LETNÁ ŠKOLA HEPATOLÓGIE 2025

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MASLD

Marek RÁC, FN Nitra

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História a súčastnosť

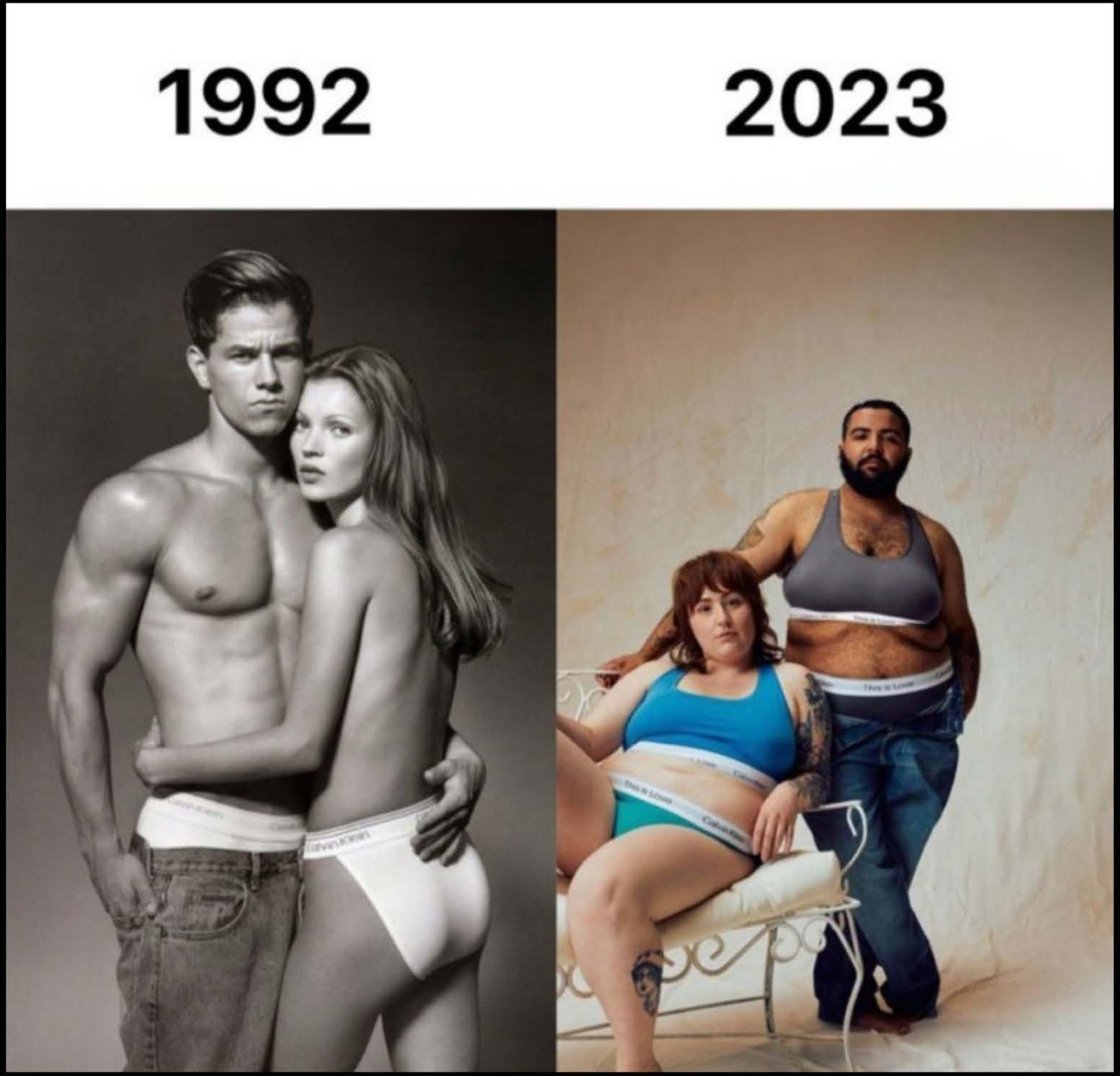

Foto:archív autora, zdroj internet

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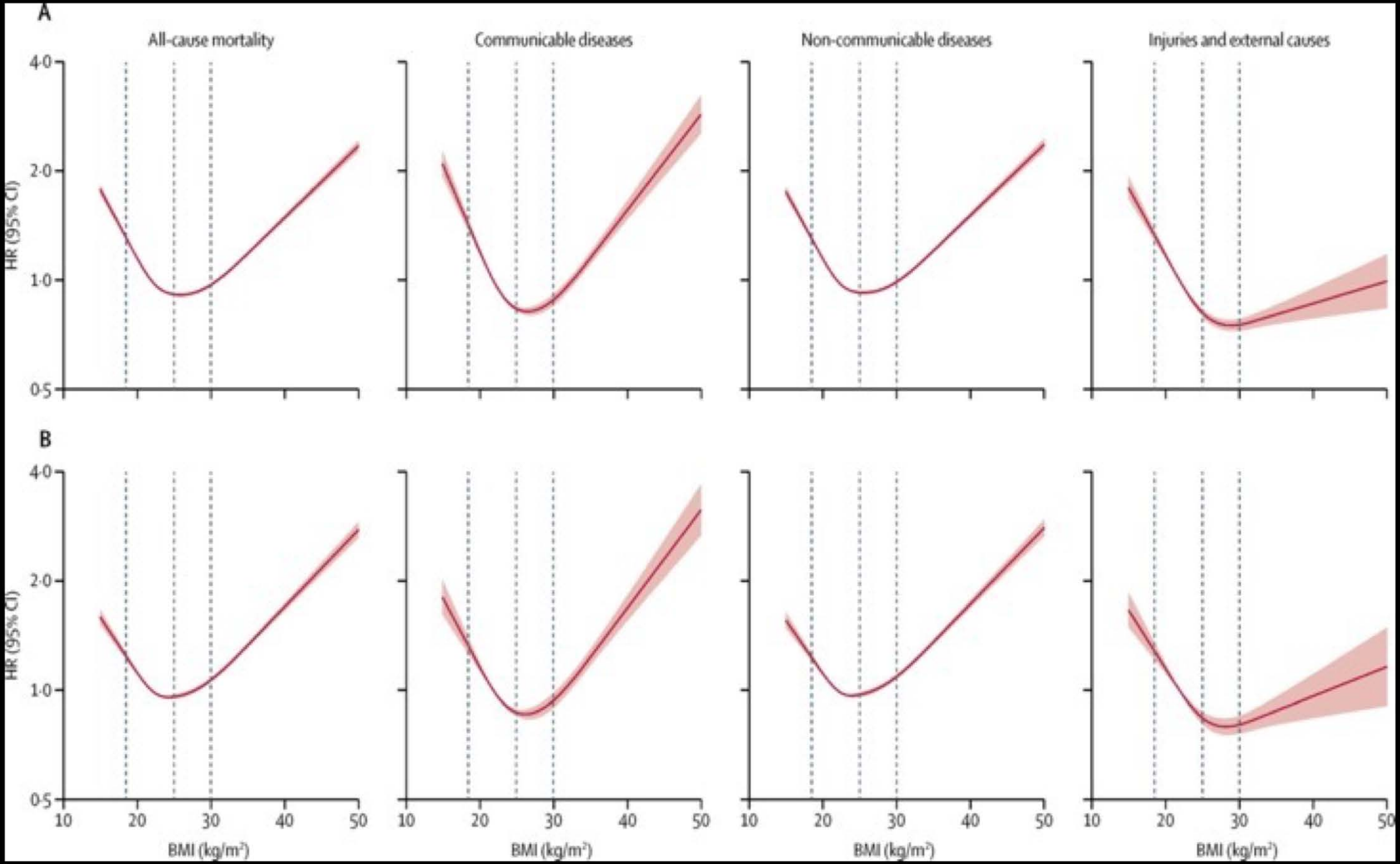
Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK

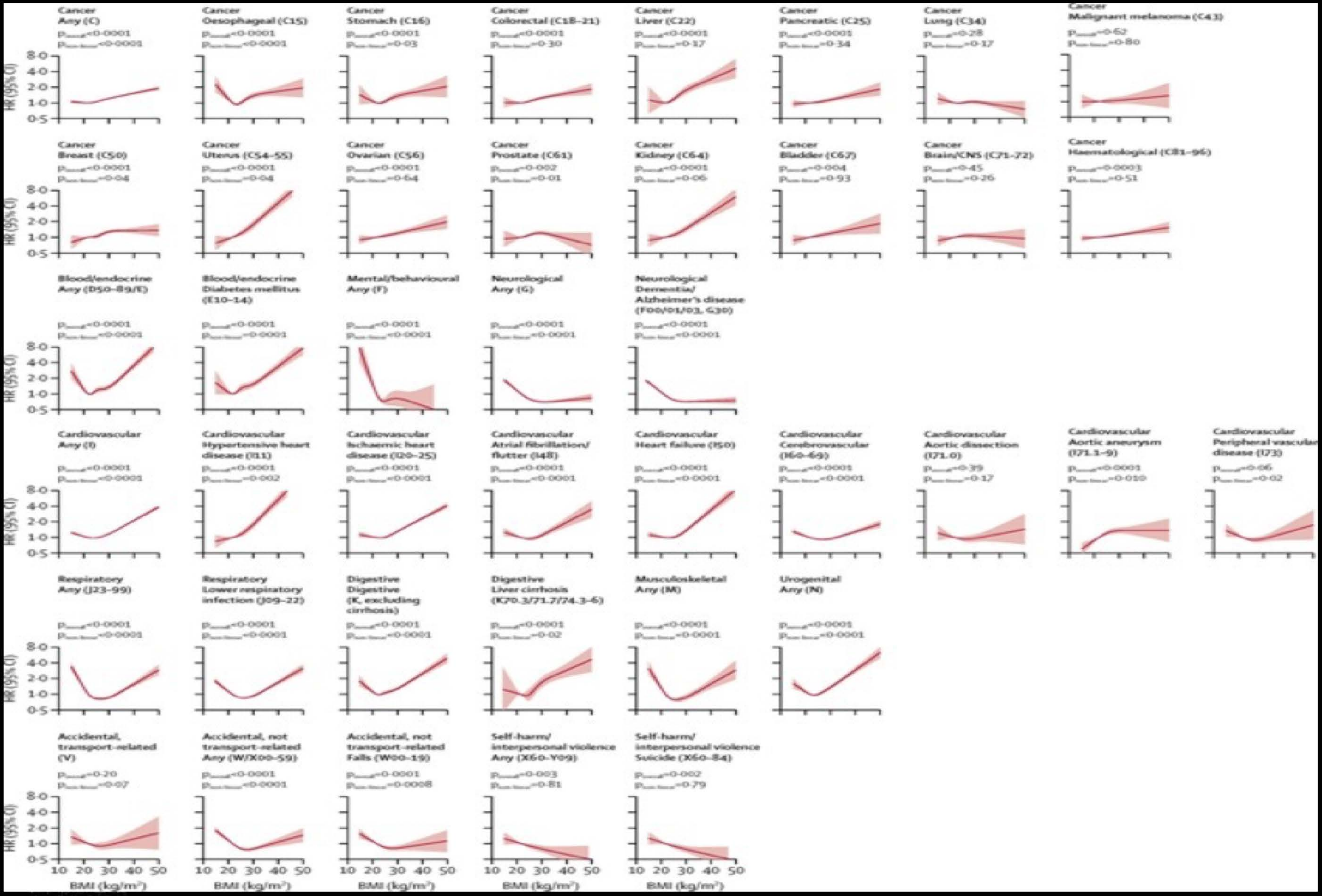
Krishnan Bhaskaran, PhD, Prof Isabel dos-Santos-Silva, PhD, Prof David A Leon, PhD, Ian J Douglas, PhD, Prof Liam Smeeth, PhD

The Lancet Diabetes & Endocrinology
Volume 6 Issue 12 Pages 944-953 (December 2018)
DOI: 10.1016/S2213-8587(18)30288-2



ELSEVIER

Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK



ELSEVIER

Komerčná determinácia (predčasných) úmrtí

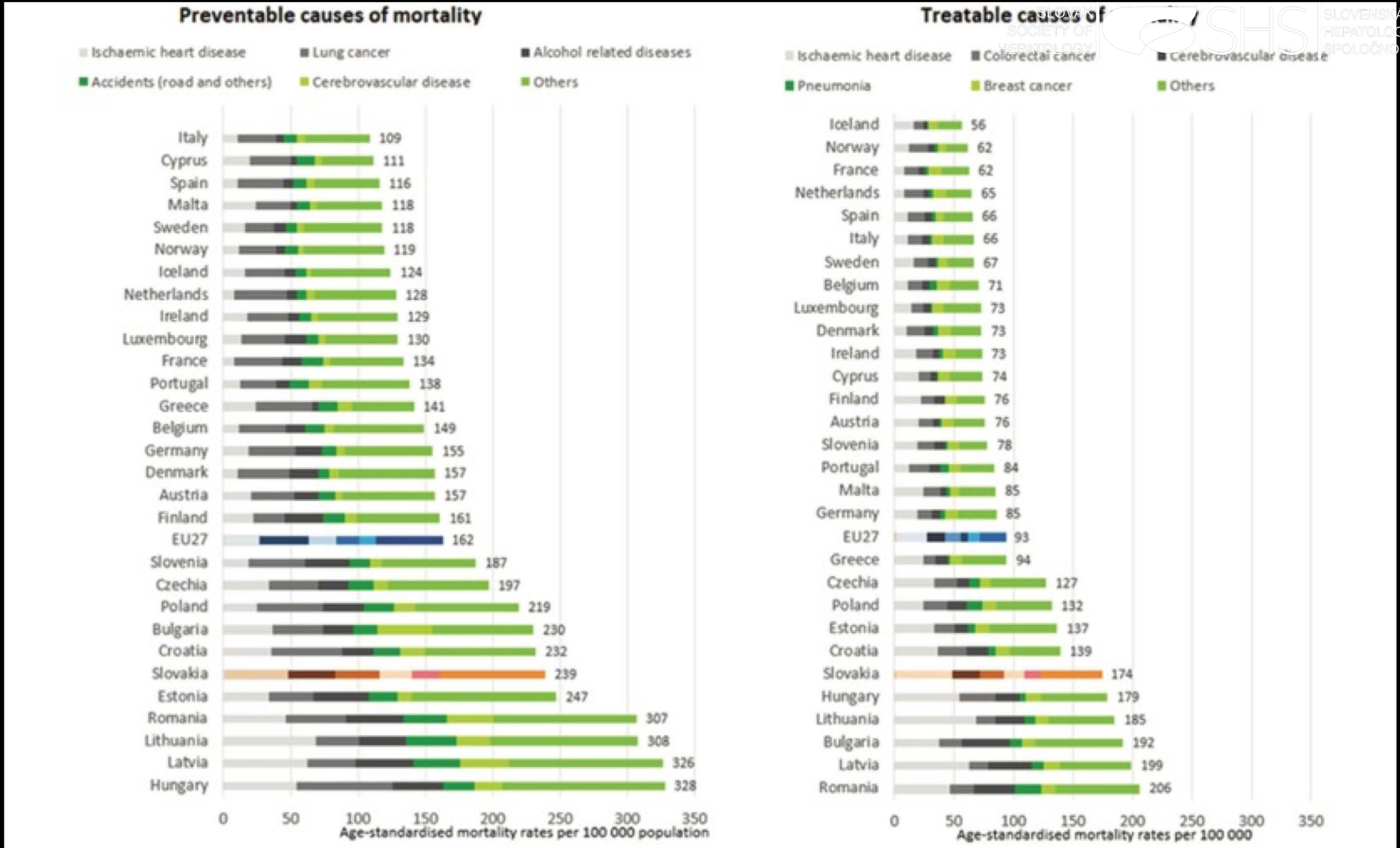
4 priemyselné odvetvia zodpovedné za minimálne 1/3 globál. úmrtí

každo_ročne ⚰️

- 🍔 **UPF/unhealthy food**
- 🍺 **EtOH**
- 🚬 fajčenie
- 🏭 fosílne palivá

Lancet 2023

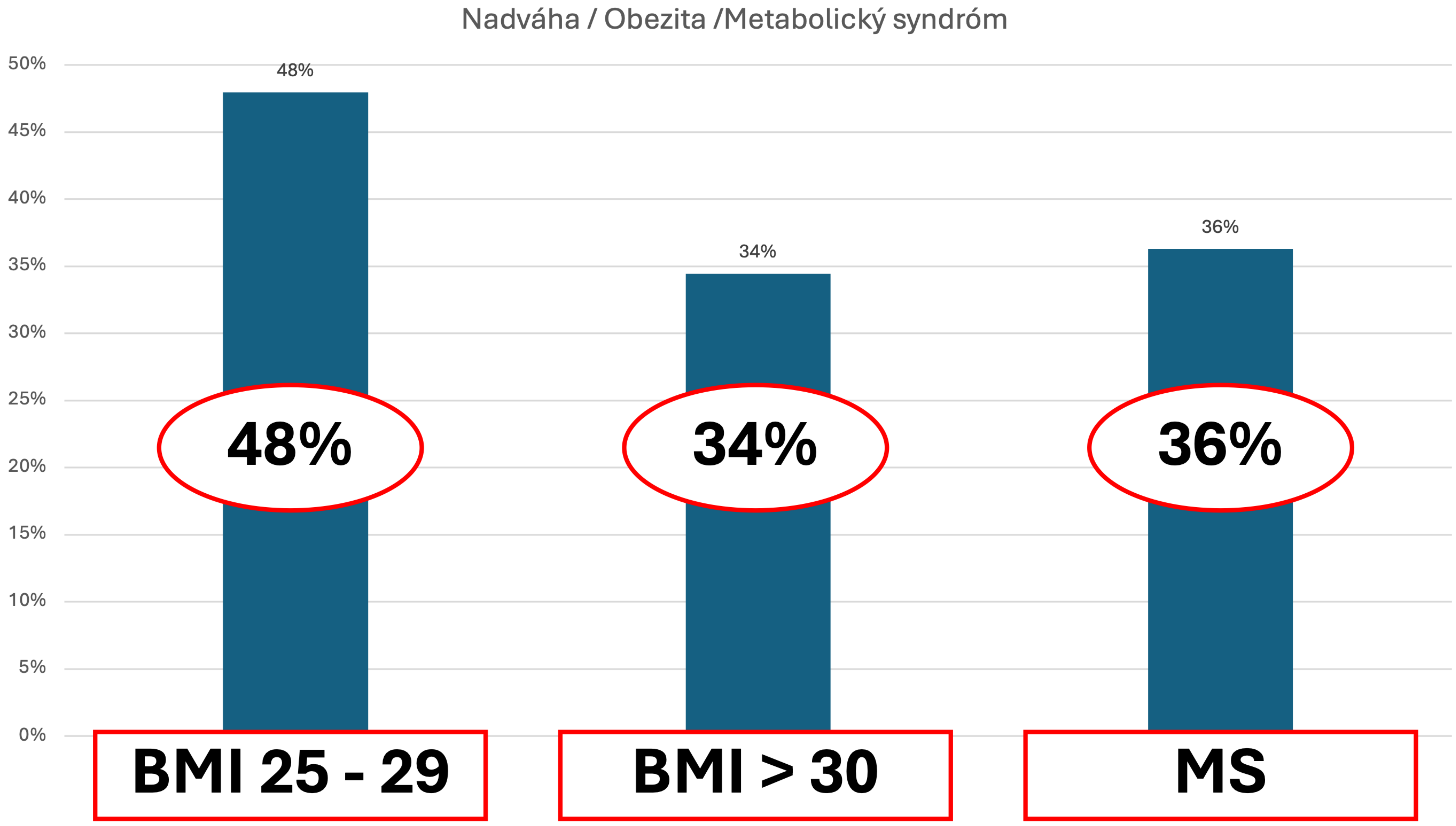
Foto:archív autora, zdroj internet



Note: Preventable mortality is defined as death that can be mainly avoided through public health and primary prevention interventions. Treatable mortality is defined as death that can be mainly avoided through health care interventions, including screening and treatment. Source: Eurostat database (data refer to 2017, except for France and the EU average 2016).

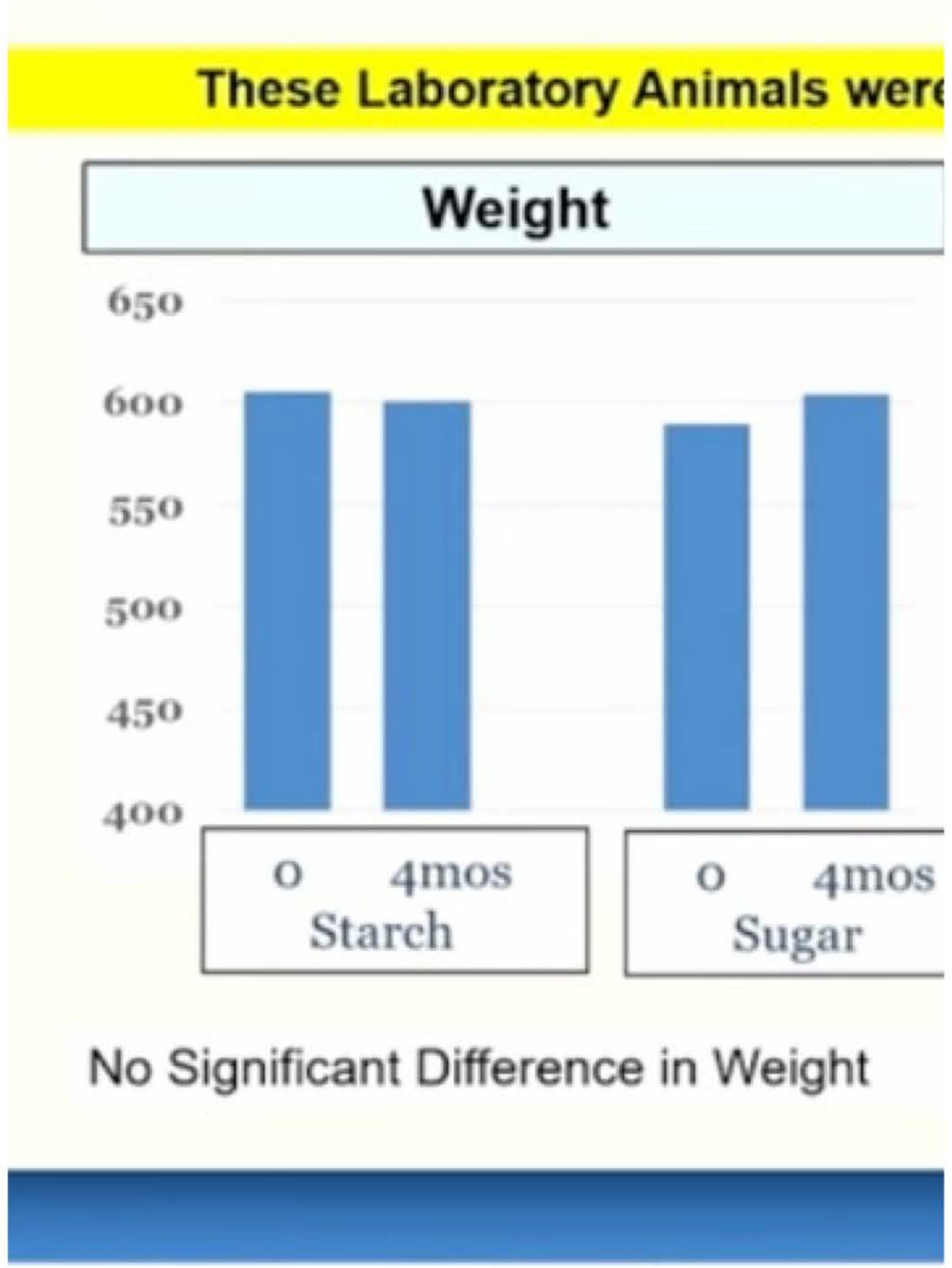
archív autora, Globsec, 2022

Komunitná vetva: nadváha / obezita / metabolický syndróm



MHD, EASLD 2025, kol sirius, vlastné dáta

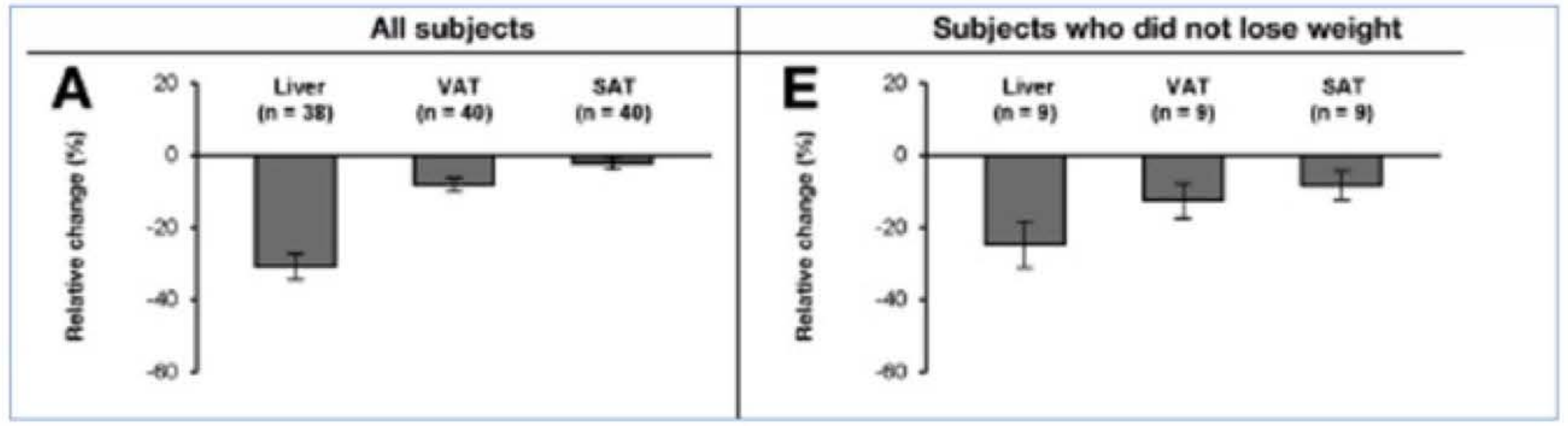
Obezitu robia kalórie, metabolickú dysfunkciu cukor



Effects of dietary fructose restriction on liver fat and De Novo lipogenesis in children with obesity

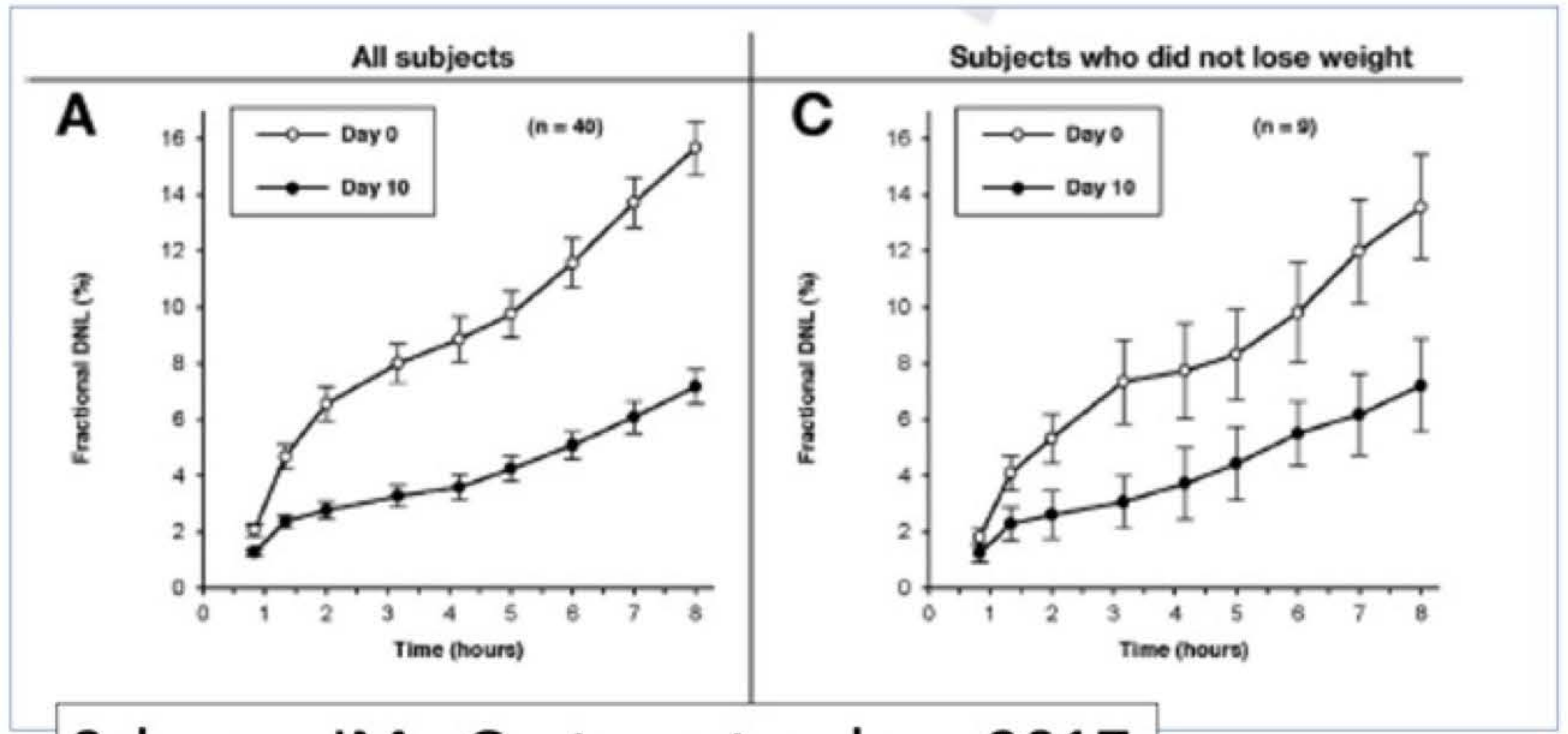
- 9 days isocaloric fructose restriction
- Obese children (n=41) with habitual high sugar consumption (fructose intake >50 g/d)

Changes in individual fat compartments



Short-term (9 days) isocaloric fructose restriction decreased liver fat, VAT, and DNL, and improved insulin kinetics in children with obesity.
These findings support efforts to reduce sugar consumption.

