MAFLD: una nuova frontiera terapeutica per i GLP-1 RA?

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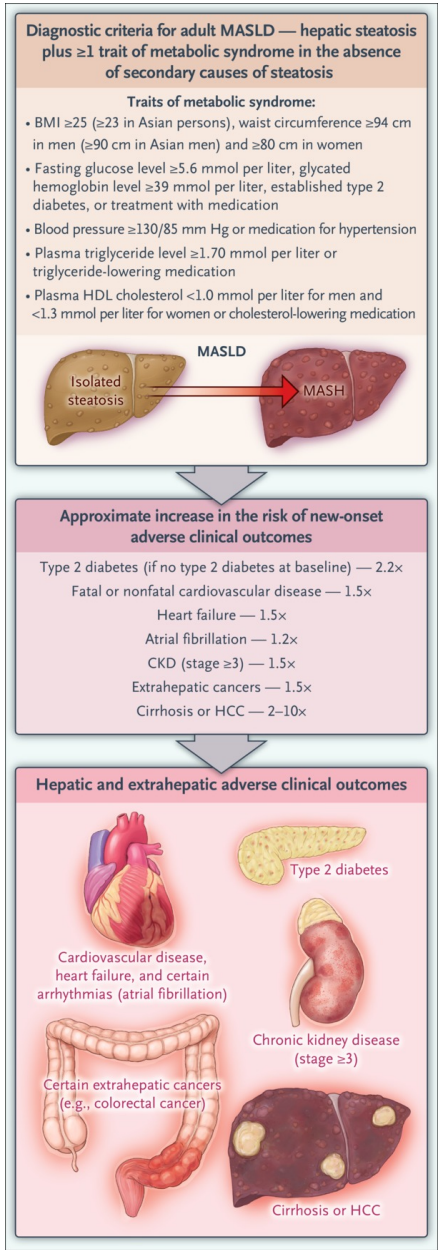
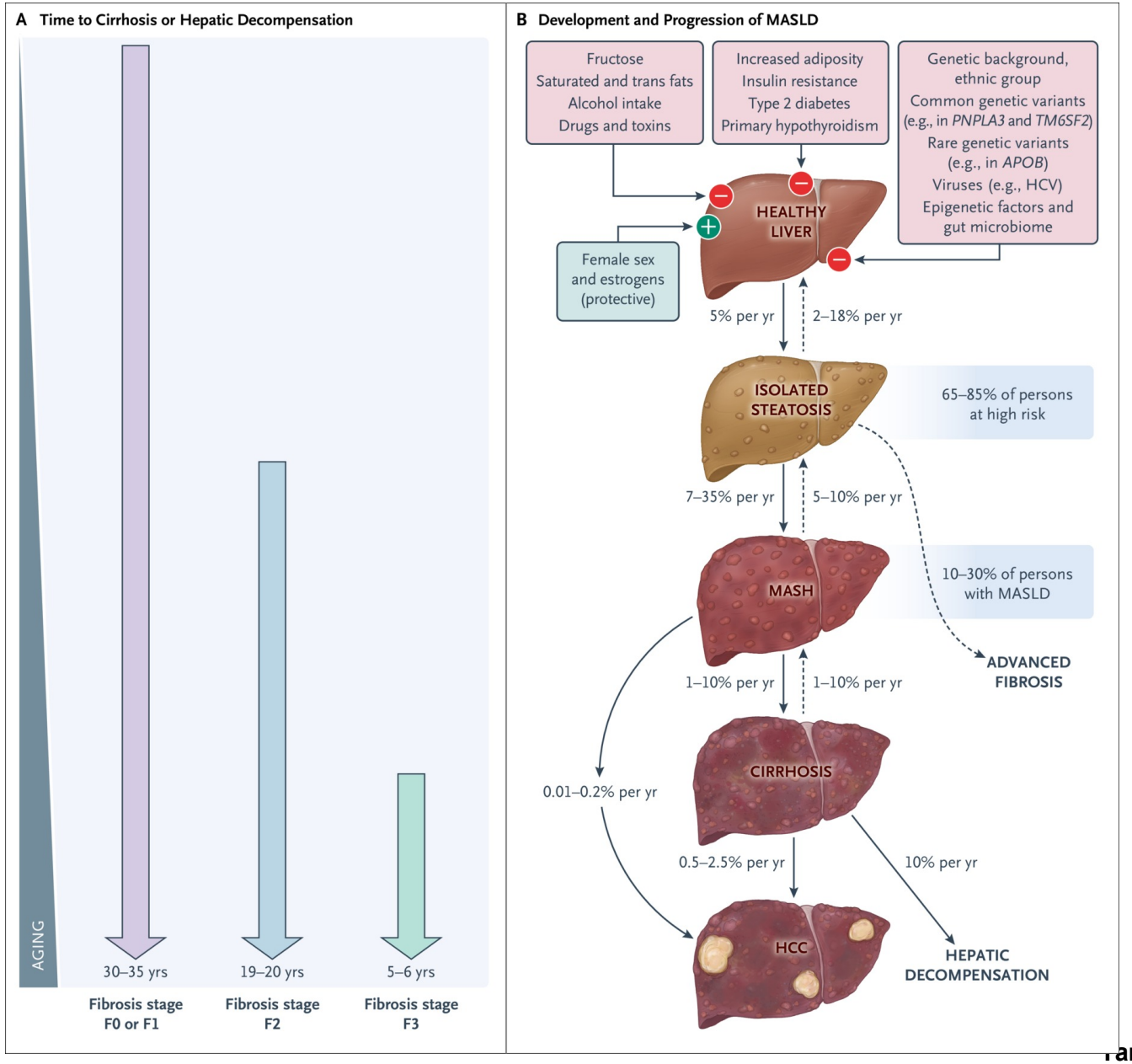
Agenda

1. Definizione ed epidemiologia di MASLD nel paziente T2D
2. Screening e Diagnosi della MASLD nel T2D: certezze ed incertezze
3. Ruolo della MASLD nel T2D: outcome epatici e outcome cardiovascolari
4. Terapia della MASLD nel T2D: ruolo di GLP-1RA

MASLD Diagnostic Criteria and Key Hepatic and Extrahepatic Clinical Outcomes.





The **prevalence of diabetes** among those with NAFLD and NASH has been estimated to be **22.51 % and 43.63 %**, respectively.

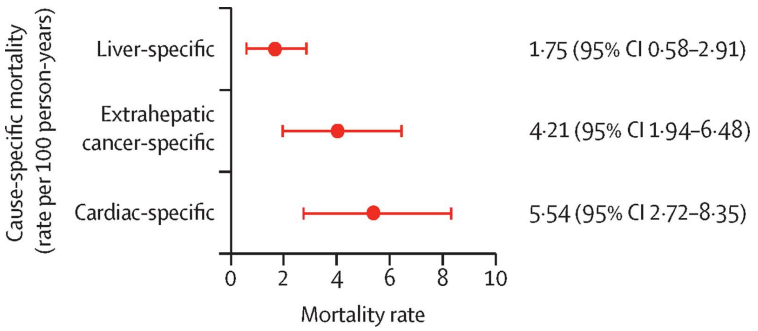
A recent global review suggested that the **prevalence of T2D could be as high as 67 %- 70 %** found in West Asia, Europe, and the United States.

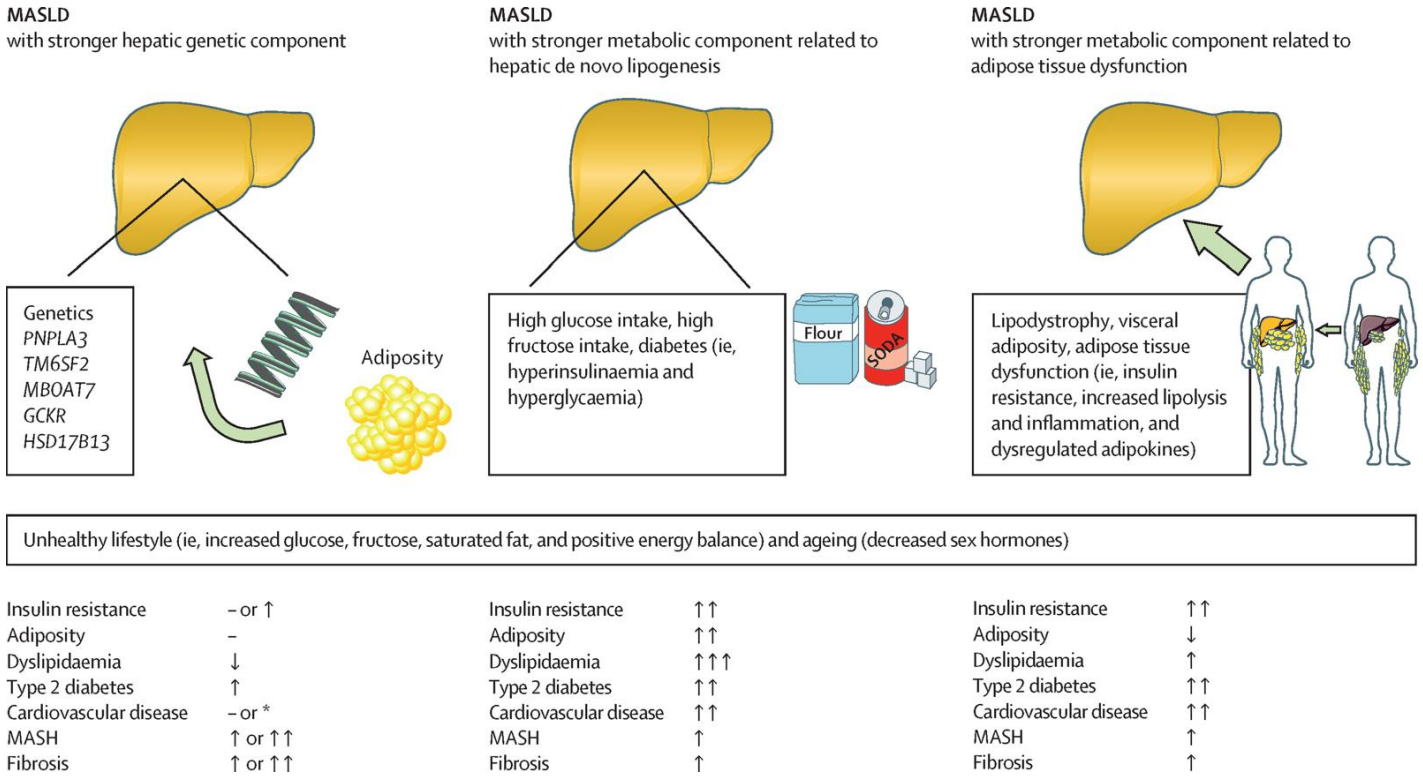
If one assesses the **prevalence of NAFLD among those with T2D**, the rates are quite high. In this context, a meta-analysis estimated the **prevalence of NAFLD among those with T2D to be about 55%** while the **prevalence for NASH was estimated at 37%** and the **prevalence of advanced fibrosis was 17%. Europe was noted to have the highest prevalence of NAFLD in those with T2D at a prevalence rate of 68.0 %.**

