Congresso Nazionale

AGGIORNAMENTI INFETTIVOLOGICI:

HIV, EPATITI & .....

Firenze, 15-17 Gennaio 2024

Centro Congressi Hotel Albani

MASLD: Inquadramento diagnostico-terapeutico

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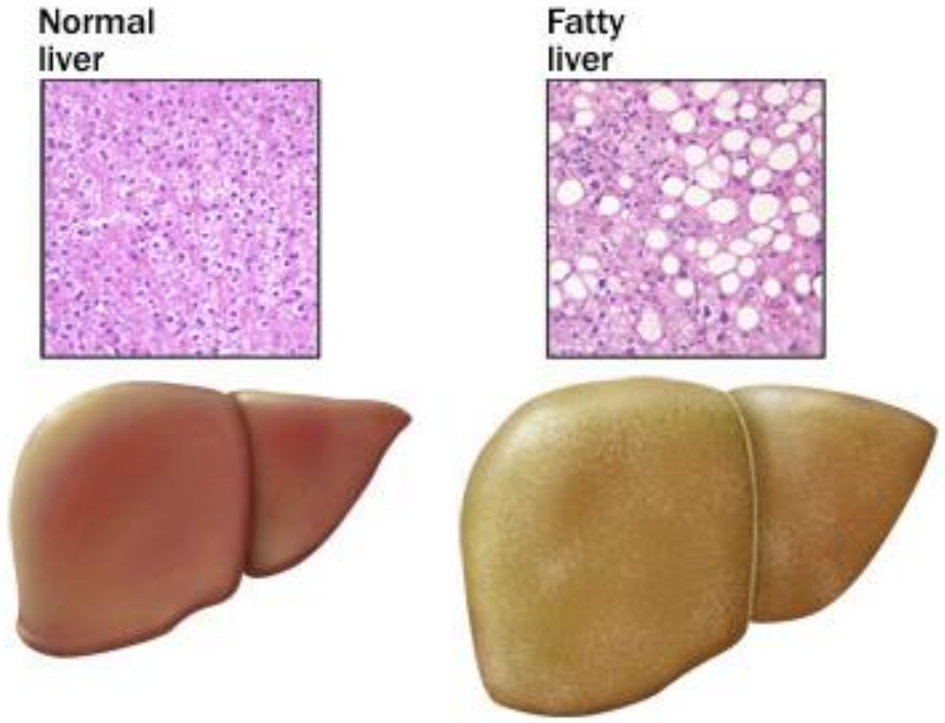
Disclosures

- **Alfasigma:** travel grants
- **AstraZeneca:** consultant fees
- **Bayer:** speaker honoraria, consultant fees, travel grants
- **Gilead:** speaker honoraria, consultant fees
- **Ipsen:** consultant fees
- **Intercept:** speaker honoraria
- **MSD/EISAI:** consultant fees
- **Menarini:** consultant fees
- **Novartis:** consultant fees
- **Novo Nordisk:** consultant fees
- **Roche:** consultant fees

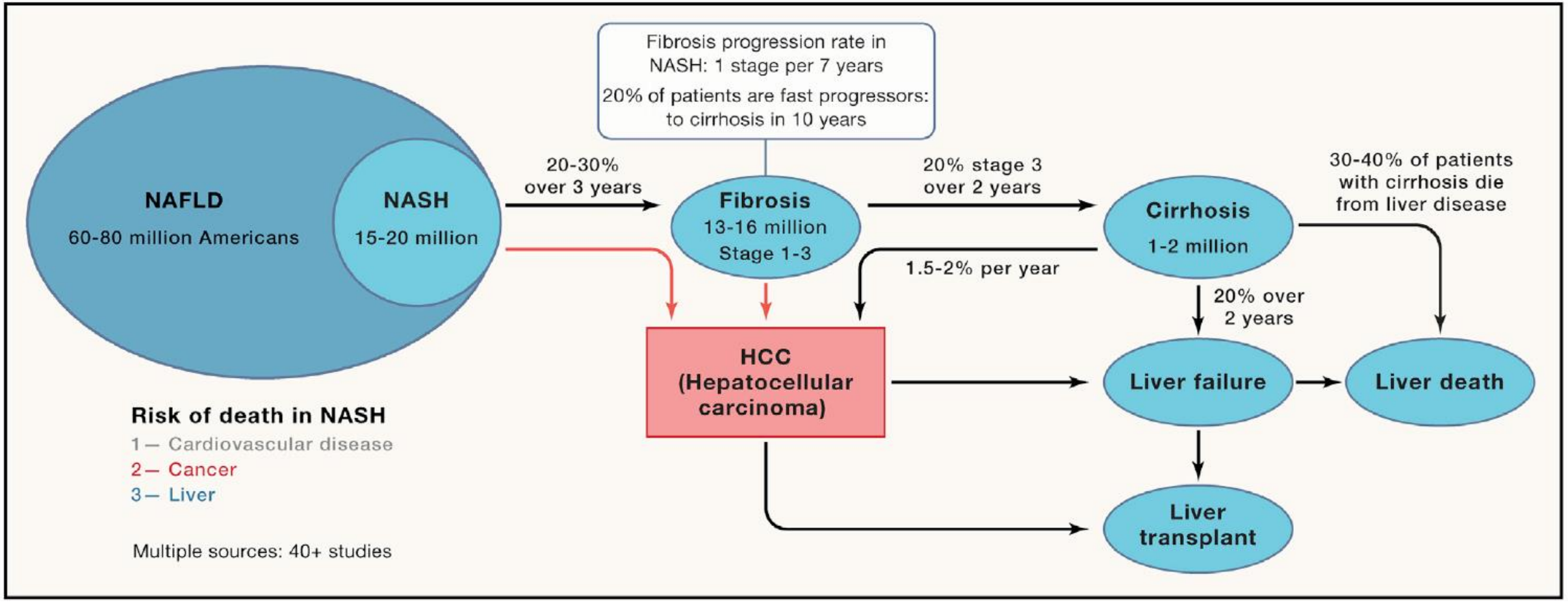
Definition and (new) nomenclature



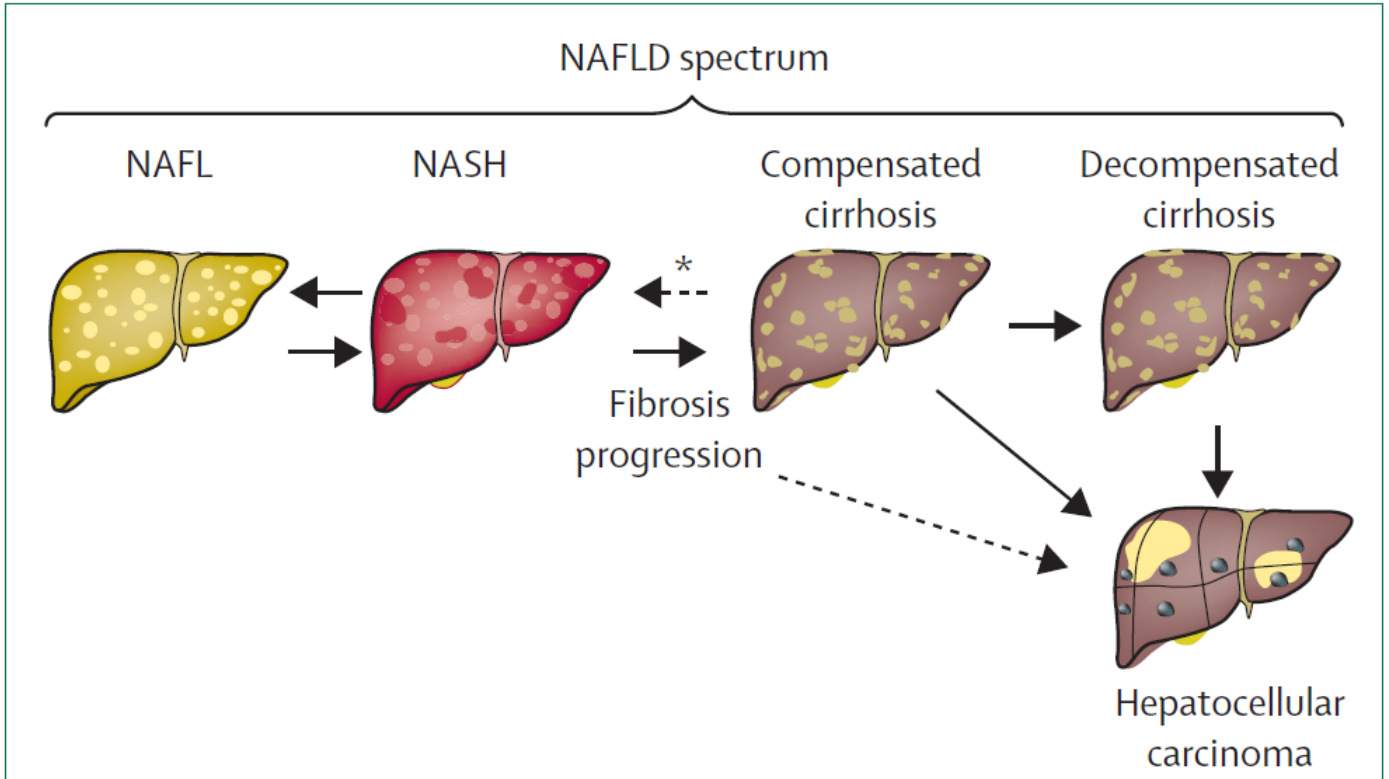
NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

- Steatosis (>5% of hepatocytes)
- **Evidence for minimal (<20g/d) alcohol consumption**
- Exclusion of other causes of liver disease

Natural history of NAFLD



Loomba et al., Cell 2021



Factors associated with NAFLD and NASH progression

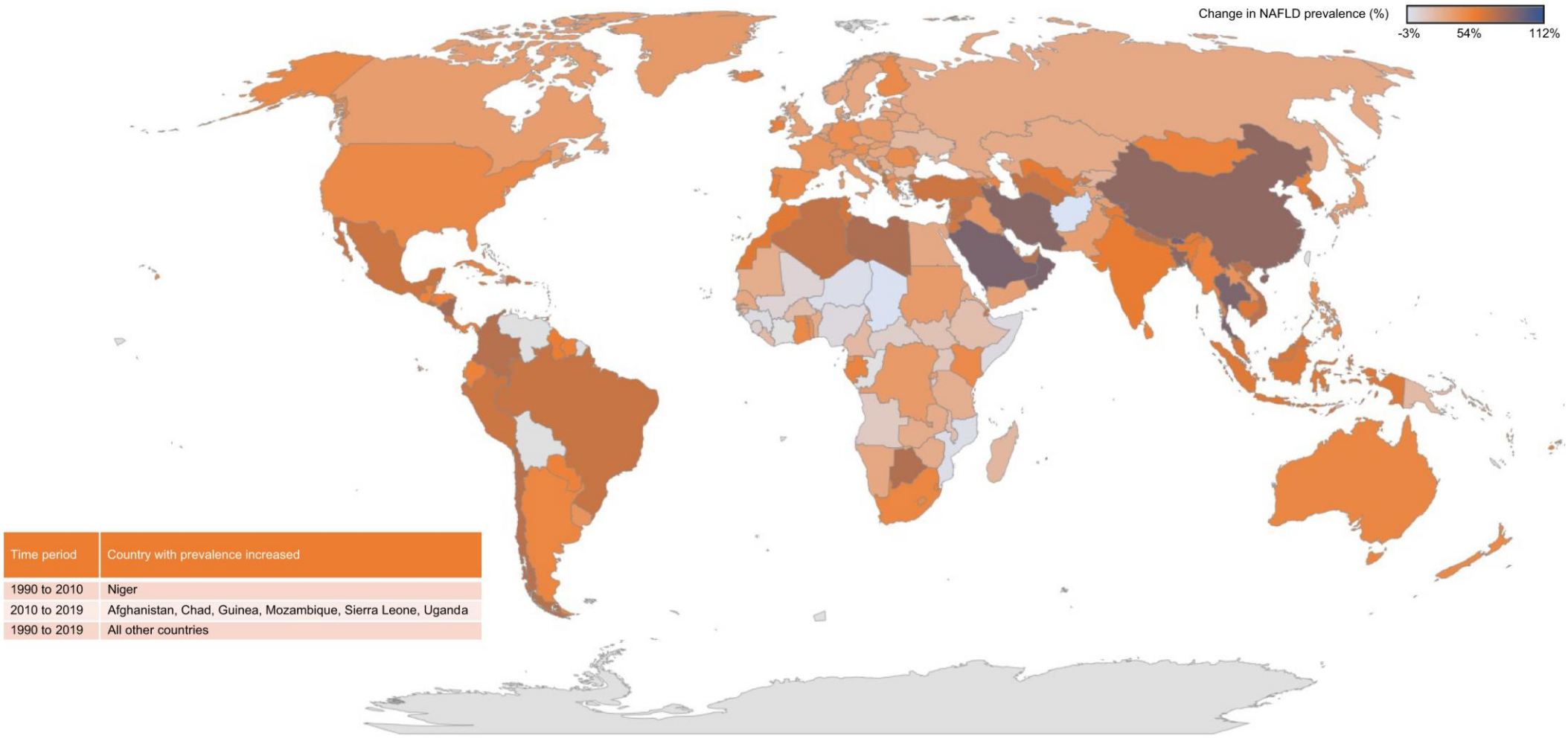
Comorbid illness
- Type 2 diabetes
- Insulin resistance
- Dyslipidaemia
- Obesity
- Hypertension
- Hypopituitarism

Genetic factors
- *PNPLA3*
- *TM6SF2*
- *GCKR*
- *MBOAT7*
- ***HSD17B13***

Environmental factors
- Fructose
- Cholesterol
- Alcohol
- **Exercise**
- **Coffee**

Powell et al., Lancet 2021

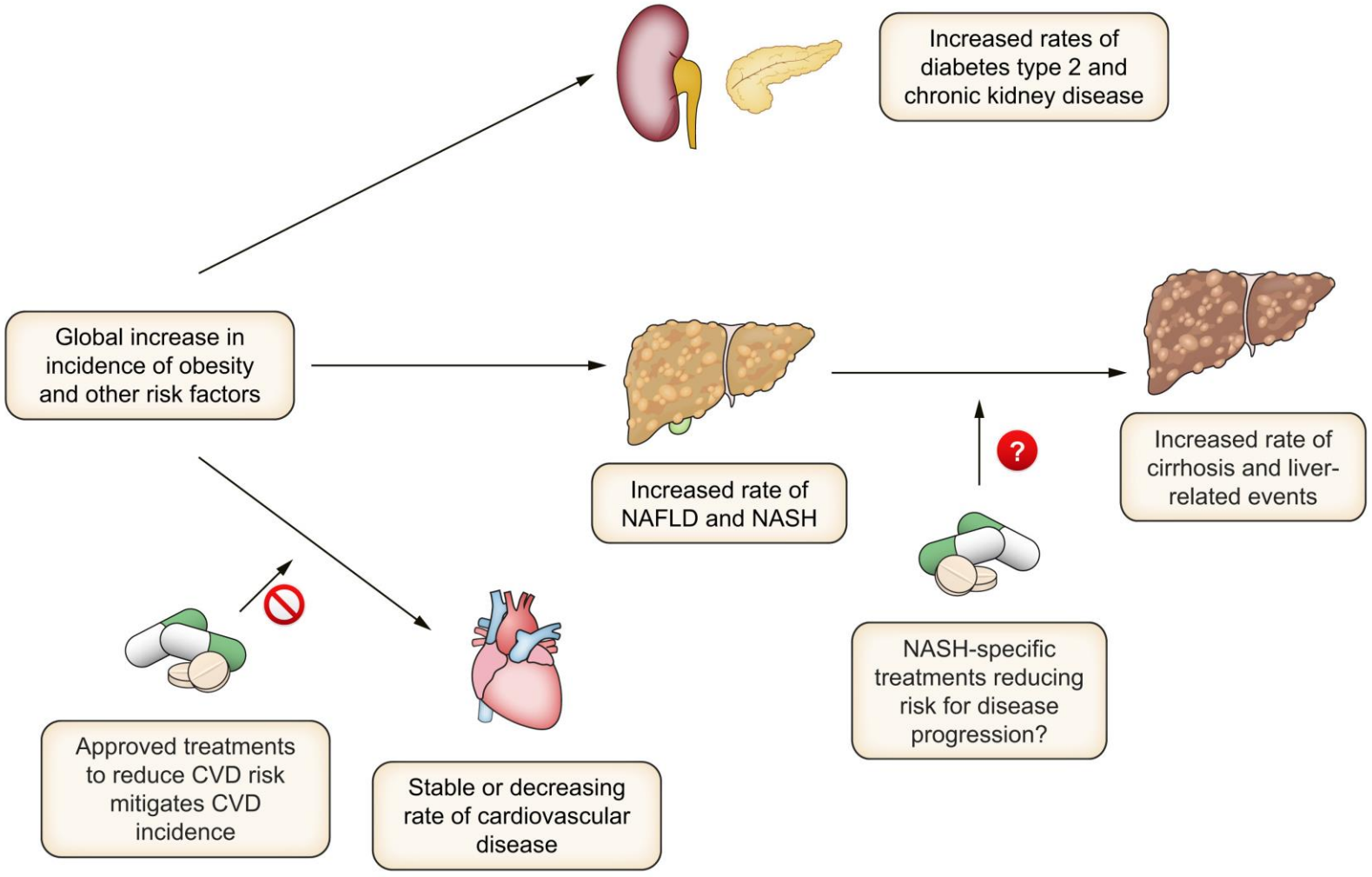
Trends in MASLD prevalence



Time period	Country with prevalence increased
1990 to 2010	Niger
2010 to 2019	Afghanistan, Chad, Guinea, Mozambique, Sierra Leone, Uganda
1990 to 2019	All other countries