Changes in postprandial DNL



Schwarz JM., Gastroenterology 2017

Fyzio & Patofyziológia

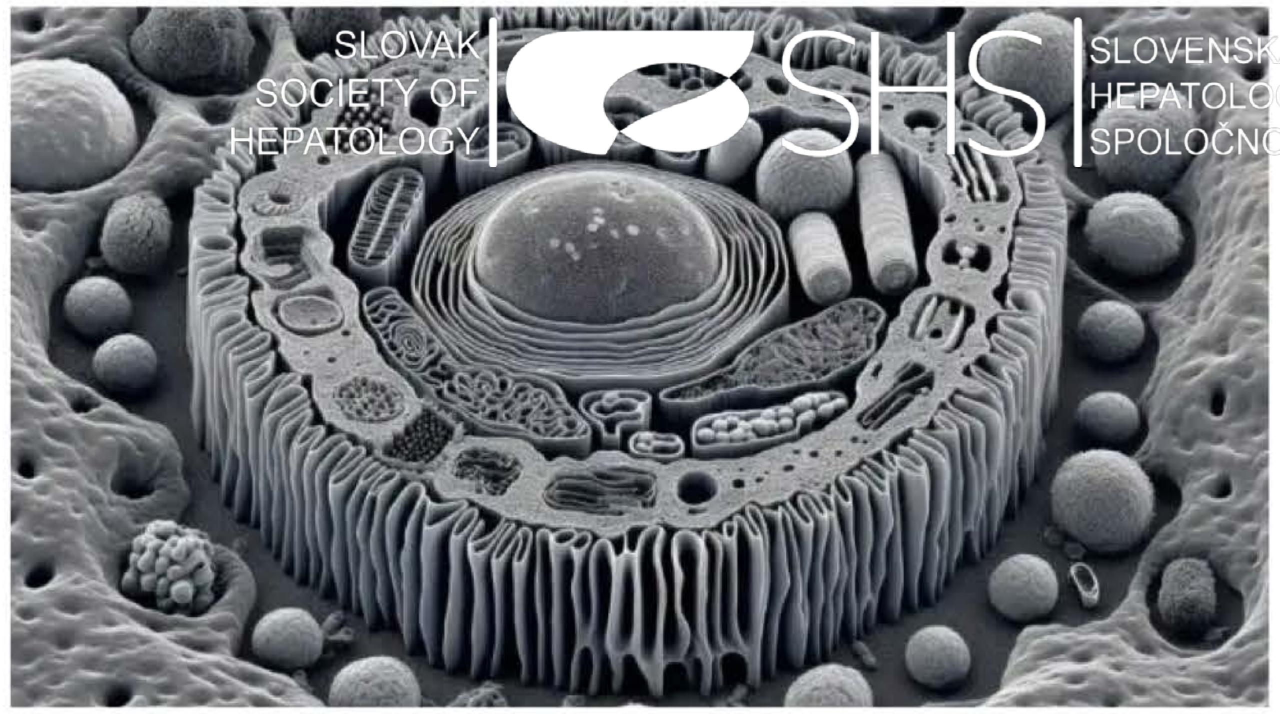


Foto:archív autora, zdroj internet

- **Metabolizmus**
  - **Glukóza** = zdroj ATP
  - Fruktóza

- **Inzulín** – rastový faktor = energy storage hormone
- **Metabolická dysfunkcia** = IR
- Inflamácia – chronická negatívna (stres, pro_zápal podnety, strava)

Metabolizmus

…ako z niečoho cudzieho z vonka urobiť telu vlastné

jedlo/potrava:

1. energia
2. rast (mozog, pečeň, kosti, svaly...tuk)

- energia/burning (determinuje mitochondria)
- rast (determinuje inzulín)

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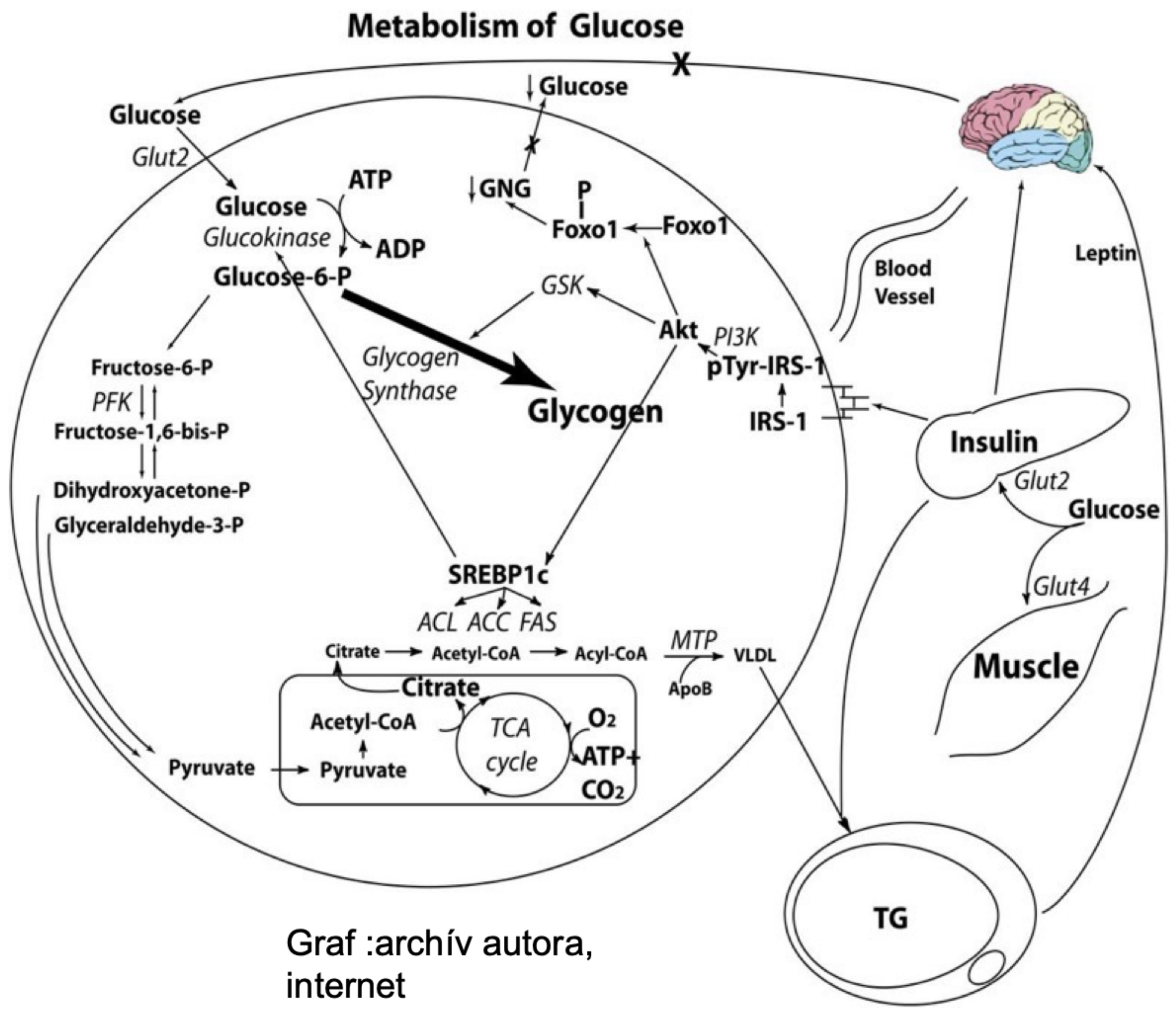
Glukóza

- **energia/vznik ATP**
- **rast/stavebné** časti (lipidy, riboza-DNA, proteíny...tkanivá, orgány)
  - 80 mg/per dcl, v 6l krvi cca 5g glukózy nalačno (malá lyžička), ak soda drink, džús tak 10 násobne viac
  - cieľ čo najnižšiu gl, za čo najnižšej hladiny INZ
    - gl nalačno reprezentuje produkciu v pečeni



Graf :archív autora, internet

Inzulín: rastový faktor = energy storage hormone

regulácia: burning or growth (kontrolný mechanizmus)

- fyziologický sy IR (deti, puberta, gravidita...)
  - hypergl – hyperinzulinémia – IR – obezita – DIA – KVCh – Ci – CKD – POSy... Ca
- INZ nezávislé tkanivá (CNS, ...), EXCES DO TUKU (more insulin = more fat)
- Sval
  - **good and bad, nikdy good or bad**

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Inzulín: rastový faktor = energy storage hormone

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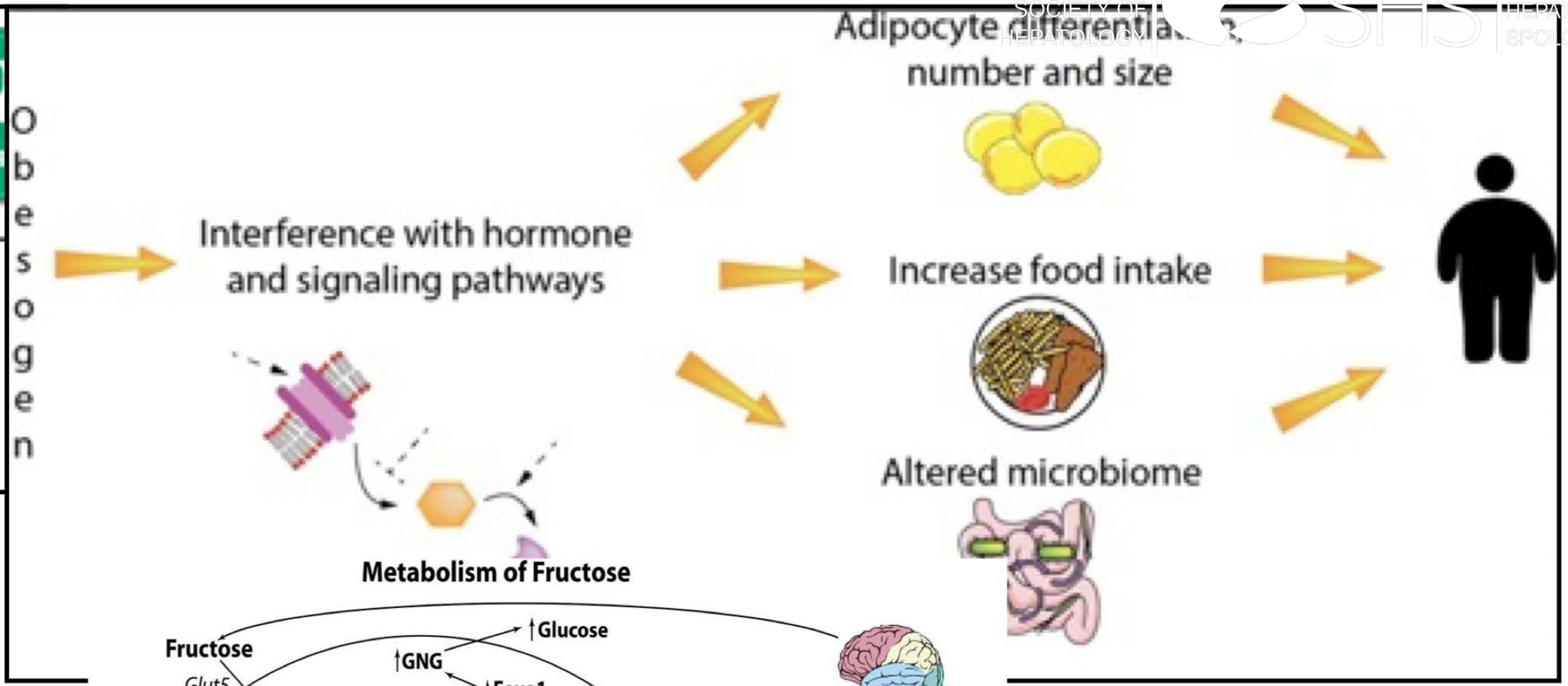
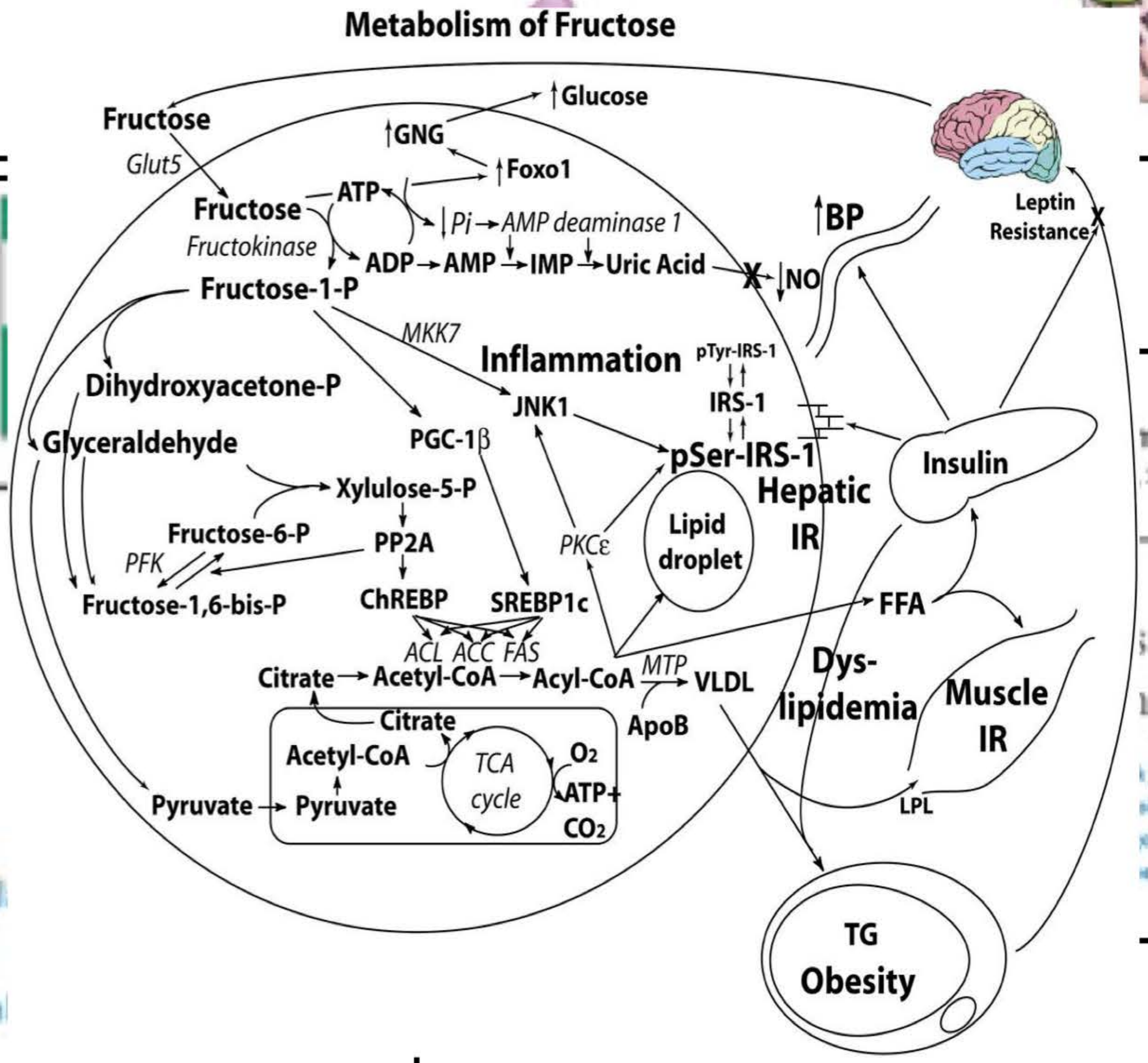
Biochemical Pharmacology
Volume 199, May 2022, 115015

Review

Obesity II: Establishing causal links between chemical exposures and obesity





Biochemical Pharmacology
Volume 199, May 2022, 115012

Review

Obesity I: Overview and molecular and biochemical mechanisms

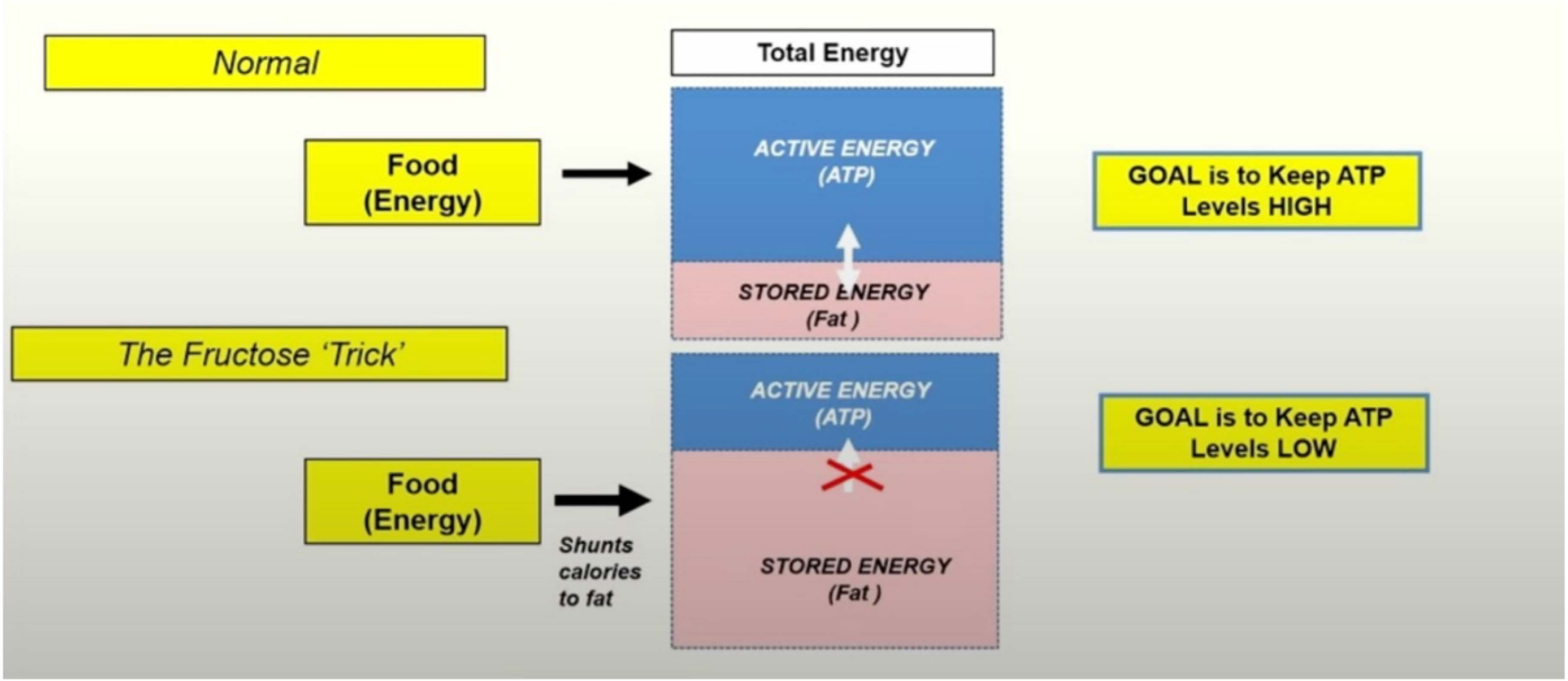
Robert H. Lustig [a], David Collier [b], Christopher Kassotis [c], Troy A. Roepke [d], Min Ji Kim [e], Etienne Bl… , Robert Barouki [f], Amita Bansal [g], Matthew C. Cave [h], Saurabh Chatterjee [i], Mahua Choudhury [j], Michael Gilbertson [k], Dominique Lagadic-Gossmann [l], Sarah Howard [m], Lars Lind [n], Craig R. Tom… , Jan Vondracek [p], Jerrold J. Heindel [m]