Diabetes Res Clin Pract. 2024 Apr:210:111648.

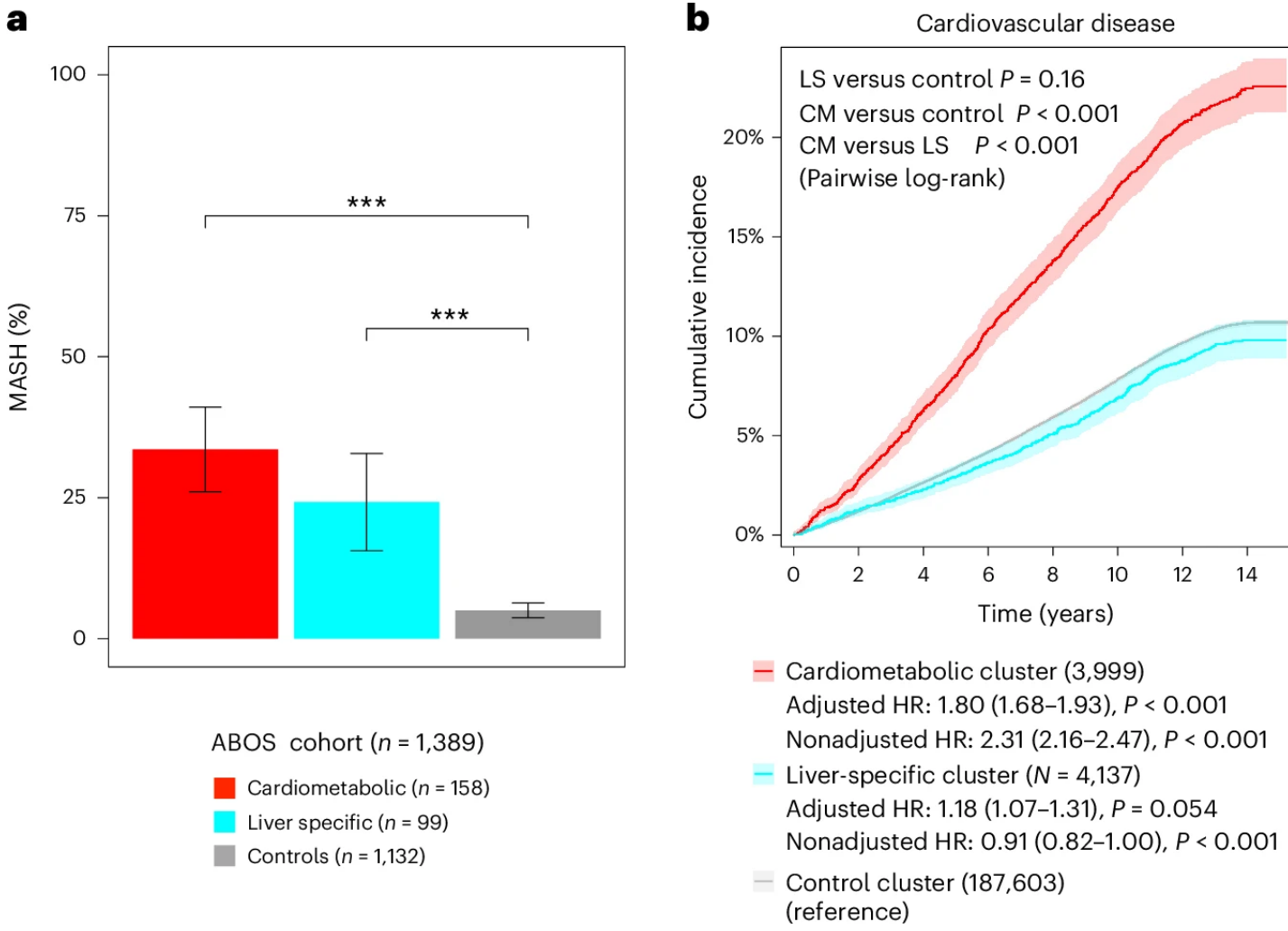
Targher G et al. N Engl J Med2025;393:683-698

Metabolic dysfunction-associated steatotic liver disease: heterogeneous pathomechanisms





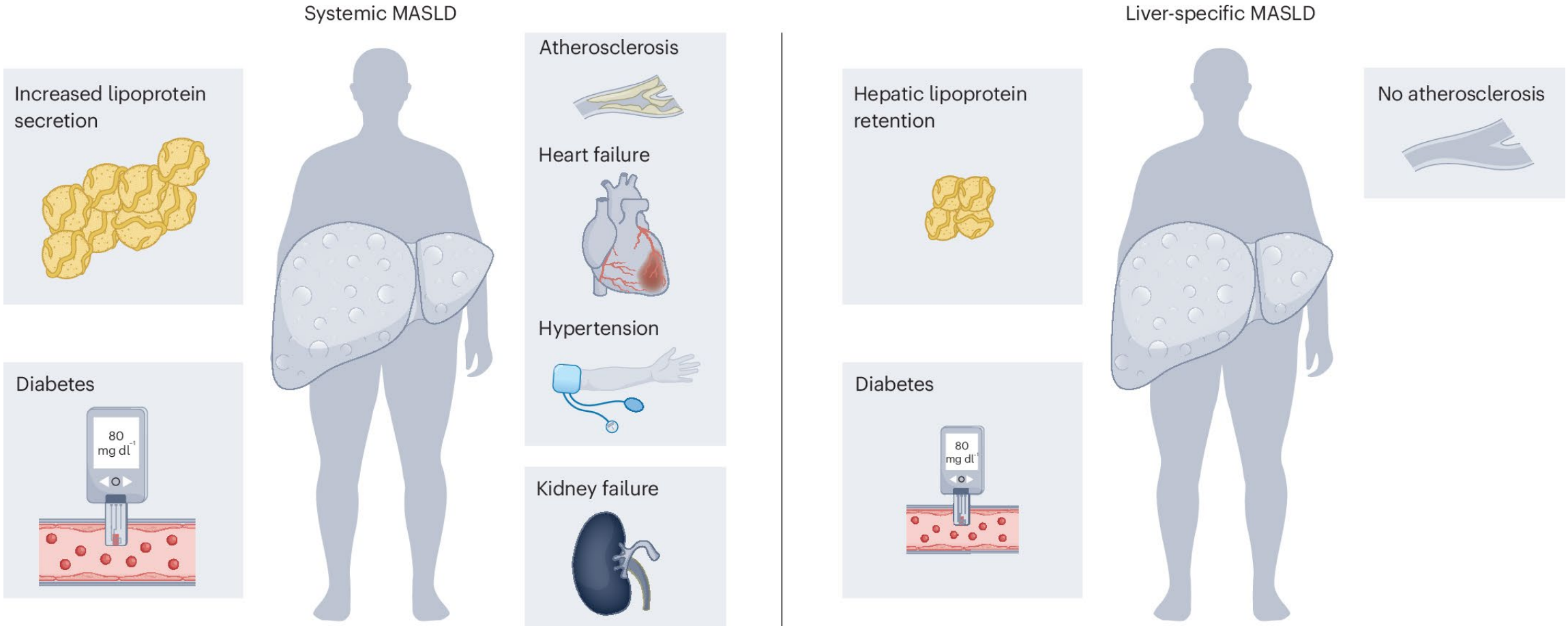
Liver histology and cardiovascular outcomes across data-driven clusters



This study unveiled the existence of at least **two distinct types of at-risk MASLD**, displaying a **similar liver phenotype at baseline**, but different biological mechanisms and **specific outcomes**, ultimately resulting in **distinct clinical trajectories**, with regard to cardiovascular disease and diabetes. Therefore, it is reasonable to state that the **search for drug treatment should reflect and selectively target these different biological pathways**. Future prospective studies are needed to assess the clinical value of these two MASLD types for guiding prevention and treatment.