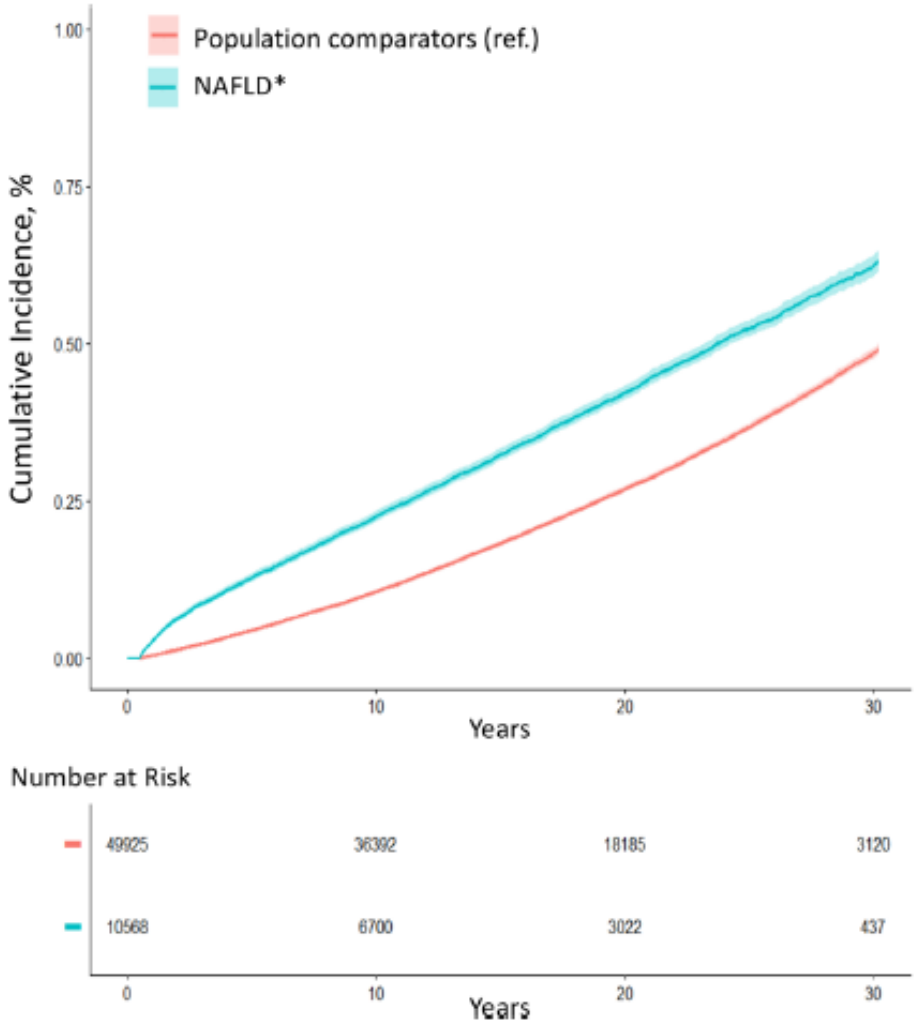
Wong et al., J Hepatol 2023

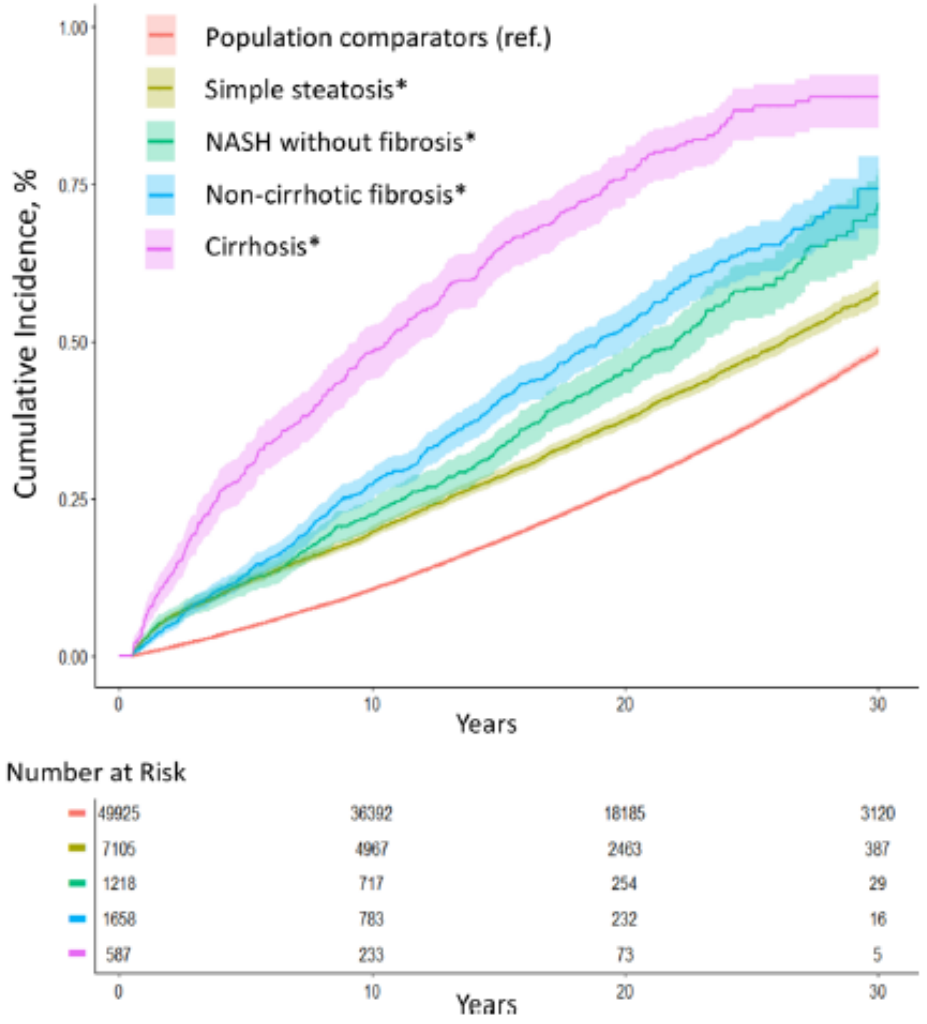
Implications of the increase in MASLD



Wong et al., J Hepatol 2023

All-cause mortality according to NASH and histological severity



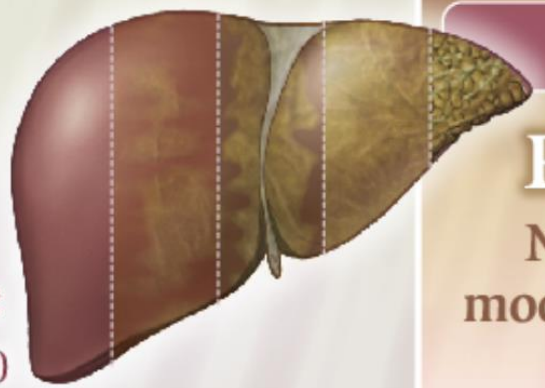


Simon et al., Gut 2020

Clinical Outcomes in Adults with Nonalcoholic Fatty Liver Disease

MULTICENTER, PROSPECTIVE STUDY

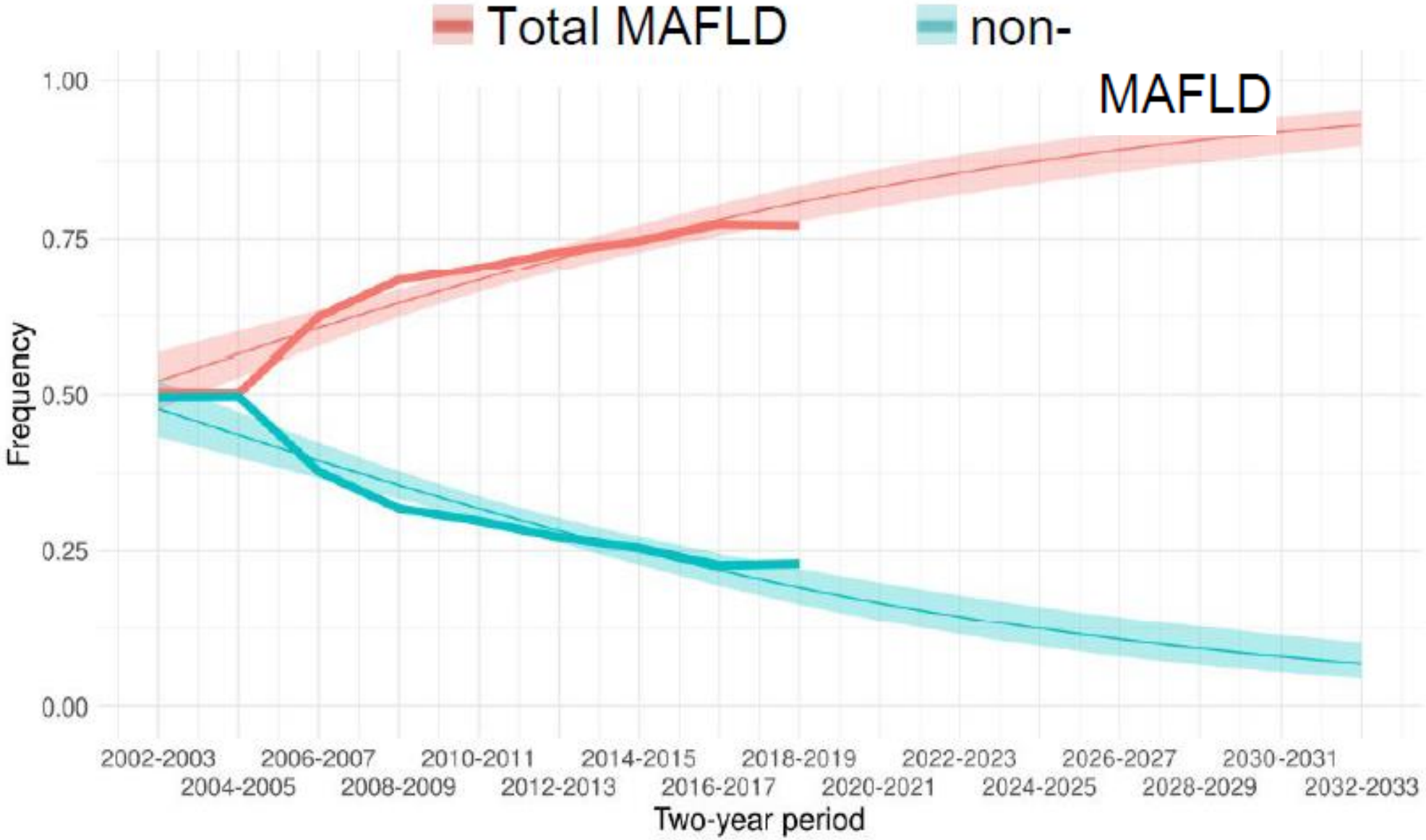
1773
Adults with nonalcoholic fatty liver disease
(median follow-up, 4 yr)



	Fibrosis Stage		
	F0 to F2 No, mild, or moderate fibrosis N=1237	**F3** Bridging fibrosis N=369	**F4** Cirrhosis N=167
Liver-related events		rate per 100 person-yr	
Variceal bleeding	0.00	0.06	0.70
Ascites	0.04	0.52	1.20
Encephalopathy	0.02	0.75	2.39
Hepatocellular carcinoma	0.04	0.34	0.14
Death from any cause	0.32	0.89	1.76

Increasing fibrosis stage is associated with increased risks of liver-related complications and death.

Sanyal et al., N Engl J Med 2021



Svegliati Baroni, Vitale et al., Gut 2022

Forms of NAFLD

✓ **"Primary" NAFLD: Associated with the metabolic syndrome**

✓ **"Secondary" NAFLD: Associated with different conditions**

Drugs: Steroids, Amiodarone, Tamoxifen, ART, chemotherapy

Metabolic or genetic alterations: Lipodystrophy, Dysbetalipoproteinemia, Weber-Christian disease

Nutritional: TPN, Rapid weight loss, Bariatric surgery, Starvation

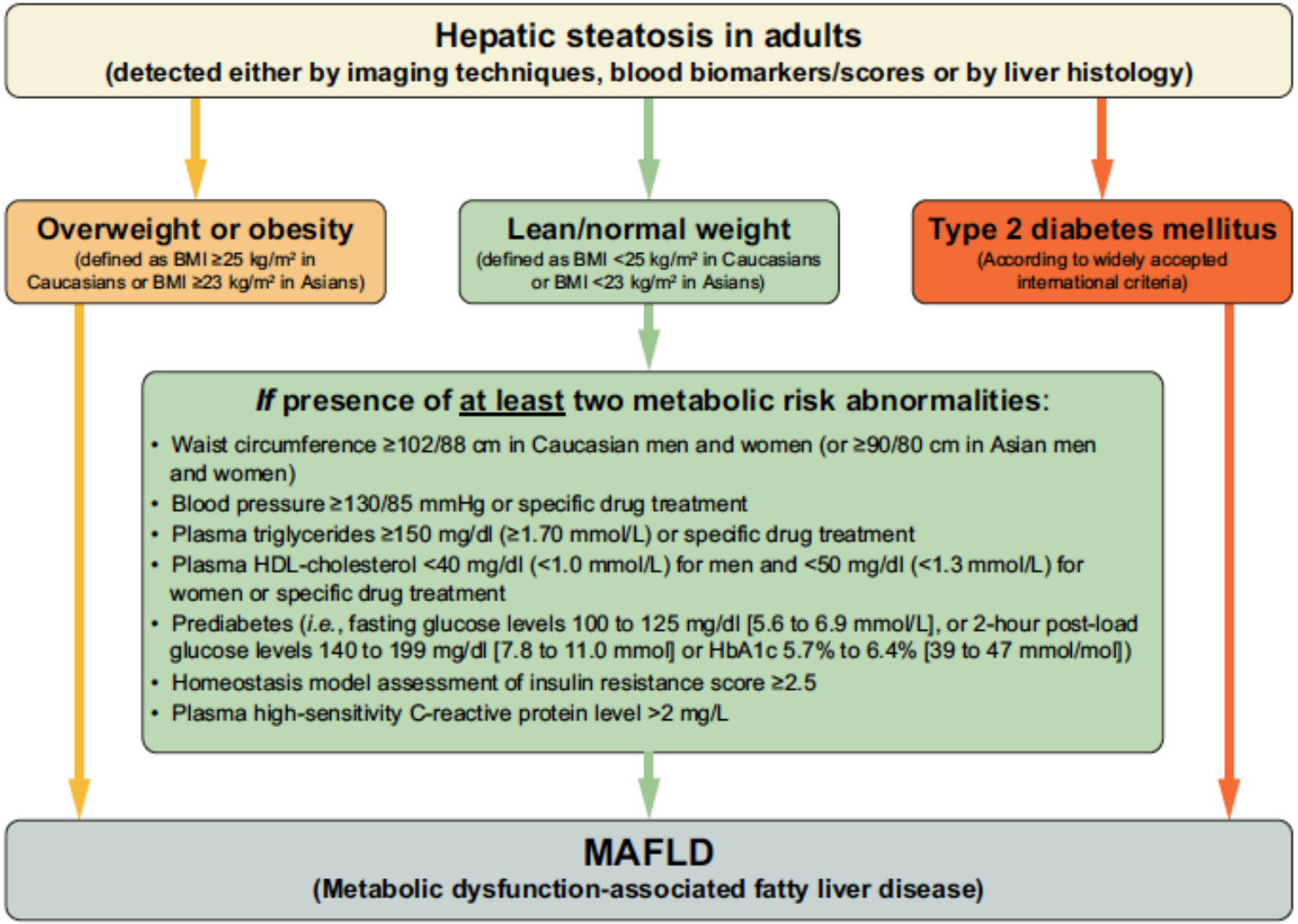
Small bowel diseases: IBD, Bacterial overgrowth