…nacology
115014

…: Limitations, …s

…J. Babin [c], Dominique Lagadic-Gossmann [d] …ine Legrand [e], Vesna Munic Kos [f] …ouët [d], Charbel Touma [e], Robert Barouki [g] …e [i], Amita Bansal [h], Sarah Howard [i] …

obrázok: archív autora
Biochem pharm 2022



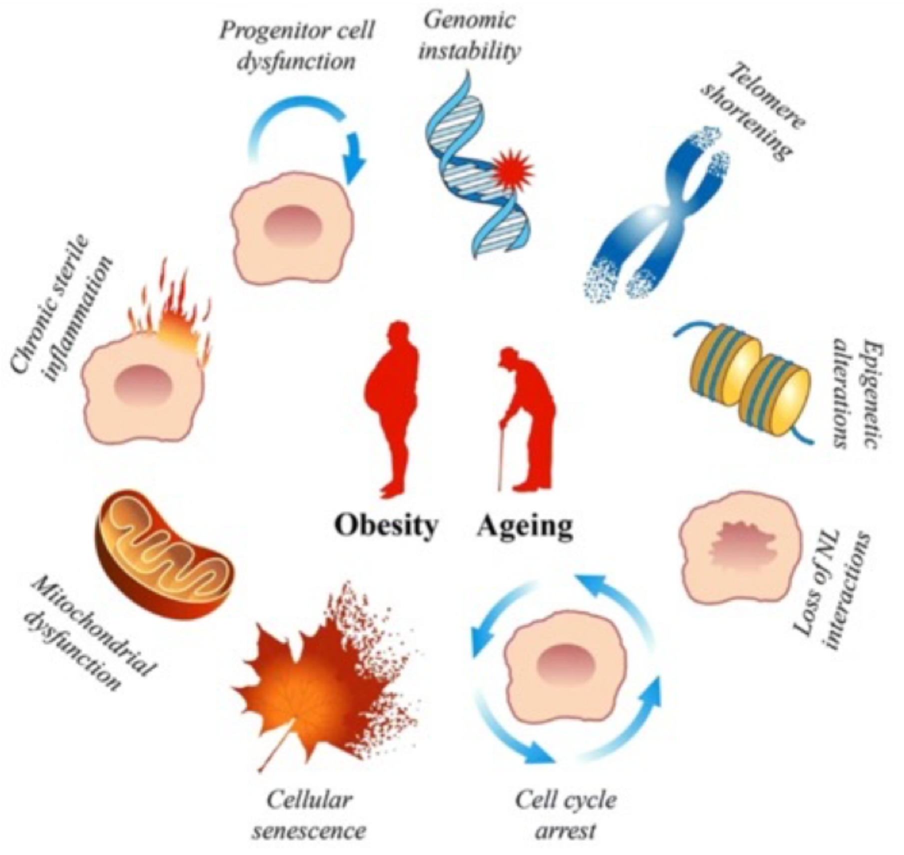
Johnson RJ et al. Adv Nutr. 2017

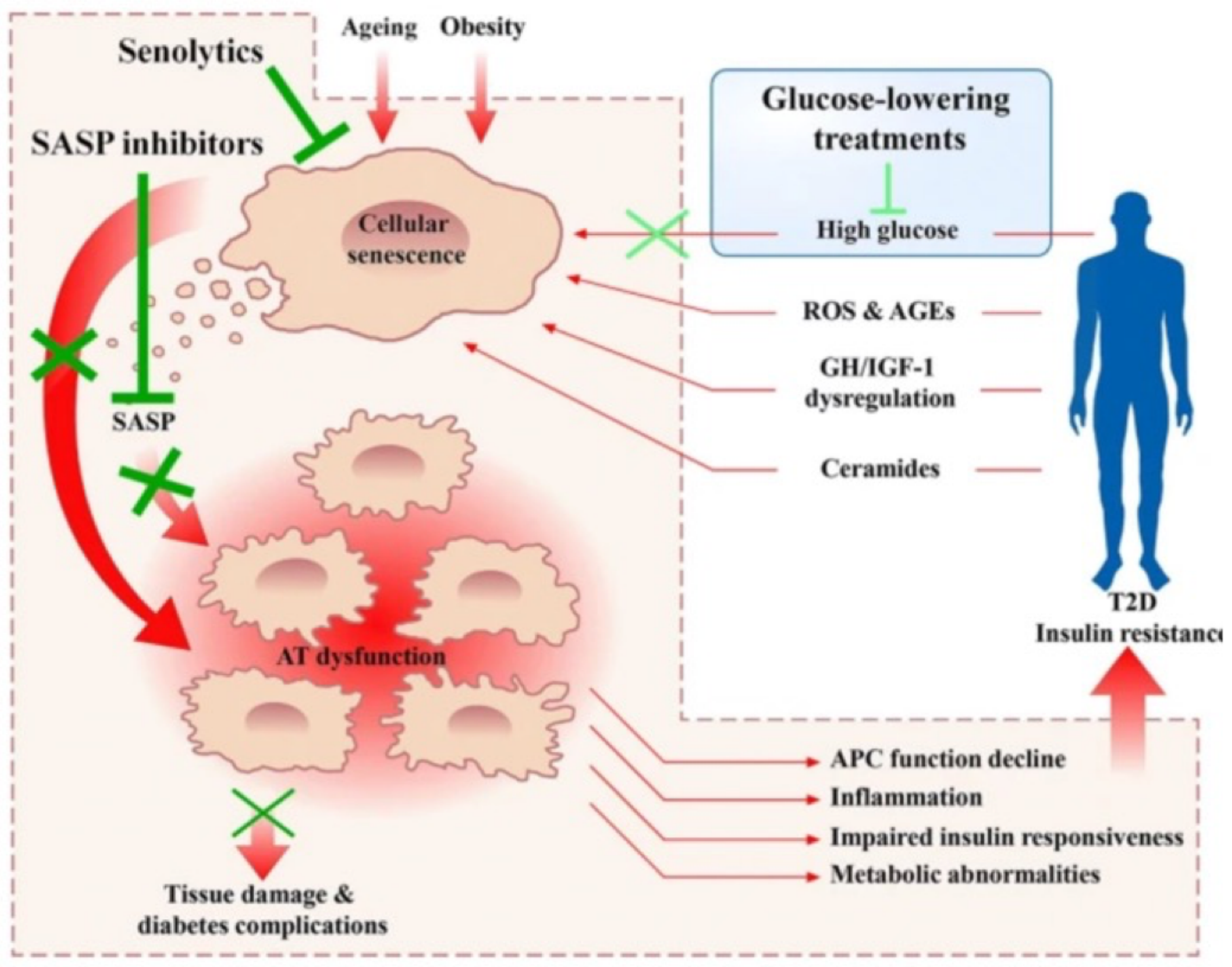
Inflamácia

inflamácia: cytokíny, REDOX, stres, aging, stres, hormóny(kortizol), predčasná smrť

- reakcia na obranu pred inváziou (enviroment, strava, toxické produkty...)
- LPS, PAMPS, DAMPS
- ...aging, civilizačné choroby

- **črevo** (bariéra proti zápalu)
  - **mikrobióm, vláknina**...
- **naša strava pro_zápalová**



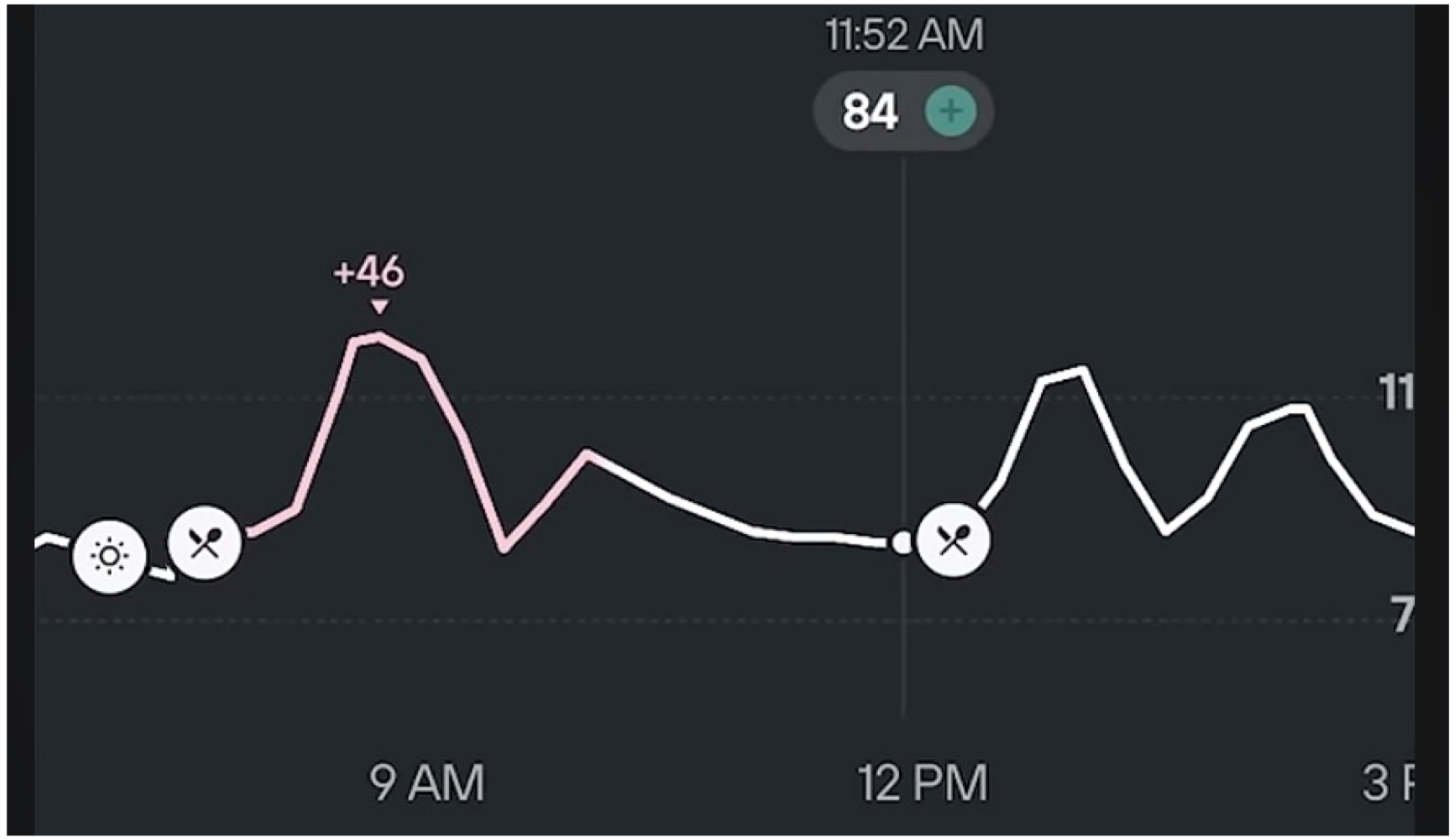


Spinelli, R., Parrillo, L., Longo, M. et al. Molecular basis of ageing in chronic metabolic diseases. J Endocrinol Invest 43, 1373–1389 (2020)

clearence glukózy a ***IR***

metabolická dysfunkcia/IR

- mnoho faktorov, vek, stres, fajčenie, genetika...VOmax, fitness
  - peak –amplitúda
  - plateau
- surrogate CGM



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Seminar

JOURNAL OF HEPATOLOGY

Global burden of liver disease: 2023 update

Harshad Devarbhavi[1], Sumeet K. Asrani[2,*], Juan Pablo Arab[3,4], Yvonne Ayerki Nartey[5], Elisa Pose[6], Patrick S. Kamath[7]

Epidemiolǵia a bremeno pečeňových chorôb

2 million deaths worldwide

1 out of 3 liver deaths among females

11th leading cause of death worldwide

15th leading cause of disability-associated life-years

Cost of liver disease in the United States (2016): $32.5 billion

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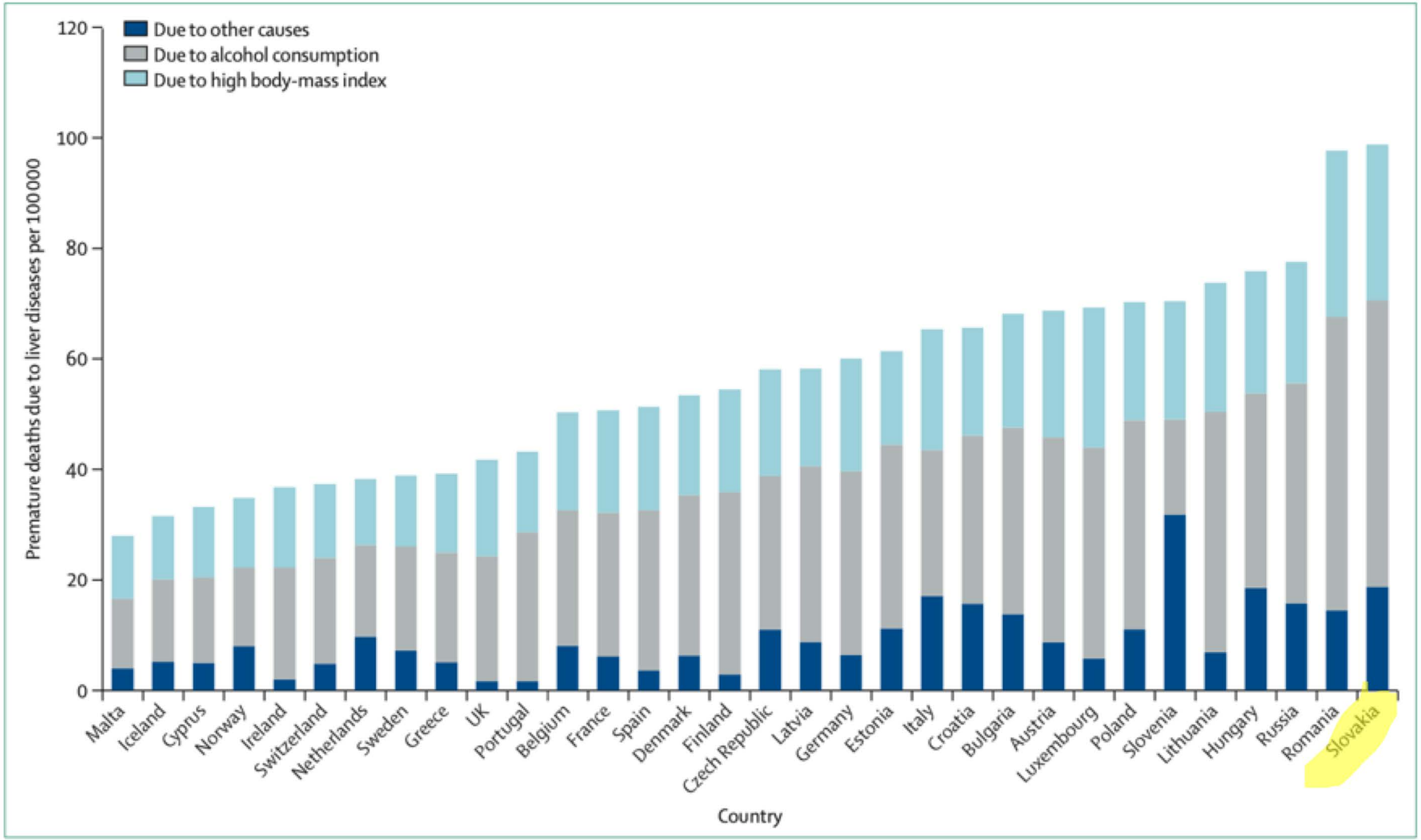
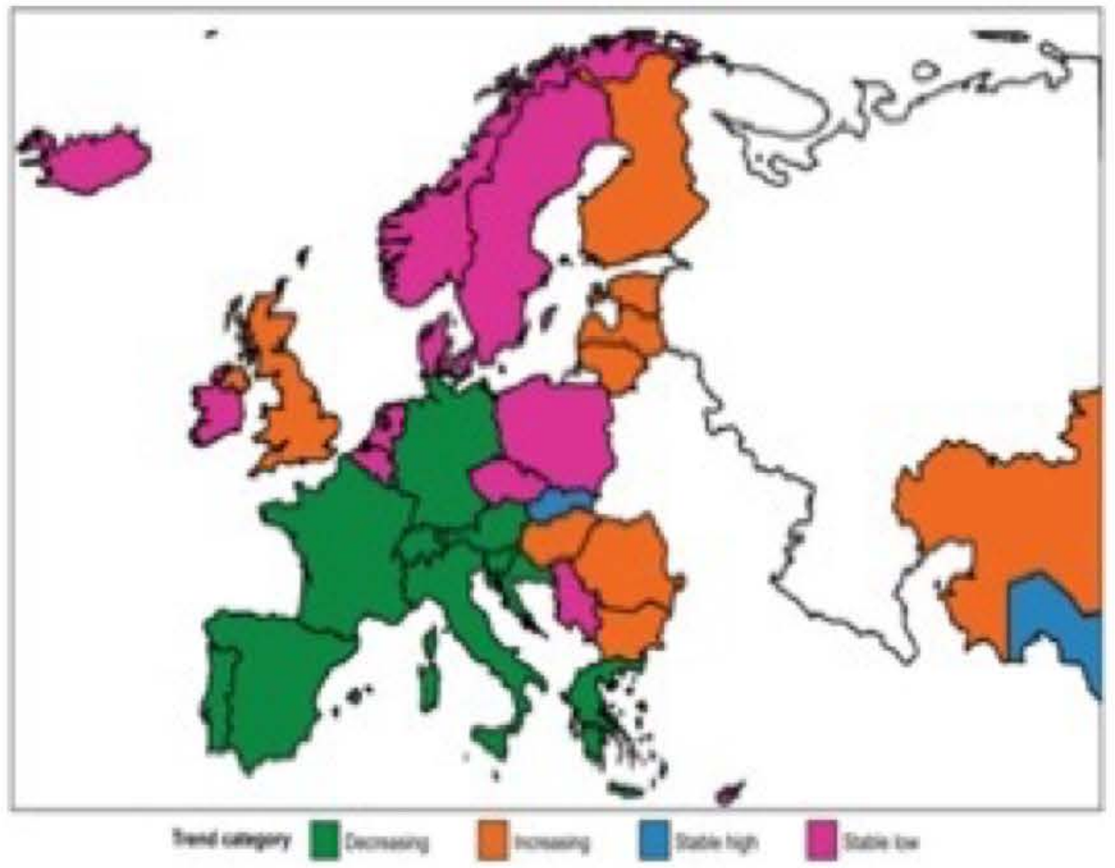
Premature deaths due to liver diseases (OECD)





Hepatology 2021

Obezita a MASLD

patofyziológia v kontexte metabolickej dysfunkcie

Genetické faktory (epigenetika) + **Enviroment**/UPF-zápal + **Psychol**ogické faktory/Stres/Spánok + CNS, hormonálne a metabolické faktory

↓

Dlhodobá **energetická nerovnováha** (príjem > výdaj) + obesogenes/ED

↓

Hypertrofia a hyperplázia adipocytov (SCFT a ektopic VAT)

↓

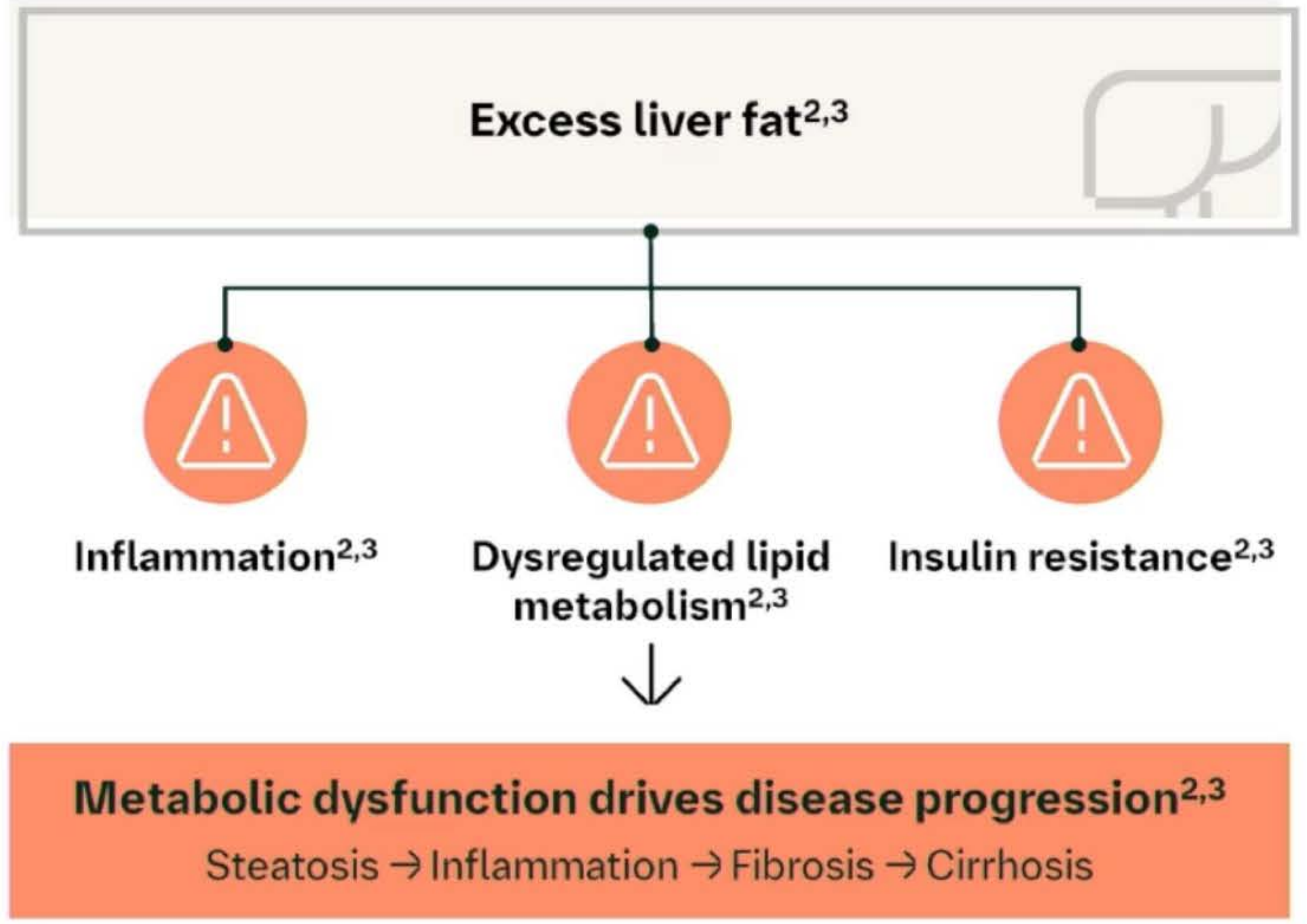
Chronický zápal ❤️‍🔥 ⇄ inzulínová rezistencia

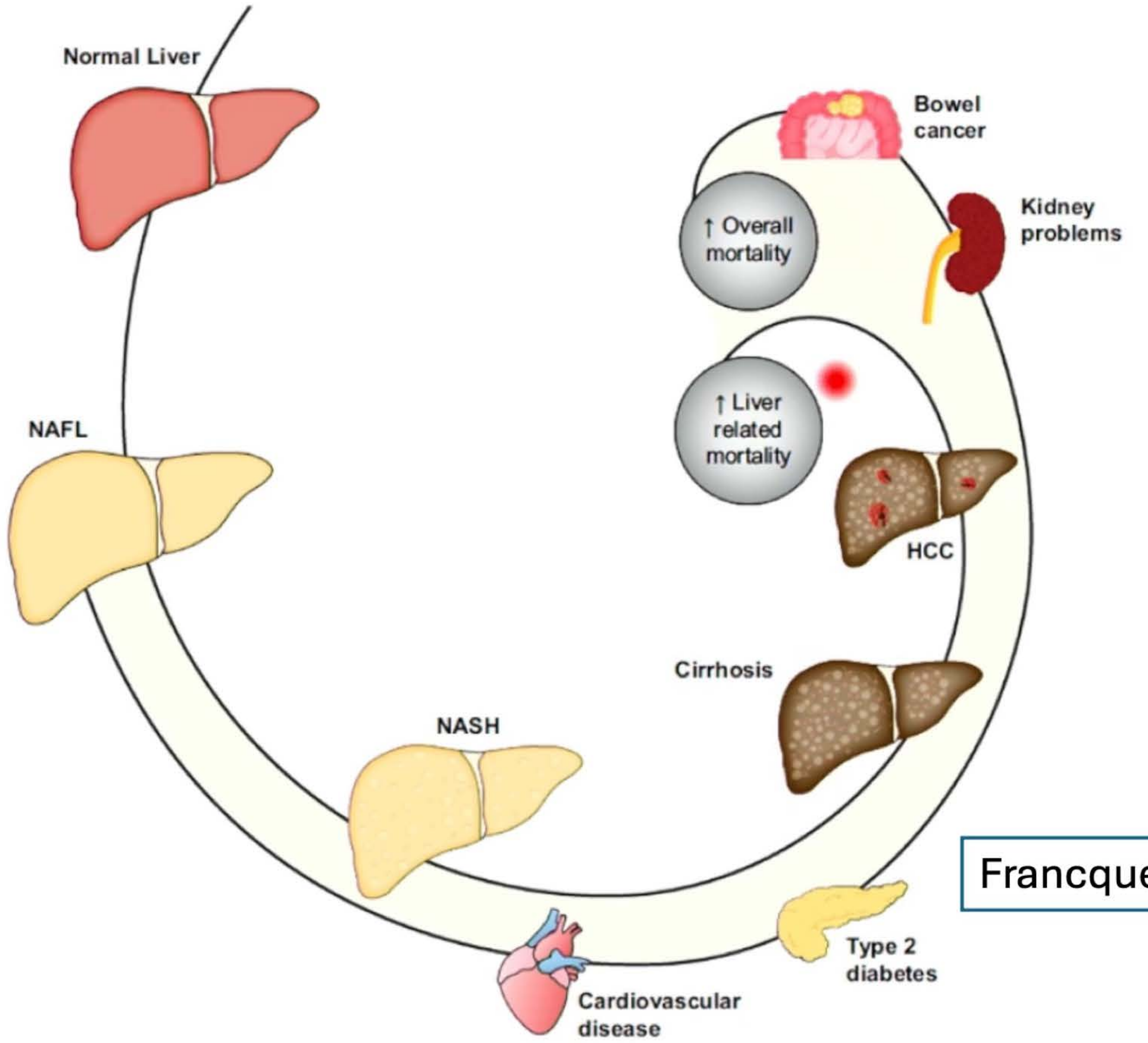
↓

Progresia obezity/metabolickej dysfunkcie → Metabolické/zdravotné komplikácie
CAREMELO

Koncept a súvislosti

- multifaktoriálne súvislosti (genet, enviro...)
- prečo liečiť MASLD/MASH
  - HCC
  - Tx
- CA-RE-ME-LO





Francque et al J Hep Rep 2021

uri N & Noureddin M. Am J Manag Care 2024;30:S159–S174; 2. Luo Y & Lin H. Immun Inflamm Dis 2021;9:59–73; 3. Qureshi K & Abrams GA. World J Gastroenterol 2007;13:3540–3553.

