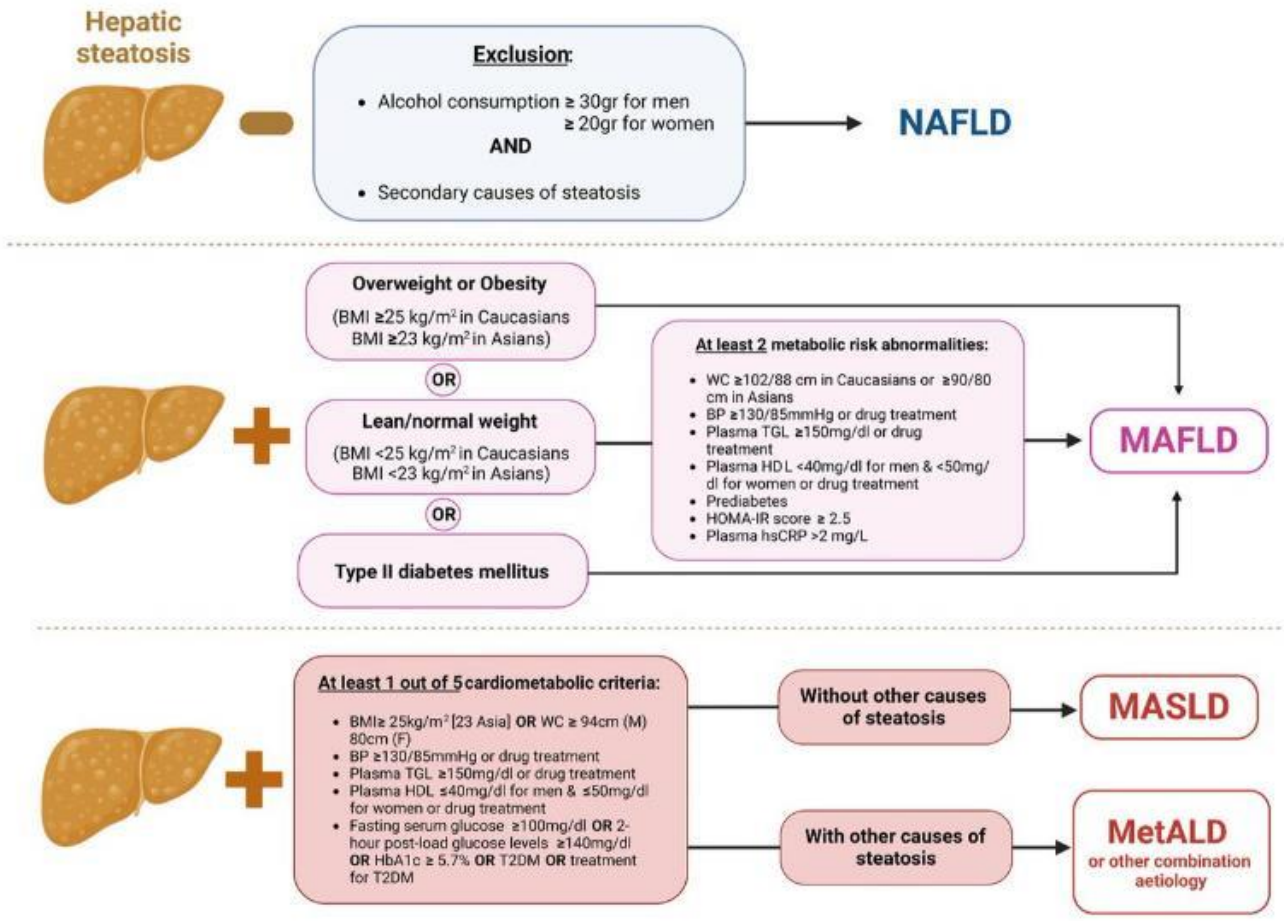