Environmental hepatotoxins: e.g. Petrochemicals

✓ **Steatosis accompanying other forms of liver disease**

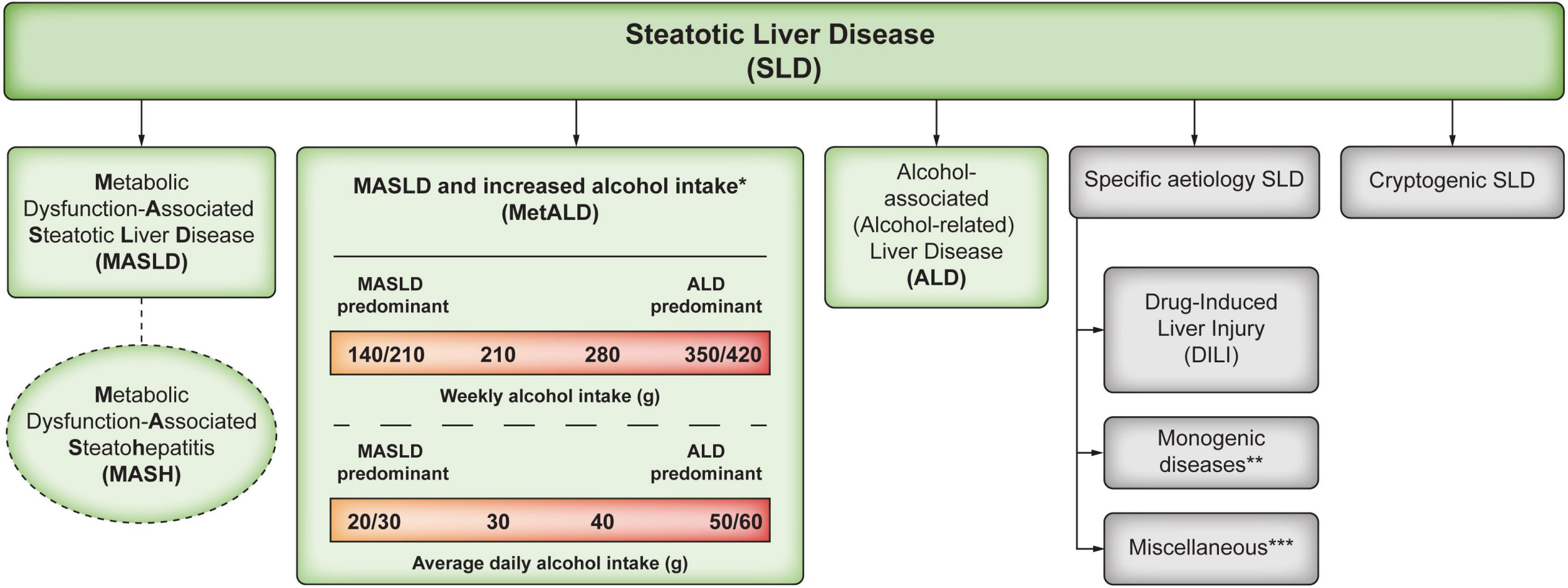
HCV genotype 3, Wilson's disease, celiac disease

‘Positive’ diagnostic criteria for MAFLD



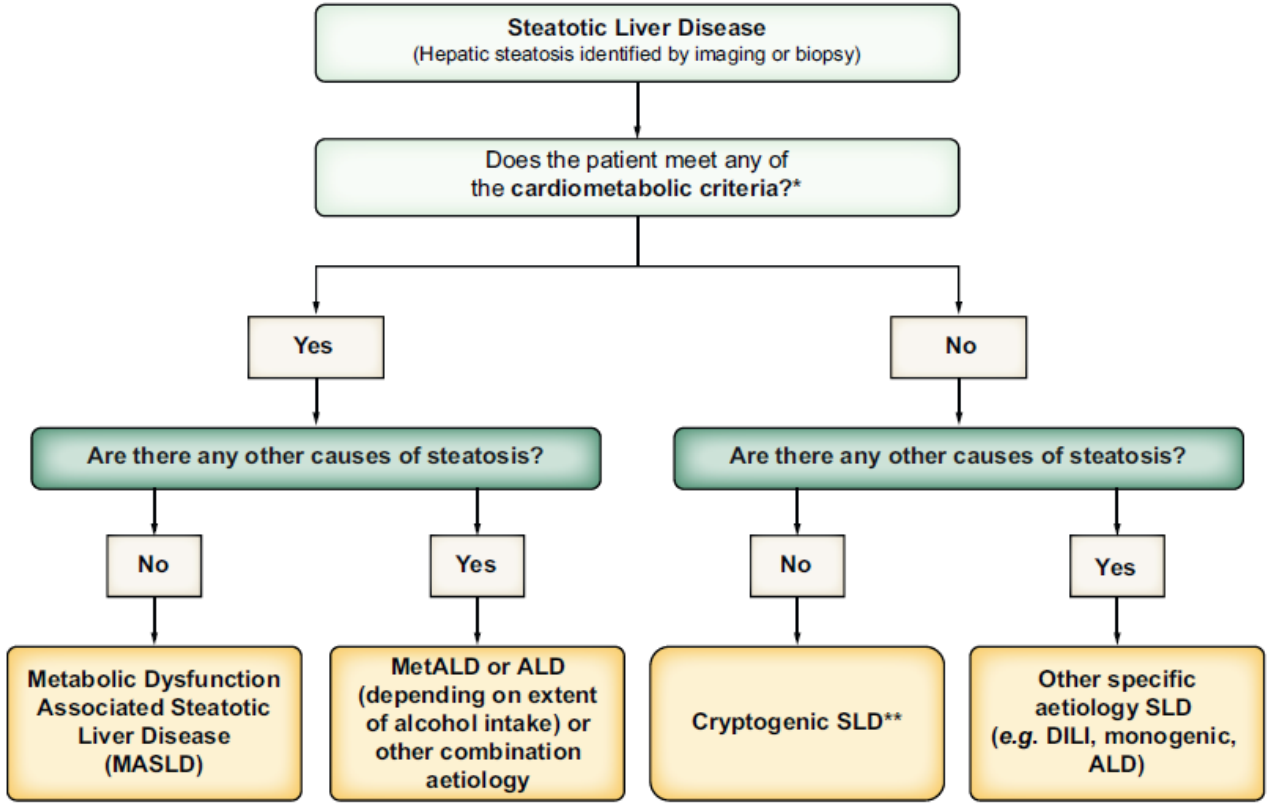
Eslam et al., J Hepatol 2020

New nomenclature for steatosis



Rinella et al., J Hepatol 2023

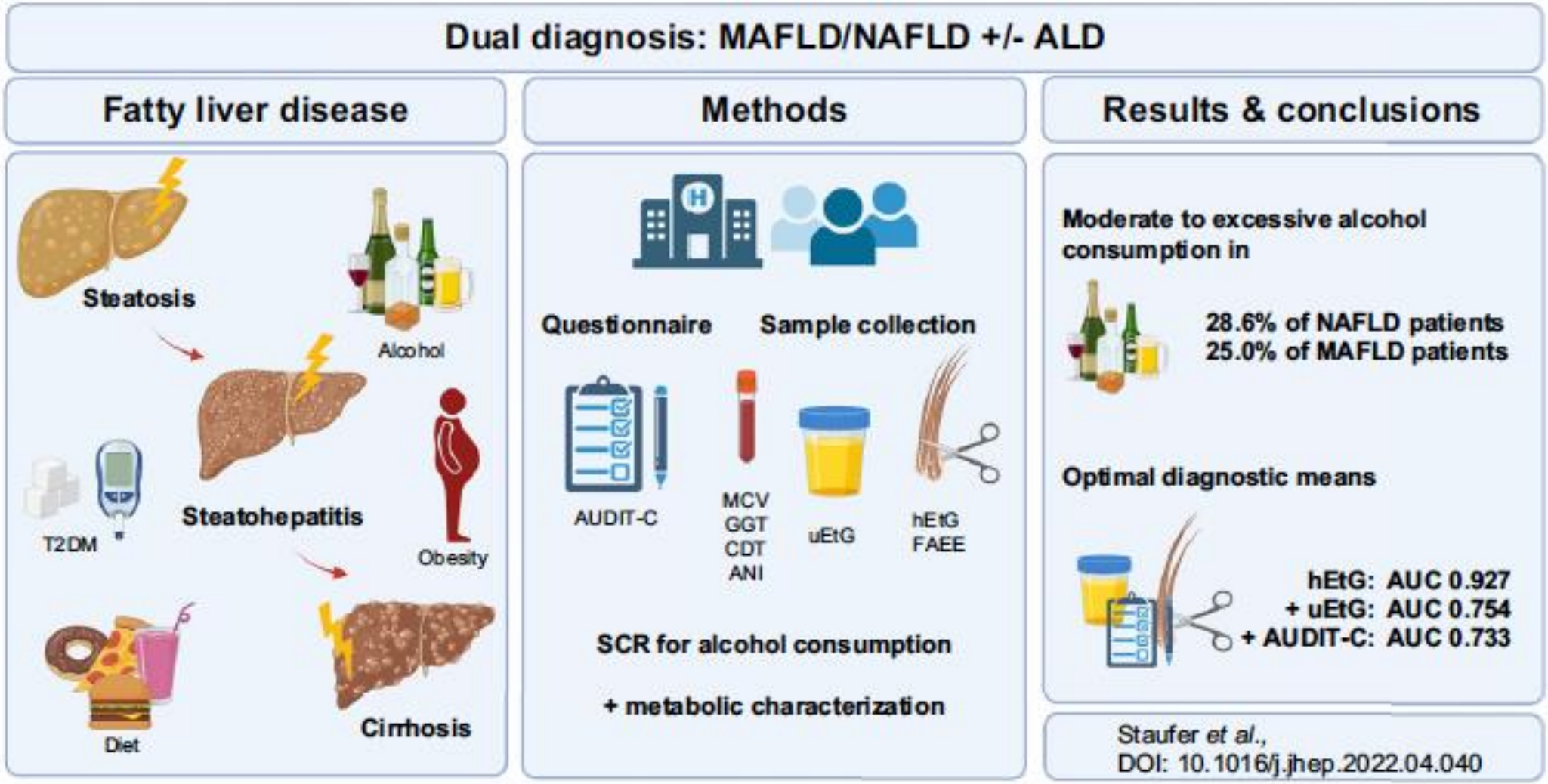
New nomenclature for steatosis



Adult criteria	Paediatric criteria
At least 1 out of 5:	At least 1 out of 5:
☐ BMI ≥25 kg/m² [23 Asia] OR WC >94 cm (M) 80 cm (F) OR ethnicity adjusted equivalent	☐ BMI ≥85th percentile for age/sex [BMI z score ≥+1] OR WC >95th percentile OR ethnicity adjusted equivalent
☐ Fasting serum glucose ≥5.6 mmol/L [100 mg/dl] OR 2-hour post-load glucose levels ≥7.8 mmol/L [≥140 mg/dl] OR HbA1c ≥5.7% [39 mmol/L] OR type 2 diabetes OR treatment for type 2 diabetes	☐ Fasting serum glucose ≥5.6 mmol/L [≥100 mg/dl] OR serum glucose ≥11.1 mmol/L [≥200 mg/dl] OR 2-hour post-load glucose levels ≥7.8 mmol [140 mg/dl] OR HbA1c ≥5.7% [39 mmol/L] OR already diagnosed/treated type 2 diabetes OR treatment for type 2 diabetes
☐ Blood pressure ≥130/85 mmHg OR specific antihypertensive drug treatment	☐ Blood pressure age <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 ≥1.70 mmol/L [150 mg/dl] OR lipid lowering 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] (M) and ≤1.3 mmol/L [50 mg/dl] (F) OR lipid lowering treatment	☐ Plasma HDL-cholesterol ≤1.0 mmol/L [≤40 mg/dl] OR lipid lowering treatment

Rinella et al., J Hepatol 2023

Alcohol consumption in presumed NAFLD

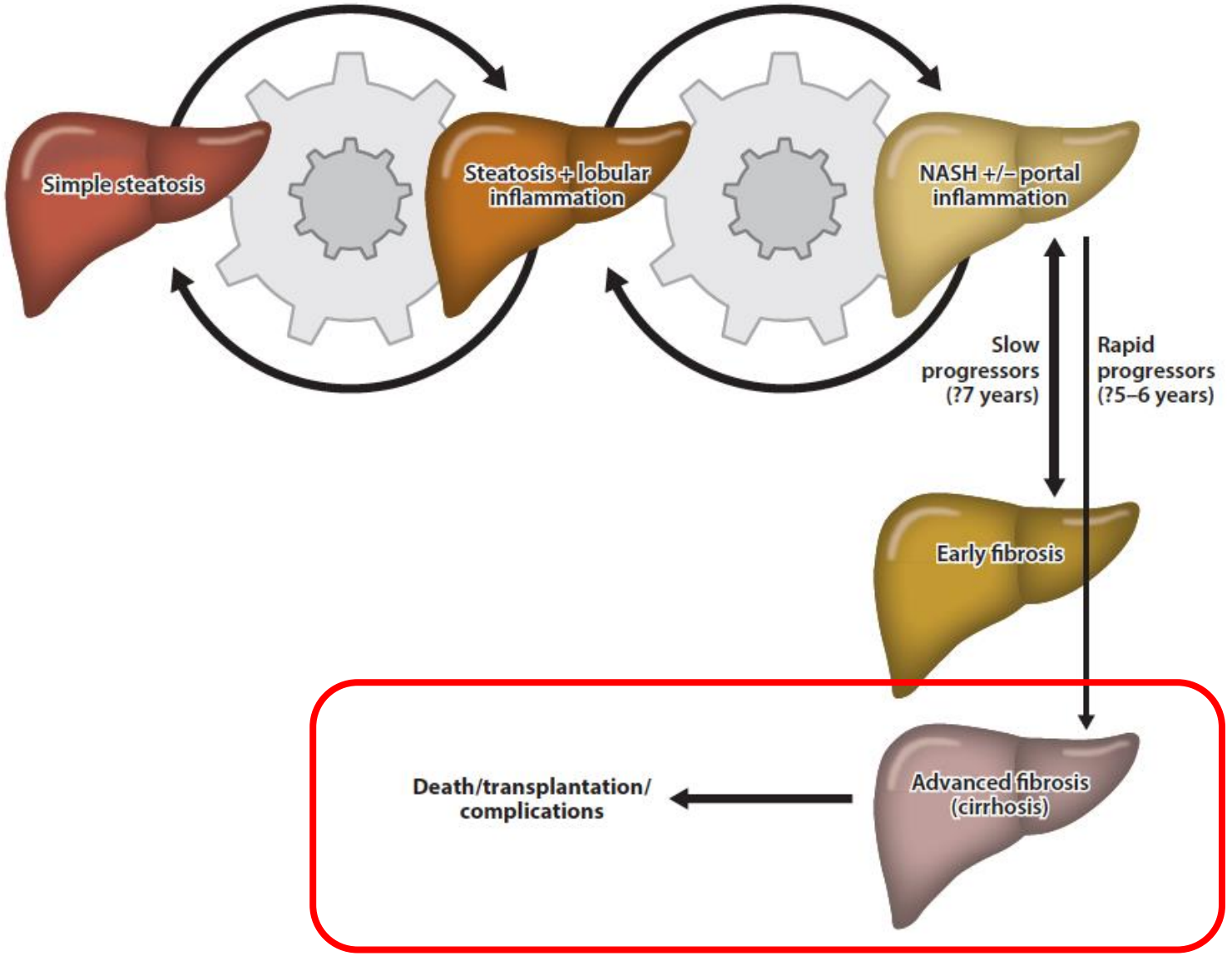


Staufer et al., J Hepatol 2022

Possible changes and pitfalls with the new nomenclature

- **Patients** → stigma removed?
- **Primary care physicians** → enforce screening of significant fibrosis
- **Drug trials** → challenges of MetALD
- **Awareness** → stimulate changes in public heath policies

Diagnostic strategies and referral



Hardy et al. Annu Rev Pathol 2017

Serum biomarkers

- AST/ALT ratio
- APRI
- FIB-4
- NAFLD fibrosis score (NFS)