Socio-ekonomická determinácia a vplyv na zdravie

(medzigeneračný presun)

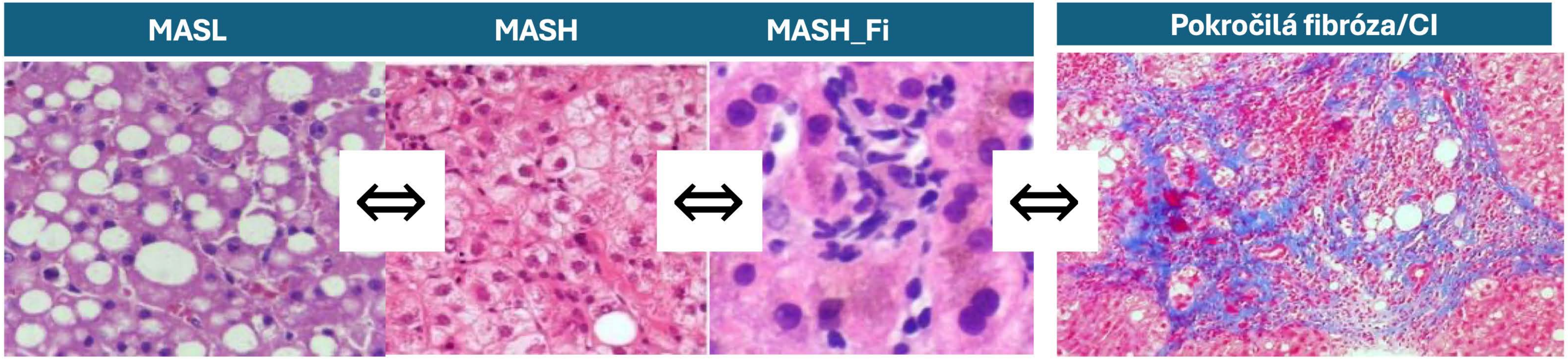
Ekonomické faktory

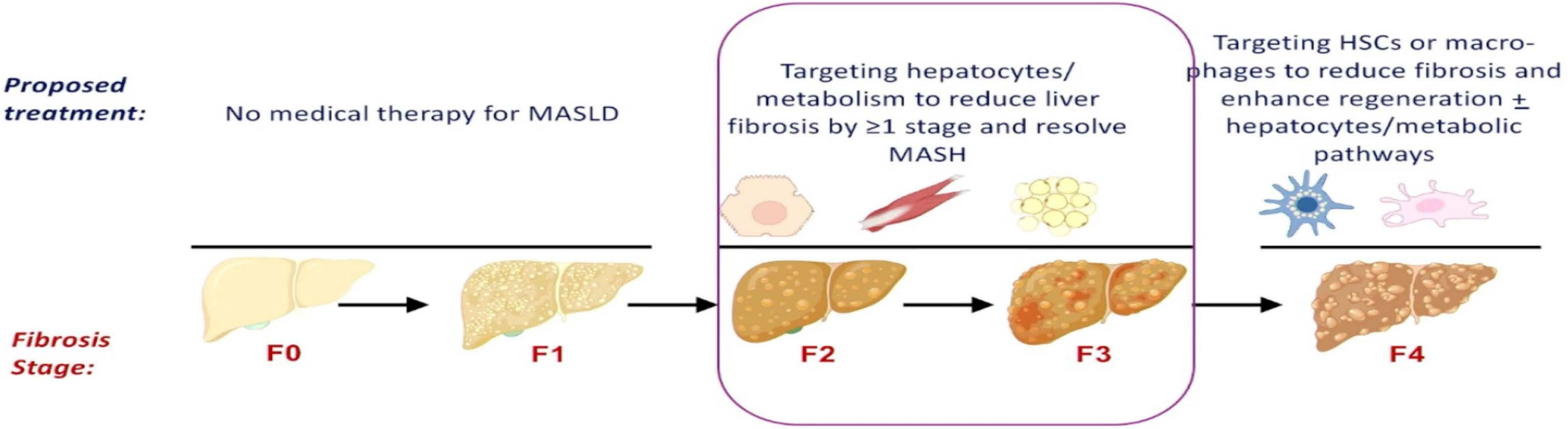
- ekonomická núdza najsilnejší prediktor obezity (Hardy et al, 2017)
- EN asoc. s obezogénnym envirometom (Verde et al, 2024)
- EN asoc. s nedostupnosťou enviromentu podporujúceho fyzickú aktivitu (Bantham, 2021)
- EN asoc. s kaloricky denznou potravou – UPF (van Erpecum, 2022)
- EN asoc. s nedostatkom zdravotníckej služby (Paulet al, 2016)
- EN kontra iné priority (deti, práca, účty)

Sociálne f.

- maltreatment v detstve (Offer et al, 2022)
- dysfunkčná rodina (Hemmingsson, 2018()
- nižšie vzdelanie (Devaux, 2011)
- bullying v detstve (Cheng et al, 2022)
- chronický stres (Kummar et al, 2023)
- stigma (Lawrence, 2021, ...)

Patofyziologické súvislosti





Schwabe et al. Antifibrotic Therapies for Metabolic Dysfunction-associated Steatotic Liver Disease
J Hep Reports 2025

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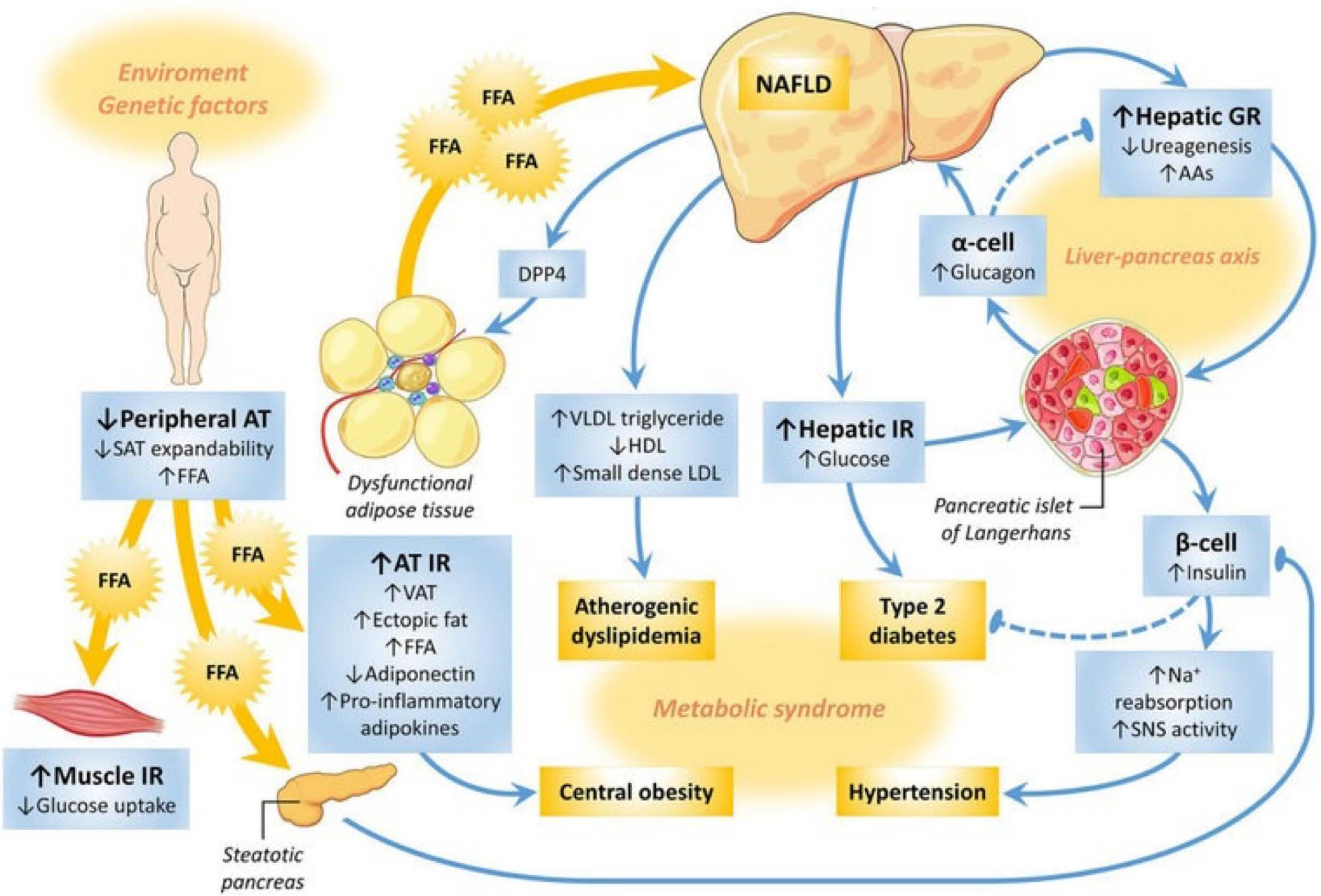
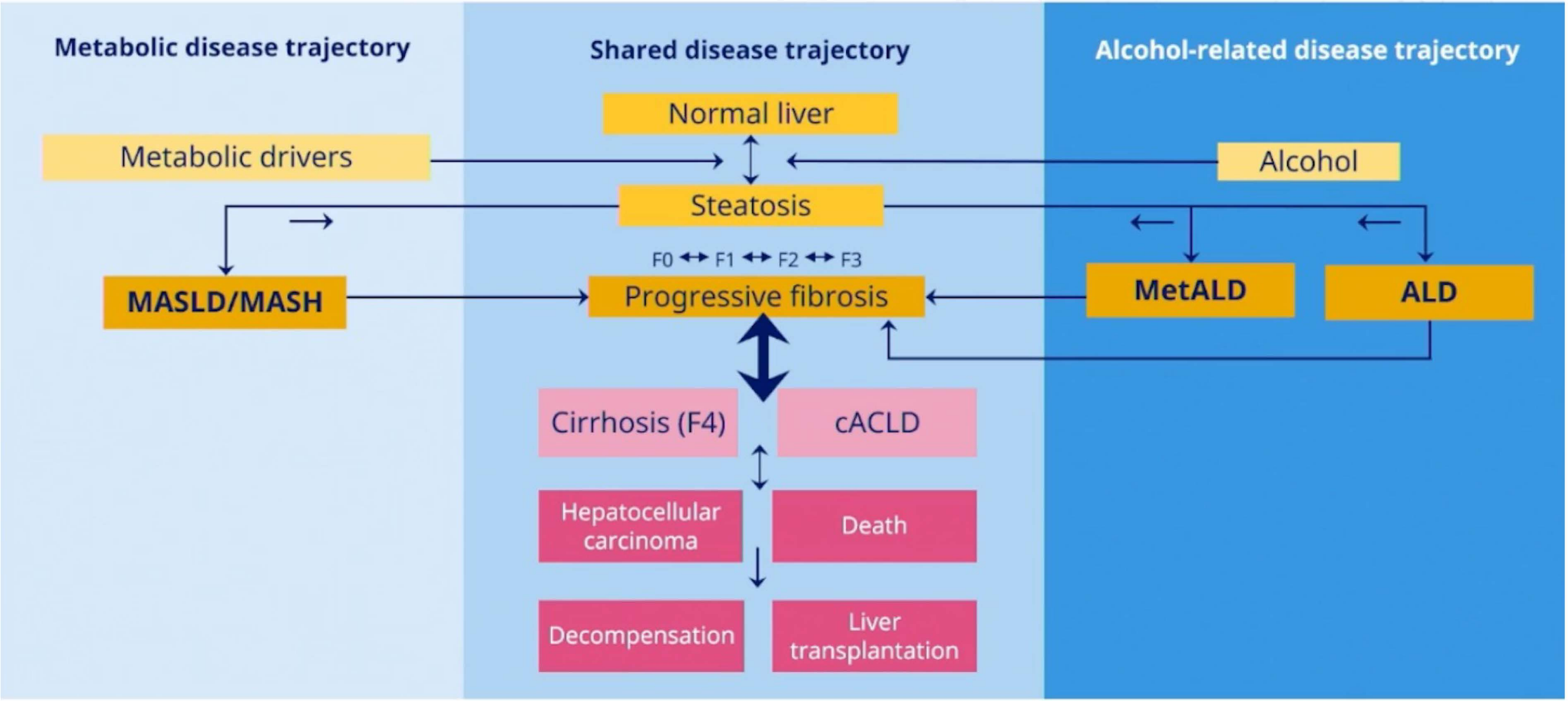
Obezita a MASLD (vzťahy a súvislosti)

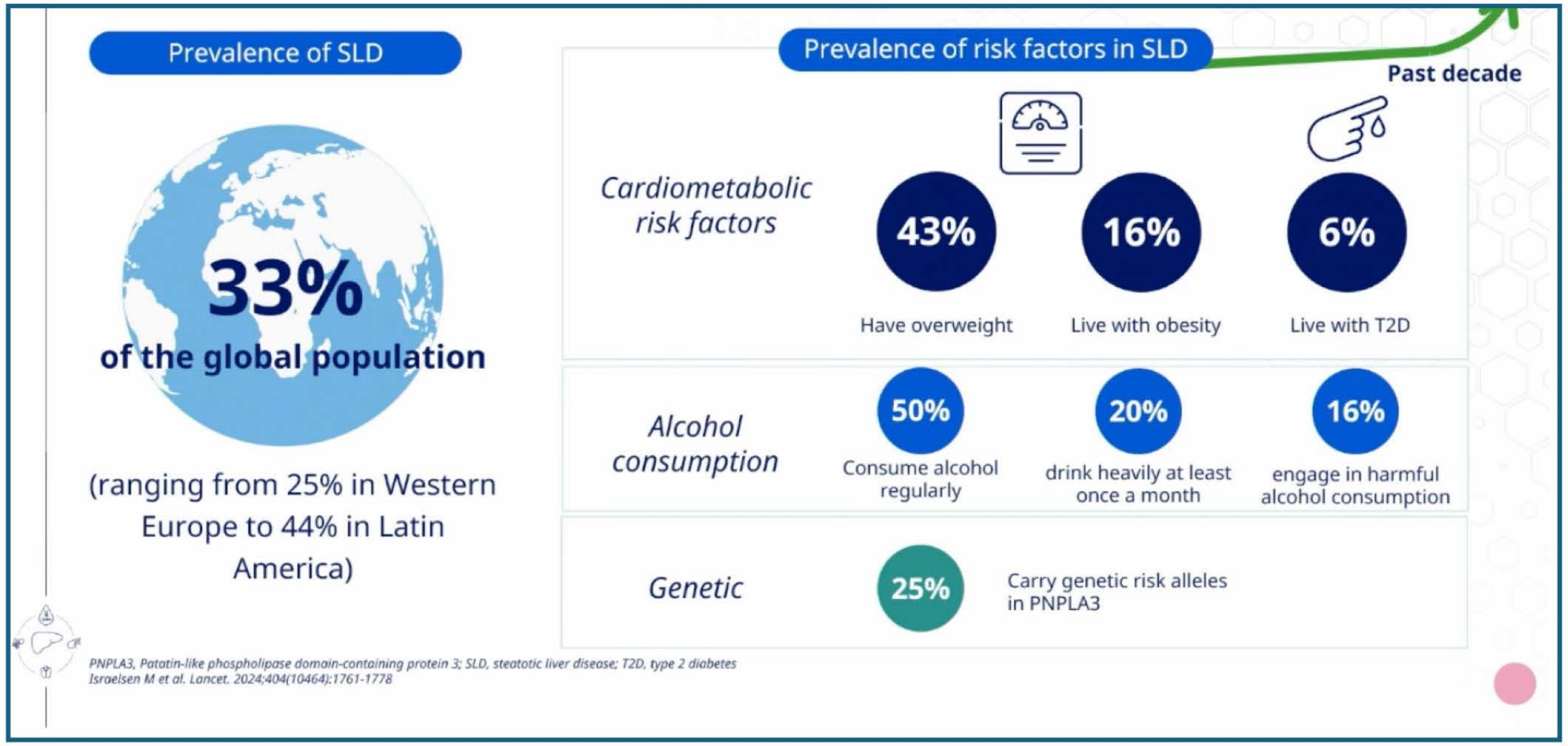


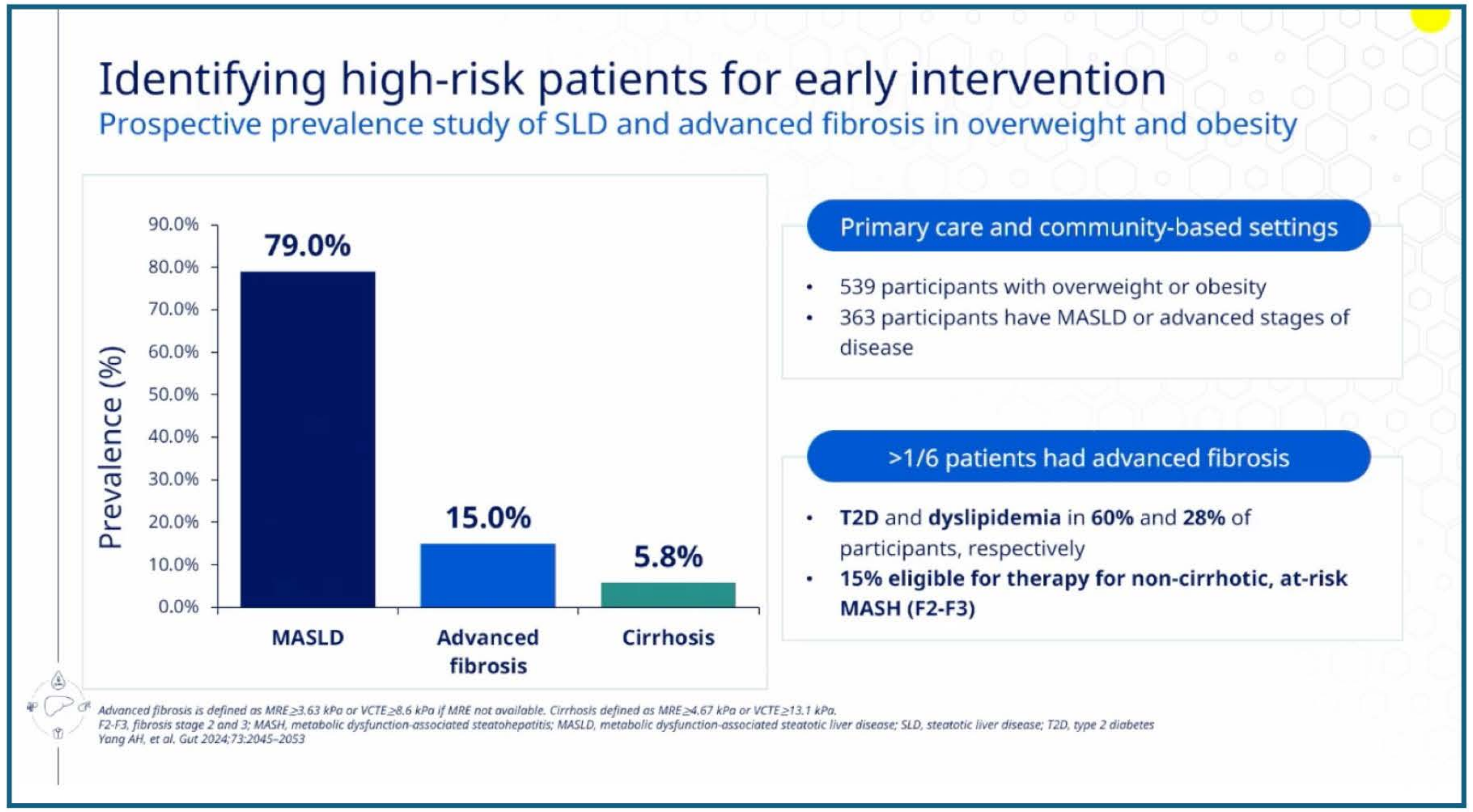
Gater et al, Rehabilitation, 2021

Etiopatogenéza, priebeh choroby



Epidemiológia MASLD, prevalencia a OBE/DIA





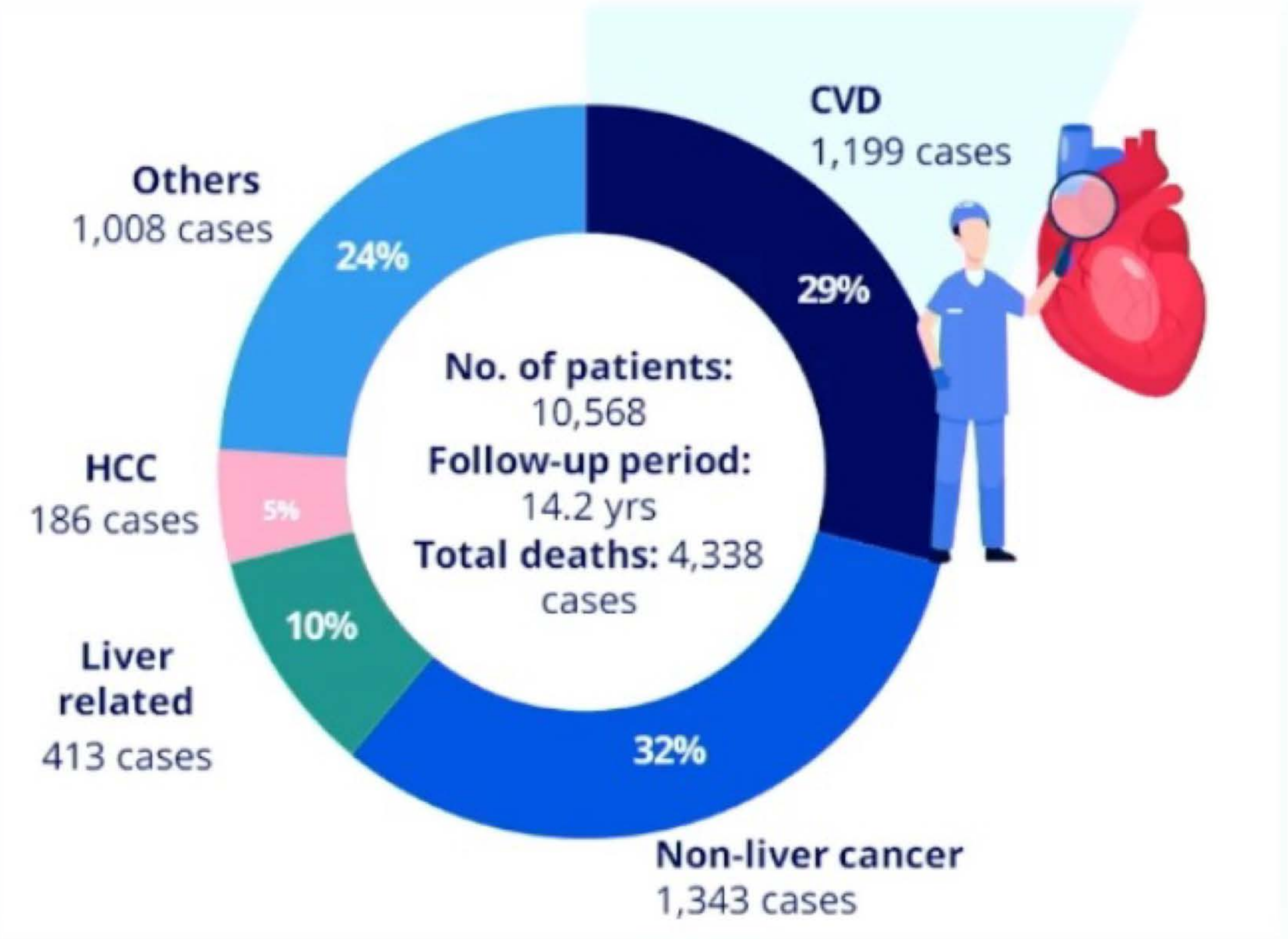
The Case for Metabolic Targeting

Causes of death in MASH

619 patients with
bx-confirmed MASLD 1975-2005
US, Europe & Thailand
12.6 years f/u (range 0.3-35.1)

Outcome	Number
Death or OLT	(n = 193)
Cardiovascular disease	74 (38.3%)
Nonliver cancer	36 (18.7%)
Cirrhosis complications	15 (7.8%)
HCC	2 (1%)
Liver transplantation	1 (0.5%)
Infections	15 (7.8)

CVD accounts for 29% of the mortality in people with MASLD[1]



10-25%
CVD

7-20%
MI

12-30%
Ischaemic stroke

14-61%
All-cause death

Angulo et al, Gastro 2015; Simon TG et al, Gut 2021; Kim K-S et al, BMJ 2024

Nomenklatúra a diagnostika MASLD 2023

Steatotická choroba pečene = Steatotic liver disease

- **Steatotická choroba pečene asociovaná s metabolickou dysfunkciou – (MASLD)**
  - Steatóza pečene asociovaná s metabolickou dysfunkciou **(MASL)**
  - Steatohepatitída asociovaná s metabolickou dysfunkciou **(MASH)**
- MASLD so zvýšenou konzumáciou alkoholu MetALD
  - Prevaha MASLD
  - Prevaha ALD

M	30	40	50	60 g/deň
Ž	20	30	40	50 g/deň

- Alkoholová choroba pečene (ALD)
  - >50/60 g/d
  - 350/420 g/t
- Špeficiká etiológia
  - Lieková steatóza pečene (DILI)
  - Monogénové Choroby**
  - Rôzne iné príčiny***
- Kryptogénna

**Deficit lyzozomálnej kyslej lipázy, hypobetalipoproteinémia, Wilsonová choroba, vrodé chyby metabolizmu
***HCV, malnutrícia, celiakia, HIV, ...

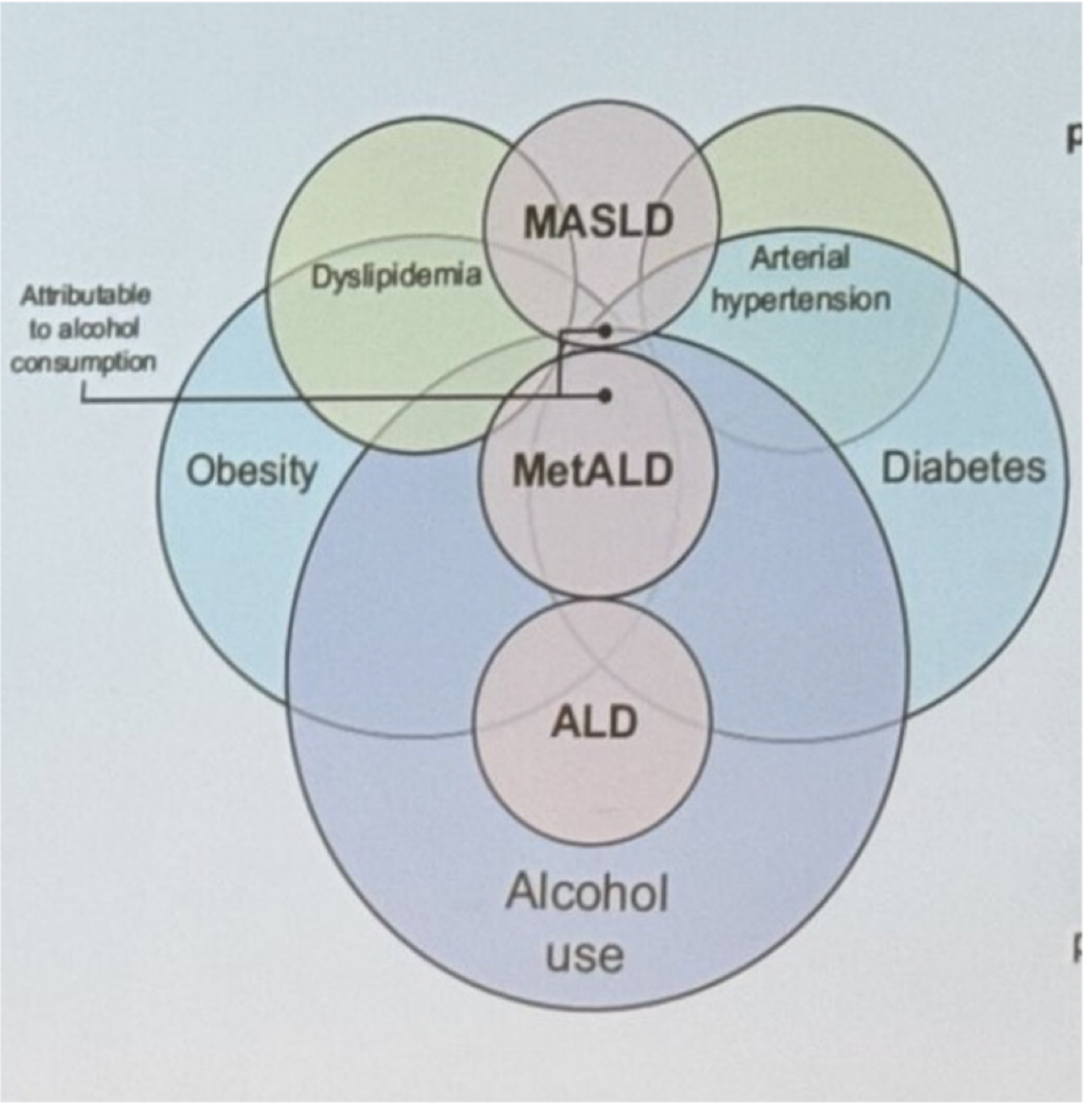
Diagnostický algoritmus steatotickej choroby pečene

Steatotická choroba pečene
Steatóza pečene podľa zobrazovacích vyšetrení alebo biopsie

↓

Aspoň 1 z 5 kardiometabolických kritérií *

- Áno → **Iná príčina steatózy?**
  - Nie → Steatotická choroba asociovaná s metabolickou dysfunkciou (MASLD)
  - Áno → MetALD alebo iné kombinované etiológie steatózy
- Nie → **Iná príčina steatózy?**
  - Nie → Kryptogénna steatotická choroba pečene
  - Áno → Iná špecifická etiológia*** Alkoholová choroba pečene, lieková, genetická** ....