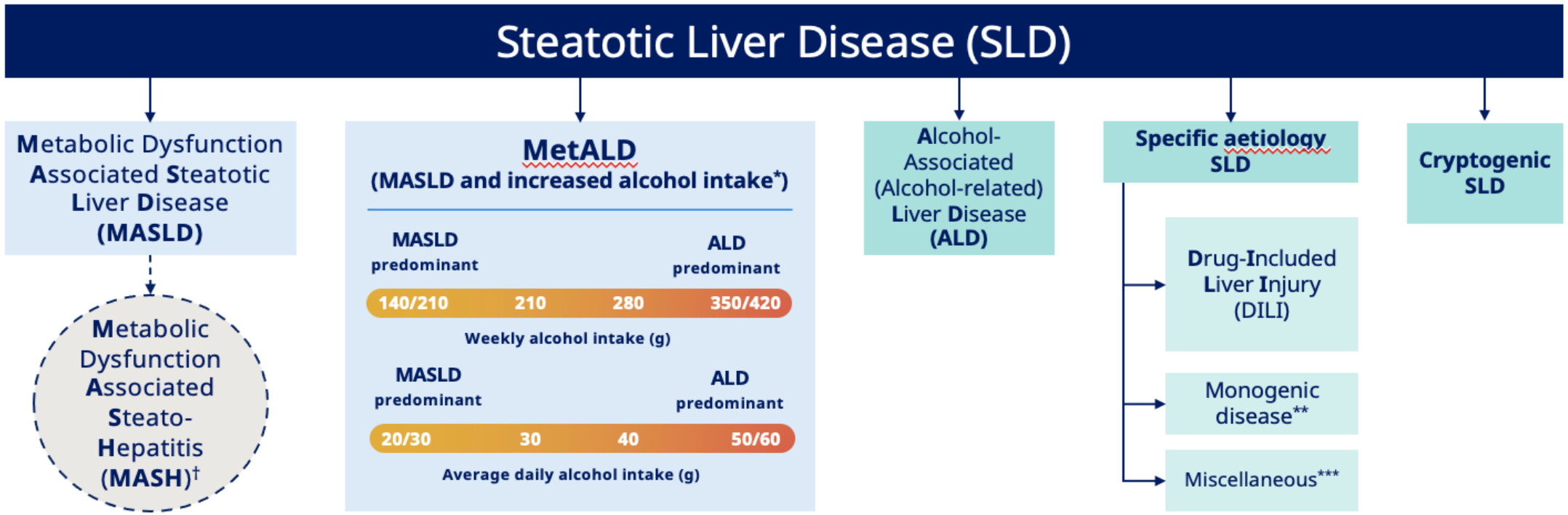