Non Patented

- FibroTest®
- ELF™
- FibroMètre®
- Hepascore

Patented

Elastography techniques

TE | ARFI / 2D SWE | MRE

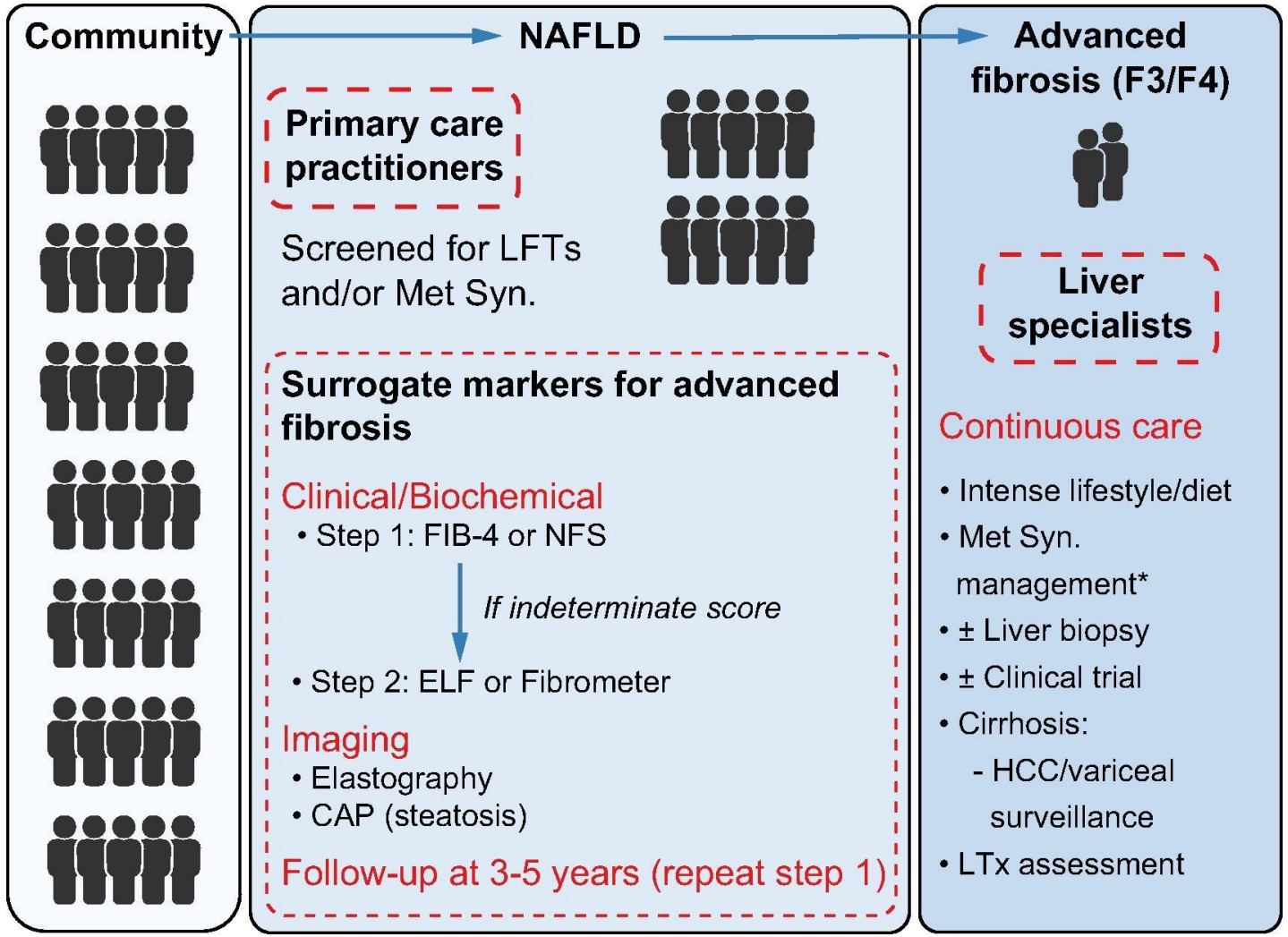
Availability

Cost

Primary care → Liver clinics

Castera, Liver Int 2020

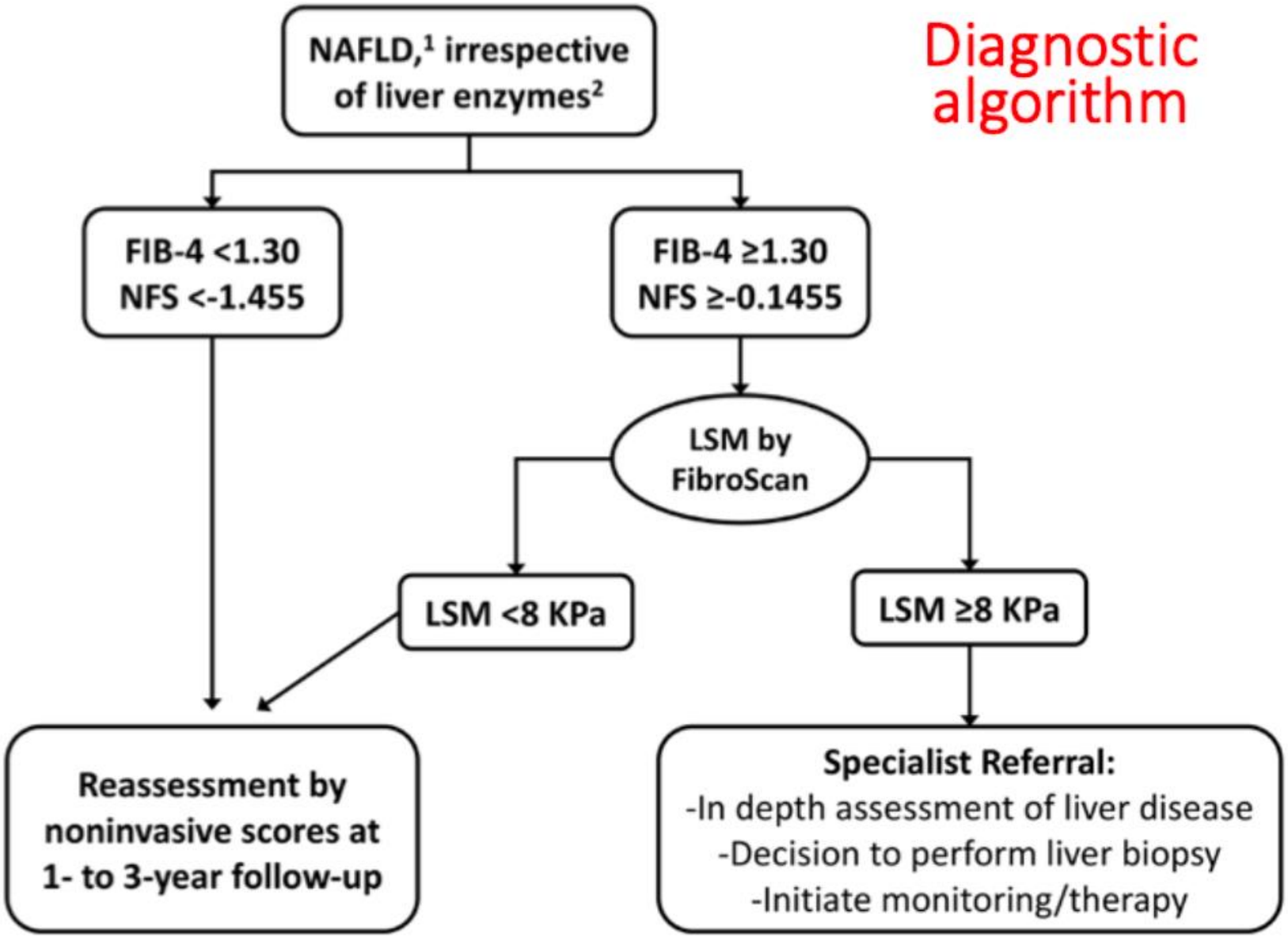
Primary care/specialist interface in NAFLD



Marchesini & Armstrong,, J Hepatol 2019

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

Diagnostic algorithm

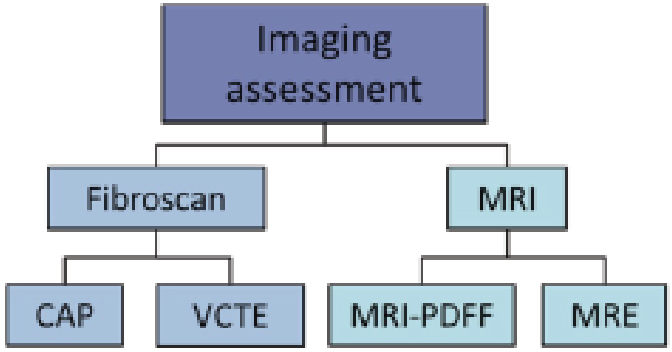


Italian NAFLD Guidelines, 2021

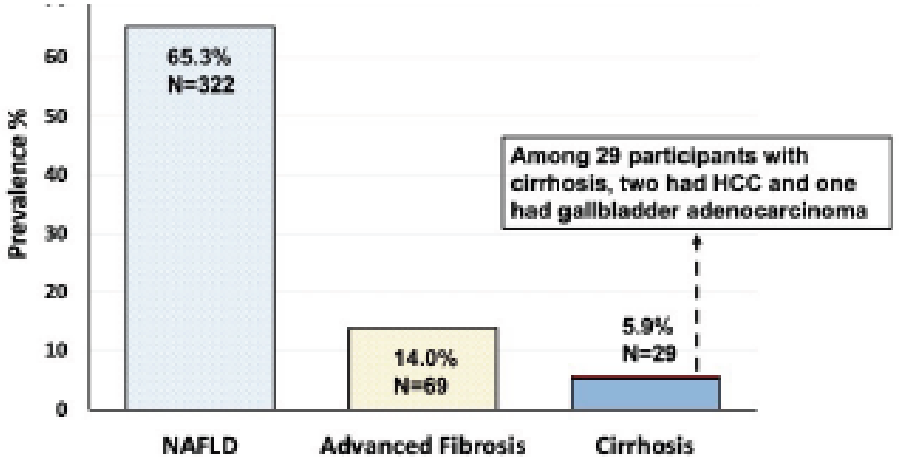
Prevalence of NAFLD, advanced fibrosis, cirrhosis and HCC in people with type 2 diabetes

Type 2 Diabetes
Age ≥ 50 years

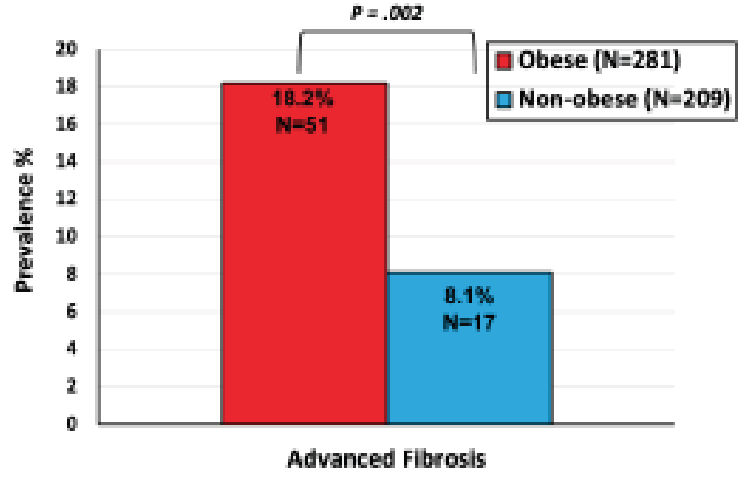
Prospectively recruited participants underwent a research examination with laboratory and clinical assessment to rule out other causes of liver disease.



The prevalence of NAFLD, advanced fibrosis and cirrhosis were 65%, 14% and 6% respectively.