* Kardiometabolické kritériá

1. BMI ≥25, alebo obvod pása M>94, Ž>80 cm
2. Glukóza nalačno ≥ 5,6 mmol/l, alebo ≥ 7,8 2 hod po záťaži glukózou, alebo HBA1C ≥ 5,7%, alebo DM2 typu, alebo liečba DM2 typu
3. Tlak krvi ≥ 130/85, alebo antihypertenzívna liečba
4. Triacylglyceroly ≥ 1.7 mmol/l, alebo hypolipidemická liečba
5. HDL-cholesterol M ≤ 1.0, Ž ≤1.3 mmol/l, alebo hypolipidemická liečba

**Deficit lyzozomálnej kyslej lipázy, hypobetalipoproteinémia, Wilsonová choroba, vrodé chyby metabolizmu
***HCV, malnutrícia, celiakia, HIV, ...

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Gastroent Hepatol 2025; 79(2): 102–105. doi: 10.48095/ccgh2025102.

Štandardný postup pre skríning chorôb pečene na Slovensku – Spoločné odporúčania Slovenskej hepatologickej spoločnosti (SHS) a Slovenskej spoločnosti všeobecného praktického lekárstva (SSVPL)

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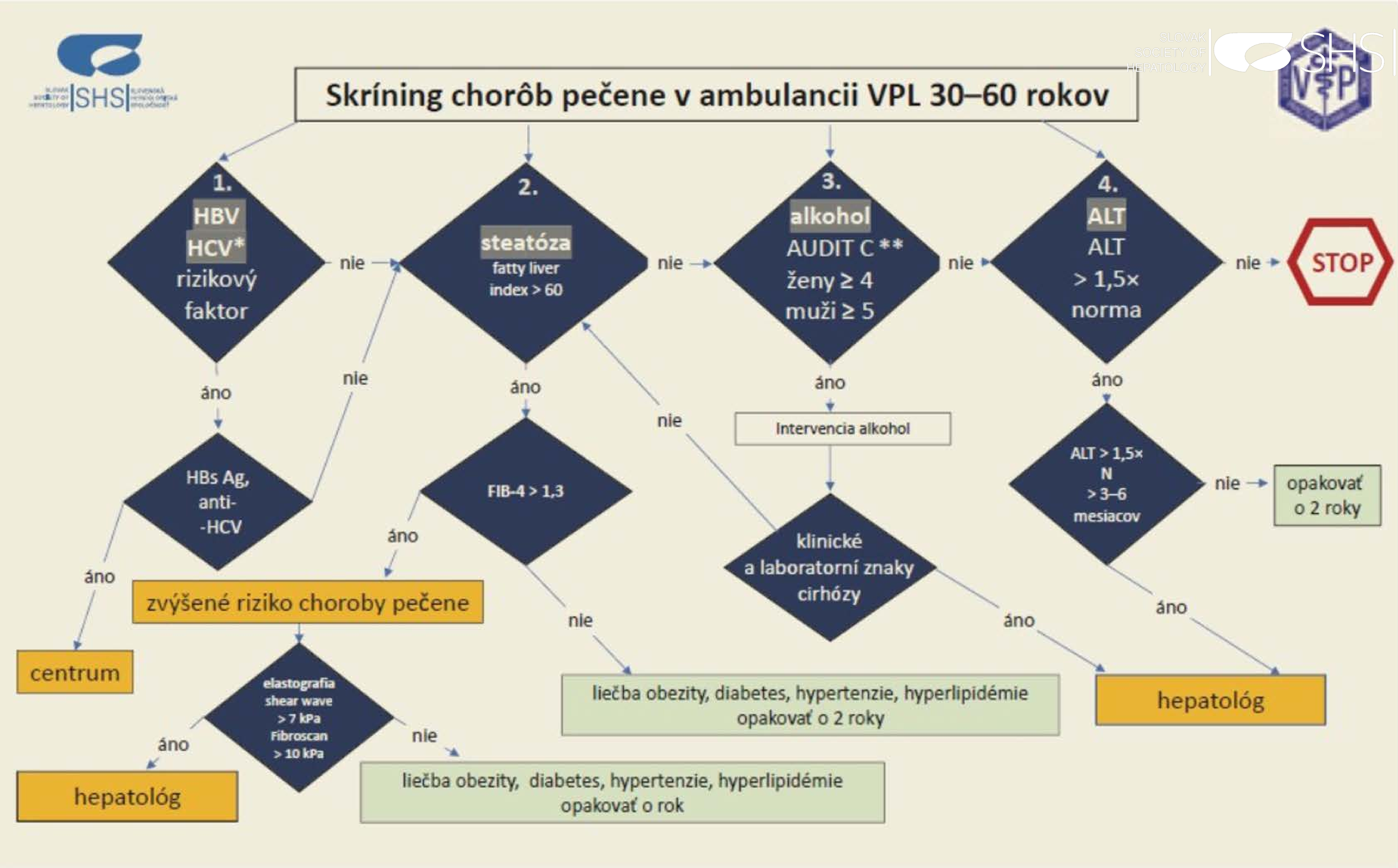
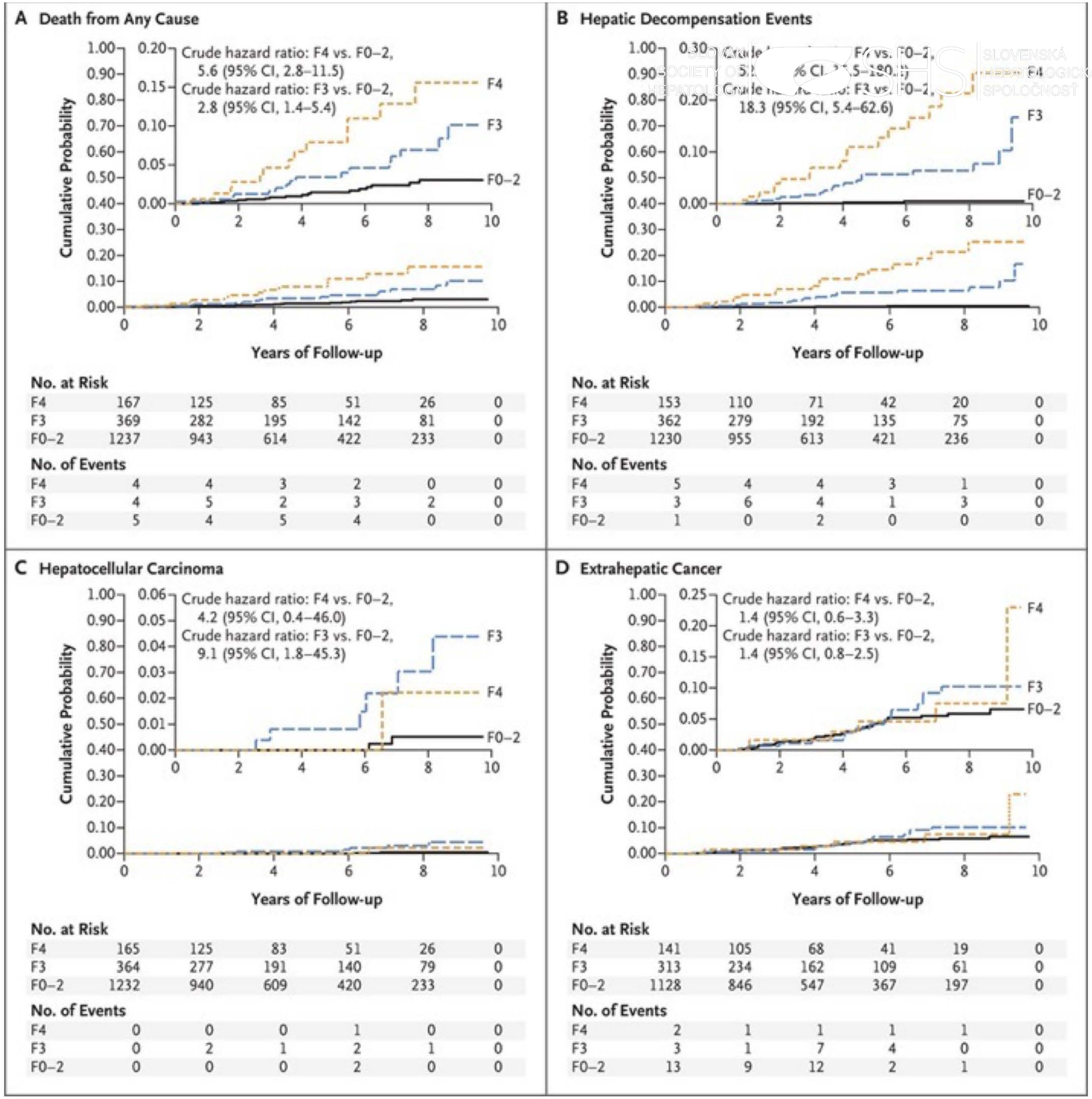


Fibróza = prognostický faktor

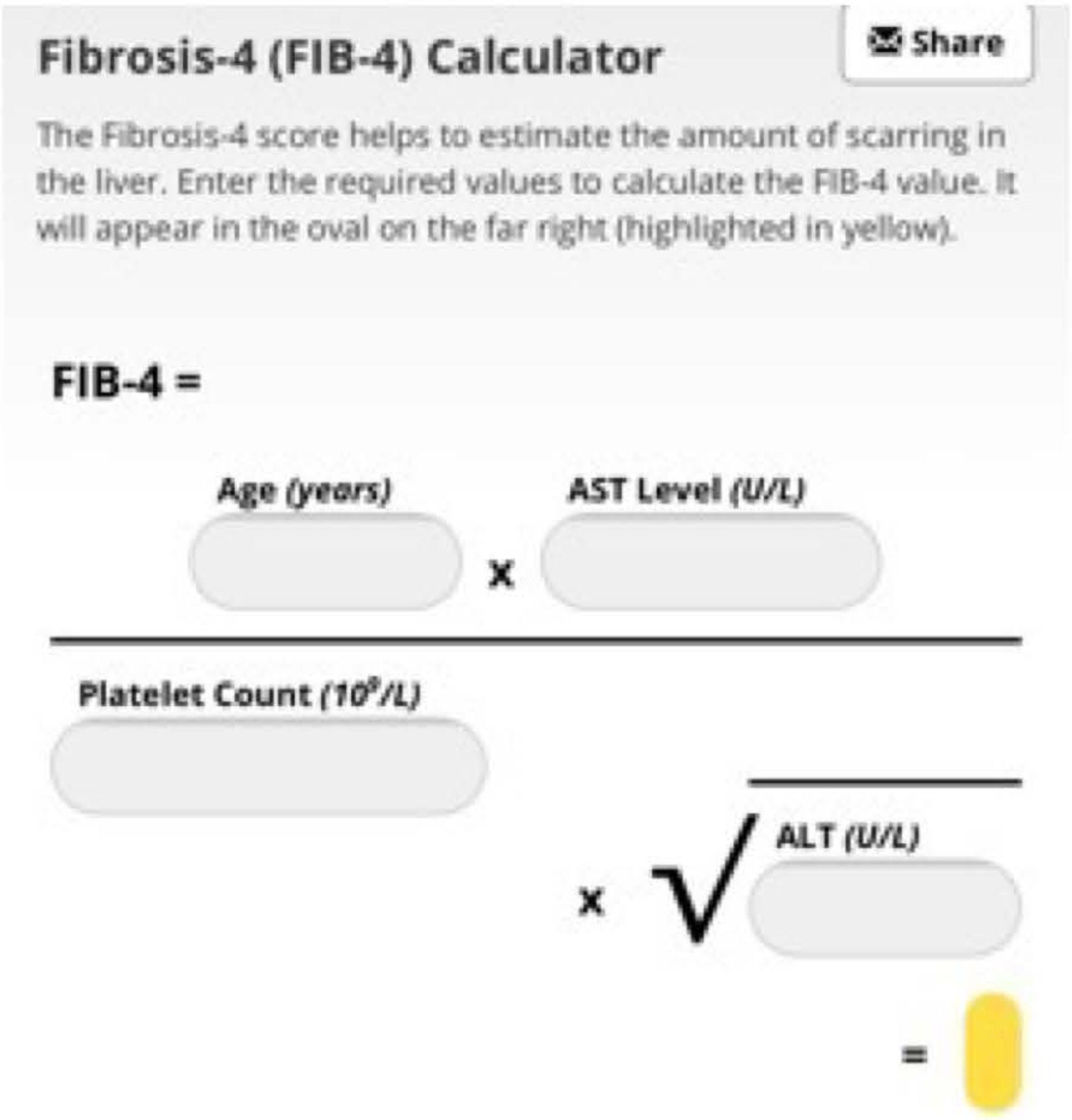
prediktor prežívania

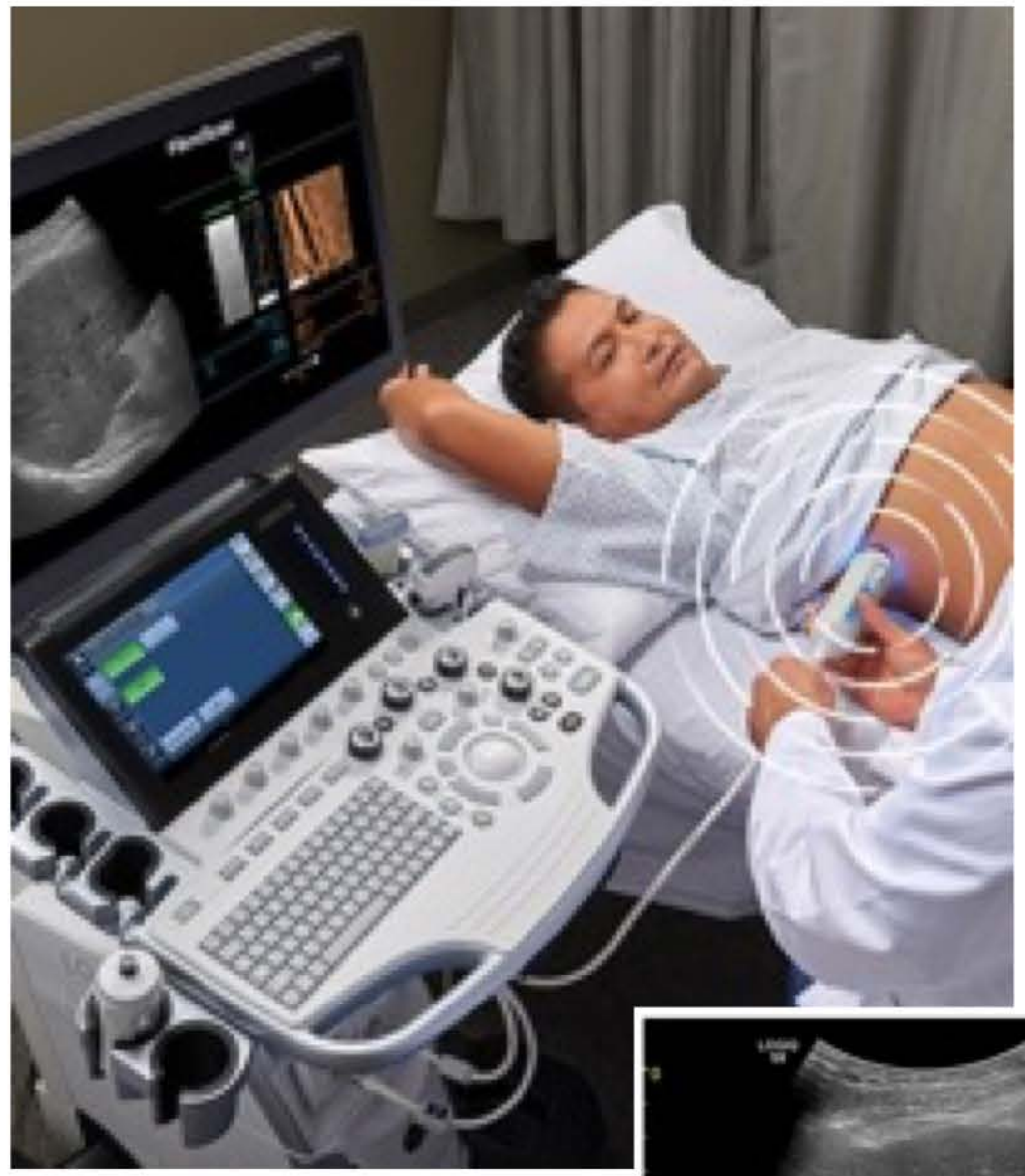


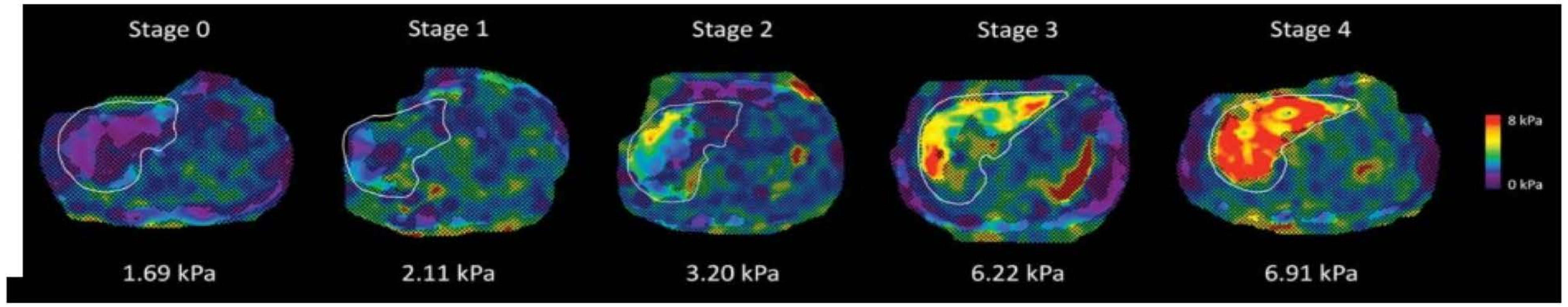
Sanyal, N Engl J Med 2021

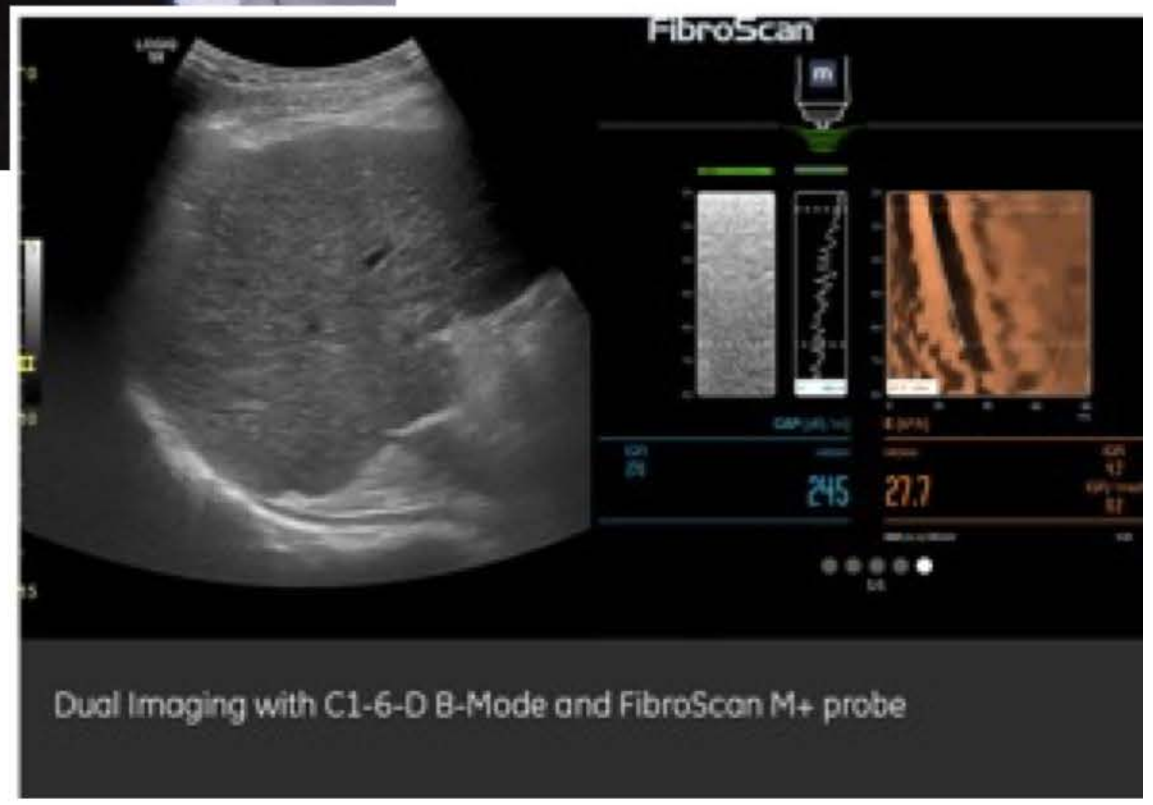
štádium fibrózy reflektuje prognózu

- diagnostika fibrózy (prevažne neinvazívna)
- prognostický faktor

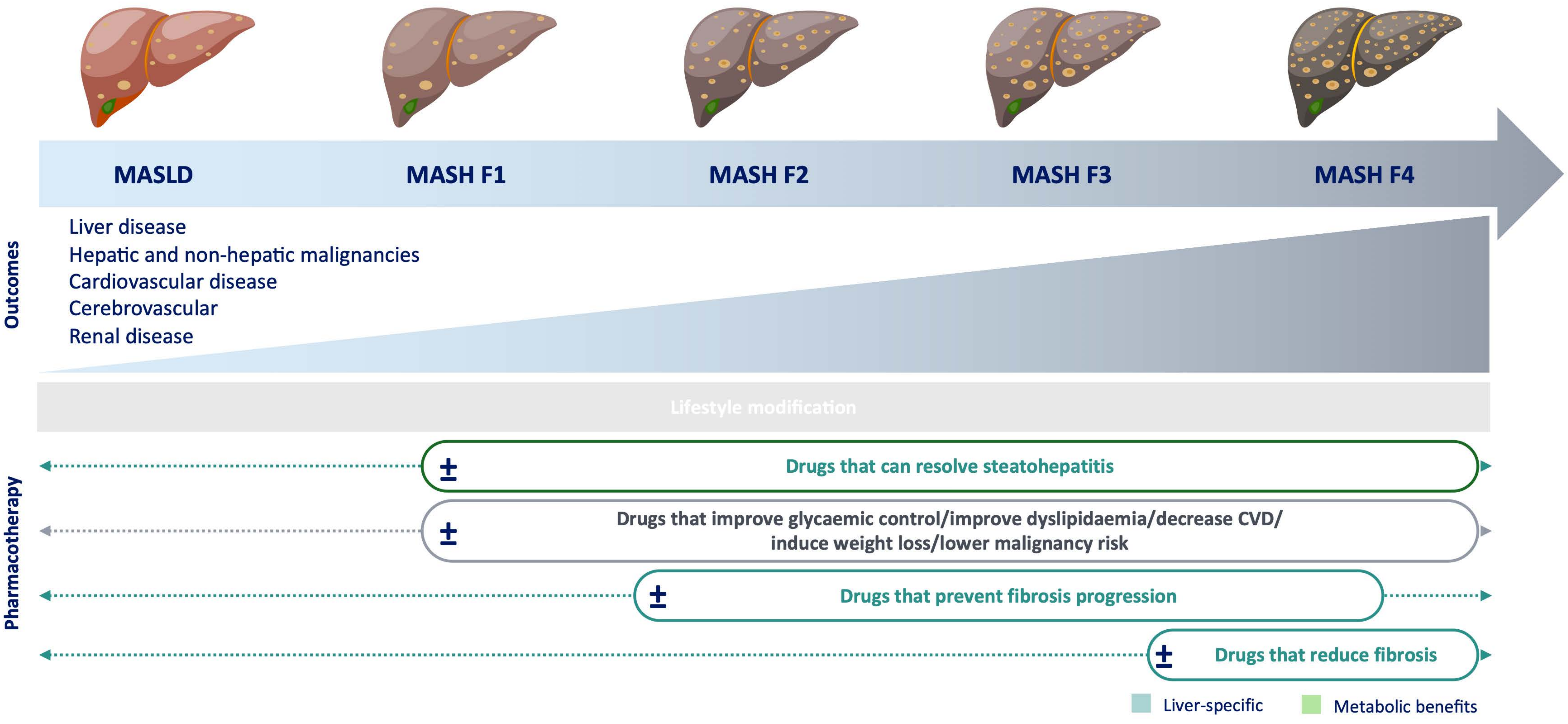








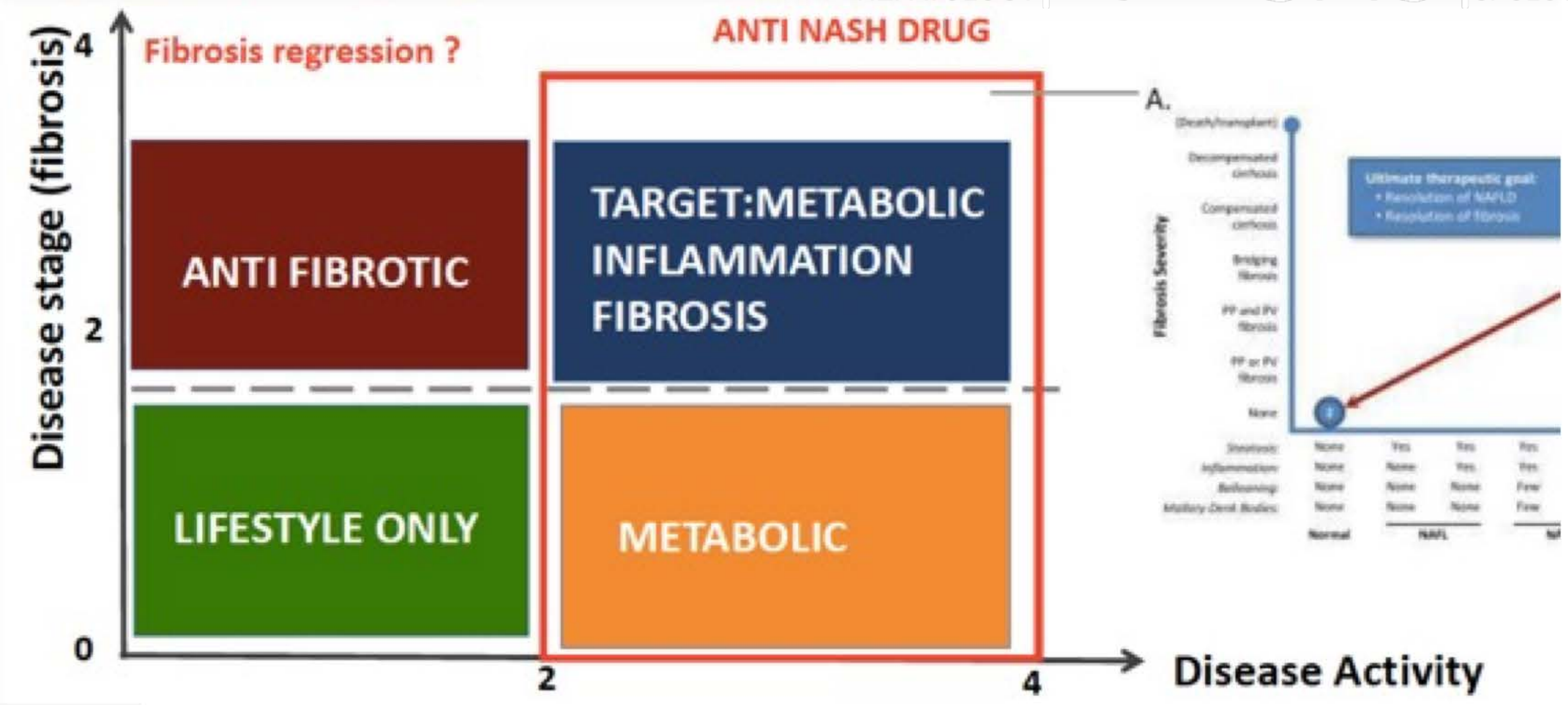
Cieľe liečby musia byť globálne/holistické (MACE, MALO, renal, onkol, …celková mortalita)