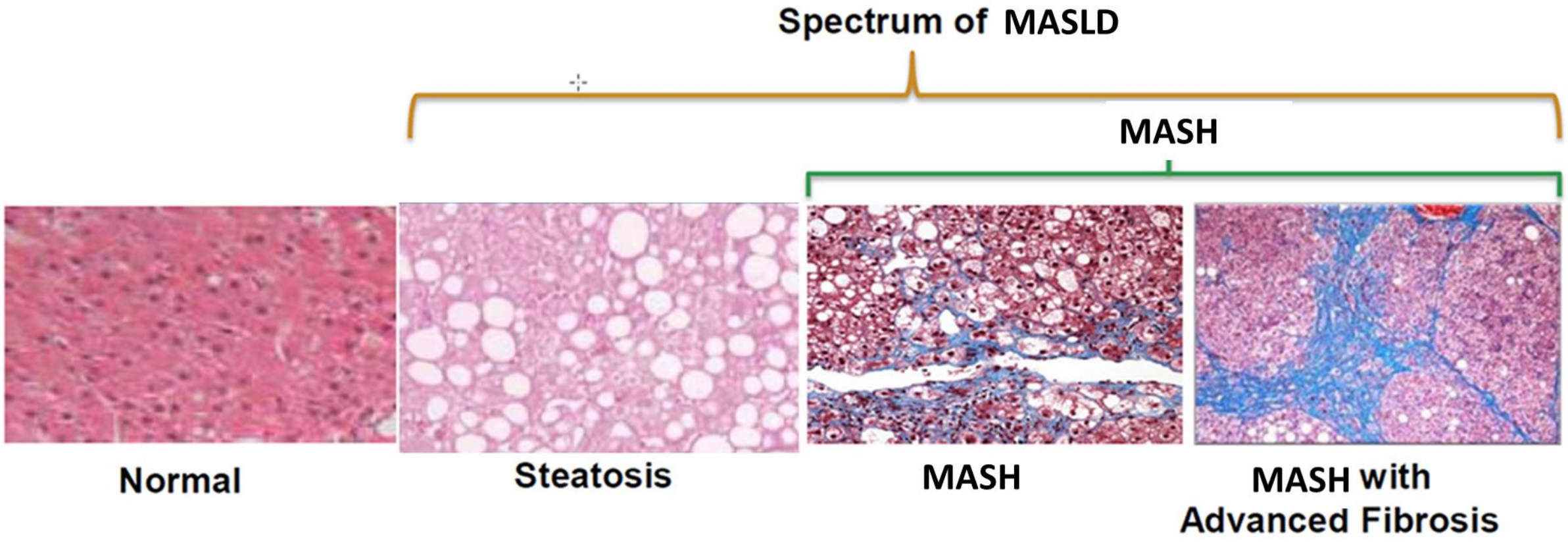
Fig. 1. Definitions of non-alcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD). BMI: body mass index, WC: waist circumference, BP: blood pressure, TGL: triglycerides, HDL: high-density lipoprotein, HOMA-IR: homeostasis model assessment – insulin resistance, hsCRP: high sensitivity C-reactive protein, T2DM: type II diabetes mellites, M: males, F: females, prediabetes: fasting glucose levels 100 to 125 mg/dl (5.6 to 6.9 mmol/L), or 2-hour post-load glucose levels 140 to 199 mg/dl (7.8 to 11.0 mmol) or HbA1c 5.7 % to 6.4 % (39 to 47 mmol/mol). Created with BioRender.com.