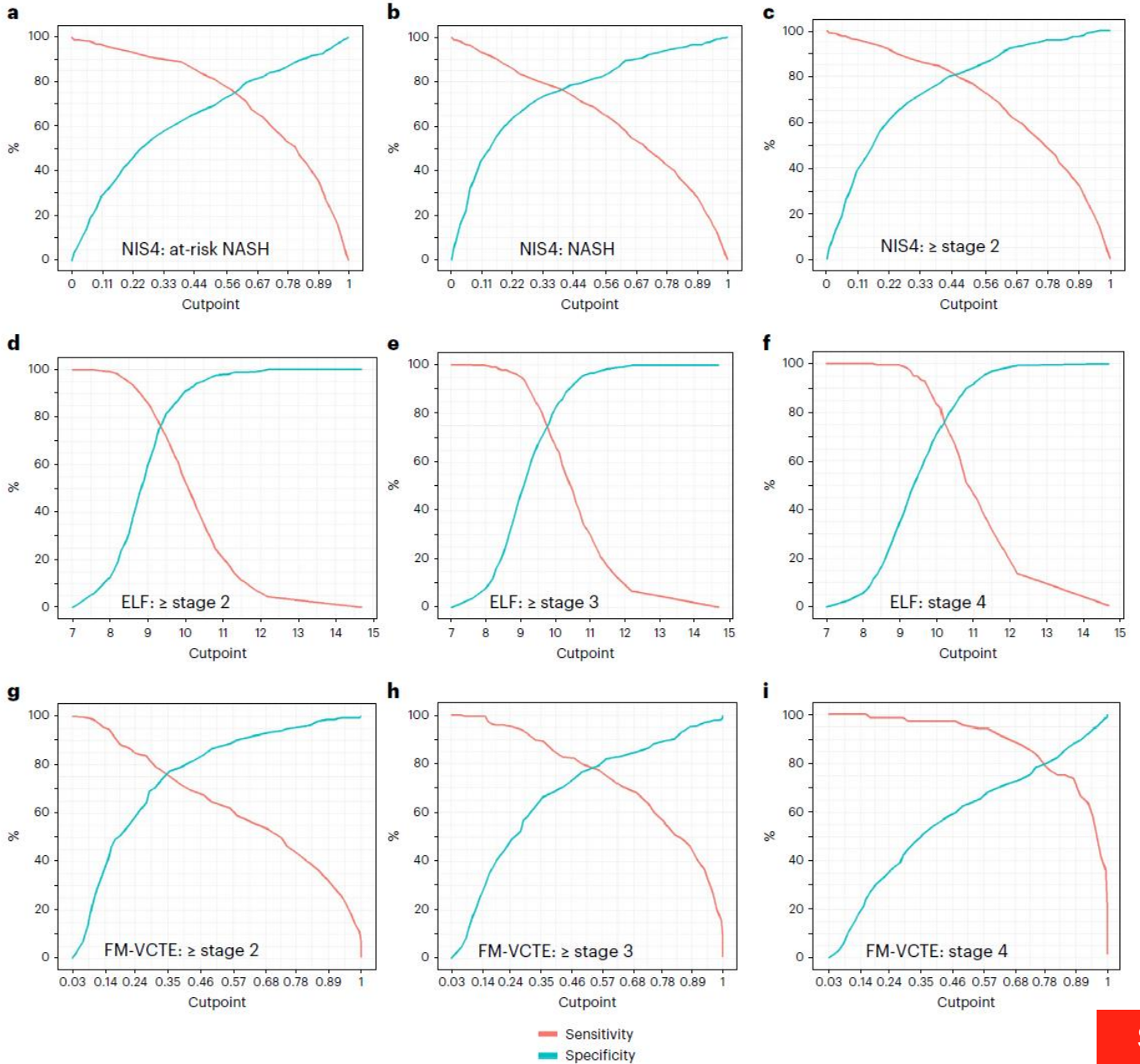


Obesity significantly increased the risk of advanced fibrosis



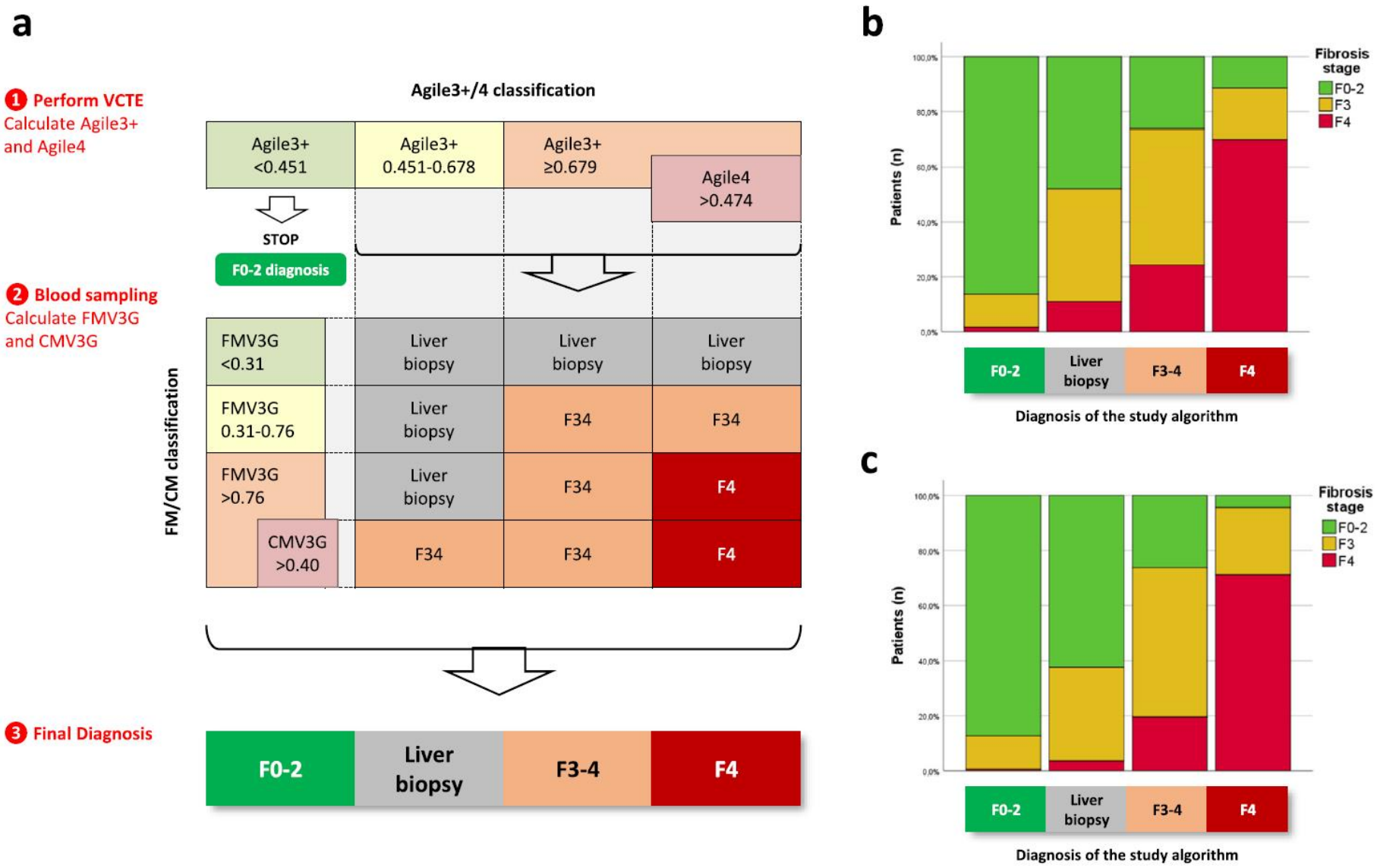
Ajmera et al., J Hepatol 2022

Performance of selected biomarker panels



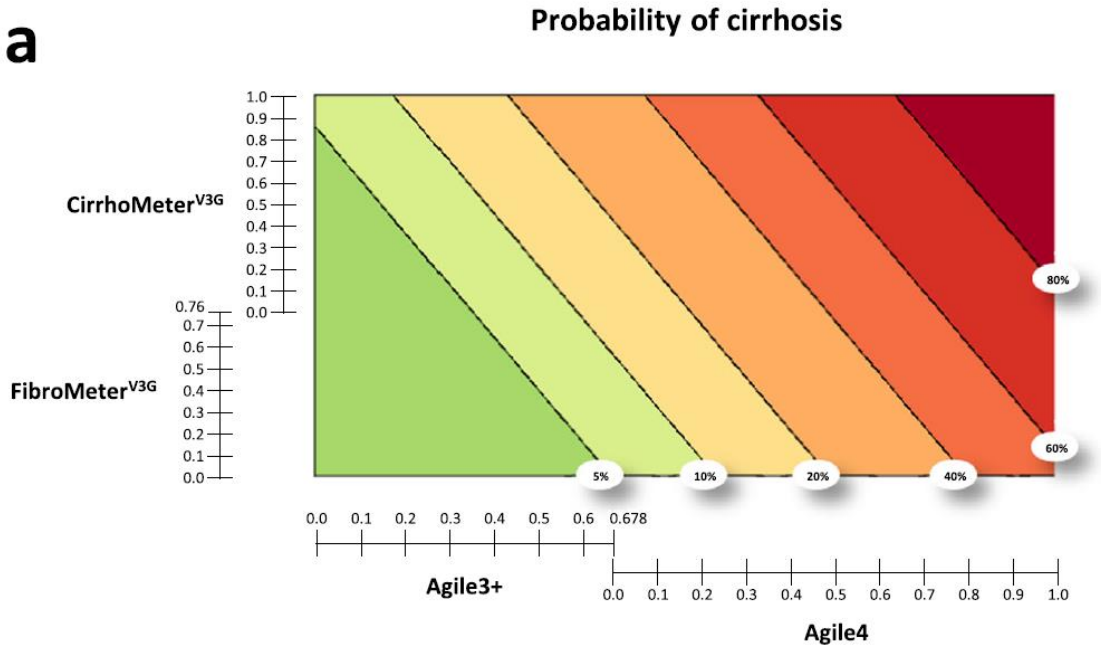
Sanyal et al., Nat Med 2023

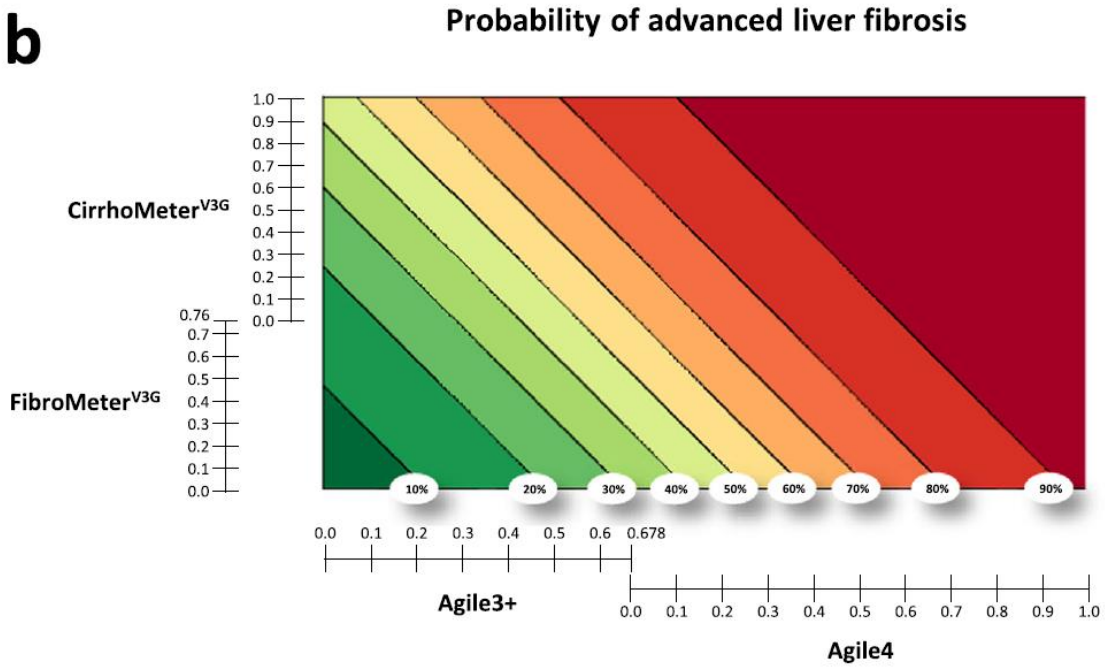
Study algorithm for the detection of MASH-cirrhosis



Boursier et al., Nat Commun 2023

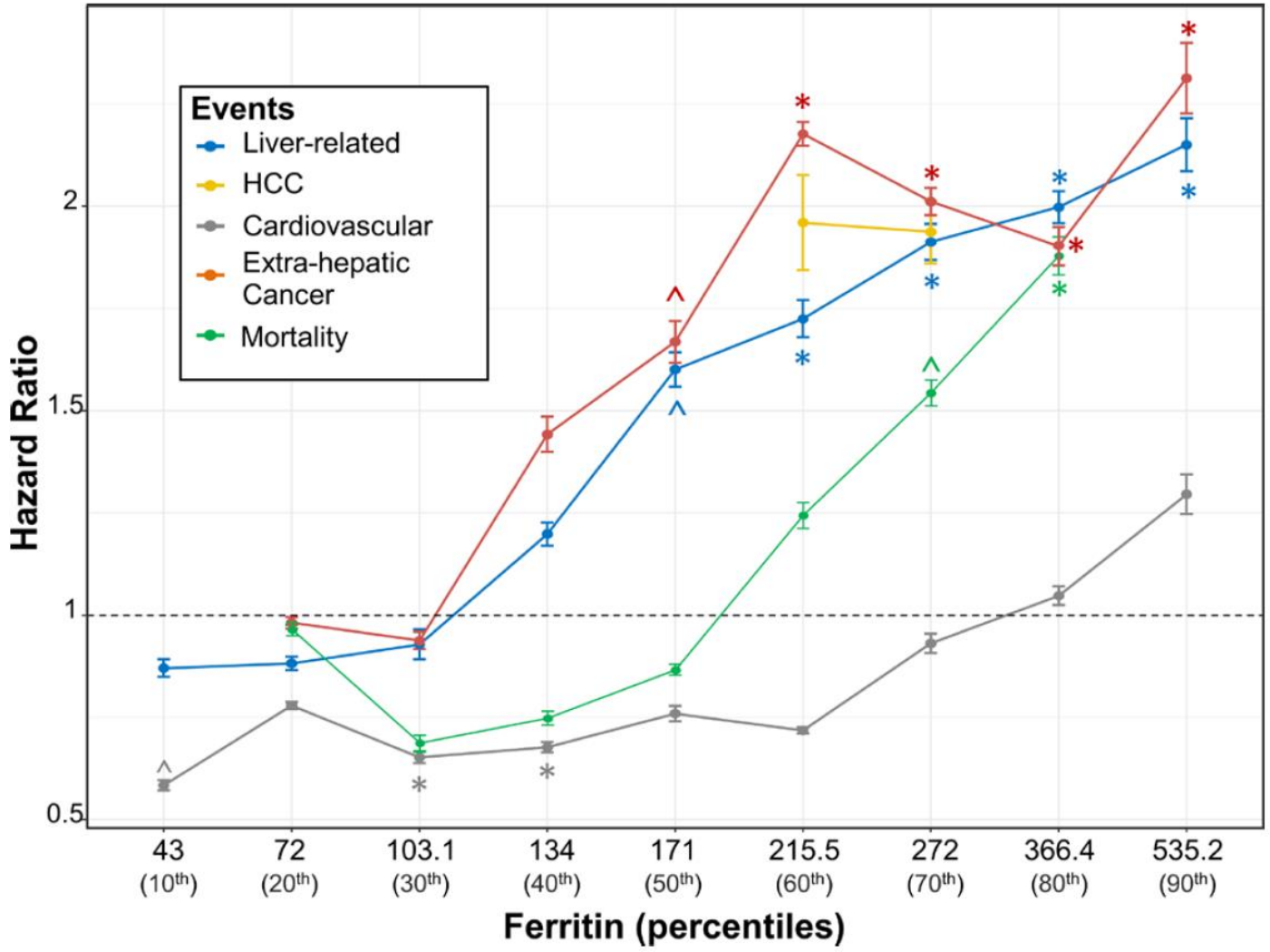
Risk prediction charts for MASH-cirrhosis





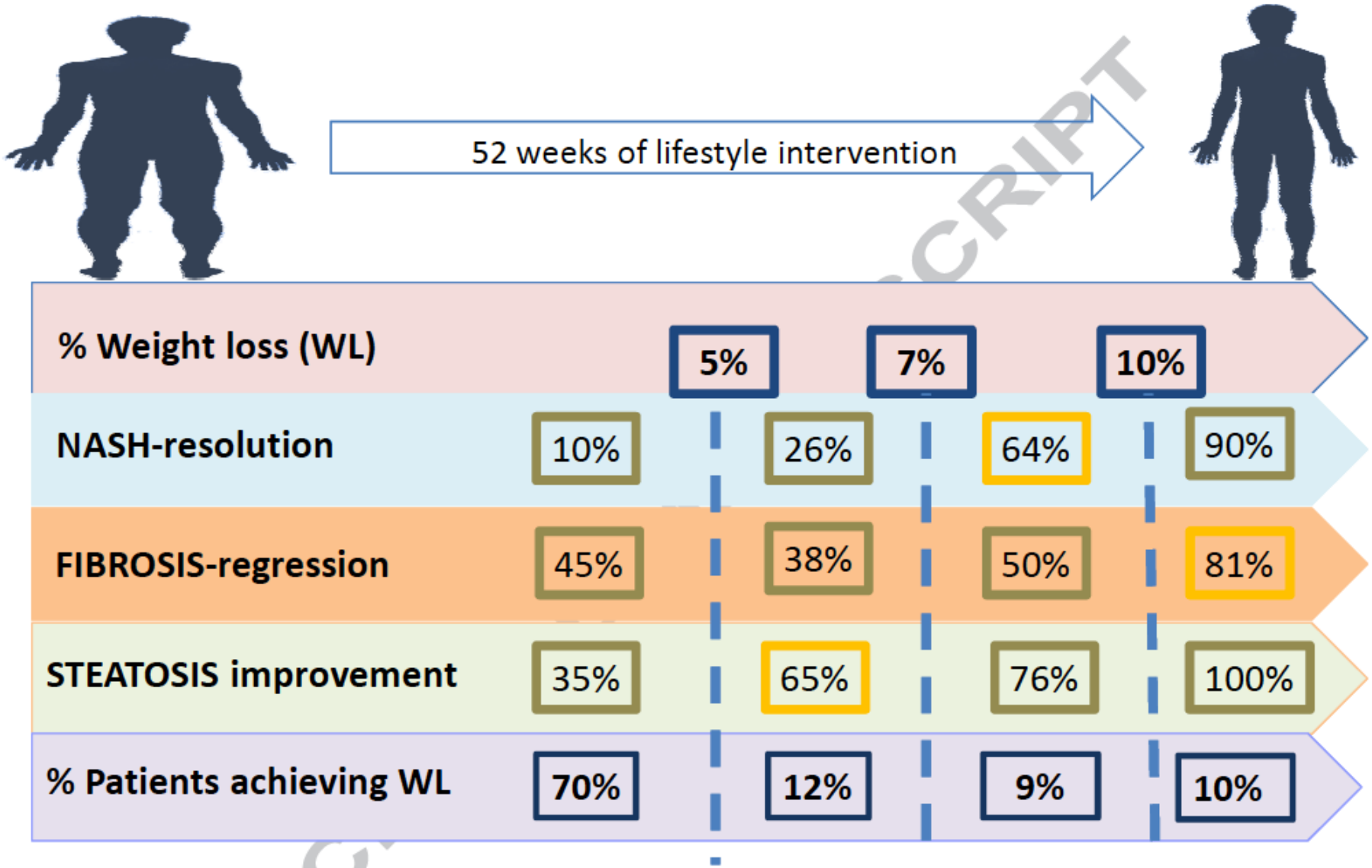
Boursier et al., Nat Commun 2023

Ferritin levels predict outcomes in MASLD



Armandi et al., Gut 2024

Current situation in NASH treatment



Data from Vilar-Gomez et al.

Romero-Gomez et al., J Hepatol 2017

Gastroenterology 2020;■:1–7

AGA Clinical Practice Update on Lifestyle Modification Using Diet and Exercise to Achieve Weight Loss in the Management of Nonalcoholic Fatty Liver Disease: Expert Review

Zobair M. Younossi,[1,2,*] Kathleen E. Corey,[3,*] and Joseph K. Lim[4]

[1]Center for Liver Diseases and Department of Medicine, Inova Fairfax Medical Campus, Falls Church, Virginia; [2]Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, Virginia; [3]Liver Center, Division of Gastroenterology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; and [4]Yale Liver Center and Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut

Best Practice Advice 2: Among patients with NASH, weight loss of ≥5% total body weight (TBW) can decrease hepatic steatosis, weight loss of ≥7% TBW can lead to NASH resolution, and weight loss of ≥10% TBW can result in fibrosis regression/stability.

5.1) Si suggerisce che i soggetti con NAFLD, inclusi quelli con *lean*-NAFLD (non obesa), siano coinvolti in programmi di correzione dello stile di vita mirati a una dieta sana e all'attività fisica abituale per una perdita di peso del 10%, associata a un miglioramento dell'istologia, inclusa la fibrosi (Forza Raccomandazione Condizionata - Qualità evidenza Bassa).

Best Practice Advice 4: Adults with NAFLD should follow the Mediterranean (Med) diet or a diet of similar design and minimize saturated fatty acid intake, specifically red and processed meat, and commercially-produced fructose consumption.

5.2) Nei pazienti con NAFLD si suggerisce che l'approccio dietetico sia mirato a favorire l'aderenza ai principi della dieta Mediterranea, compreso un ridotto apporto di zuccheri raffinati e industriali, che sono stati associati alla riduzione del contenuto di grassi epatici e alla riduzione del rischio cardiovascolare (Forza Raccomandazione Condizionata - Qualità evidenza Molto Bassa).