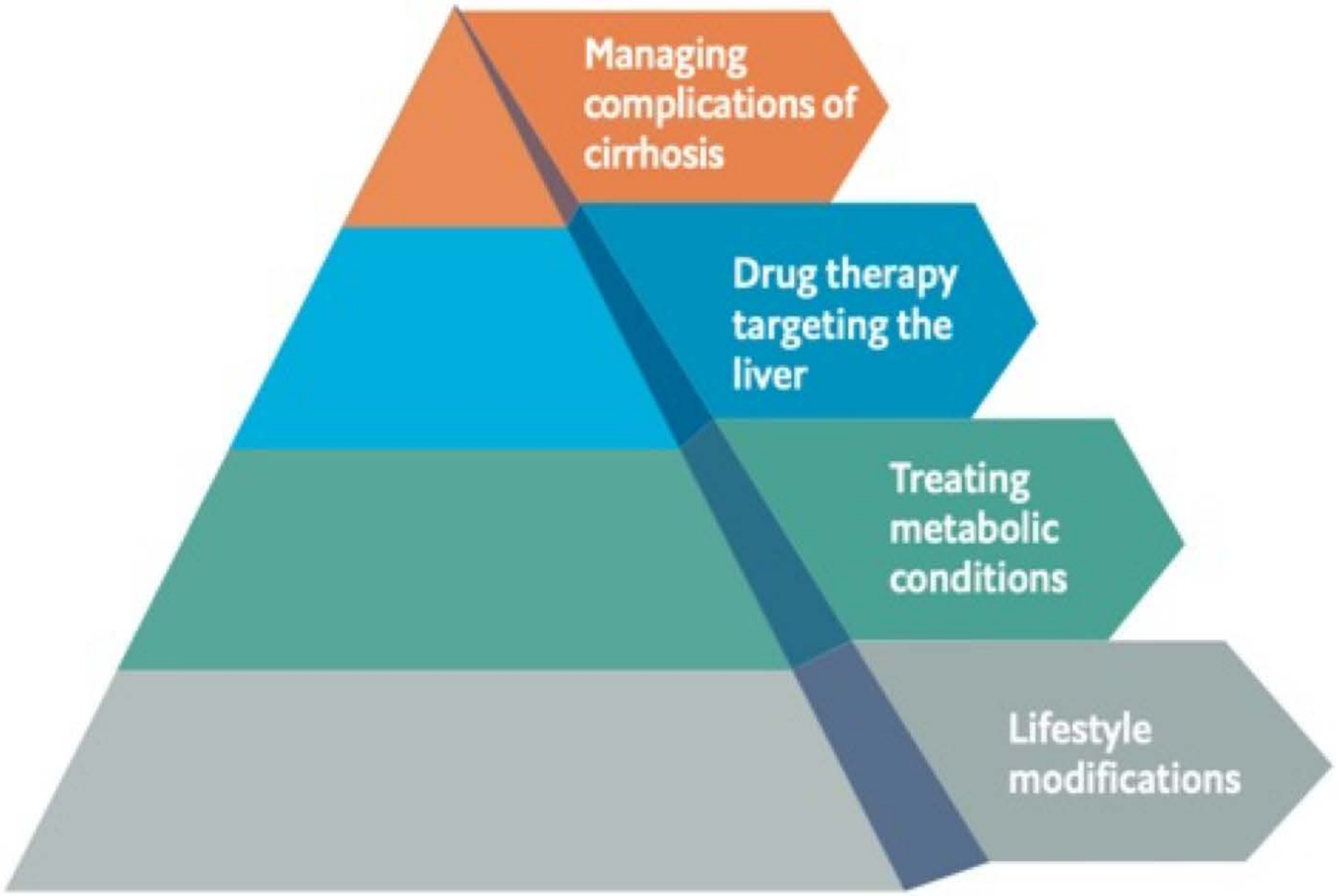


SLC
SOCIET
HEPATOL

MAFLD - liečba

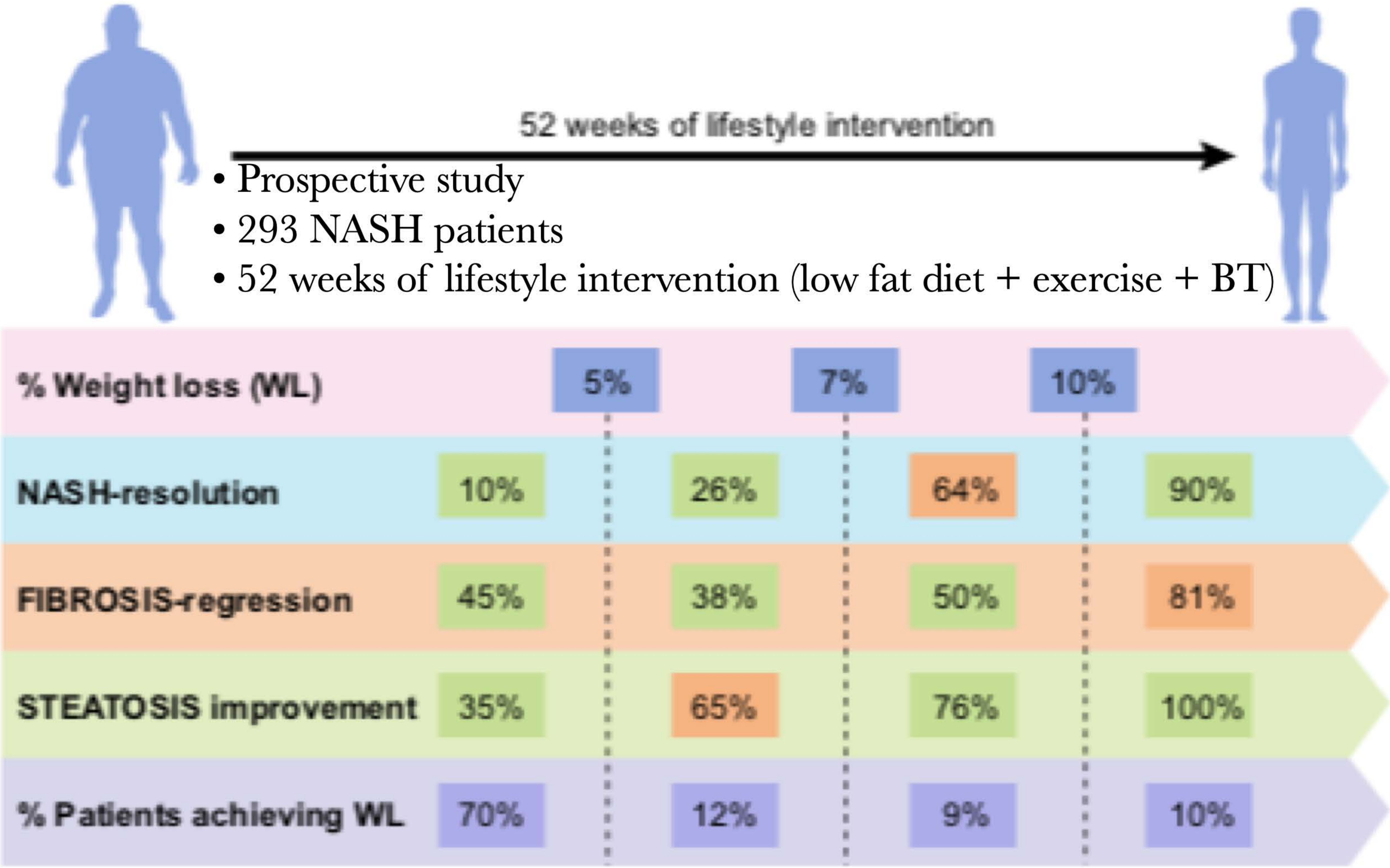
- Diéta
- Aktivita a cvičenie
- Farmakologická liečba
- Bariatrická/metabolická chirurgia





Weight loss by lifestyle modification needed to reach NASH resolution and FIBROSIS regression

- Prospective study
- 293 NASH patients
- 52 weeks of lifestyle intervention (low fat diet + exercise + BT)



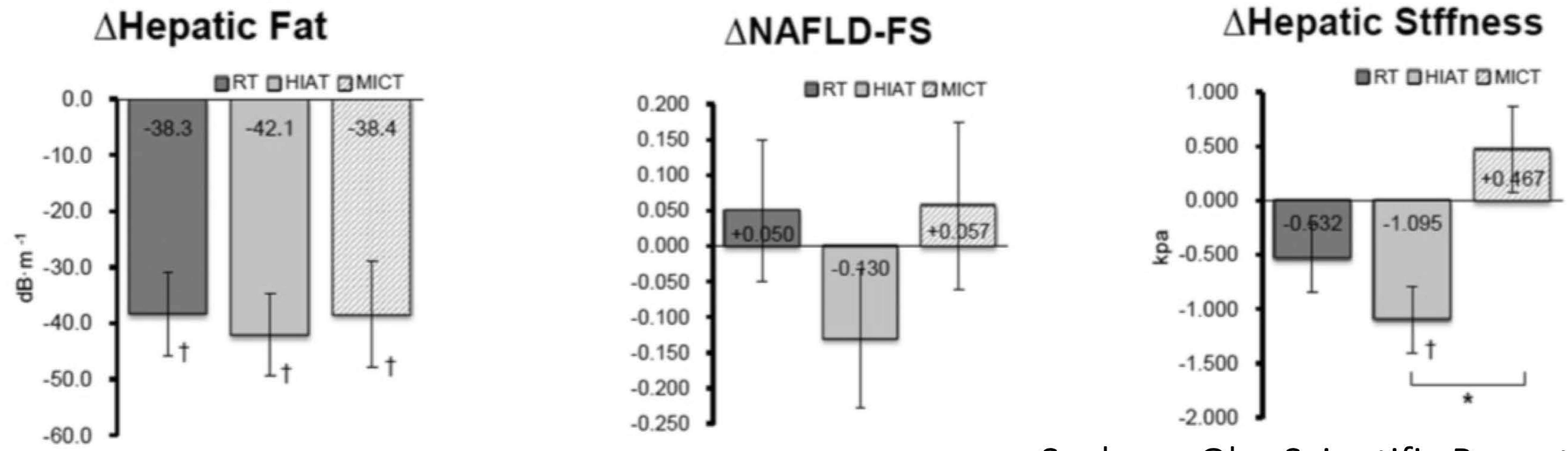
Vilar-Gomez E., Gastroenterology 2015

High-intensity aerobic exercise improves liver fat and stiffness

52 NAFLD, 12 W follow-up, MRS, CAP, transient elastography

- Resistance training X 3/W (RT) n=19
- High-intensity interval aerobic training 85% VO2Max (HIAT) X 3/W/13 min n=20
- Moderate-intensity continuous aerobic training 65% VO2Max (MICT) X 3/W/40 min n=13

No significant changes in weight, visceral fat or energy intake



Sechang Oh., Scientific Reports 2017

Noureddin M *Hepatology* 2024

GLP-1 receptor agonist trial achieved both the primary endpoints

Phase 3 ESSENCE trial: (Part 1) 72 weeks

ESSENCE part 1 trial information

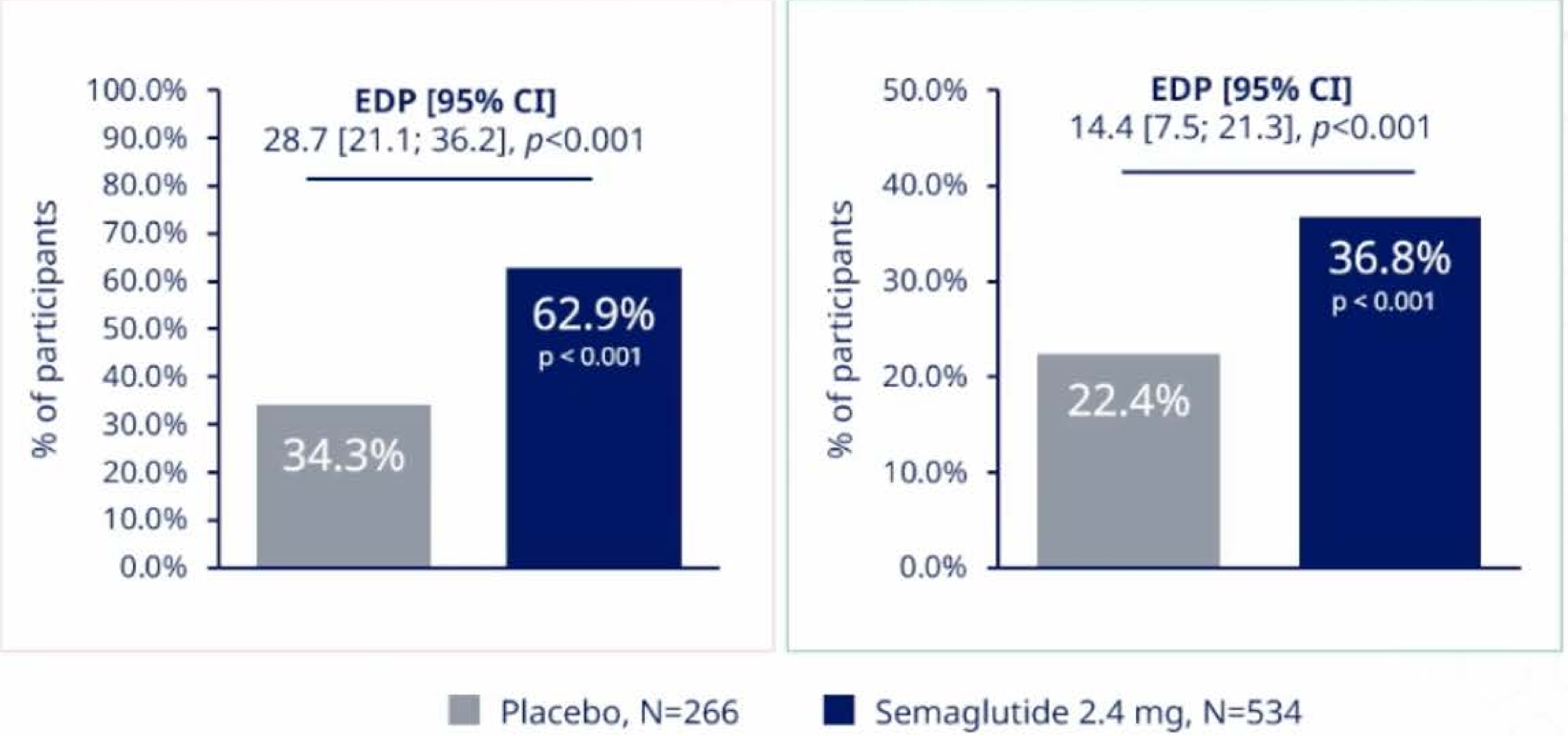
800 participants
Biopsy-confirmed F2-F3 MASH, NAS ≥4

Cardiometabolic parameters
- **>99%** met ≥1 MASLD cardiometabolic criteria
- **43.3%** met all five cardiometabolic risk factors

Safety profile (N=1200): GI side effects, mild to moderate nausea, diarrhoea, constipation and vomiting

Resolution of steatohepatitis
with no worsening of liver fibrosis

Reduction in liver fibrosis
with no worsening of steatohepatitis



CI, confidence interval; EDP, estimated difference in responder proportions; F, fibrosis stage; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NAS, non alcoholic fatty liver disease activity score. Sanyal AJ, Newsome PN, et al. N Engl J Med. Published online April 30, 2025. doi: 10.1056/NEJMoa2413258

The NEW ENGLAND JOURNAL of MEDICINE

Tirzepatide for MASH with Liver Fibrosis

A PLAIN LANGUAGE SUMMARY

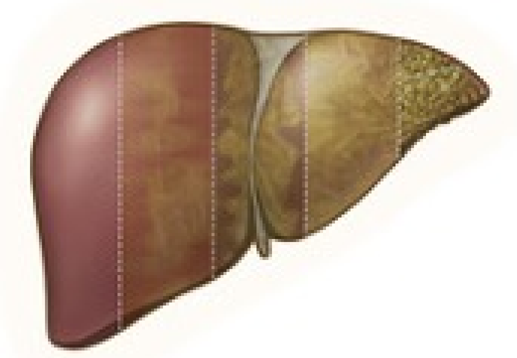
Based on the NEJM publication: Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis by R. Loomba et al. (published June 8, 2024)

In this trial, researchers assessed the efficacy and safety of once-weekly tirzepatide in persons with metabolic dysfunction–associated steatohepatitis (MASH) and moderate or severe fibrosis.

MASH, formerly known as NASH (nonalcoholic steatohepatitis), is a progressive liver disease characterized by excess fat in the liver, hepatic inflammation, and hepatocyte injury, with or without fibrosis.

WHY WAS THE TRIAL DONE?

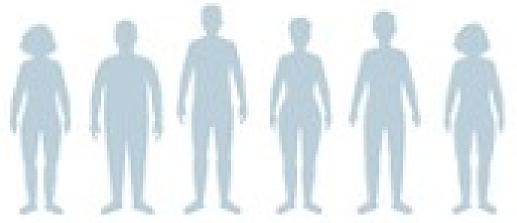
MASH is associated with liver-related complications and death. Tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist, has been shown to reduce liver fat and improve biomarkers of MASH and fibrosis in persons with type 2 diabetes. The efficacy and safety of tirzepatide in persons with MASH and moderate or severe fibrosis are unclear.



HOW WAS THE TRIAL CONDUCTED?

190 adults with a body-mass index (BMI) between 27 and 50, histologically confirmed MASH, and moderate or severe fibrosis received once-weekly subcutaneous tirzepatide at one of three doses (5 mg, 10 mg, or 15 mg) or placebo for 52 weeks. The primary end point was resolution of MASH without worsening of fibrosis at week 52.

PARTICIPANTS



WHO	190 participants
	18 to 80 years of age
	Women: 57%; Men: 43%
CLINICAL STATUS	Biopsy-confirmed MASH
	Stage 2 or 3 fibrosis
	BMI, 27 to 50
	With or without type 2 diabetes mellitus

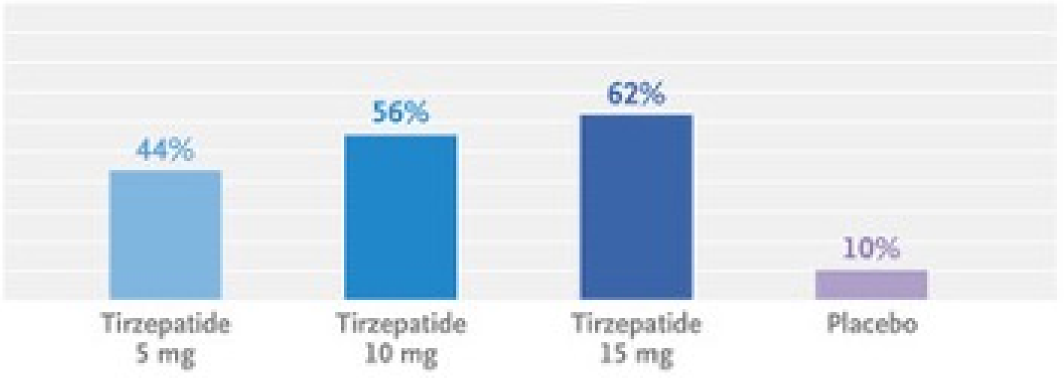
TRIAL DESIGN

- PHASE 2
- MULTICENTER
- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- LOCATION: 10 COUNTRIES

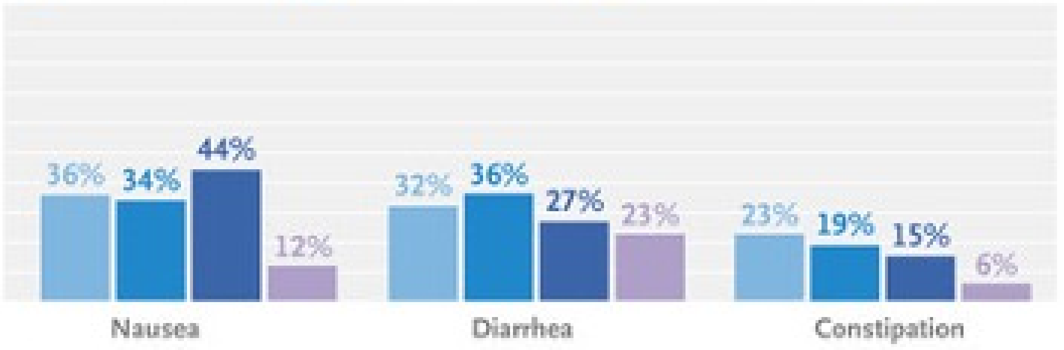
The NEW ENGLAND JOURNAL of MEDICINE

RESULTS

The percentage of participants who had resolution of MASH without worsening of fibrosis was significantly higher in all three tirzepatide groups than in the placebo group.

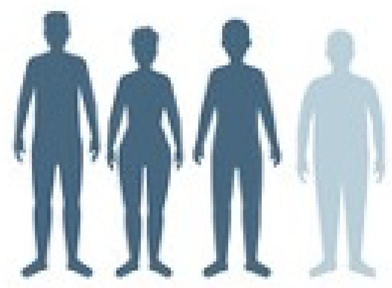


Gastrointestinal events were the most common adverse events with tirzepatide and were mostly mild or moderate in severity.



FIBROSIS STAGE

The percentage of participants who had an improvement (decrease) of at least one fibrosis stage without worsening of MASH (a key secondary end point) also favored the tirzepatide groups.



LIMITATIONS AND REMAINING QUESTIONS

- The small sample size did not provide adequate statistical power to evaluate the effect of tirzepatide on fibrosis.
- The trial was too short to assess the effect of tirzepatide on major adverse liver outcomes.
- Persons with MASH that had progressed to cirrhosis were not included in the trial.