Steatotic Liver Disease is the overarching term



†MASH is under the umbrella term, MASLD
**weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male);*
***e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism;*
****e.g. Hepatitis C virus (HCV), malnutrition, celiac disease*
HCP, health care professionals. Modified from Rinella, ME et al. Hepatology. 2023. doi: 10.1097/HEP.0000000000000520

No Change in Histologic Disease Definition

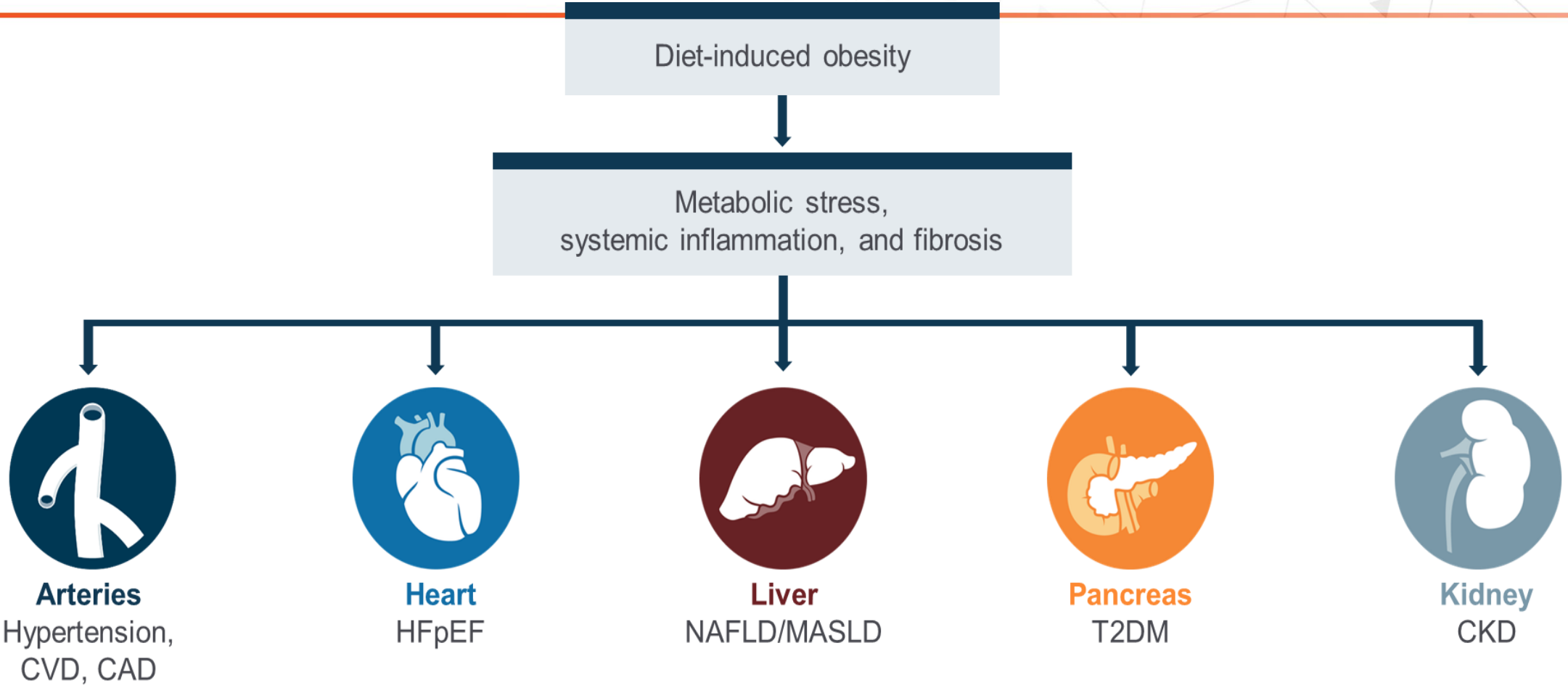


Summary: Pathophysiology in MASH

- Great (99%) overlap in NAFLD and MASLD, therefore, no anticipated change in disease pathogenesis or associated pathophysiology
- Complex inter-organ cross talk with adipose tissue being a key regulator of signaling pathways → MASLD / MASH
- A maladaptive metabolic response, potentially starting within the adipocytes → insulin resistance and cellular stress.
- Patient heterogeneity is influenced by genetic and epigenetic modifiers with this interaction warranting further investigation
- Therapies the address the underlying metabolic disease/ insulin resistance and/or adipocyte biology may be best
  - Treatments focused on inflammation/death pathways have not worked

Ref

MASH is a component of a multi-system disorder



CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, nonalcoholic fatty liver disease.

1. Friedman SL, et al. Nat Med. 2018;24:908-922; 2. Pan American Health Organization. Accessed May 26, 2023. https://www.paho.org/en/enlace/overweight-and-obesity#:~:text=Overweight%20and%20obesity%20is%20one,and%20gout%2C%20and%20pulmonary%20diseases; 3. Jam SA, et al. BMC Nephrol. 2022;23:233; 4. Godoy-Matos AF, et al. Diabetol Metab Syndr. 2020;12:60; 5. Tourki B, et al. Front Cardiovasc Med. 2021;8:695952.

AASLD clinical practice algorithm

2023

Clinical Suspicion for Fatty Liver Disease

Primary Care or Non-GI/Hepatology Care

Goal: Exclude advanced fibrosis in low-prevalence populations

Primary risk assessment, e.g., FIB-4

FIB-4 ≥1.3

No

Reassess periodically:
FIB-4 every 1–2 years if T2D/preT2D or ≥2 metabolic risk factors*

Yes

FIB-4 >2.67
Consider referral

Persistent ↑ ALT and AST

Risk Level	VCTE or ELF	
Low	< 8.0	<7.7
Intermediate	8–12	7.7 - 9.8
High	>12	>9.8

All patients:
- Cardiometabolic risk reduction & preferential use of meds with potential NAFLD benefit
- Ongoing assessment of alcohol intake
- Lifestyle management

Referral

GI/Hepatology care

Goal: Identify/manage patients with 'at risk' NASH or cirrhosis

- Review/perform primary/secondary risk assessment
- Consider additional stratification with MRE, cT1