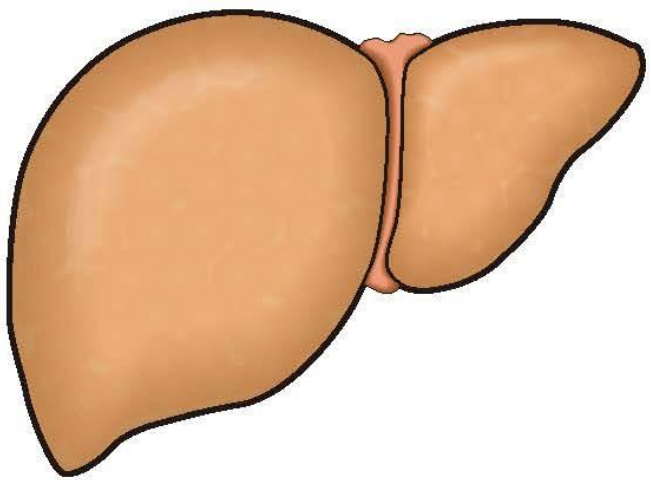
Aerobic exercise

1. Activation of lypolysis
2. Up-regulation of UCP-1 and PPARγ
3. Alteration in adipocytokine

Resistance exercise

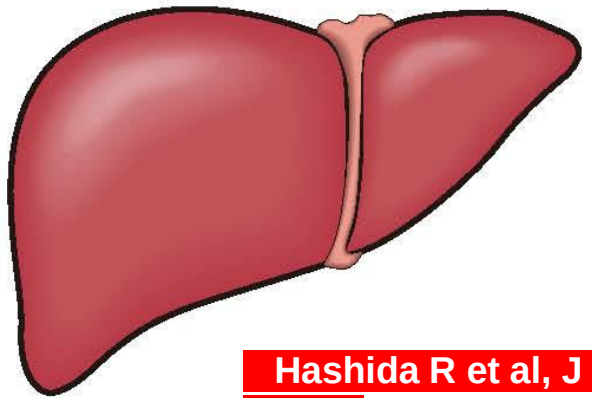
1. Hypertrophy of type II muscle fibers
2. Activation of GLUT4, AMPK, and caveolins
3. Alteration in myokines

[NAFLD]



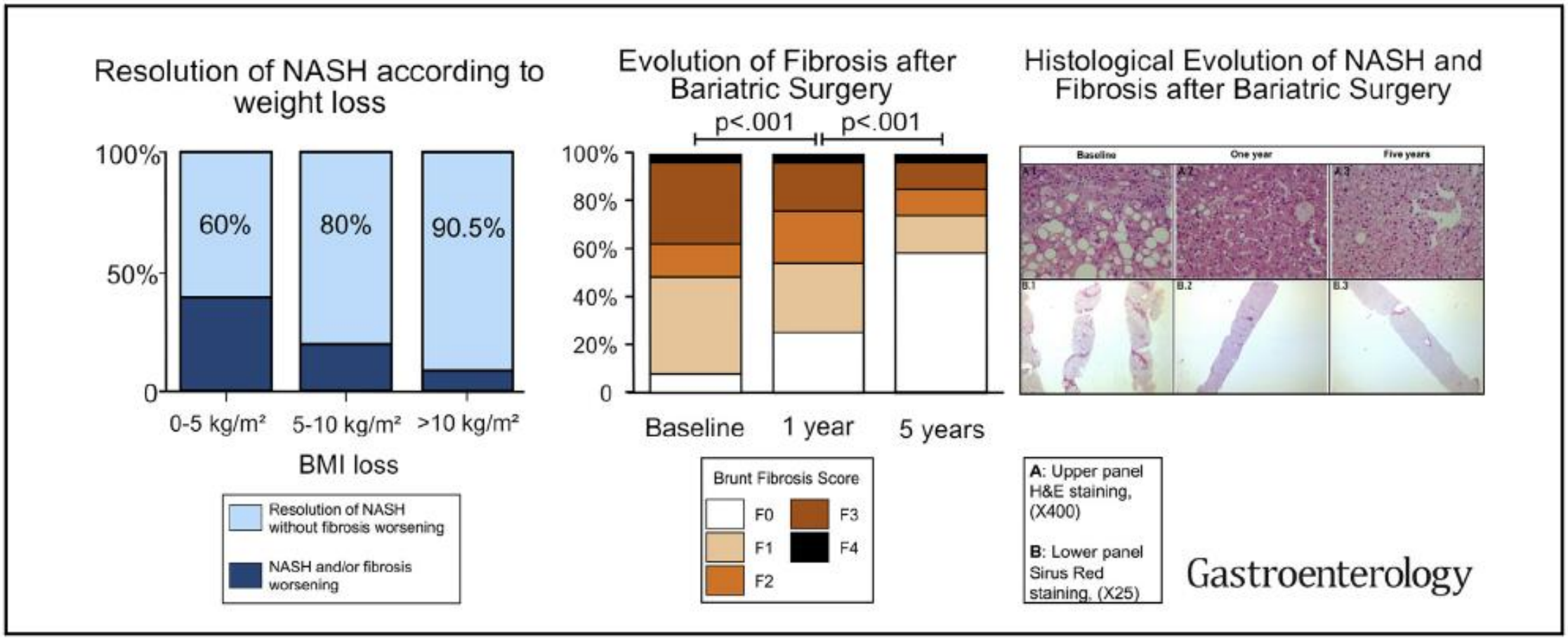
Improvement

[Normal Liver]



Hashida R et al, J Hepatol 2017

Bariatric surgery provides resolution of NASH and regression of fibrosis



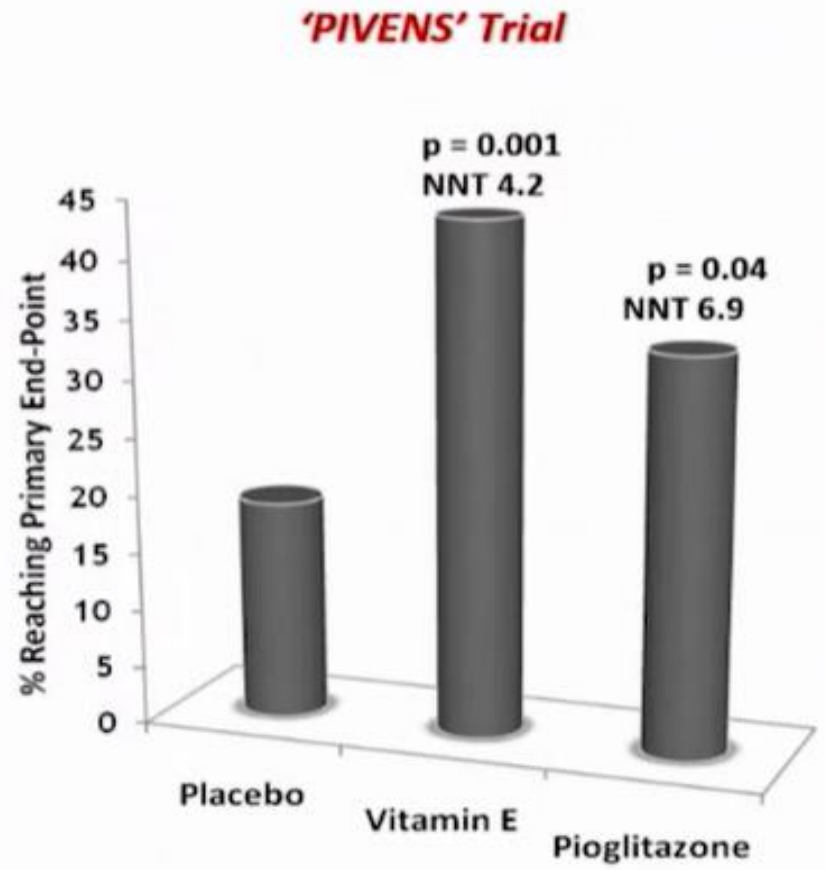
Lassailly et al., Gastroenterology 2020

NASH: whom to treat

- Biopsy-proven NASH patients
- Presence of fibrosis ≥F2
- Early-stage NASH with risk of fibrosis progression
  (age >50 years; diabetes, MetS, increased ALT)
- Active NASH with high necroinflammatory activity
- NASH cirrhosis may be an indication for selected drugs

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

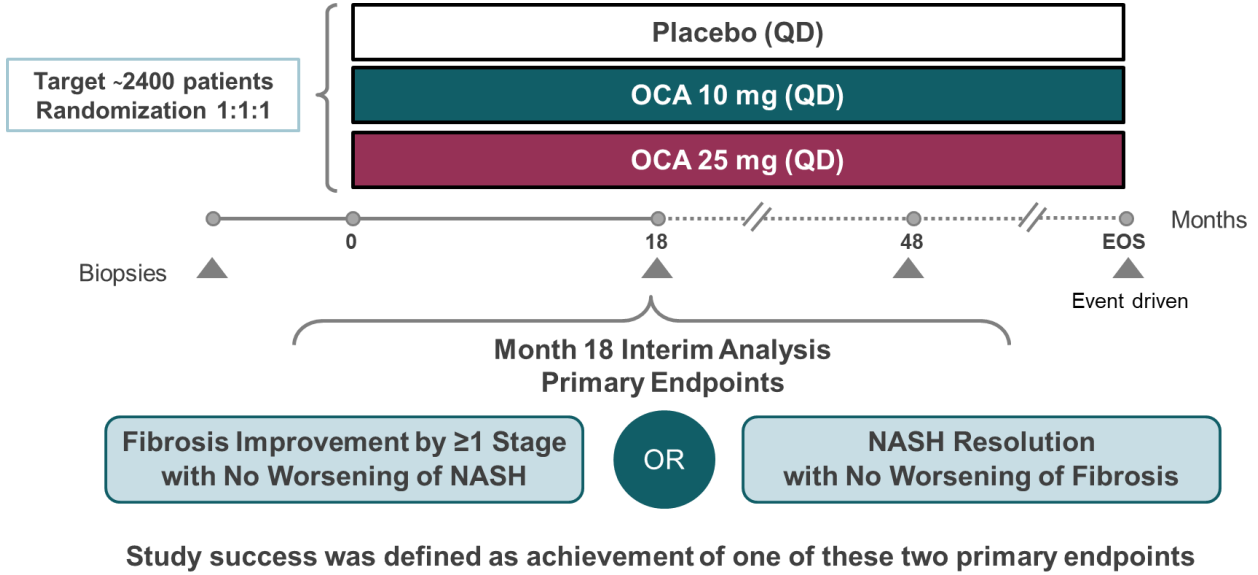
- 247 non-diabetic adults with NASH
  - **30mg Pioglitazone**
  - **800IU Vitamin E**
  - **Placebo**
- Liver biopsy at 96 Weeks
- Both agents improved steatosis & inflammation scores
- Only Vitamin E reduced ballooning
- Neither agent reduced fibrosis
- BUT resolution of NASH in 30-40% of patients treated
- High-dose vitamin E linked to increased all-cause mortality, hemorrhagic stroke and prostate cancer



Sanyal N Engl J Med 2010; 362:1675-1685

REGENERATE: a Phase 3 trial of obeticholic acid (OCA) for NASH

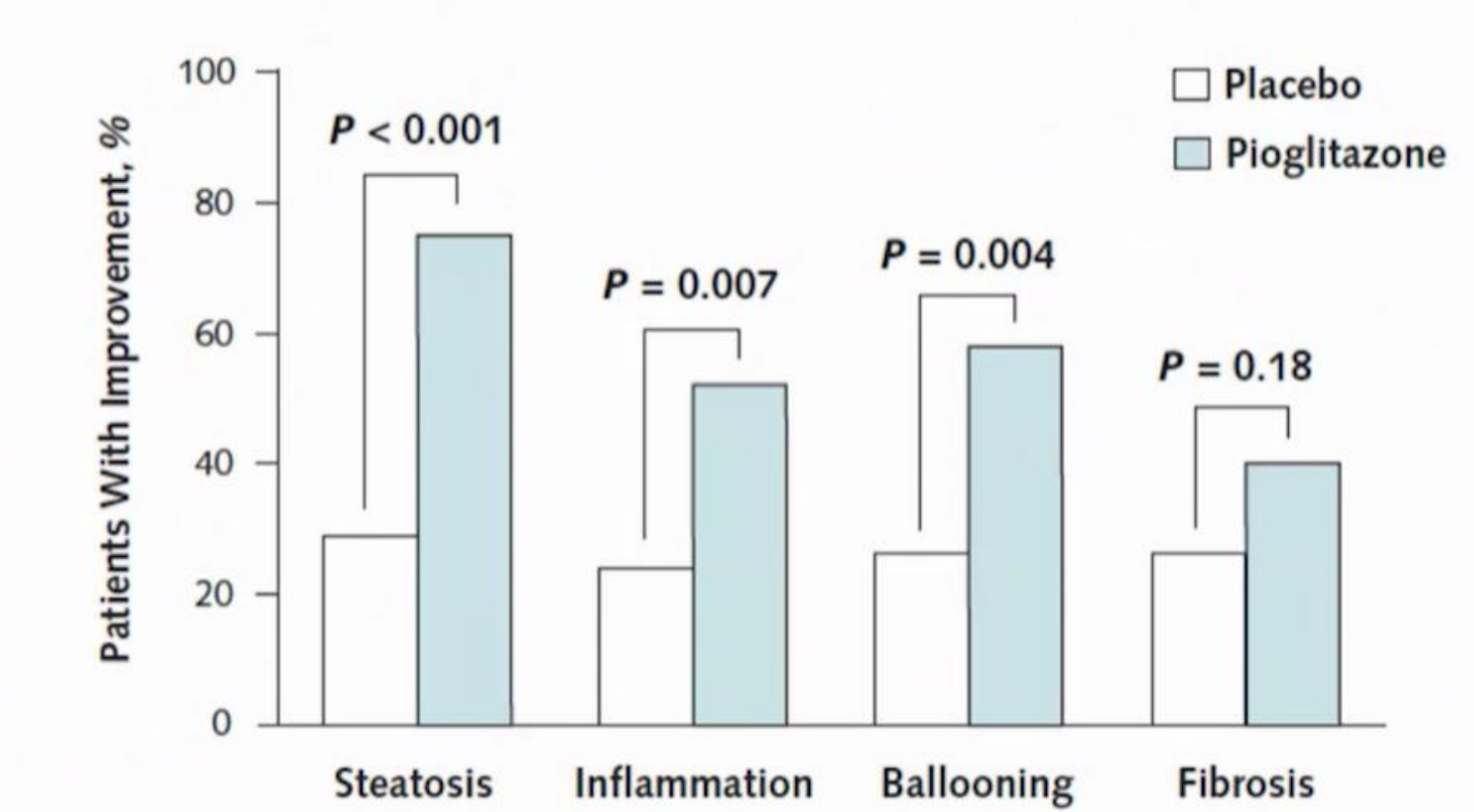
- In the Phase 2b FLINT study, the potent FXR agonist OCA 25 mg for 72 weeks improved fibrosis and other histological features of NASH
- Month 18 interim analysis of REGENERATE evaluated OCA on liver histology in NASH patients with F2/F3 fibrosis



Study success was defined as achievement of one of these two primary endpoints

Younossi, EASL 2019

Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial



* In patients with paired biopsies (n = 82)

Cusi et al, Ann Intern Med 2016

Figure 2. Liver fat and insulin sensitivity before and after 18 mo of pioglitazone or placebo in patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus.

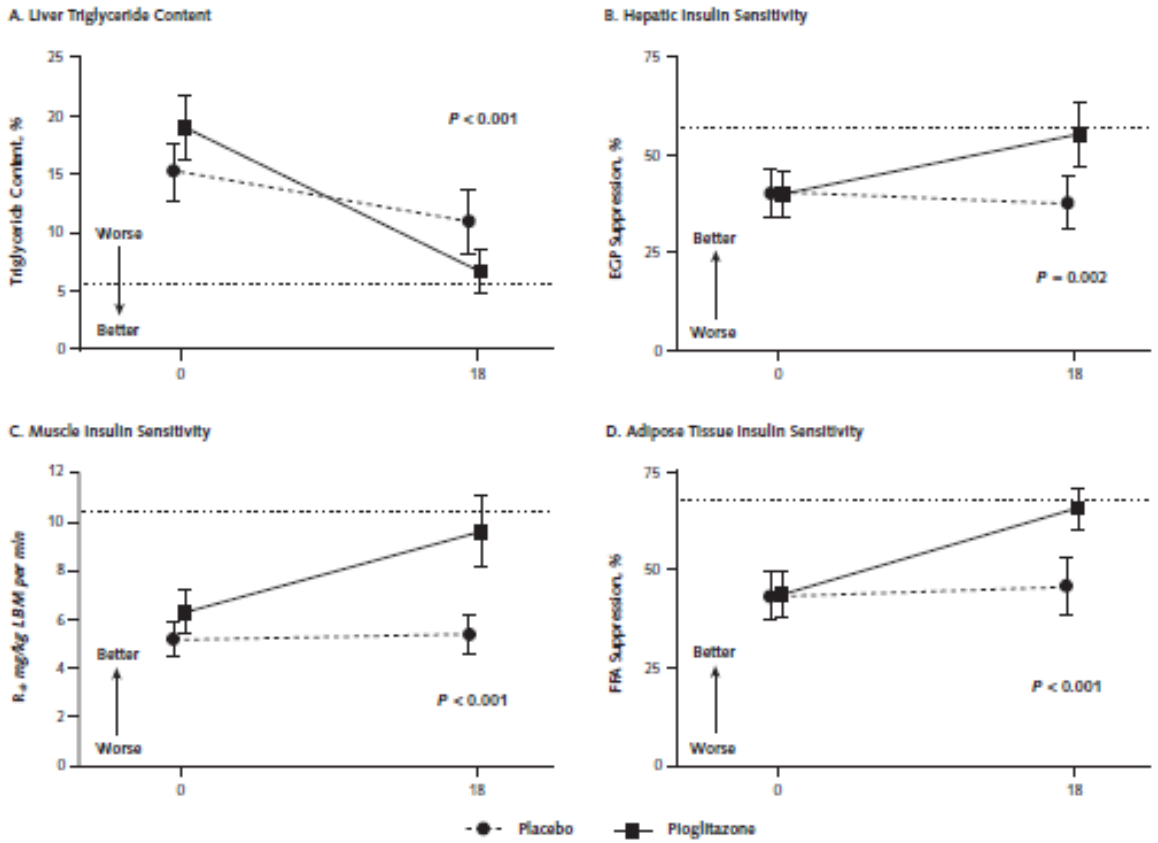
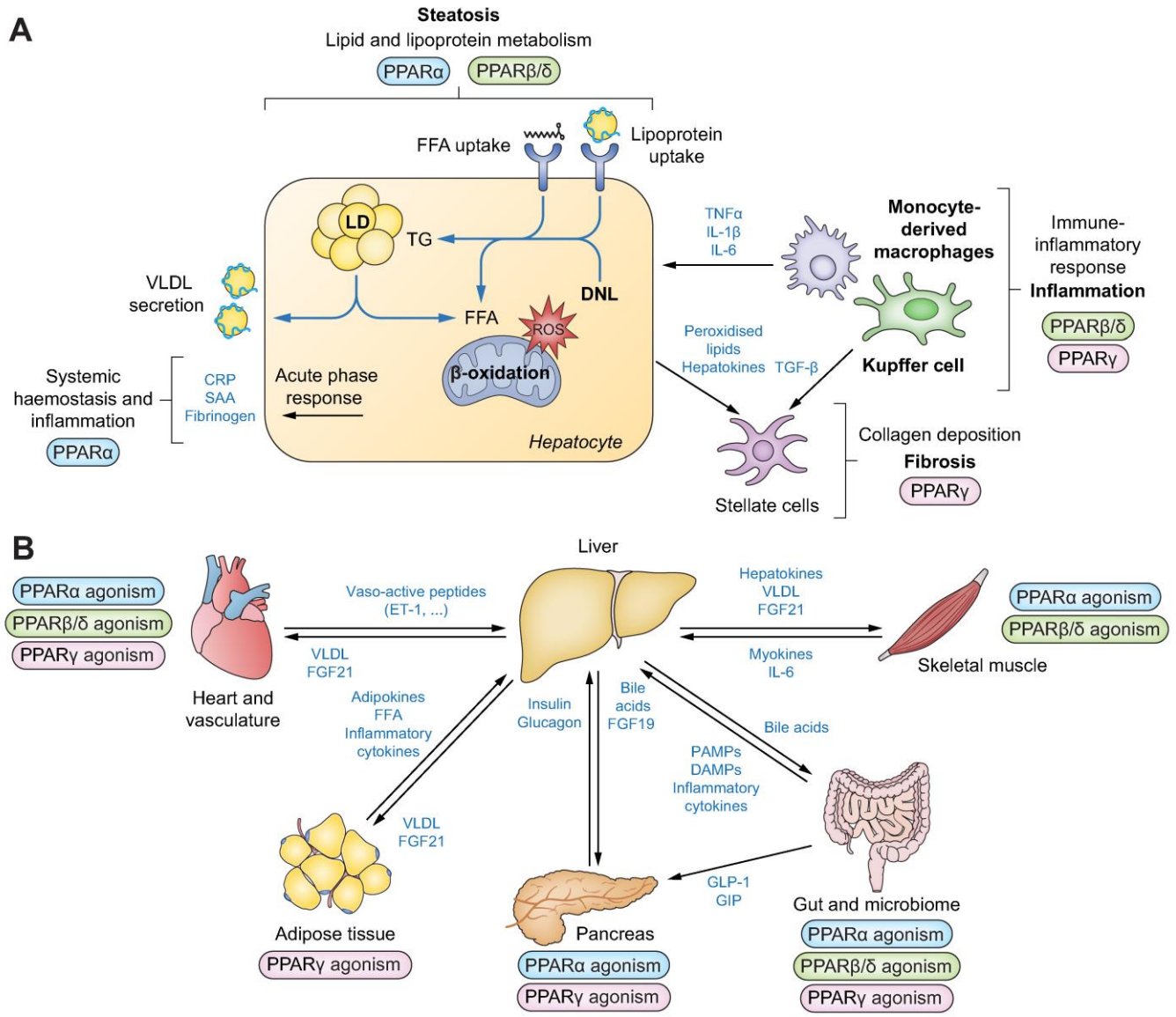