Nat Med. 2024 Dec;30(12):3624-3633.

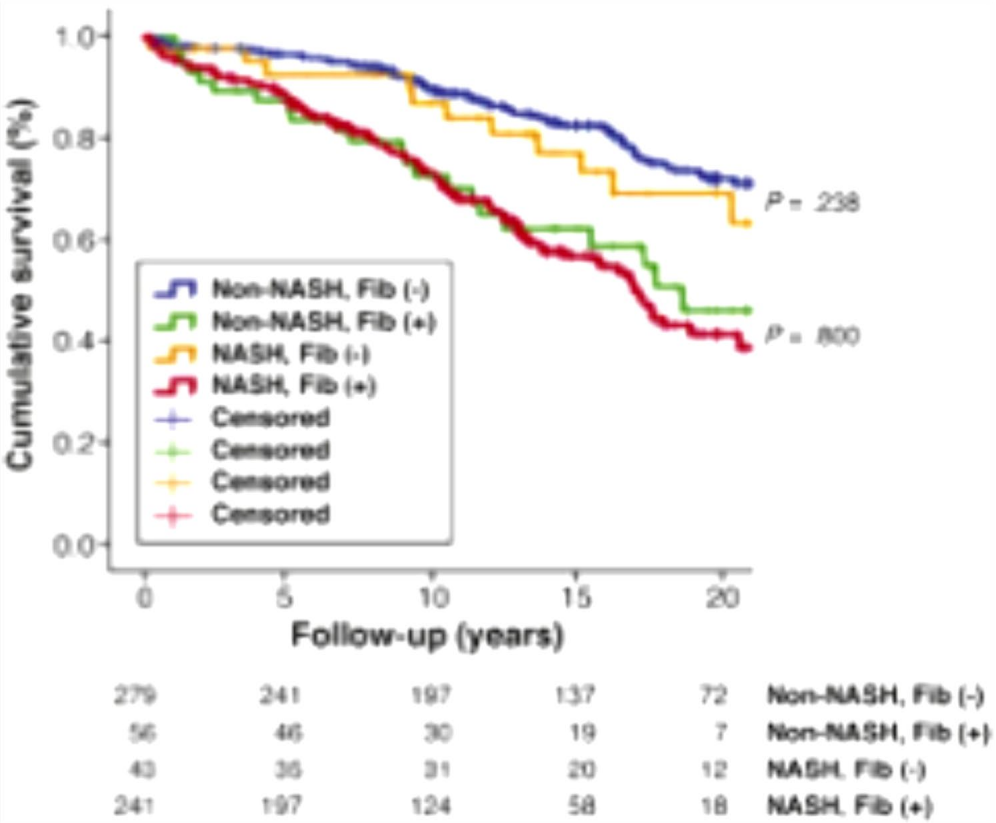
Different clinical trajectories in systemic MASLD and liver-specific MASLD



Systemic MASLD is characterized by increased hepatic lipoprotein secretion and is associated with higher risks of cardiovascular disease, kidney failure and T2D. **Liver-specific MASLD** is associated with modestly increased risk of T2D and rapid progression of liver disease due to hepatic lipoprotein retention, which, in turn, protects against CVD.

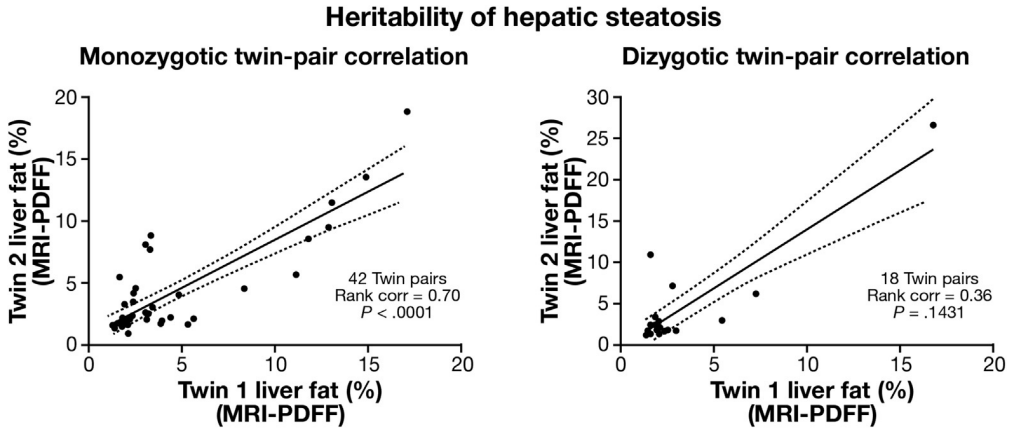
Nat Metab 2025 Oct 17. doi: 10.1038/s42255-025-01394-8

Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With NAFLD

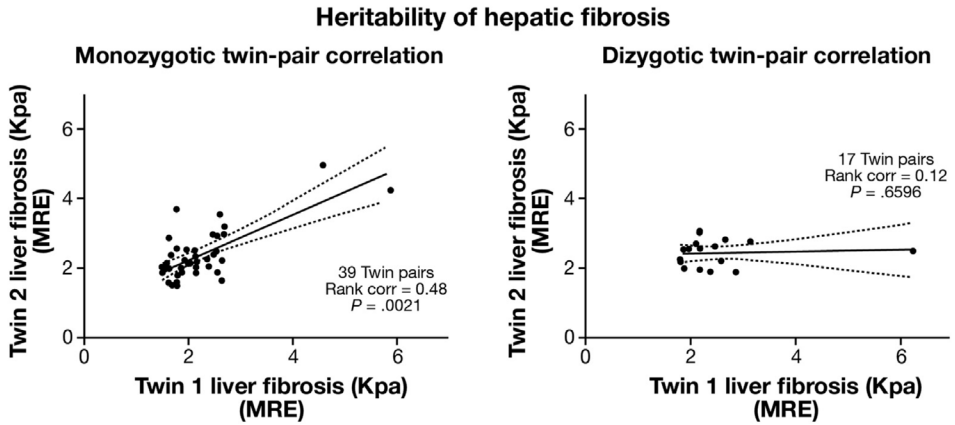


Gastroenterology 2015;149:389–397

Heritability of Hepatic Fibrosis and Steatosis Based on a Prospective Twin Study



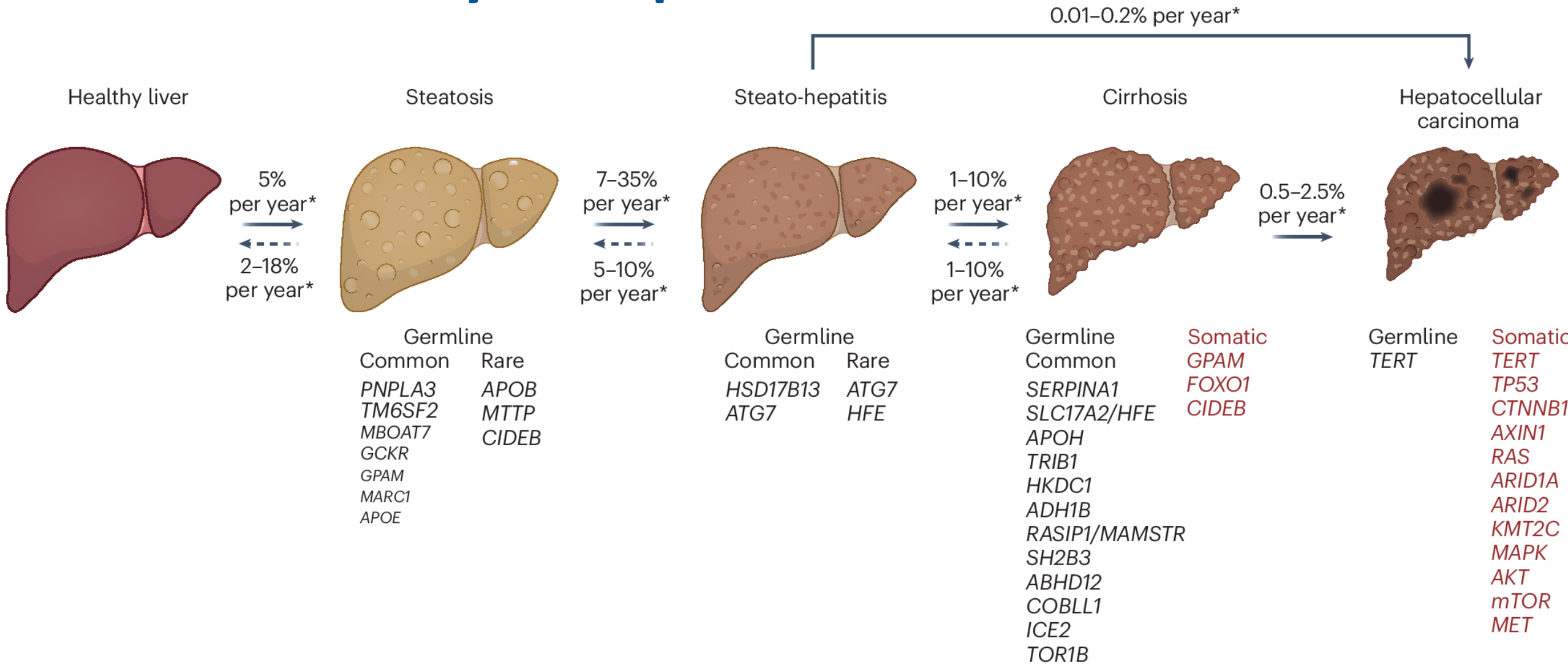
Heritability estimate of hepatic steatosis (as assessed by MRI-PDFF) was 0.52 (95% confidence interval (CI): 0.31–0.73, $P < 1.1 \times 10^{-11}$)