CONCLUSIONS

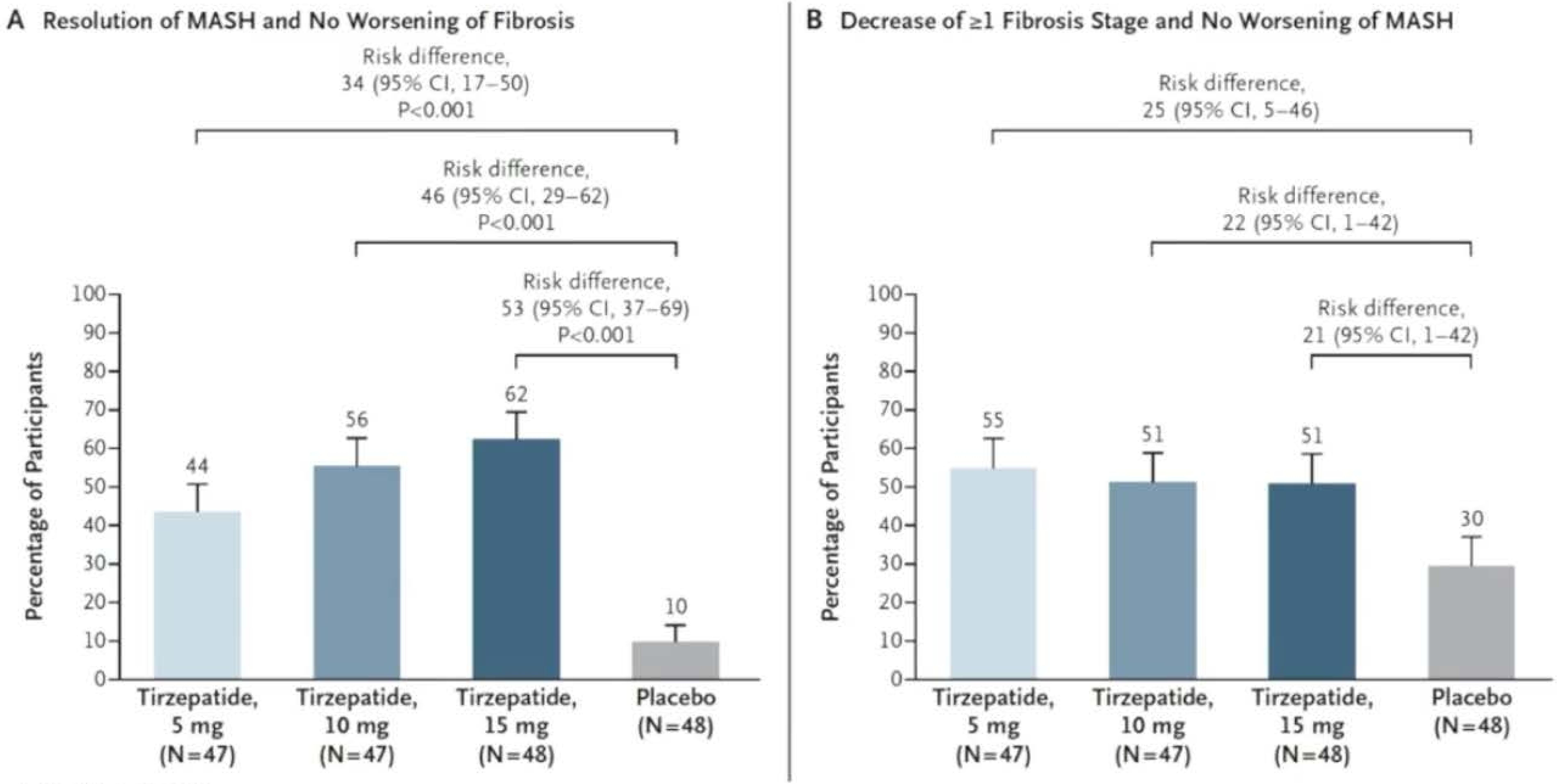
In participants with MASH and moderate or severe fibrosis, once-weekly tirzepatide at a dose of 5 mg, 10 mg, or 15 mg was more effective than placebo for resolution of MASH without worsening of fibrosis.

LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

FURTHER INFORMATION

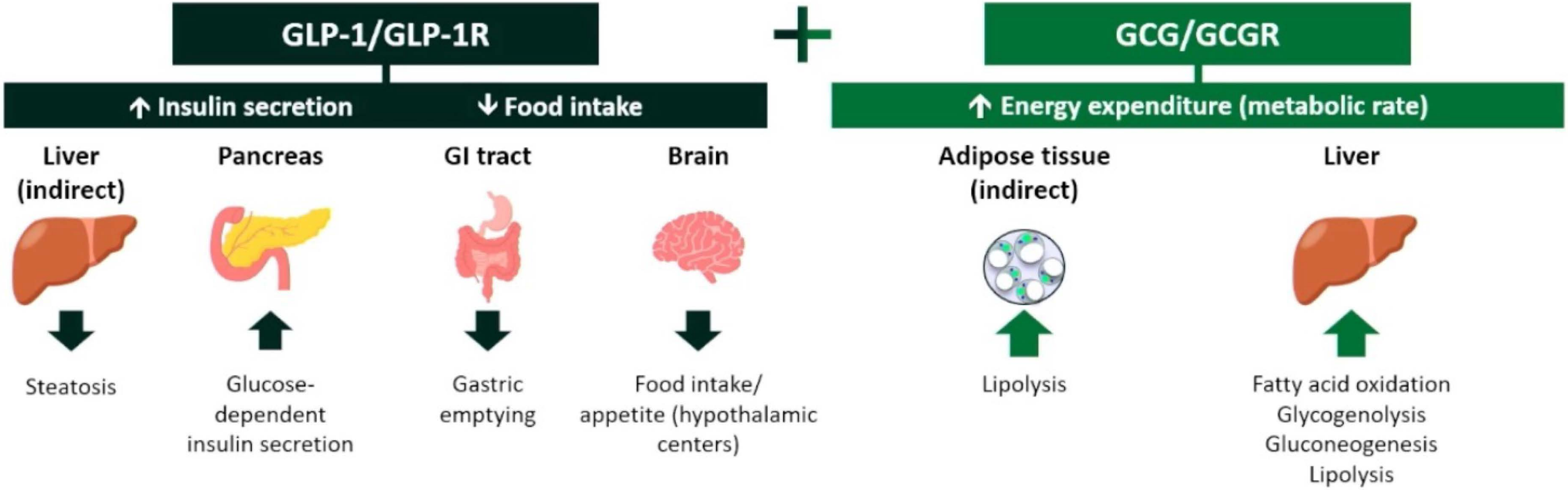
Trial registration: ClinicalTrials.gov number, NCT04166773
Trial funding: Eli Lilly
Full citation: Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for metabolic dysfunction–associated steatohepatitis with liver fibrosis. N Engl J Med 2024;391:299-310. DOI: 10.1056/NEJMoa2401943

Liver Outcomes Driven by Metabolic Improvement: Tirzepatide Phase 2 SYNERGY trial



Loomba et al NEJM 2025

GLP-1 Glucagon combinations



GLP1:GLG ratio	Pemvidutide (1:1)	Cotadutide (5:1)	Survodutide (8:1)

The NEW ENGLAND JOURNAL of MEDICINE

Phase 2 Trial of Survodutide in MASH and Fibrosis

A PLAIN LANGUAGE SUMMARY

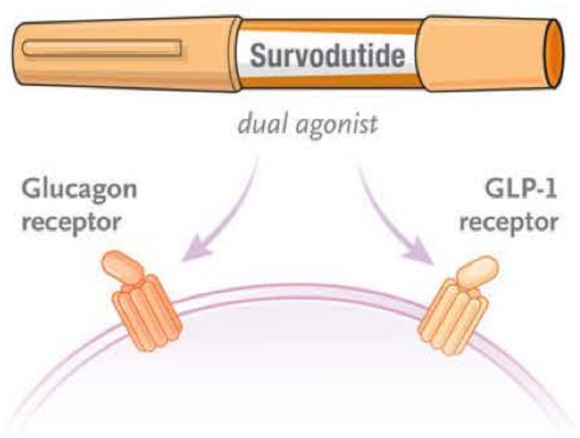
Based on the NEJM publication: A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis
by A.J. Sanyal et al. (published June 7, 2024)

In this trial, researchers evaluated the efficacy and safety of multiple subcutaneous doses of survodutide, a dual agonist of the glucagon receptor and glucagon-like peptide-1 (GLP-1) receptor, in participants with metabolic dysfunction–associated steatohepatitis (MASH) and liver fibrosis.

MASH, previously called NASH (nonalcoholic steatohepatitis), is associated with increased morbidity and mortality. The prevalence of MASH is predicted to increase worldwide.

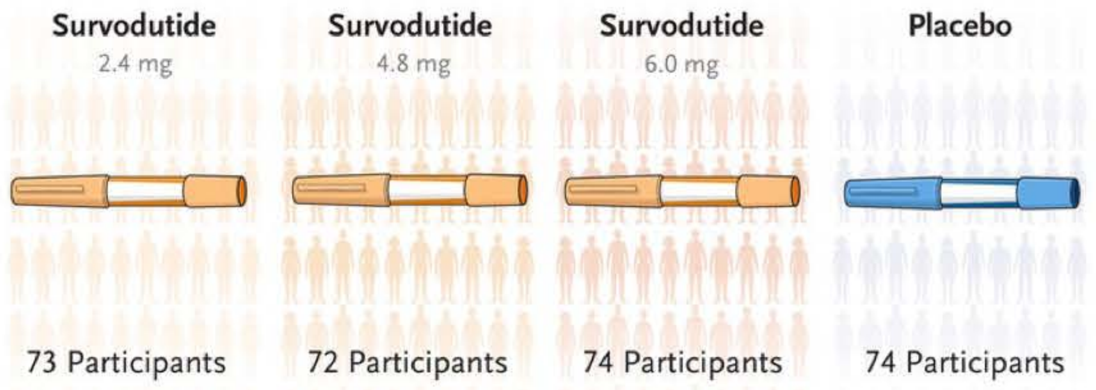
WHY WAS THE TRIAL DONE?

Compounds in development for treating MASH include GLP-1 receptor agonists. However, dual agonism of the glucagon and GLP-1 receptors may be more effective than GLP-1 receptor agonism alone, because the extrahepatic benefits of GLP-1 receptor agonism are combined with the direct hepatic effects of glucagon receptor agonism.



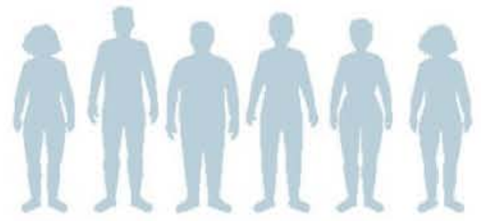
HOW WAS THE TRIAL CONDUCTED?

293 adults with biopsy-confirmed MASH and fibrosis stage F1 through F3 were randomly assigned to receive once-weekly subcutaneous survodutide, at a target dose of 2.4, 4.8, or 6.0 mg, or placebo. A 24-week rapid-dose-escalation phase was followed by a 24-week maintenance phase. The primary end point was histologic improvement (reduction) in MASH with no worsening of fibrosis at week 48.



24-week rapid-dose-escalation phase followed by a 24-week maintenance phase

PARTICIPANTS



WHO	293 adults
	18–80 years of age
	Women: 53%; Men: 47%
CLINICAL STATUS	Biopsy-confirmed MASH
	Fibrosis stage F1 through F3

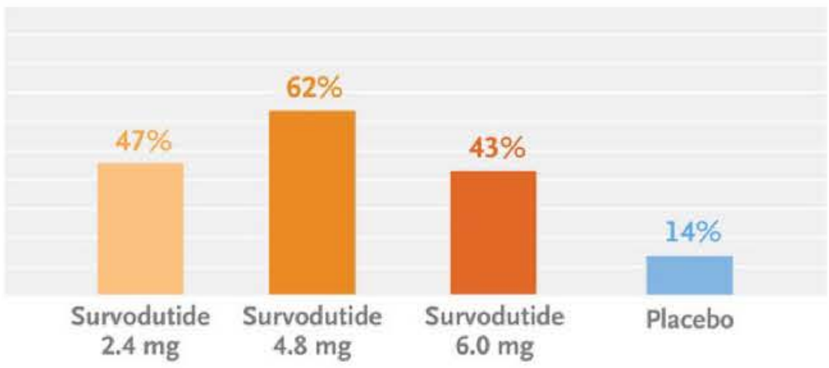
TRIAL DESIGN

- PHASE 2
- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- DOSE-FINDING
- LOCATION: 155 SITES IN 25 COUNTRIES

RESULTS

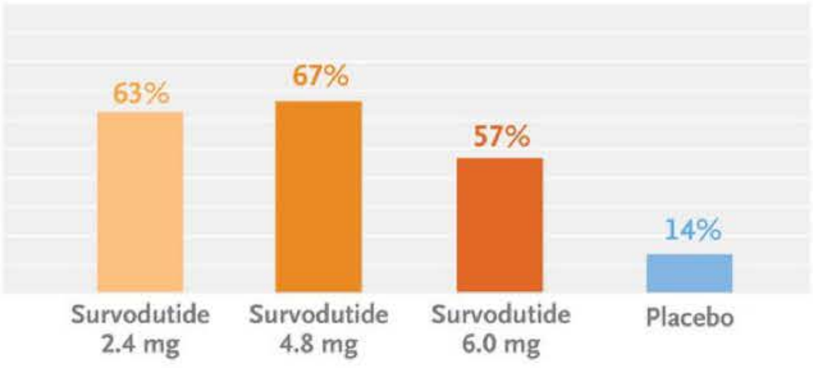
Survodutide was associated with significant improvement in MASH with no worsening of fibrosis at 48 weeks as compared with placebo.

Histologic Improvement in MASH
(P<0.001)



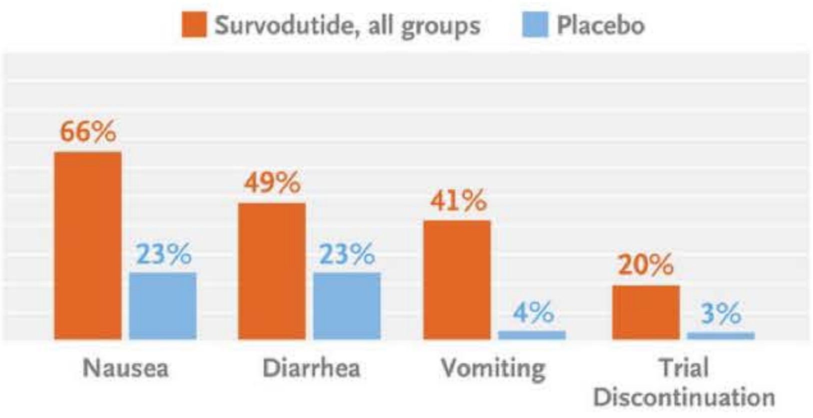
A decrease in liver fat content by at least 30% — a secondary end point — was more common with survodutide than with placebo.

Decrease in Liver Fat Content by at Least 30%



The most common adverse events were nausea, diarrhea, and vomiting, all of which occurred more frequently with survodutide than with placebo. Trial discontinuation due to adverse events also occurred more often with survodutide than with placebo.

Adverse Events



LIMITATIONS AND REMAINING QUESTIONS

- Most participants were White, which may restrict the generalizability of the findings.
- The benefit of survodutide with respect to fibrosis will need to be examined in future studies.

CONCLUSIONS

In a phase 2 trial involving participants with MASH and liver fibrosis, survodutide was superior to placebo with respect to improvement in MASH without worsening of fibrosis over 48 weeks.

LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

FURTHER INFORMATION

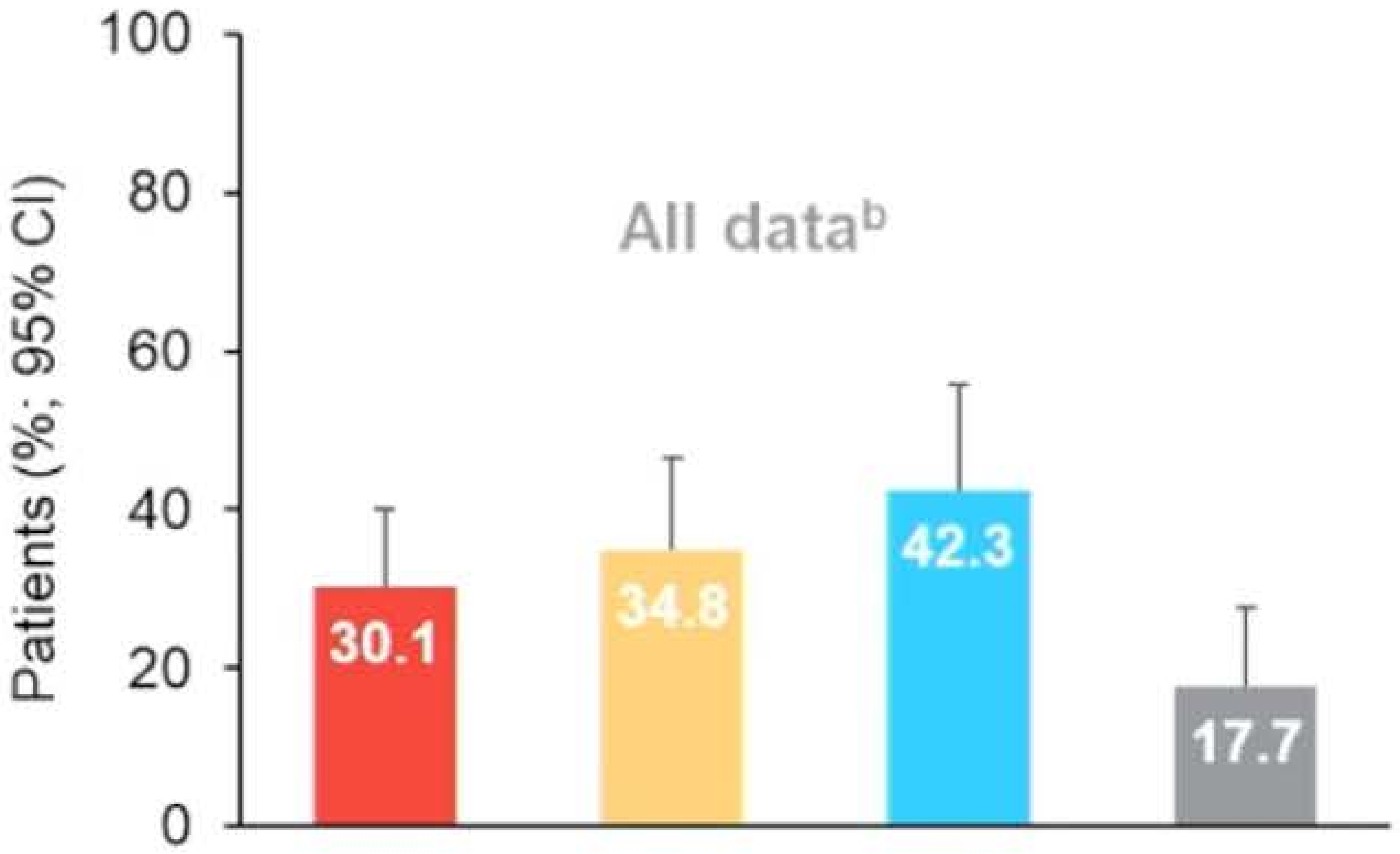
Trial registration: ClinicalTrials.gov number, NCT04771273; EudraCT number, 2020-002723-11

Trial funding: Boehringer Ingelheim

Full citation: Sanyal AJ, Bedossa P, Fraessdorf M, et al. A phase 2 randomized trial of survodutide in MASH and fibrosis. N Engl J Med 2024;391:311-9. DOI: 10.1056/NEJMoa2401755

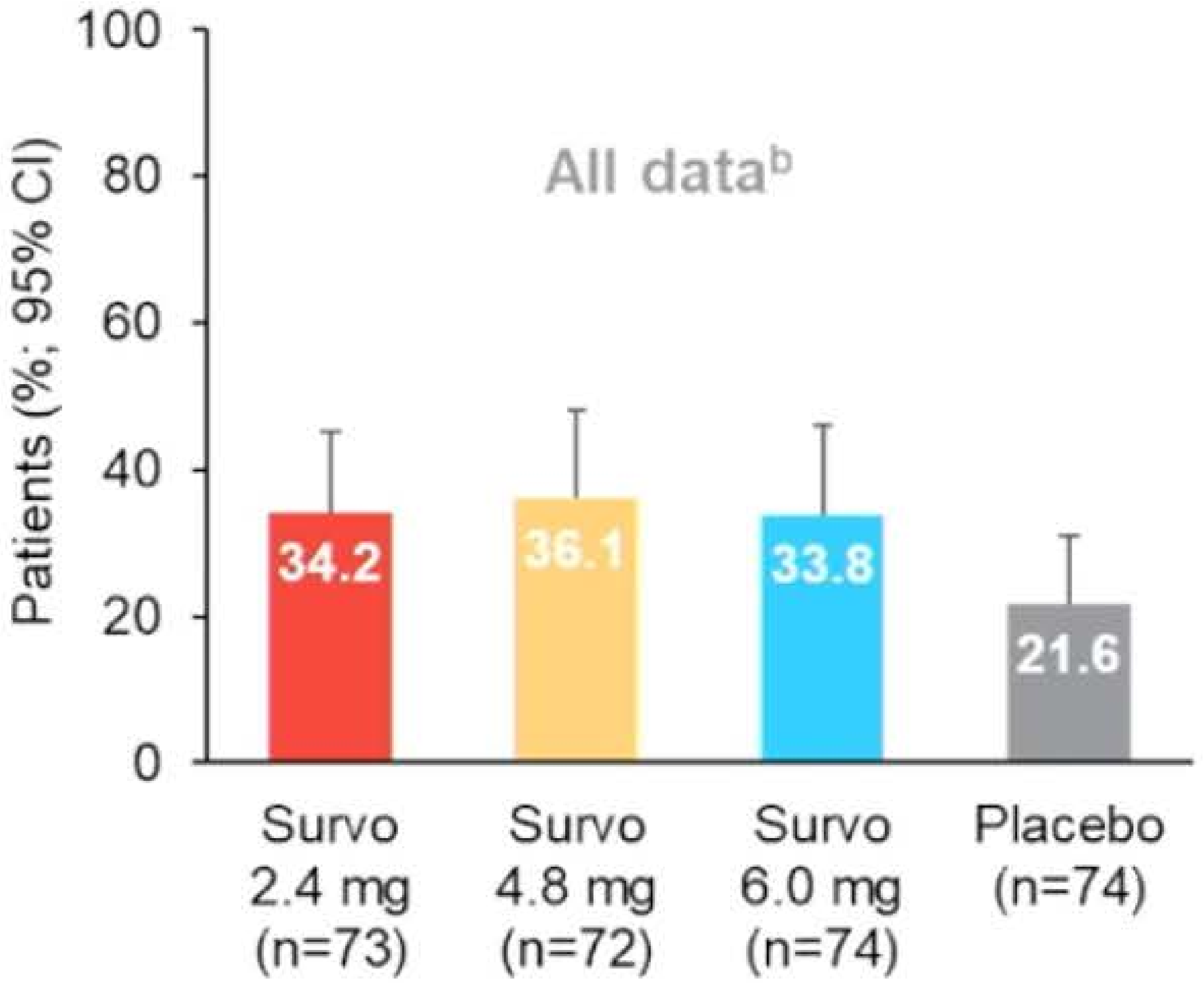
Survodutide – Phase 2 trial

Actual treatment: Improvement in liver fibrosis with no worsening in MASH[a] (F1–F3 population)



	Survo 2.4 mg (n=93)	Survo 4.8 mg (n=69)	Survo 6.0 mg (n=52)	Placebo (n=79)
Paired biopsy results[c]:	50.0%	45.3%	50.0%	21.1%
Nominal P-values:	0.0587	0.0181	0.0011	

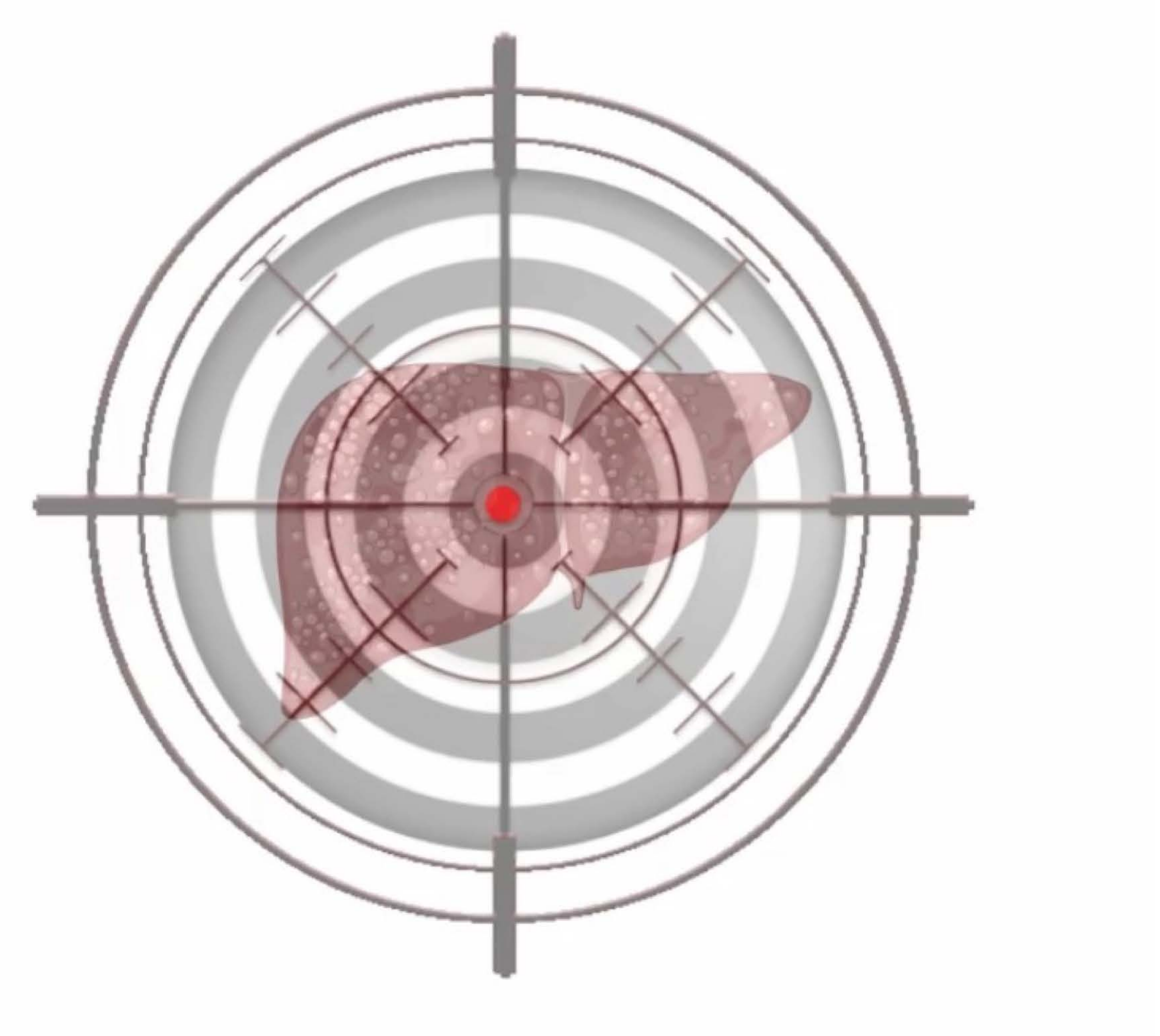
Planned treatment: ≥1-stage decrease in fibrosis (F1-F3 population)



Sanyal AJ, et al. EASL ILC 2024/ NEJM 2024.