Table 3. Metabolic and Hepatic Characteristics After 18 mo of Pioglitazone Treatment

Characteristic	Mean Value After 18 mo (SD)		Treatment Difference (95% CI)*	P Value*
	Placebo	Pioglitazone		
Weight, *kg*	99.5 (16.7)	99.4 (16.6)	2.5 (0.4 to 4.5)	0.020
Body mass index, *kg/m²*	34.6 (5.0)	34.6 (4.8)	0.9 (0.1 to 1.6)	0.019
Total body fat by DXA, %	36 (8)	36 (7)	2 (1 to 3)	<0.001
Fasting plasma glucose level				0.020
mmol/L	6.6 (1.3)	6.1 (0.8)	−0.6 (−1.1 to −0.1)	
mg/dL	119 (24)	110 (14)	−11 (−19 to −2)	
2-h plasma glucose level				<0.001
mmol/L	12.0 (3.8)	9.6 (3.9)	−2.7 (−3.8 to −1.6)	
mg/dL	216 (69)	173 (70)	−48 (−69 to −28)	
Hemoglobin A_{1c} level, %				
Patients without T2DM	5.8 (0.3)	5.6 (0.3)	−0.1 (−0.3 to 0.0)	0.124
Patients with T2DM	6.5 (0.7)	6.2 (0.7)	−0.6 (−1.1 to −0.2)	0.009
Fasting plasma insulin level				0.041
pmol/L	102 (96)	48 (90)	−36 (−72 to 0)	
μU/mL	17 (16)	8 (15)	−6 (−12 to 0)	
Free fatty acid level, *mmol/L*	0.46 (0.17)	0.36 (0.16)	−0.04 (−0.14 to 0.05)	0.38
Liver fat content, %	11 (7)	7 (5)	−7 (−10 to −4)	<0.001
Aspartate aminotransferase level, *U/L*	38 (31)	29 (10)	−14 (−22 to −6)	0.001
Alanine aminotransferase level, *U/L*	44 (33)	27 (12)	−24 (−35 to −12)	<0.001
Triglyceride level				0.018
mmol/L	1.7 (0.8)	1.4 (0.7)	−0.6 (−1.0 to −0.1)	
mg/dL	149 (72)	127 (63)	−50 (−92 to −9)	
Total cholesterol level				0.92
mmol/L	3.9 (0.9)	4.0 (0.9)	0.0 (−0.5 to 0.5)	
mg/dL	149 (36)	153 (34)	1 (−18 to 19)	
LDL cholesterol level				0.59
mmol/L	2.0 (0.7)	2.2 (0.7)	0.1 (−0.3 to 0.6)	
mg/dL	79 (28)	84 (28)	5 (−13 to 22)	
HDL cholesterol level				<0.001
mmol/L	1.0 (0.2)	1.1 (0.3)	0.1 (0.1 to 0.2)	
mg/dL	40 (9)	44 (10)	5 (3 to 8)	

Cusi et al, Ann Intern Med 2016

PPAR agonists and MASLD

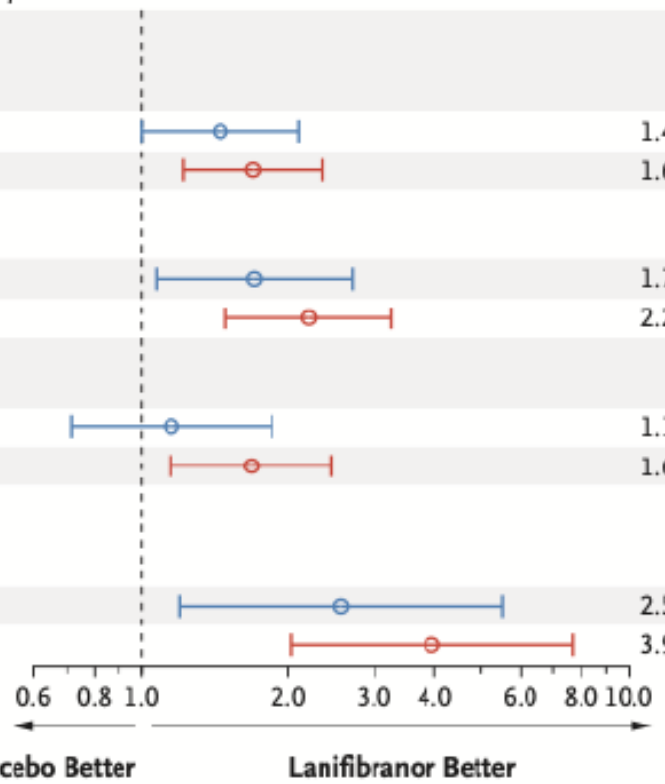


Staels et al., J Hepatol 2023

The pan-PPAR agonist lanifibranor in NASH

Phase 2b, double-blind, RCT in 247 patients with noncirrhotic, highly active NASH assigned to 1200 or 800 mg of lanifibranor or PL once daily for 24 weeks. 103 (42%) had T2D and 188 (76%) had significant or advanced fibrosis.

End Point	Placebo	Lanifibranor	Risk Ratio (95% CI)	P Value
	percent of patients with response			
Primary end point: reduction of ≥2 points in SAF-A score and no worsening of fibrosis				
Lanifibranor, 800 mg	33	48	1.45 (1.00–2.10)	0.07
Lanifibranor, 1200 mg	33	55	1.69 (1.22–2.34)	0.007
Secondary end point: resolution of NASH without worsening of fibrosis				
Lanifibranor, 800 mg	22	39	1.70 (1.07–2.71)	
Lanifibranor, 1200 mg	22	49	2.20 (1.49–3.26)	
Secondary end point: improvement in fibrosis stage of ≥1 without worsening of NASH				
Lanifibranor, 800 mg	29	34	1.15 (0.72–1.85)	
Lanifibranor, 1200 mg	29	48	1.68 (1.15–2.46)	
Composite secondary end point: resolution of NASH and improvement in fibrosis stage of ≥1				
Lanifibranor, 800 mg	9	25	2.57 (1.20–5.51)	
Lanifibranor, 1200 mg	9	35	3.95 (2.03–7.66)	

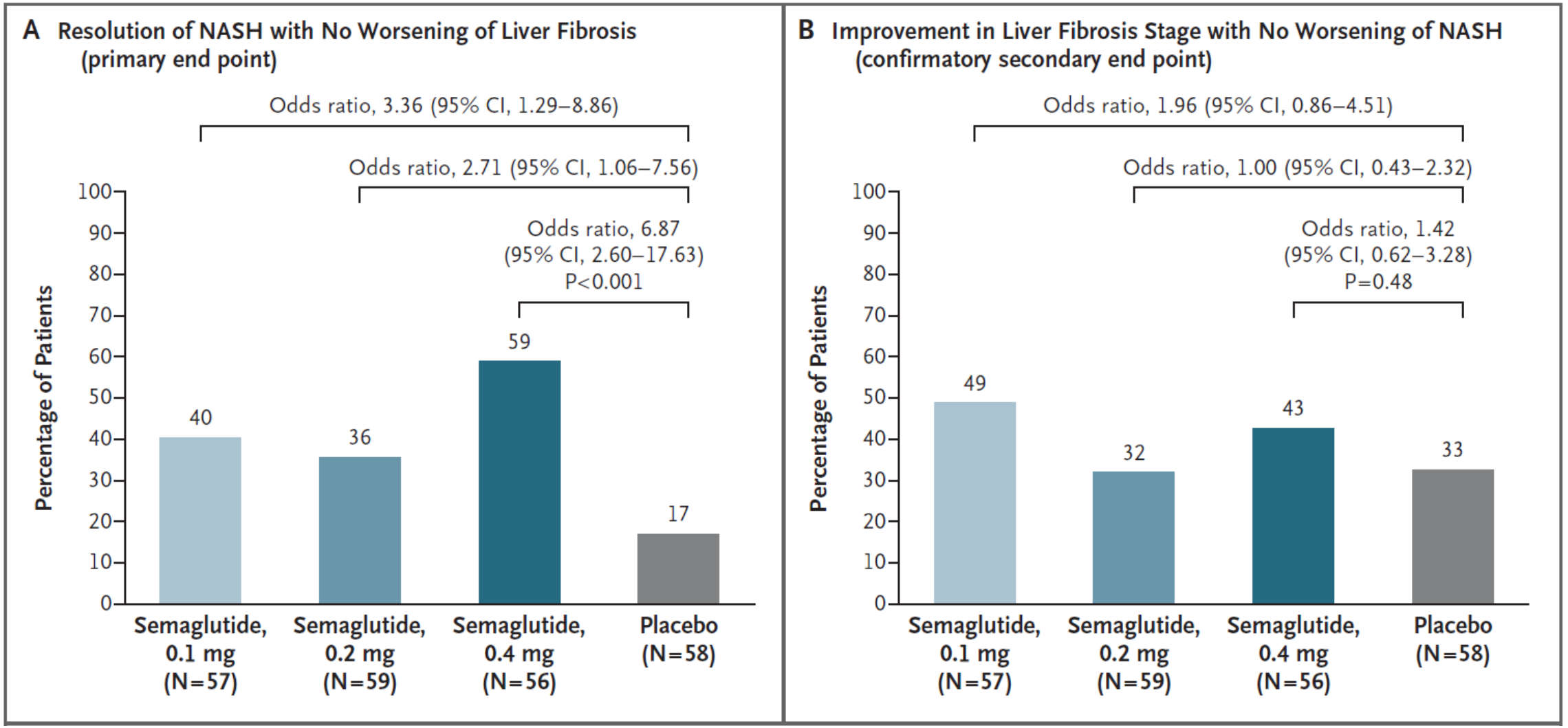


Primary end point:
- decrease of at least 2 points in the SAF-A score (ballooning and inflammation) without worsening of fibrosis

Secondary end points:
- surrogate biomarkers, resolution of NASH and regression of fibrosis.