Heritability estimate of hepatic fibrosis (as assessed by MRE) was 0.5 (95% confidence interval (CI): 0.31–0.73, $P < 1.1 \times 10^{-11}$)

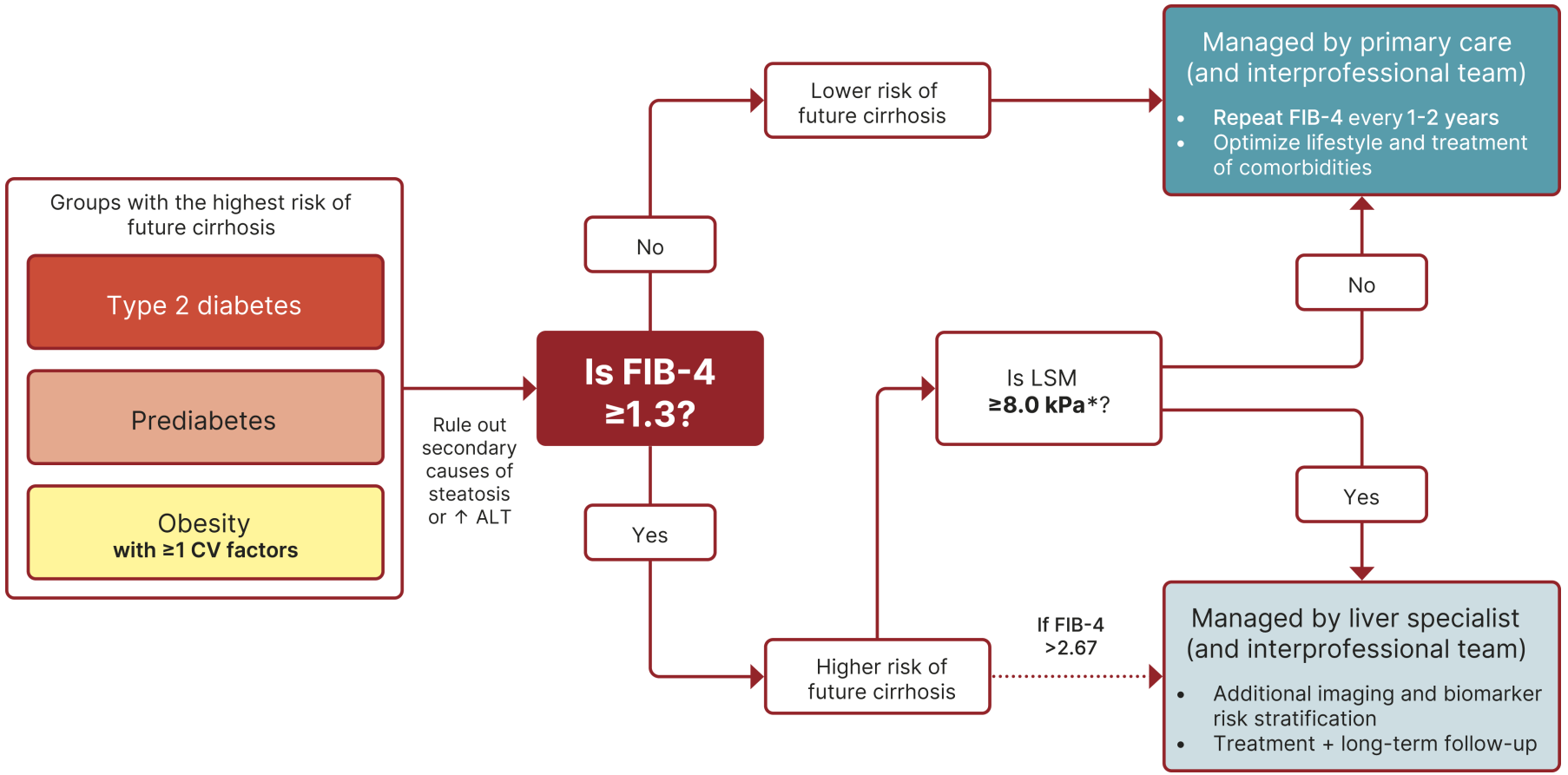
Gastroenterology Volume 149, Issue 7, December 2015, Pages 1784-1793

Heritability of Hepatic Fibrosis and Steatosis



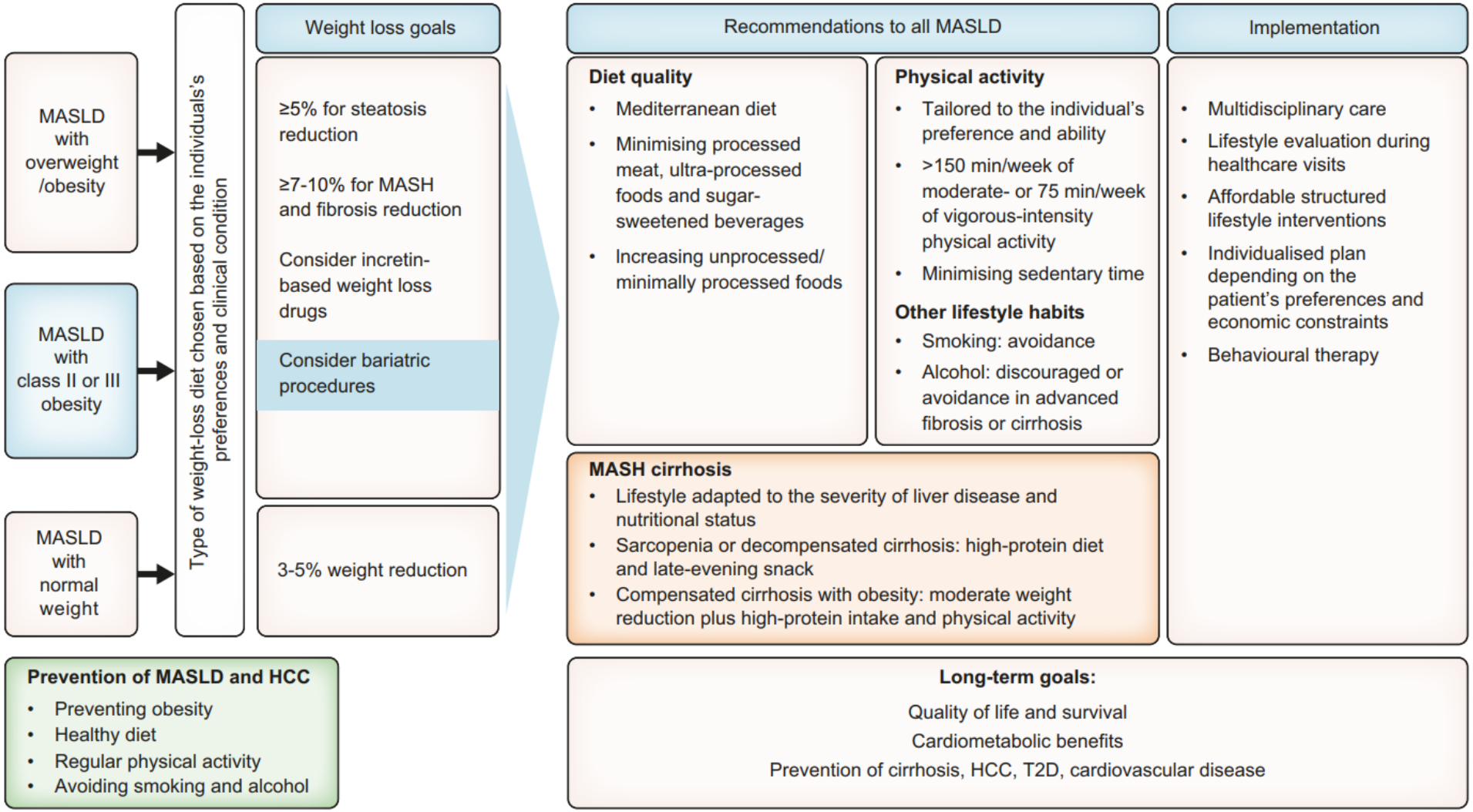
Nat Metab 2025 Oct 17. doi: 10.1038/s42255-025-01394-8

Diagnostic algorithm for risk stratification and the prevention of cirrhosis in individuals with MASLD