PCP follow-up or reassess

Low risk

Intermediate/high risk

Consider liver biopsy
- Indeterminate NITs
- Diagnostic uncertainty
- Persistently ↑ ALT and AST

Suspect cirrhosis (clinical, imaging or ELF >11.3)

Biopsy Staging

Stage 0-1	Stage 2-3	Stage 4
Reassess in 2-3 years	• Reassess annually • Consider pharmacotherapy	Cirrhosis-based management

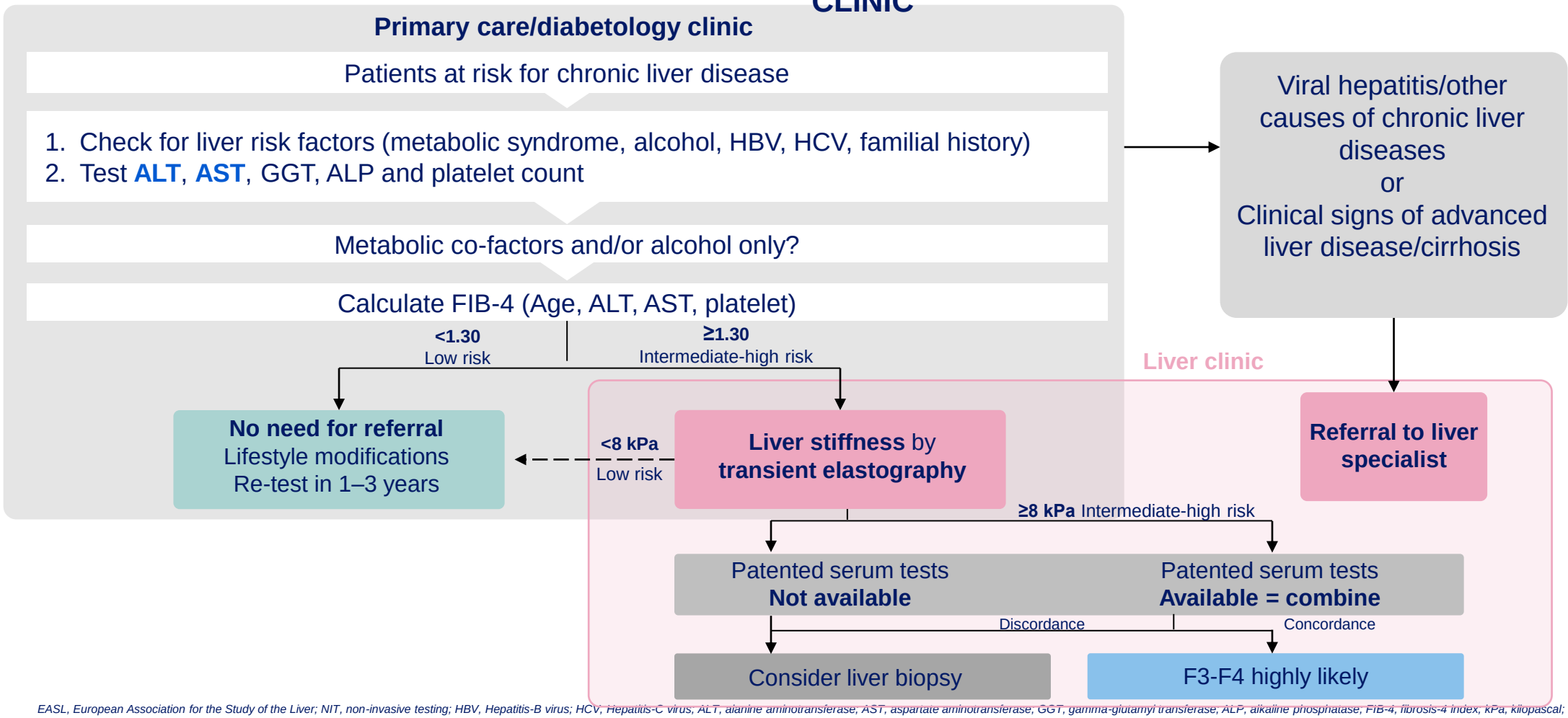
*AASLD, American Association for the Study of Liver Disease; GI, gastrointestinal; FIB-4, fibrosis-4 index; T2D, type 2 diabetes; *, FIB-4 every 2–3 years if no T2D and <2 metabolic risk factors; ALT, alanine aminotransferase; AST, aspartate aminotransferase; VCTE, vibration controlled transient elastography; ELF, enhanced liver fibrosis test; NAFLD, non-alcoholic fatty liver disease; MRE, magnetic resonance enterography; cT1, iron-corrected T1 relaxation time; PCP, primary care physician; NIT, non-invasive testing*