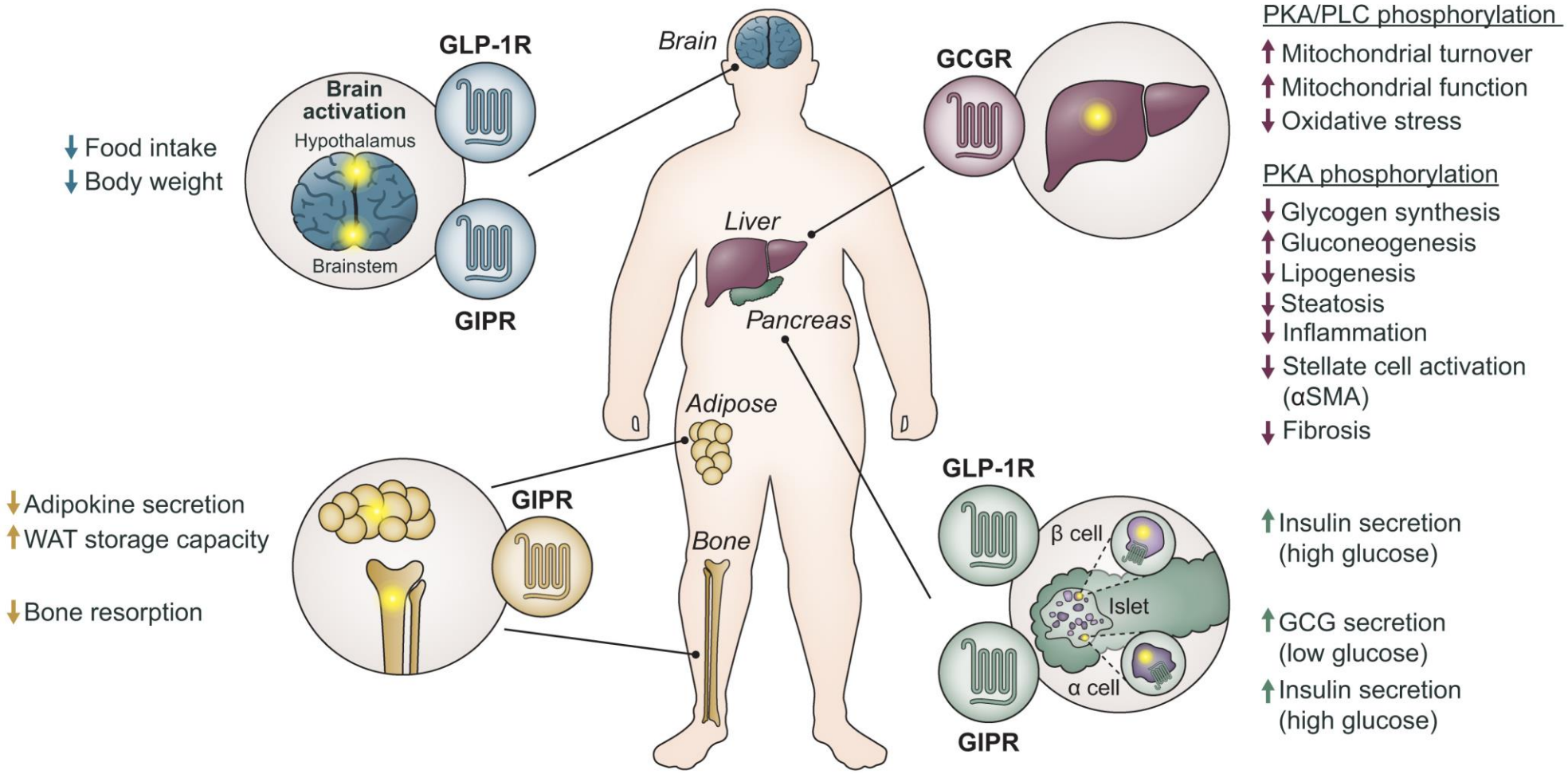
Francque et al., N Engl J Med 2021

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis



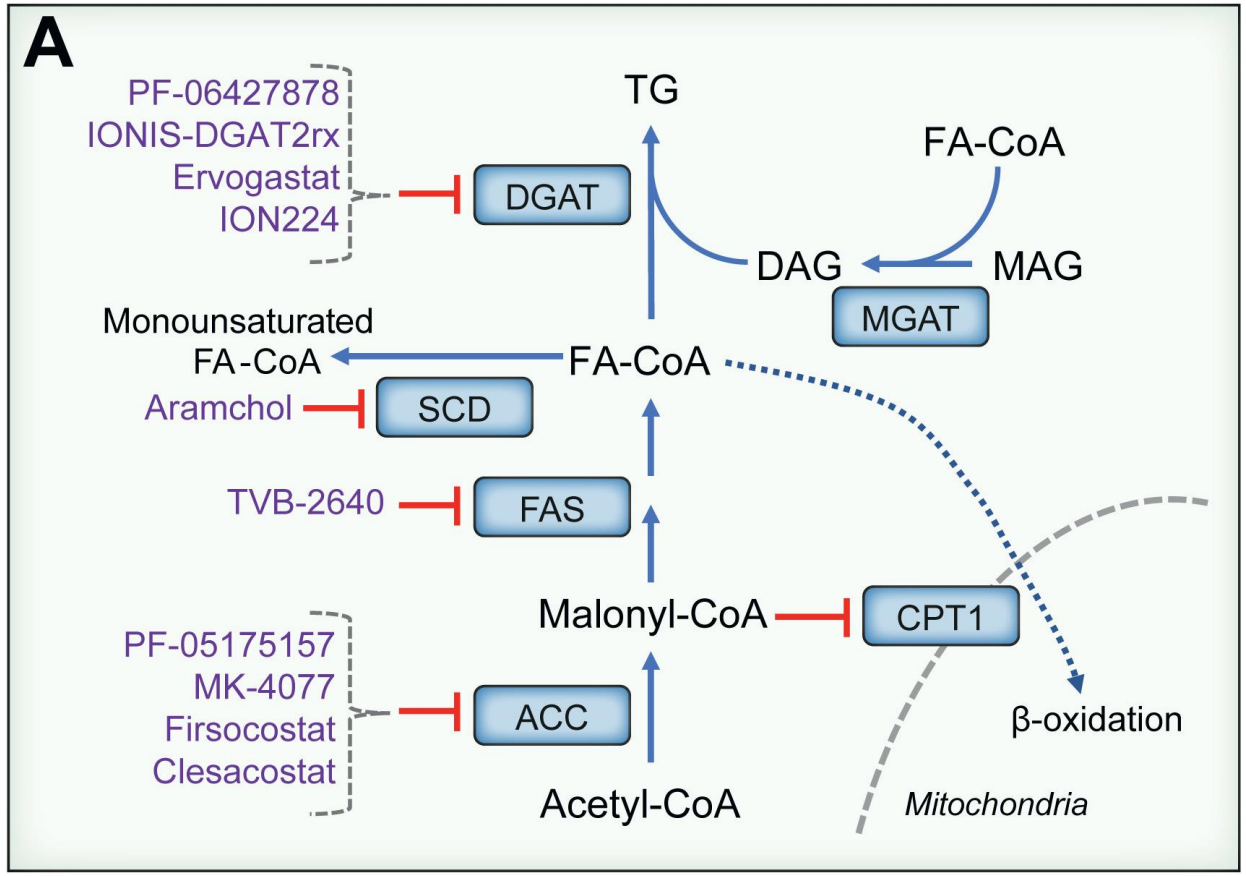
Newsome P et al, NEJM 2021

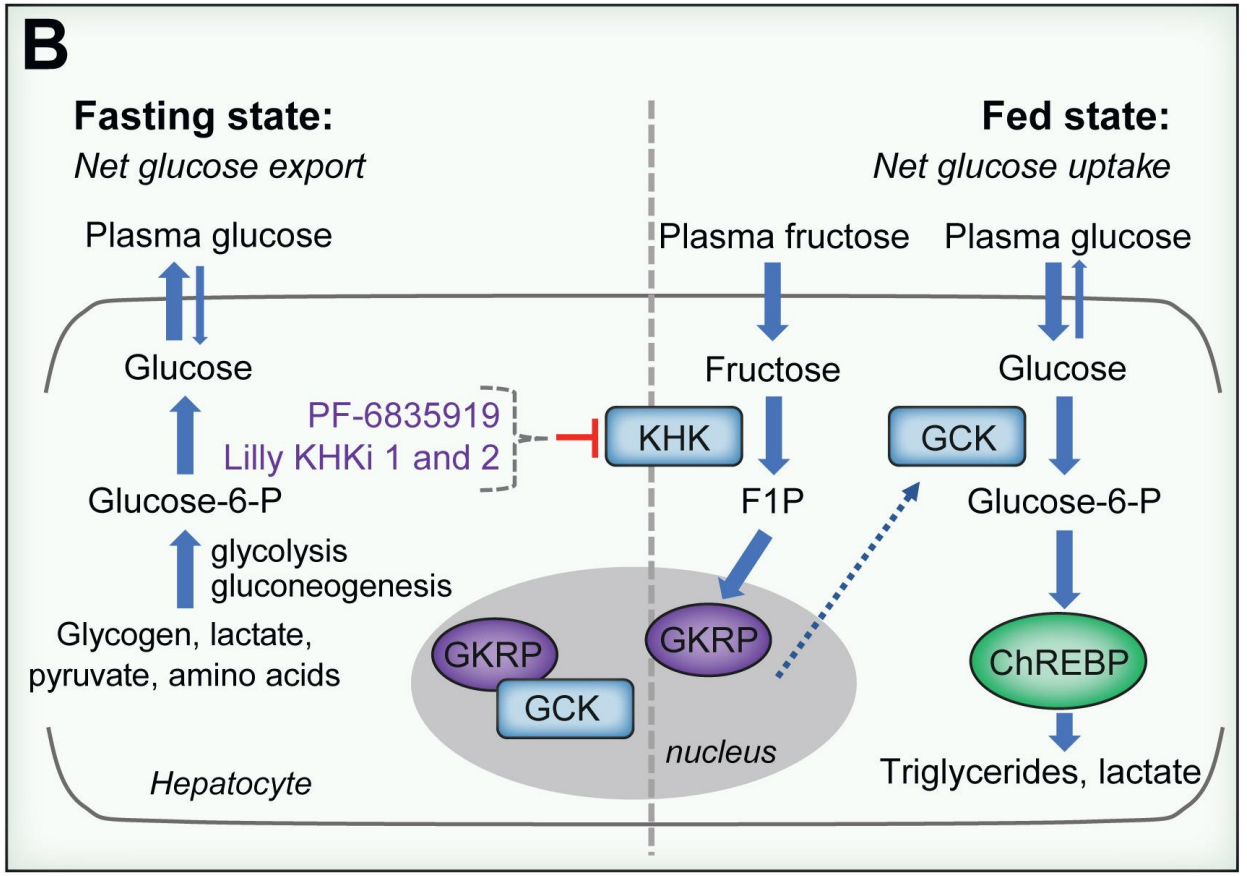
Incretins and MASLD



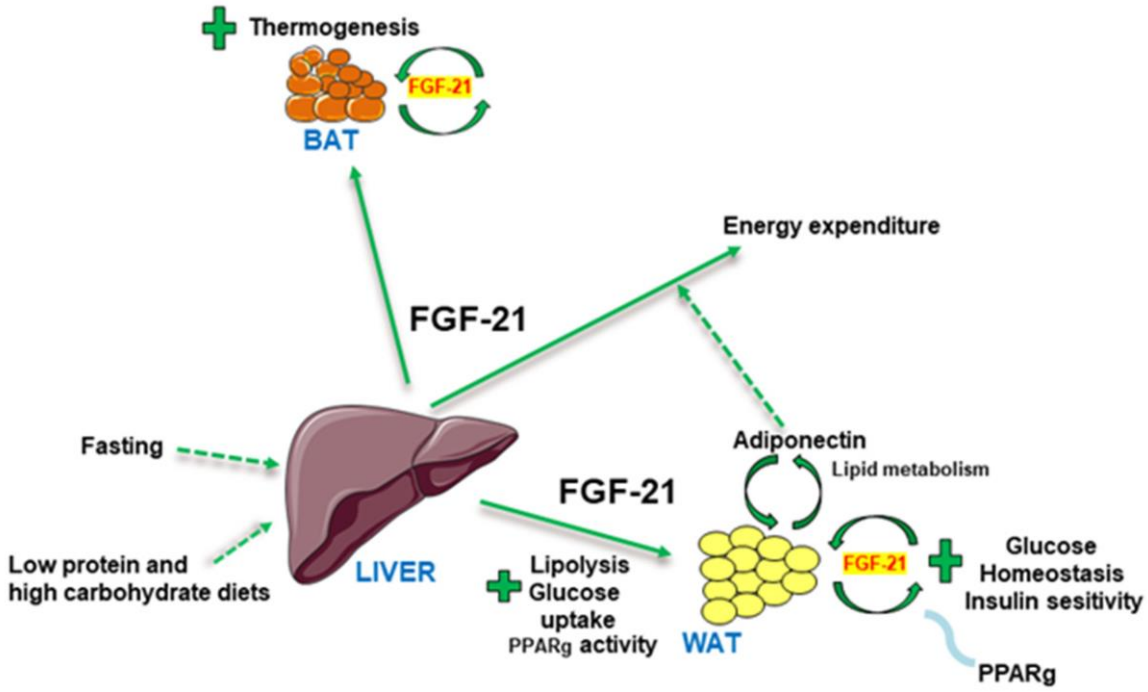
Newsome & Ambery, J Hepatol 2023

Inhibition of lipogenesis for the treatment of MASLD





Esler & Cohen, J Hepatol 2023



RESEARCH SUMMARY

Randomized, Controlled Trial of the FGF21 Analogue Pegozafermin in NASH

Loomba R et al. DOI: 10.1056/NEJMoa2304286

CLINICAL PROBLEM

For patients with nonalcoholic steatohepatitis (NASH), the development of clinically significant fibrosis is associated with worse liver-related outcomes (e.g., progression to cirrhosis and hepatocellular carcinoma), cardiovascular events, and death. No pharmacologic treatment has been approved for NASH.

CLINICAL TRIAL

Design: A phase 2b, multicenter, double-blind, 24-week, randomized, placebo-controlled trial assessed the efficacy and safety of pegozafermin — a long-acting glycopegylated fibroblast growth factor 21 (FGF21) analogue — in adults with biopsy-confirmed NASH and moderate or severe fibrosis.

Intervention: 222 patients were assigned to receive subcutaneous pegozafermin (15 or 30 mg weekly or 44 mg once every 2 weeks) or placebo (weekly or once every 2 weeks). The primary end points, evaluated at week 24, were an improvement in fibrosis (defined as a reduction by ≥1 stage on a scale of 0 to 4) without worsening of NASH and NASH resolution without worsening of fibrosis.

RESULTS

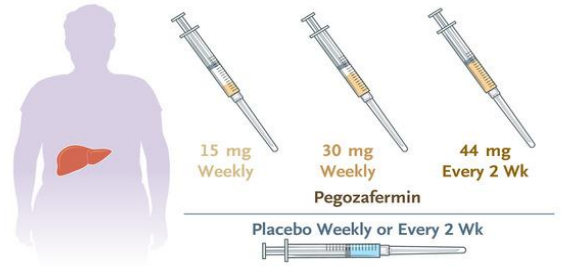
Efficacy: Treatment with the weekly 15-mg or 30-mg dose or every-2-week 44-mg dose of pegozafermin led to greater improvements in fibrosis than placebo.

Safety: The most common adverse events were nausea, diarrhea, and injection-site erythema. No adverse events with a severity above grade 3 or deaths were reported.

LIMITATIONS AND REMAINING QUESTIONS

- Patients with newly diagnosed type 2 diabetes, or any illness that might affect the results of the trial or pose an additional risk to the participant, were excluded.
- Most of the patients were White, limiting the generalizability of the data.
- Longer-term data on safety and noninvasive biomarker assessments are needed.

Links: Full Article | NEJM Quick Take | Editorial



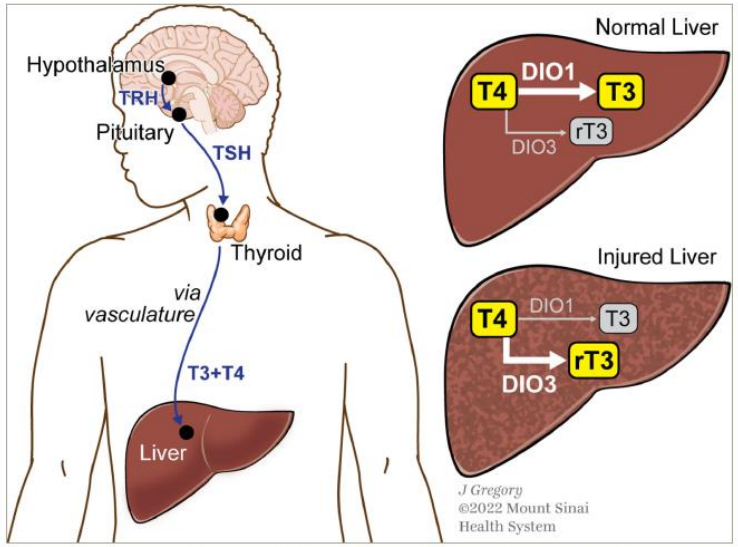
CONCLUSIONS

In patients with biopsy-confirmed NASH, pegozafermin treatment either weekly or every 2 weeks led to improvements in fibrosis over 24 weeks.

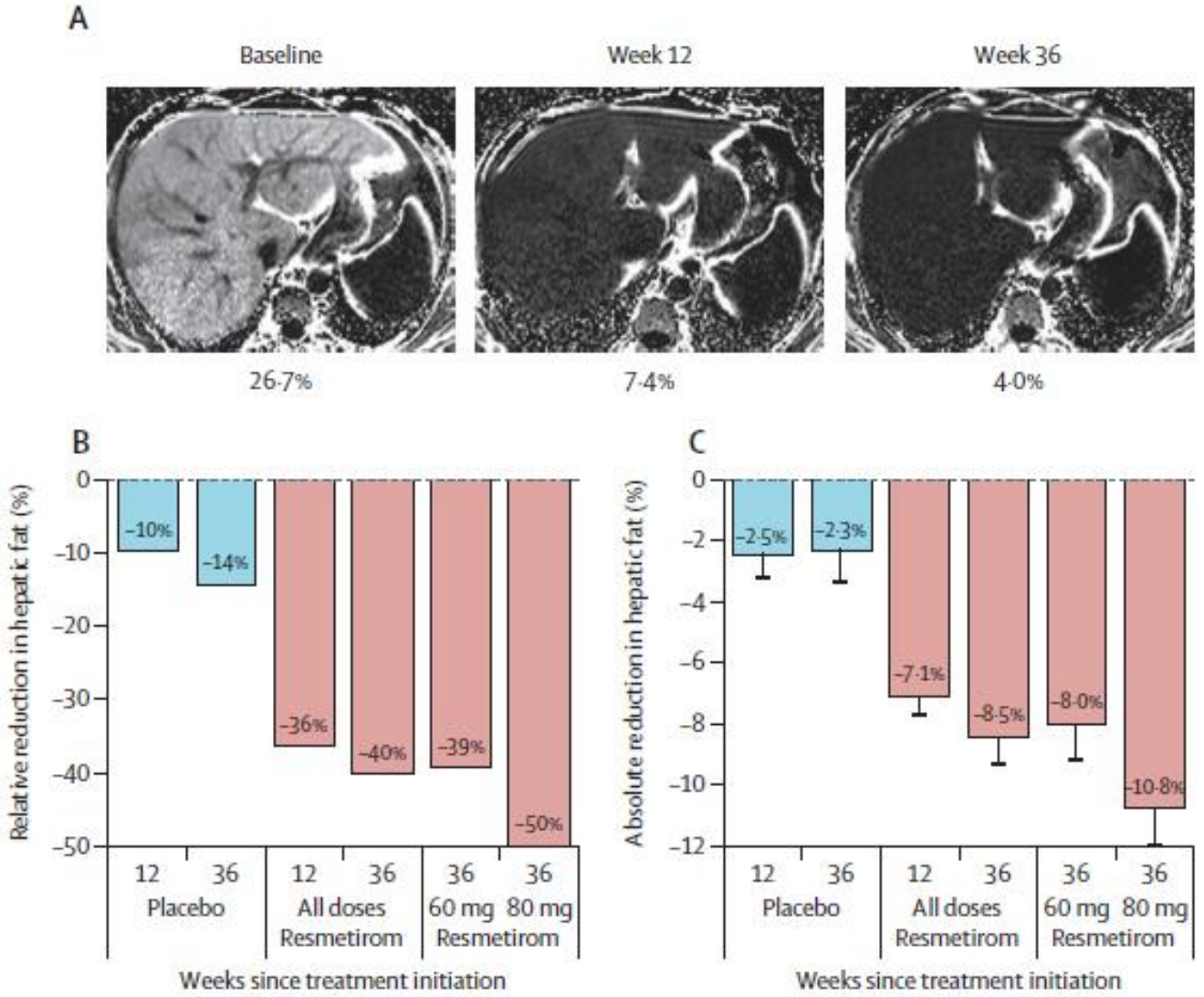
Loomba et al. NEJM 2023

Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis

Figure 2: Changes in deiodinase type 1 and deiodinase type 3 in chronic liver injury drives intrahepatic hypothyroidism



In the normal liver, DIO1 activity, an intrahepatic enzyme, drives the conversion of T4 to active T3. In chronic liver injury, a decrease in DIO1 activity coupled with an increase in DIO3 activity leads to increased conversion of T4 to inactive reverse T3, subsequently leading to accumulation of lipotoxic species, cyclic liver injury and local intrahepatic hypothyroidism. Used with permission from ©Mount Sinai Health System.
DIO1 = deiodinase type 1; DIO3 = deiodinase type 3; rT3 = reverse triiodothyronine; T3 = triiodothyronine; T4 = thyroxine; TRH = thyroid-releasing hormone; TSH = thyroid-stimulating hormone.



Harrison et al, Lancet 2019