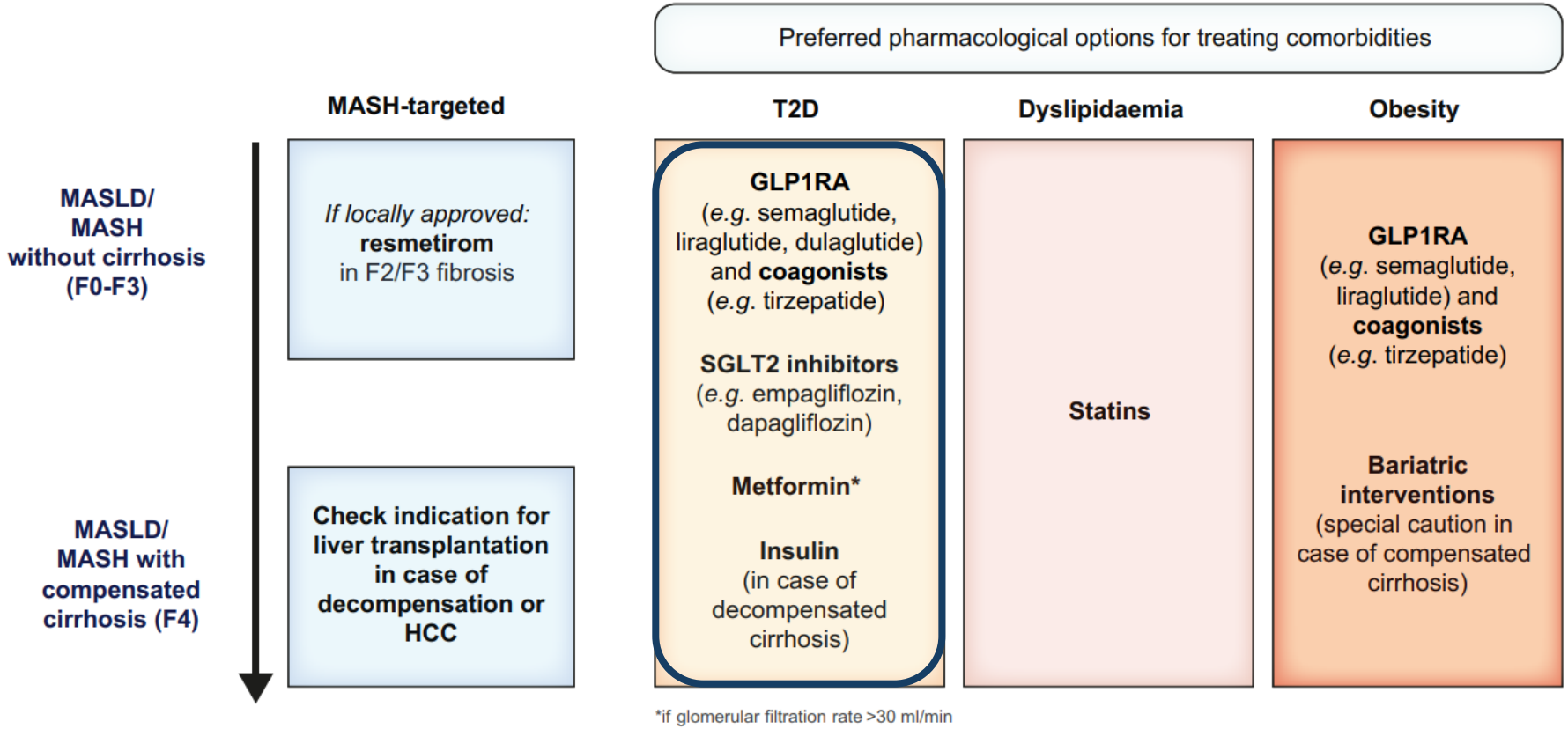
Kenneth Cusi, et al; Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) in People With Diabetes: The Need for Screening and Early Intervention. A Consensus Report of the American Diabetes Association. Diabetes Care 20 June 2025; 48 (7): 1057–1082

Lifestyle management algorithm for MASLD



EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)
Journal of Hepatology, September 2024. vol. 81 / 492-542

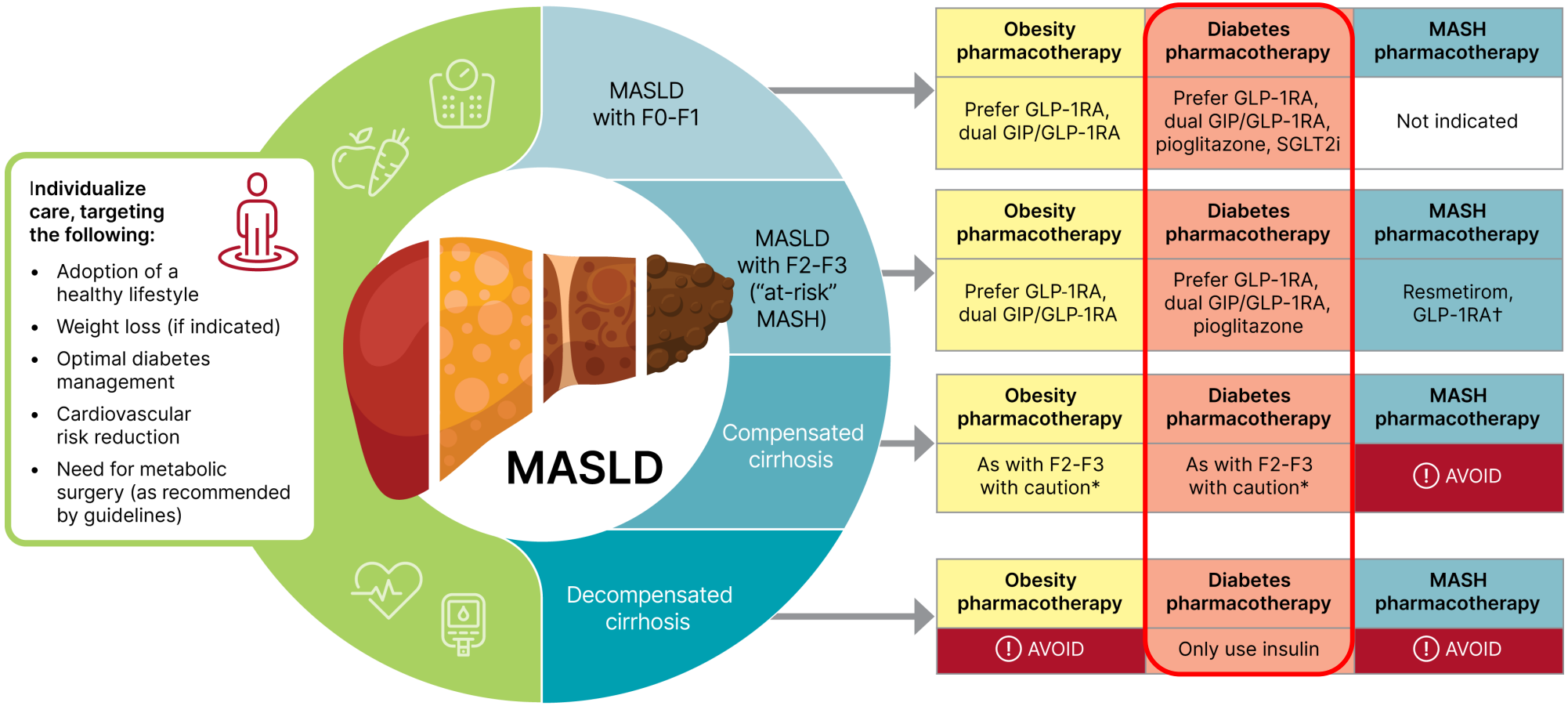
Treatment recommendations beyond lifestyle modification in MASLD/MASH



In the absence of a formal demonstration of histological improvement in large, well conducted, phase III trials, glucagon-like peptide 1 receptor agonists (GLP1RA) cannot currently be recommended as MASH-targeted therapies (**LoE 5, strong recommendation**).	98%
GLP1RAs are safe to use in MASH (including compensated cirrhosis) and should be used for their respective indications, namely type 2 diabetes and obesity, as their use improves cardiometabolic outcomes (**LoE 2, strong recommendation**).	98%

EASL–EASD–EASO Clinical Practice Guidelines on the management of MASLD
Journal of Hepatology, September 2024. vol. 81 / 492-542

MASLD treatment algorithm for individuals with prediabetes or diabetes



Kenneth Cusi, et al; 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. Diabetes Care 20 June 2025; 48 (7): 1057–1082

Liver and cardiorenal effects of glucose-lowering medications

	Effect in MASLD and MASH*				Cardiovascular, renal, and other relevant clinical effects			
Medication	Hepatic steatosis	Steatohepatitis	Fibrosis regression	Reduction of fibrosis progression	ASCVD*	CKD*	HF*	Hypoglycemia¶
Semaglutide**	Beneficial	Beneficial	Beneficial	Potential benefit	Beneficial	Beneficial	Beneficial	Low risk
Tirzepatide***†	Potential benefit	Potential benefit	Potential benefit	Potential benefit	?	?	Beneficial	Low risk
Pioglitazone†	Potential benefit	Potential benefit	Potential benefit	Potential benefit	Beneficial	Neutral	Not recommended in HF stage B, C, or D	Low risk
SGLT2 inhibitors	Potential benefit	?	?	?	Beneficial	Beneficial	Beneficial	Low risk
Metformin¶	Neutral	Neutral	Neutral	Neutral	Potential benefit?	Neutral	Neutral	Low risk
DPP-4 inhibitors¶	Neutral	?	?	?	Neutral	Neutral	Neutral (except	Low risk

Kenneth Cusi, et al; 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. Diabetes Care 20 June 2025; 48 (7): 1057–1082

The NEW ENGLAND JOURNAL of MEDICINE

Semaglutide in Metabolic-Related Steatohepatitis

A Research Summary based on Sanyal AJ et al. | 10.1056/NEJMoa2413258 | Published on April 30, 2025

WHY WAS THE TRIAL DONE?