Adapted from Rinella ME et al. Hepatology. 2023;doi: 10.1097/HEP.0000000000000323.

EASL clinical practice guidelines

2021

PROPOSED USE OF NITs IN PATIENTS OBSERVED IN PRIMARY CARE OR OUTSIDE THE LIVER CLINIC

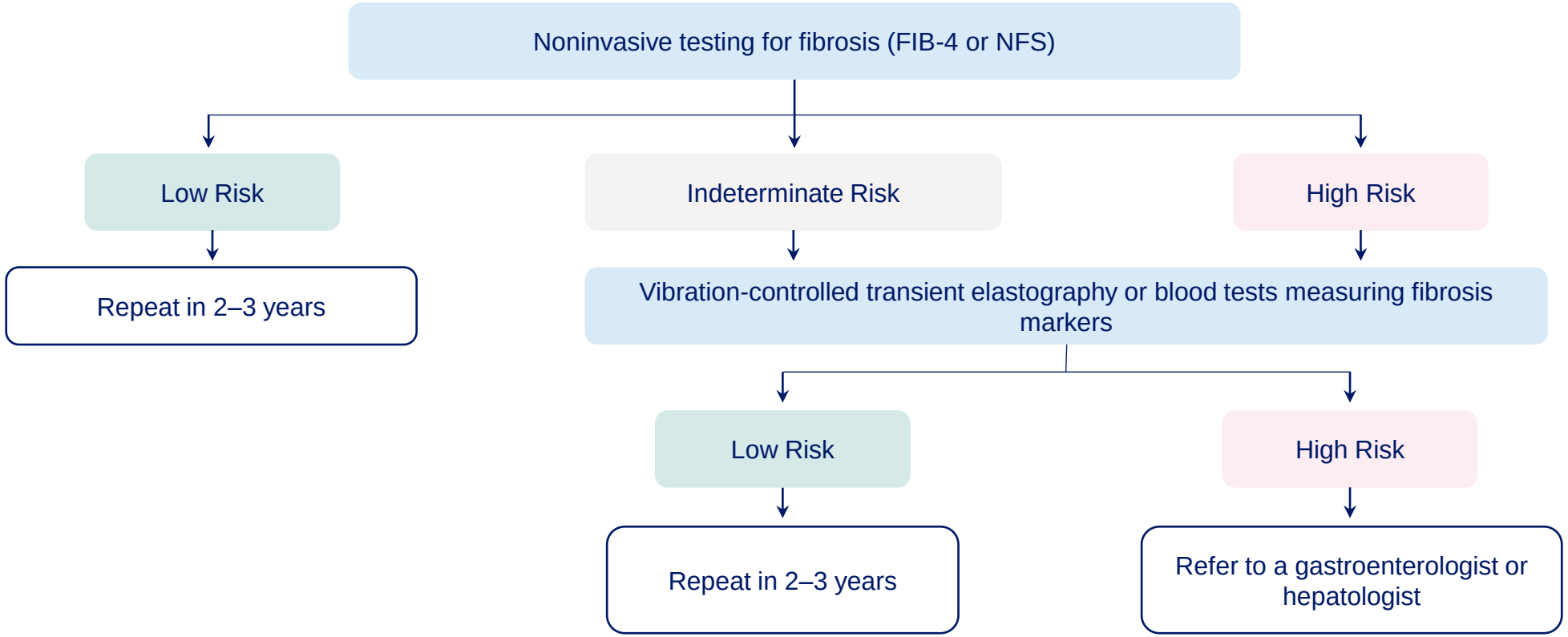


EASL, European Association for the Study of the Liver; NIT, non-invasive testing; HBV, Hepatitis-B virus; HCV, Hepatitis-C virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; FIB-4, fibrosis-4 index; kPa, kilopascal; F3-F4, liver fibrosis stage 3-4.