Metabolic dysfunction–associated steatohepatitis (MASH) is a severe form of metabolic dysfunction–associated steatotic liver disease characterized by steatosis, hepatocyte damage, and inflammation. In a previous phase 2 trial involving patients with MASH, treatment with semaglutide, a glucagon-like peptide-1 receptor agonist, resulted in better outcomes than placebo.

HOW WAS THE TRIAL CONDUCTED?

1197 adults with biopsy-defined MASH and fibrosis stage 2 or 3 were randomly assigned to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo for 240 weeks. The primary end points were the resolution of steatohepatitis with no worsening of liver fibrosis and a reduction in liver fibrosis with no worsening of steatohepatitis.

TRIAL DESIGN

- Phase 3
- Randomized
- Double-blind
- Placebo-controlled
- Location: 253 clinical sites in 37 countries

RESULTS

At a planned interim analysis at week 72 involving the first 800 patients, resolution of steatohepatitis with no worsening of liver fibrosis occurred in a higher percentage of patients treated with semaglutide than with placebo. Reduction in liver fibrosis with no worsening of steatohepatitis was also reported in a higher percentage of patients treated with semaglutide than with placebo. The most common adverse events in both groups were gastrointestinal disorders, including nausea, diarrhea, and constipation.

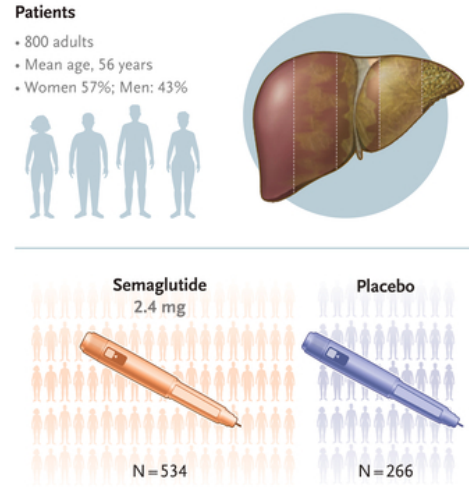
LIMITATIONS AND REMAINING QUESTIONS

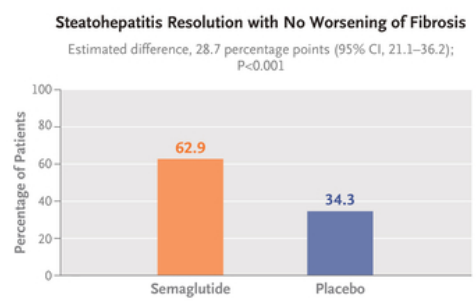
- More than two thirds of the patients were White, which may limit the generalizability of the results.
- Data regarding biomarkers of alcohol consumption were lacking.
- Given the small number of lean patients, definitive conclusions about benefit in this population cannot be drawn.

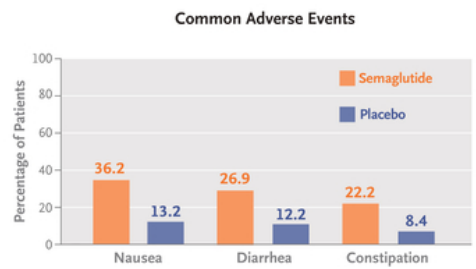
CONCLUSIONS

In an interim analysis of a phase 3 trial involving patients with MASH and moderate or advanced liver fibrosis, once-weekly semaglutide improved liver histologic results over 72 weeks.

NEJM QUICK TAKE | EDITORIAL

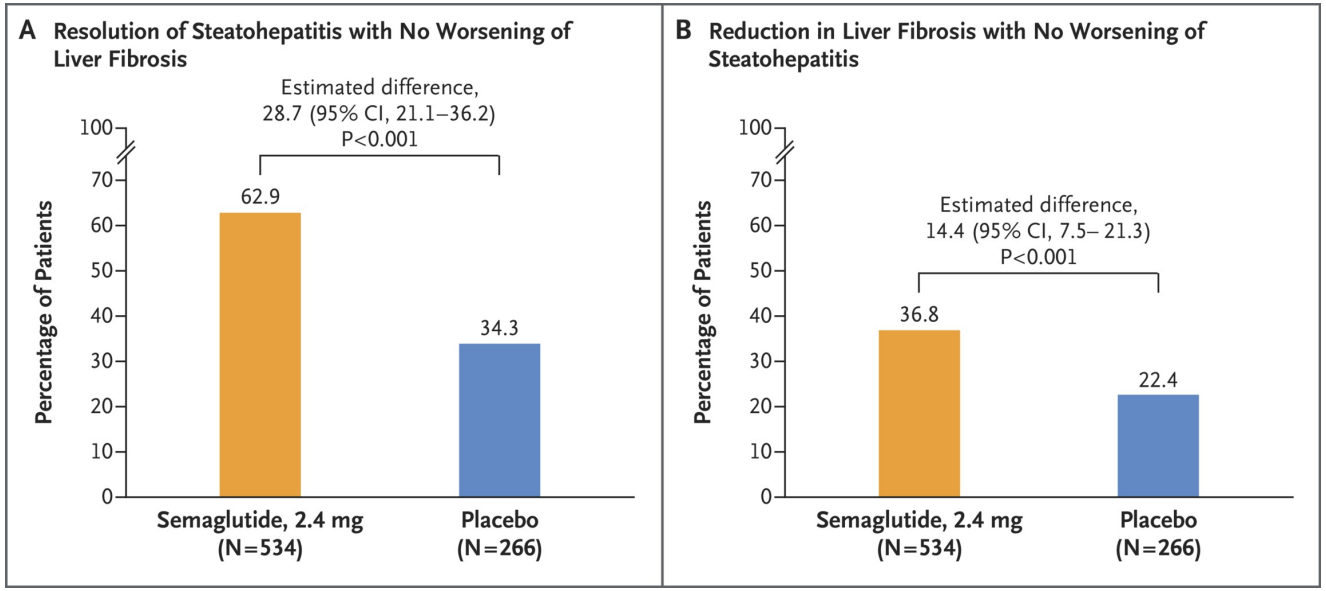


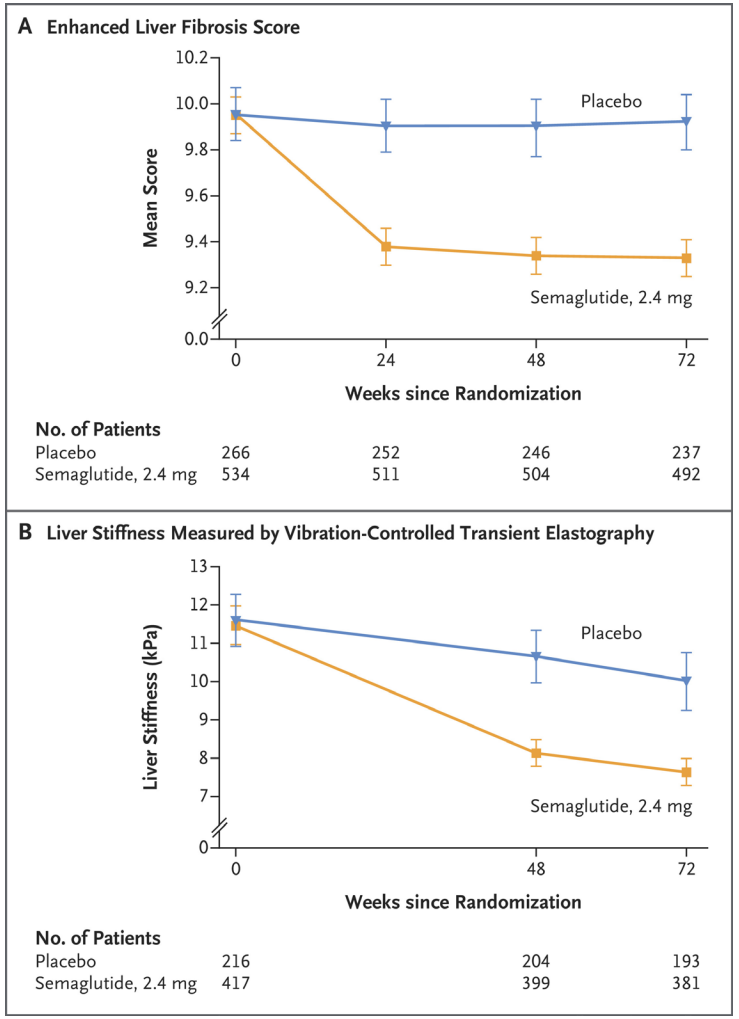




Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis

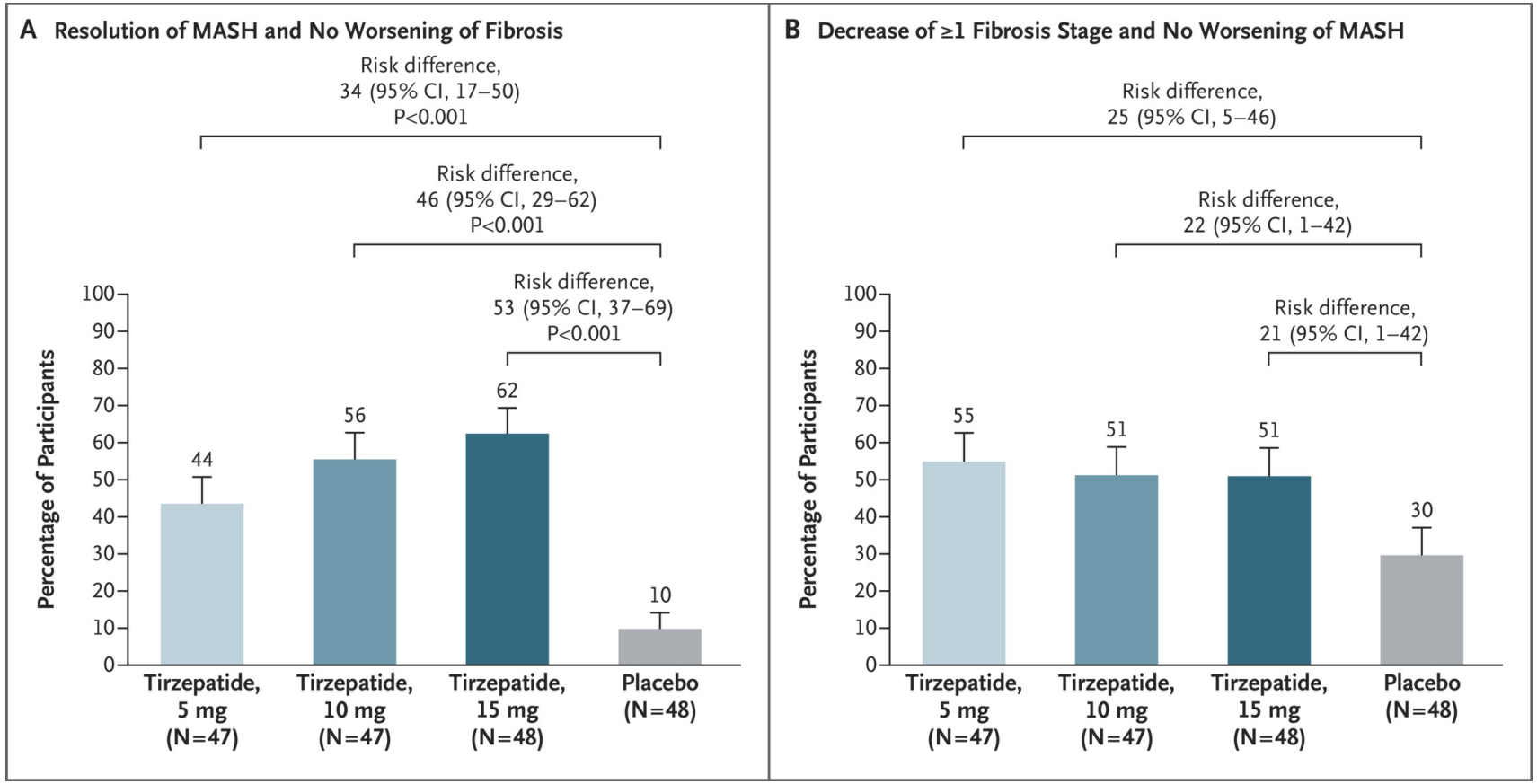
Semaglutide





N Engl J Med Volume 392(21):2089-2099June 5, 2025

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis (phase 2)



Loomba R et al. N Engl J Med 2024;391:299-310

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

Harrison SA et al. DOI: 10.1056/NEJMoa2309000

CLINICAL PROBLEM

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease characterized by ≥5% hepatic steatosis with hepatocellular damage and inflammation. There are currently no approved pharmacologic treatments for NASH. Resmetirom is an oral, liver-directed, thyroid hormone receptor beta–selective agonist in development for the treatment of NASH.

CLINICAL TRIAL

Design: An ongoing, phase 3, multinational, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of resmetirom in adults with biopsy-confirmed NASH and liver fibrosis.

Intervention: 966 patients with NASH and fibrosis of stage F1B, F2, or F3 were assigned in a 1:1:1 ratio to receive once-daily resmetirom (80 mg or 100 mg) or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points; scores range from 0 to 8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by ≥1 stage with no worsening of the NAFLD activity score.

RESULTS

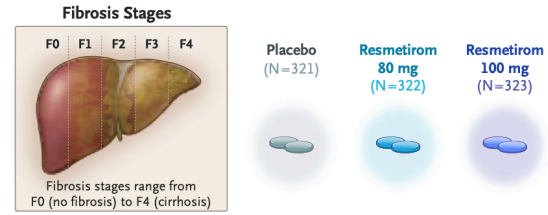
Efficacy: Among evaluable patients, both doses of resmetirom were superior to placebo with respect to the two primary end points.

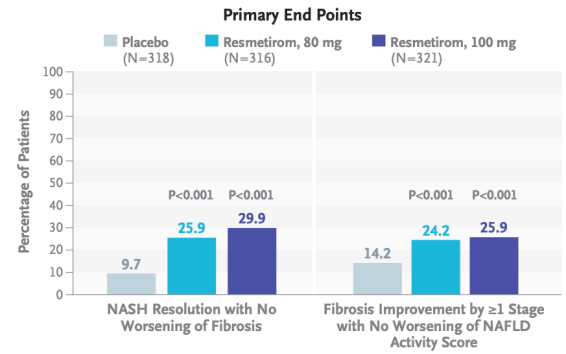
Safety: More than 90% of the patients in each group had adverse events, most of which were mild or moderate in severity. Diarrhea and nausea occurred more often with resmetirom than with placebo. The incidence of serious adverse events was similar among the groups.

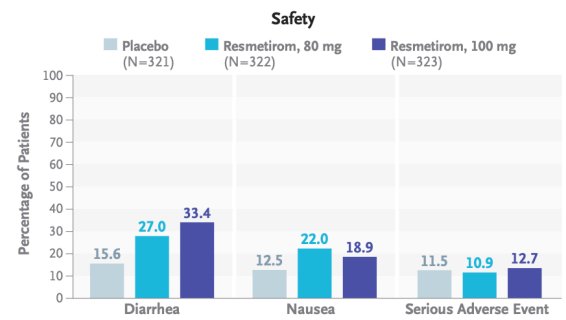
LIMITATIONS AND REMAINING QUESTIONS

- The trial lacked clinical-outcomes data to correlate with the histologic data. The trial is planned to continue to 54 months to evaluate liver-related outcomes, including progression to cirrhosis.
- Almost 90% of the participants were White, which limits the generalizability of the findings to other racial or ethnic groups.