Adapted from Berzigotti A et al. J. Hepatol. 2021;75:659–89.

ADA referral pathway

2023



American Diabetes Association Professional Practice Committee. Diabetes Care. 2023;46:S49–S67.

Patients who should be screened for NAFLD/NASH

Summary of global guidelines

Associations in the US, Europe and Japan recommend screening for NAFLD and NASH in[1–7]:

Patients with T2D

Patients with obesity/MetS*

Patients with liver steatosis

Patients with abnormal liver enzymes

High-risk individuals†

AASLD recommends screening for advanced fibrosis within high-risk populations

JSGE/JSH also recommends screening high-risk individuals for HCC

AACE, ADA & DGVS recommend evaluation of individuals with T2D and elevated liver enzymes for NASH[5-7]

**AASLD and EASL; †Definition of high-risk varies across guidelines.*
AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; AASLD, American Association for the Study of Liver Disease; DGVS; German Society of Gastroenterology; HCC, hepatocellular carcinoma; JSGE/JSH, Japanese Society of Gastroenterology/Japanese Society of Hepatology; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2D, type 2 diabetes.

1. Rinella ME et al. Hepatology. 2023;doi: 10.1097/HEP.0000000000000323; 2. Marchesini G et al. J Hepatol. 2016;64:1388–1402; 3. Kanwal F et al. Gastroenterology. 2021:1–13; 4. Tokushige K et al. J Gastroenterol. 2021;56:951–63; 5. American Diabetes Association Professional Practice Committee. Diabetes Care. 2023;46:S49-S67. 6. Endocrine Practice. American Association of Clinical Endocrinology. 2022; 28:455-564; 7. Tacke F et al. Deutsche Gesellshaft fur Gastroenterologie–und Stoffwechselkrankheiten. 2022;1–149.

Lack of awareness of NAFLD/NASH

Summary of global guidelines

NAFLD affects approximately 30% and NASH affects 5% of the global population

Overall, there is a lack of recognition of NASH as a **chronic progressive metabolic disease**

Majority of individuals are **undiagnosed** or diagnosed at a much **later stage** due to:

- Silent and non-specific symptoms
- Lack of understanding of the disease
- Limitations in diagnostic methods

HCPs lack an understanding of NASH or do not consider NASH a **high priority**

Due to the **increased prevalence** of NAFLD/NASH in patients with **T2D, obesity** and other metabolic syndrome, there is a need for **active evaluation** in these patients

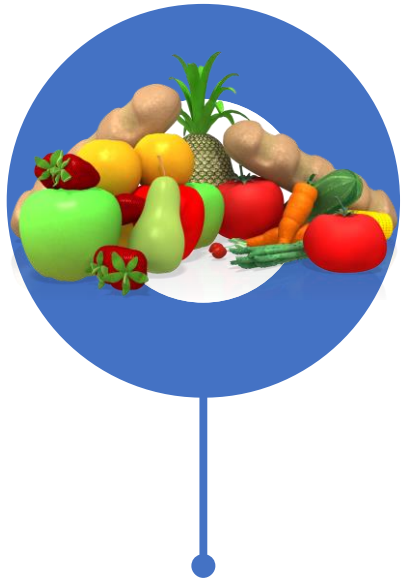
HCPs, healthcare professionals; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NIT, non-invasive tests; T2D, type 2 diabetes.

1. Younossi ZM et al. Hepatology. 2023; 10.1097/HEP.0000000000000004; 2. Rinella ME et al. Hepatology. 2023;doi: 10.1097/HEP.0000000000000323; 3. Marchesini G et al. J Hepatol. 2016;64:1388–1402; 4. Kanwal F et al. Gastroenterology. 2021:1–13; 5. Tokushige K et al. J Gastroenterol. 2021;56:951–63; 6. American Diabetes Association Professional Practice Committee. Diabetes Care. 2023;46:S49-S67.