Links: Full Article | NEJM Quick Take | Editorial



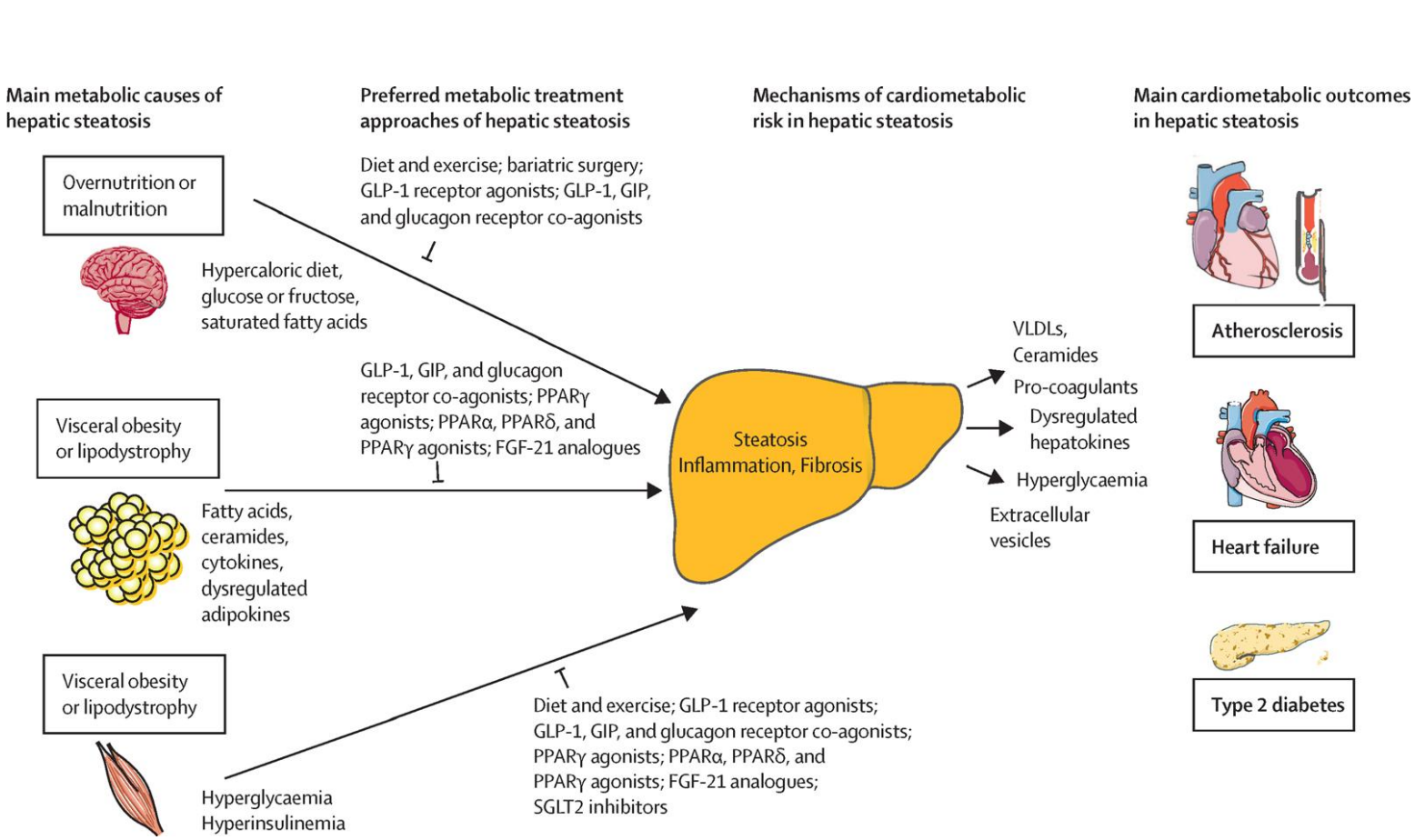


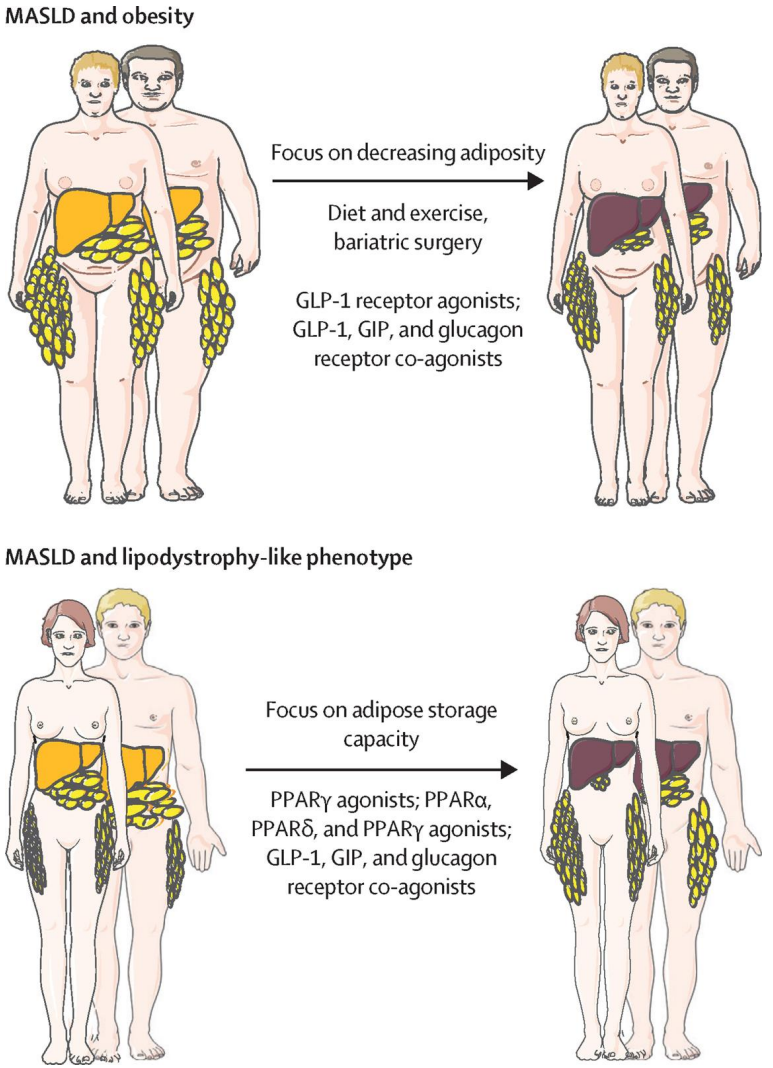


CONCLUSIONS

In patients with NASH and liver fibrosis, once-daily treatment with resmetirom was superior to placebo with respect to NASH resolution and fibrosis improvement by ≥1 stage at 52 weeks of follow-up.

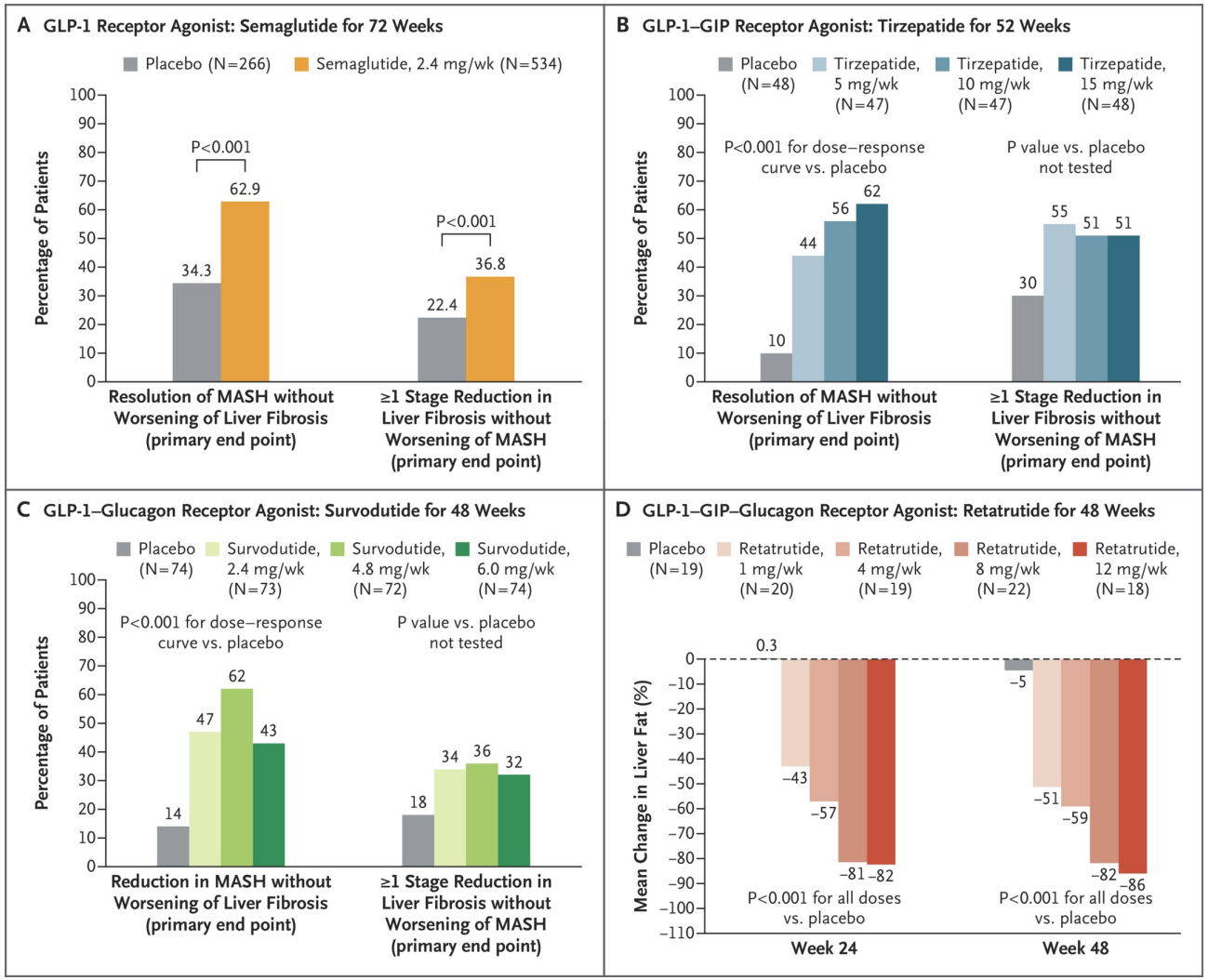
Metabolic dysfunction-associated steatotic liver disease: heterogeneous pathomechanisms and effectiveness of metabolism-based treatment





Lancet Diabetes & Endocrinology Volume 13, Issue 2 P134-148February 2025

Possible Hepatoprotective Effects of GLP-1 Receptor Agonists or Other Dual or Triple Incretin–Based Receptor Agonists in Adults with MASLD or MASH and Fibrosis.



Targher G et al. N Engl J Med 2025;393:683-698

CONCLUSIONI

- La MASLD è una malattia multisistemica che è diventata un problema di salute pubblica in tutto il mondo. Per affrontare il crescente onere clinico della MASLD sarà necessario creare un gruppo di lavoro multidisciplinare e un quadro di riferimento per sviluppare e adottare nuove modalità di lavoro collaborative volte a fornire un'assistenza e un trattamento olistici e incentrati sulla persona ai pazienti con MASLD.
- data l'eterogeneità della MASLD e il ruolo della predisposizione genetica nel far pendere la bilancia verso le complicanze epatiche (in contrapposizione alle complicanze cardiometaboliche), valutare se i punteggi di rischio poligenico o i pannelli di biomarcatori possano identificare in modo affidabile i pazienti con MASLD che presentano un rischio più elevato di eventi avversi epatici sarà importante per stabilire le priorità e, possibilmente, per un trattamento più precoce.
- Le modifiche dello stile di vita dovrebbero essere parte di qualsiasi approccio terapeutico, ma resmetirom è il primo farmaco approvato per il trattamento di adulti con MASH non cirrotico e fibrosi da moderata ad avanzata
- I farmaci a base di incretine e altre farmacoterapie basate sul metabolismo si stanno rivelando promettenti come opzioni terapeutiche non solo per la malattia epatica steatosica, ma anche per le complicazioni cardiovascolari, renali e metaboliche che sono strettamente correlate a MASLD e MASH.