Goals of Any Treatment for MASH

- Improve metabolic abnormalities
- Decrease inflammation
- Prevent / arrest / reverse liver fibrosis
- Prevent liver failure, liver cancer and liver-related outcomes
- Improve systemic outcomes (eventually) including risk for new incident diabetes mellitus, CVD, and CKD
- Acceptable safety profile

Lifestyle recommendations for treating MASH



Caloric intake reduction
of ≥30% or
~750-1,000 kcal/day improved insulin resistance and hepatic steatosis.

Limit consumption of fructose-enriched beverages.

Weight loss
of 3-5% can improve steatosis, but 6-10% is needed to improve MASH/fibrosis.

Exercise
alone may reduce steatosis, but the effect on other histologic features is unknown.

No heavy alcohol consumption
Insufficient data to guide recommendations regarding nonheavy alcohol consumption.

Drink ≥2 cups of caffeinated coffee daily.

Sources: Chalasani N *et al.* The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology.* 2018 Jan;67(1):328-357.

50 years since first report to FDA Approval !

From crawl, to walk, to a run (with a few stumbles along the way) to a final “win”

The RACE is on!

Discovery 1960-1970	1980 Mayo series Ludwig et al.	1985- Basic science	1992 Epidemiology	2010 PIVENS	2014 FLINT	2014-present Phase 2/3 Clinical studies	2024 FDA approves Resmetirom

MASH Emerging Landscape 2024

Objectives

- Discuss newly FDA-approved therapy, resmetirom, a thyroid hormone receptor-β (THR-β) agonist for MASH
  - Efficacy
  - Safety
  - FDA approved label for use
- Emerging therapies in phase 3 studies on the short-term horizon
  - GLP1: Semaglutide
  - Pan-PPAR: Lanifibranor
  - FGF-21 agonist: Efruxifermin
  - FGF-21 agonist: Pegozafermin
  - Highlight promise of dual and triple agonists

Shifting the needle on a neglected public health threat

A global issue

MASLD affects >33% of adults around the world.

A significant impact

MASLD has serious health, economic, and social implications.

A complex Challenge

MASLD requires us to work across disciplines and sectors to find solutions.

A silent condition

MASLD has received little attention from policy-makers or the public health community.

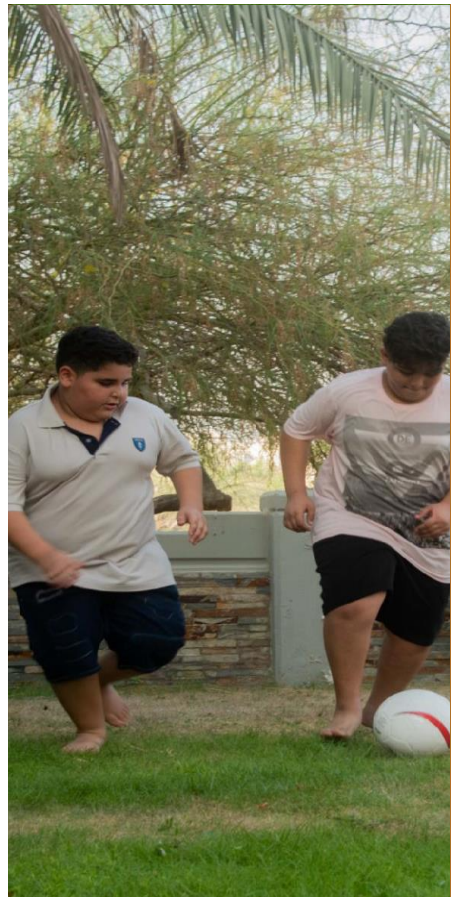


Photo credit: The World Obesity Federation.

@JVLazarus

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- **SBÜ Adana Şehir Eğitim ve Araştırma Hastanesi**
- **İç Hastalıkları Kliniği**
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