Liečba hepatocentrická

- predpokladaný efekt na inflamáciu a fibrózu
    - THR beta RA
    - Fibroblast Growth Factor 21 (FGF 21) RA
    - FA Syntase Inhibitor



EMA Recommends Rezdiffra for MASH Liver Fibrosis

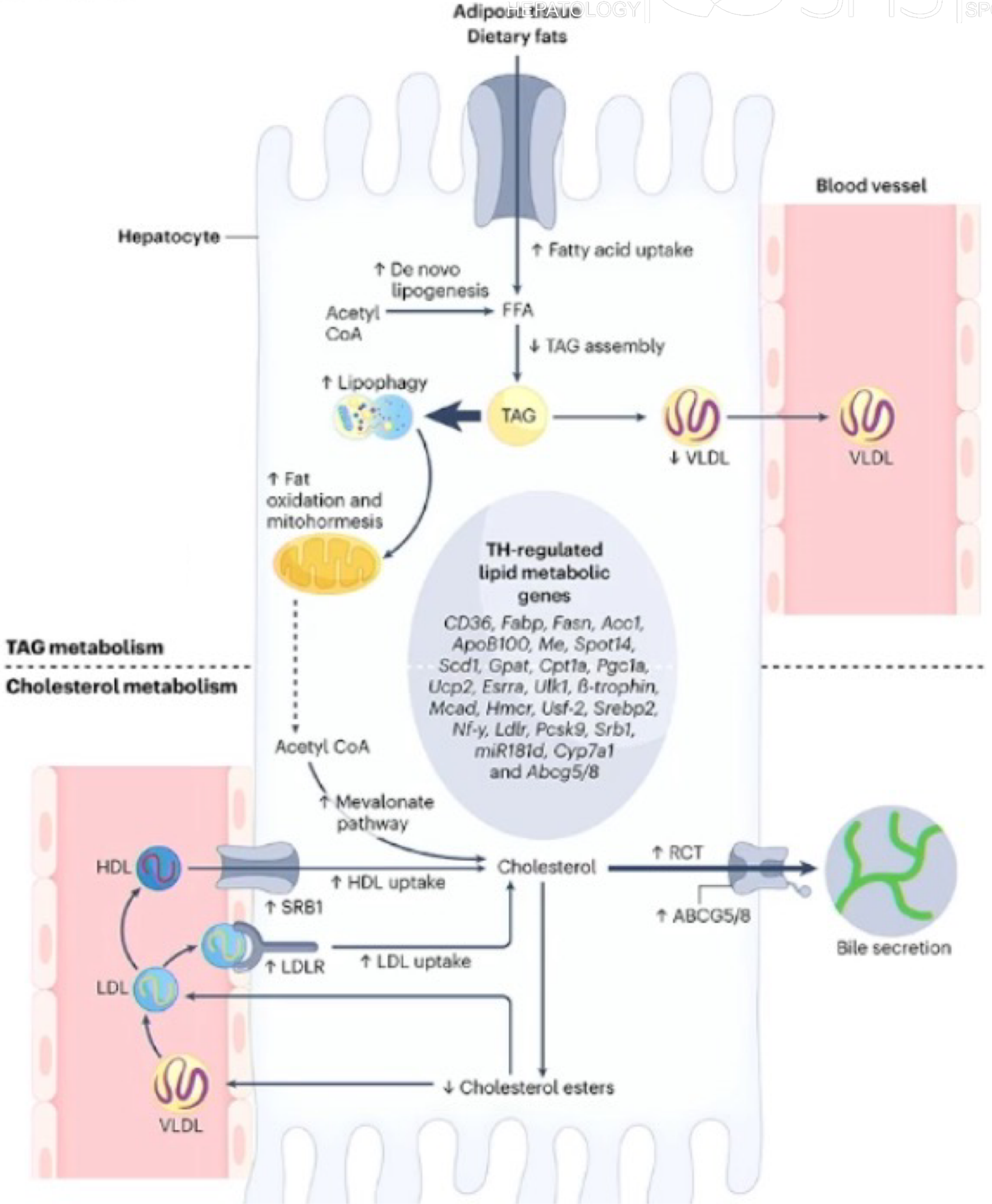
Annie Lennon
June 20, 2025

Tyreomimetiká/THR beta RA

úprava metabolickej dysregulácie a nastolenie homeostázy

- beta R v pečeni
- downregulation aktivity DIO (deiodinázy)
- redukcia konverzie T4 → T3 (úprava IH hypotyreóz

- THR beta RA rieši lipidovú homeostázu ⇧:
  - lipofágie, beta oxidácie FA
  - regenerácia/novotvorba – zlepšenie funkcie mitochondrií
  - clearance cholesterolu, FA
- v konečnom dôsledku
  - ⇩ IH steatózy,
  - nekroinflamácie –MASH resolution, ⇩ LDL-C, ⇩ TG



Sinha et al. *Nat Rev Gastroenterol Hepatol* 2025

THR-β agonist achieved both the primary endpoints

Phase 3 MAESTRO-NASH trial: 52 weeks

MAESTRO-NASH trial information

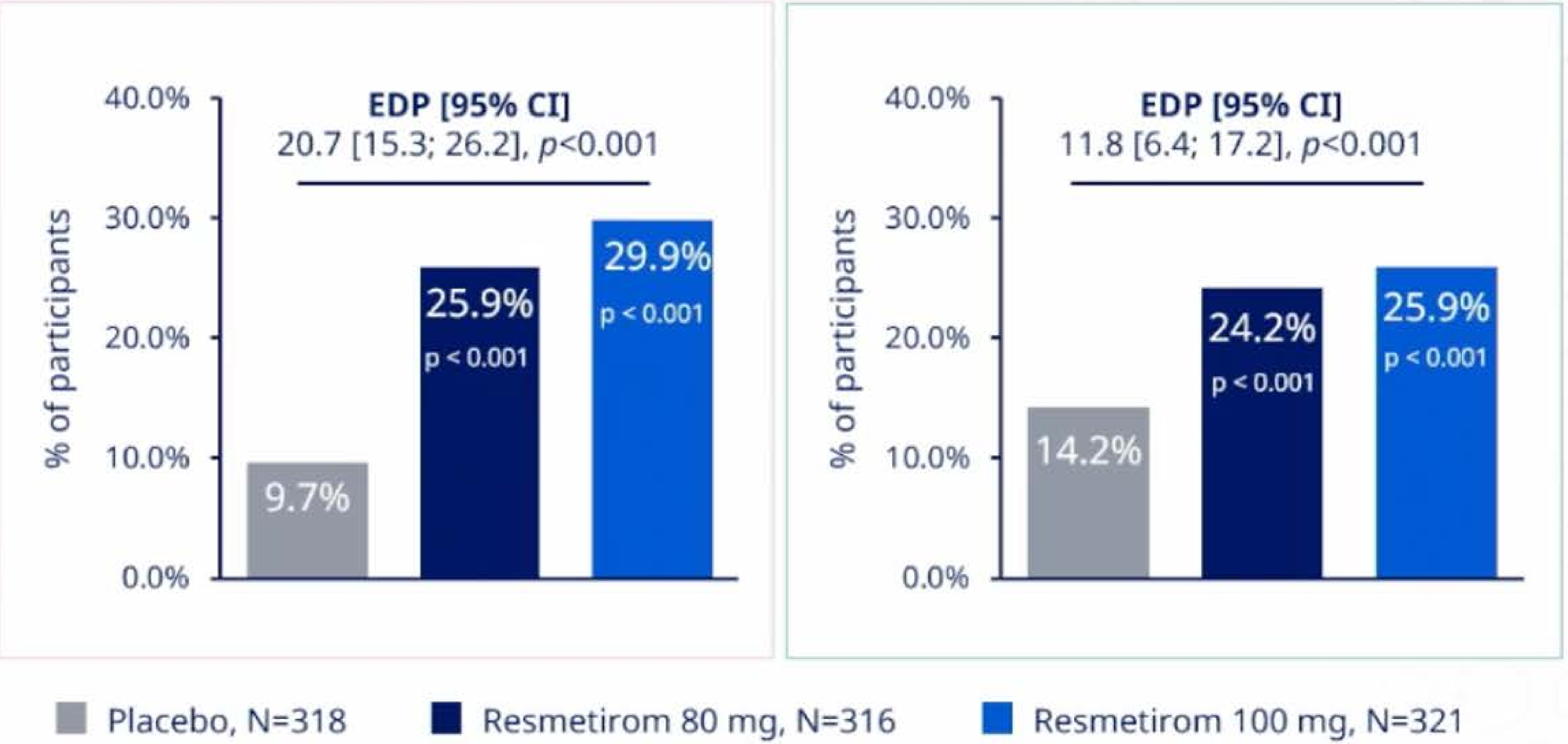
966 participants
Biopsy-confirmed F1-F3 MASH, NAS ≥4

Cardiometabolic parameters
- HTN: **78.1%**;
- Dyslipidaemia: **71.3%**
- T2D: **67.0%**

Safety profile: GI side effects, mild to moderate diarrhoea and nausea

MASH Resolution with no worsening of fibrosis

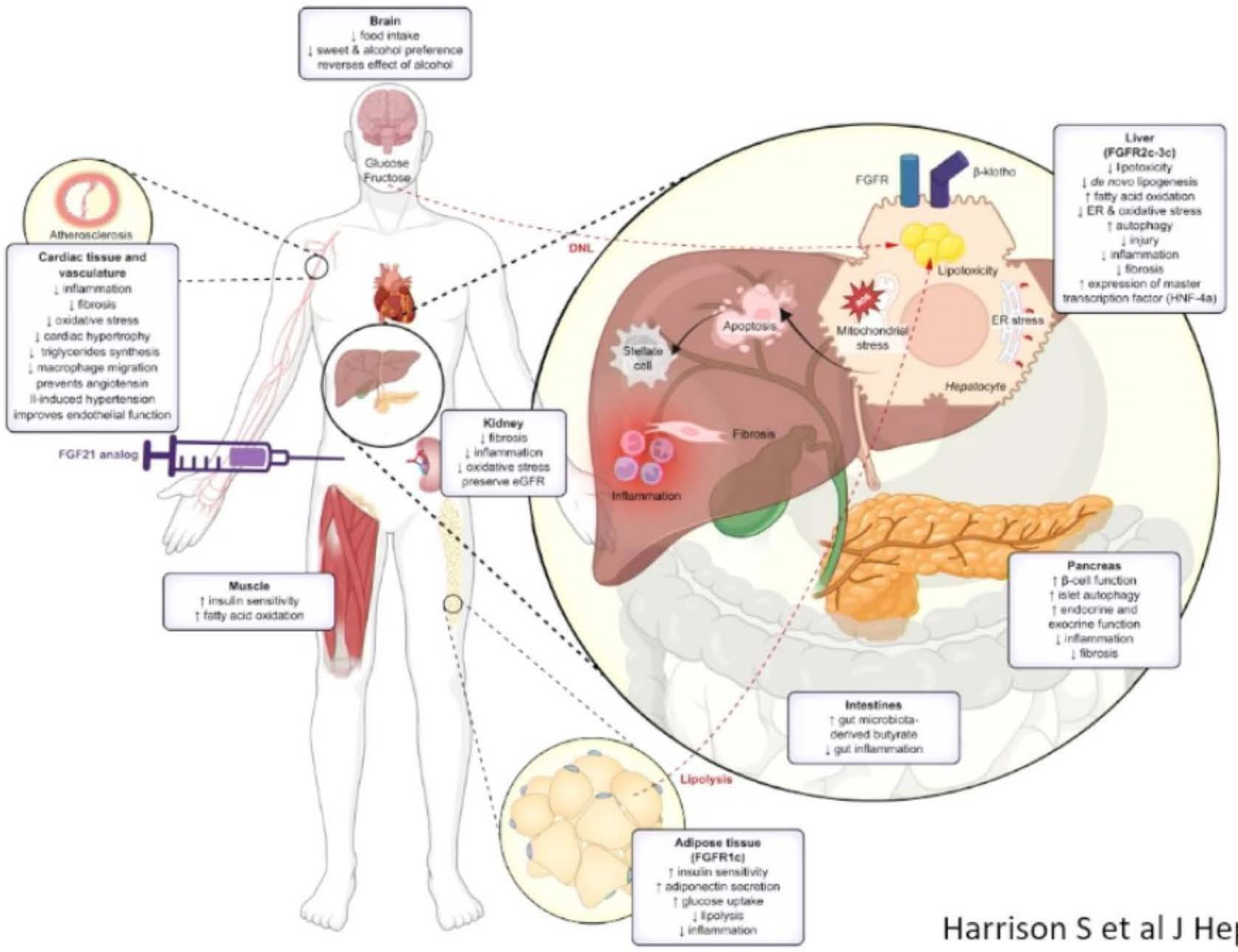
Fibrosis Improvement (≥ 1 stage) with no worsening of NAS



CI, confidence interval; EDP, estimated difference in percentage points; F, fibrosis stages; GI, gastrointestinal; HTN, hypertension; MASH, metabolic dysfunction-associated steatohepatitis; NAS, non alcoholic fatty liver disease activity score; T2D, type 2 diabetes; THR-β, thyroid hormone receptor β
Harrison SA et al. N Engl J Med 2024;390:497-509

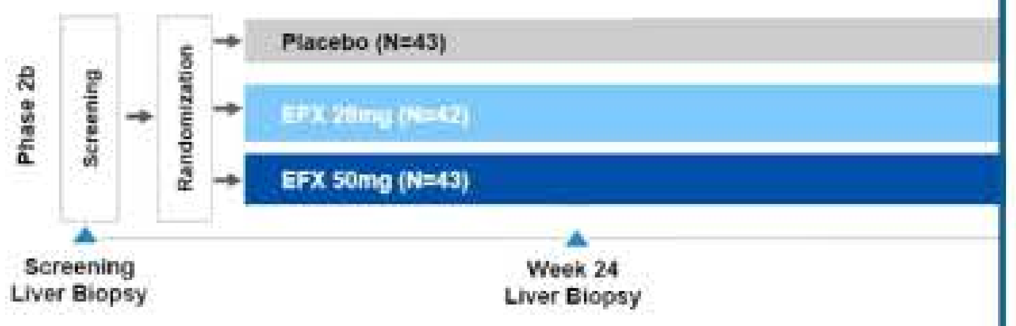
Fibroblast Growth Factor 21 (FGF 21) RA

- primárnym cieľom metabolická alterácia
  - reguluje výdaj energie, metabolizmus sacharidov a lipidov
- redukuje LFC
- regresia inflamácie/fibrózy
- efekt na HSCs a makrofágy
- pleitropický efekt



Harrison S et al J Hepatol 2024

Efruxifermin shows sustained fibro
through 96 weeks



Conventional Histopathology:
Fibrosis Improvement ≥1 Stage
& No Worsening of MASH (LBAS-24 or LBAS-96[1])

Week 96 ITT Analysis[2]

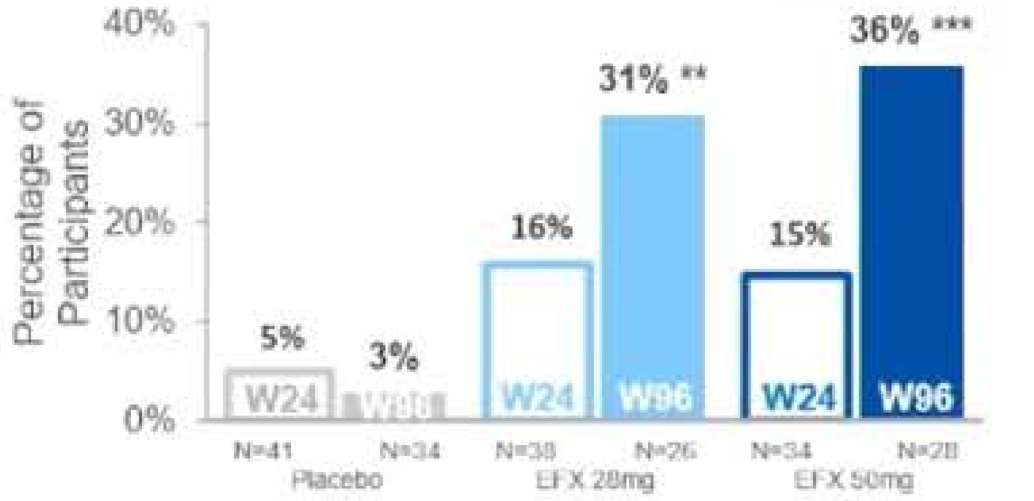
Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
19%	30%	49%**

[1] All participants with biopsies at baseline and specified timepoint; [2] Missing biopsy = non-responder; [3] All participants with unstained sli
† p<0.05, ††† p<0.001 versus placebo at W24; *p<0.05, *** p<0.001, versus placebo at W96 (Coc

Noureddin et al, presented at AASLD TLM 2024

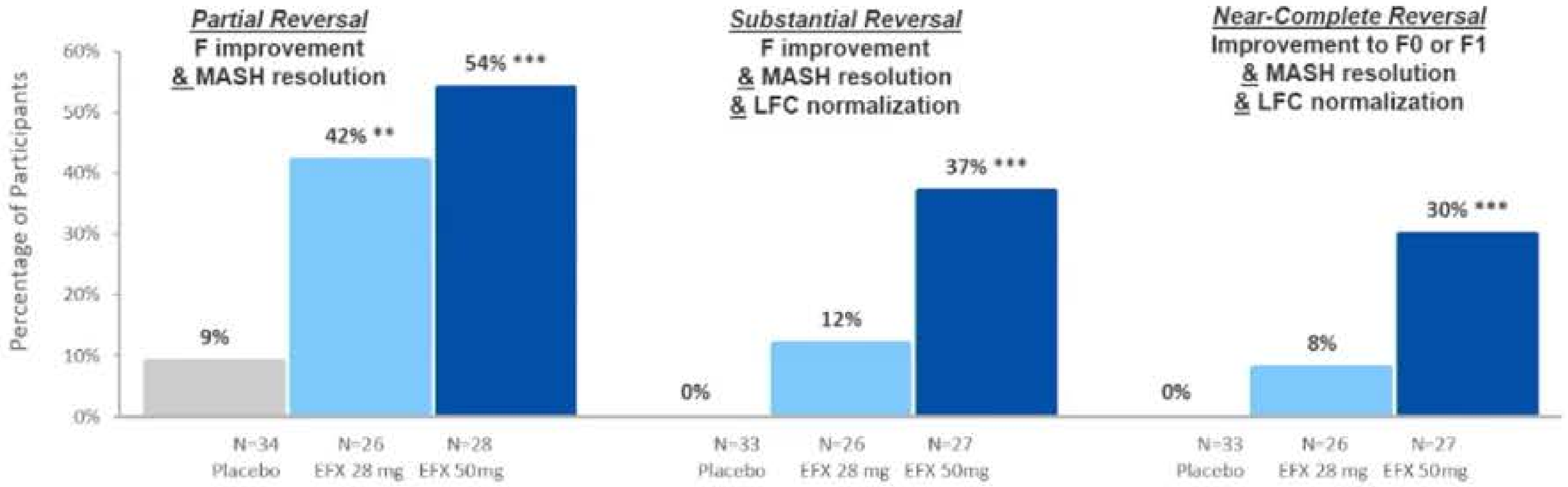
Efruxifermin: evidence of disease reversal after 96 weeks

2-Stage Fibrosis Improvement
& No Worsening of MASH (LBAS-24 or LBAS-96)

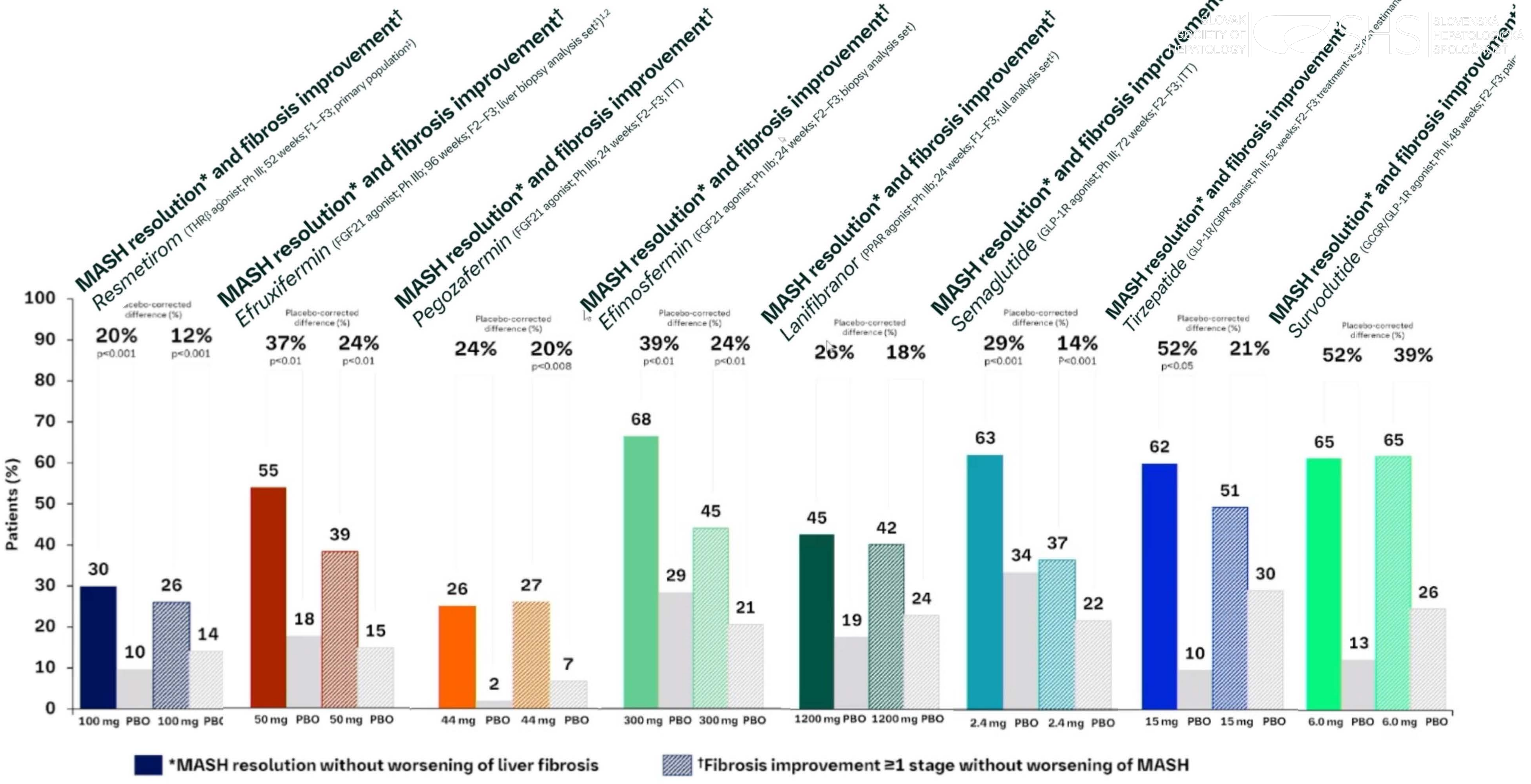


Responder Type at W96 (Proportion of Participants)[1]	Placebo (N=32)	EFX 28 mg (N=26)	EFX 50 mg (N=24)
ELF (≥0.5 absolute reduction in score)	25%	58%	71%
Liver Stiffness (≥30% relative reduction by FibroScan VCTE)	19%	50%	71%
ELF + Liver Stiffness	6%	38%	54%
ELF + Liver Stiffness + Histopathology[2]	0%	19%	42%

[1] Based on those patients with baseline and Week 96 measurements of ELF Score, Liver Stiffness (Fibroscan), and conventional histopathology
[2] ELF + Liver Stiffness AND Fibrosis Improvement ≥1 stage without MASH worsening, by conventional histopathology



Noureddin et al, presented at AASLD TLM 2024



MASH resolution* and fibrosis improvement†
Resmetirom (THRβ agonist; Ph III; 52 weeks; F1–F3; primary population‡)
MASH resolution* and fibrosis improvement†
Efruxifermin (FGF21 agonist; Ph IIb; 96 weeks; F2–F3; liver biopsy analysis set‡)
MASH resolution* and fibrosis improvement†
Pegozafermin (FGF21 agonist; Ph IIb; 24 weeks; F2–F3; ITT)
MASH resolution* and fibrosis improvement†
Efimosfermin (FGF21 agonist; Ph IIb; 24 weeks; F2–F3; biopsy analysis set)
MASH resolution* and fibrosis improvement†
Lanifibranor (PPAR agonist; Ph IIb; 24 weeks; F1–F3; full analysis set‡)
MASH resolution* and fibrosis improvement†
Semaglutide (GLP-1R agonist; Ph III; 72 weeks; F2–F3; ITT)
MASH resolution* and fibrosis improvement†
Tirzepatide (GLP-1R/GIPR agonist; Ph II; 52 weeks; F2–F3; treatment-regimen estimand‡)
MASH resolution* and fibrosis improvement†
Survodutide (GCGR/GLP-1R agonist; Ph II; 48 weeks; F2–F3
Placebo-corrected difference (%)
20% p<0.001
12% p<0.001
37% p<0.01
24% p<0.01
24%
20% p<0.008
39% p<0.01
24% p<0.01
26%
18%
29% p<0.001
14% P<0.001
52% p<0.05
21%
52%
39%
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
30
10
26
14
55
18
39
15
26
2
27
7
68
29
45
21
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42
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63
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37
22
62
10
51
30
65
13
65
26
100 mg
PBO
100 mg
PBO
50 mg
PBO
50 mg
PBO
44 mg
PBO
44 mg
PBO
300 mg
PBO
300 mg
PBO
1200 mg
PBO
1200 mg
PBO
2.4 mg
PBO
2.4 mg
PBO
15 mg
PBO
15 mg
PBO
6.0 mg
PBO
6.0 mg
PBO
*MASH resolution without worsening of liver fibrosis
†Fibrosis improvement ≥1 stage without worsening of MASH

EASL-EASD-EASO Treatment Guidelines

Preferred pharmacologic options for treating comorbidities

MASH-targeted

MASLD/MASH without cirrhosis (F0-F3)
If locally approved:
Resmetirom
in F2/F3 fibrosis

MASLD/ MASH with compensated cirrhosis (F4)
Check indication for liver transplantation in case of decompensation or HCC

T2D

GLP-1RA
(eg, semaglutide, liraglutide, dulaglutide) and co-agonists (eg, tirzepatide)

SGLT2 inhibitors
(eg, empagliflozin, dapagliflozin)

Metformin[a]

Insulin
(in case of decompensated cirrhosis)

Dyslipidemia

Statins

Obesity

GLP-1RA
(eg, semaglutide, liraglutide) and co-agonists (eg, tirzepatide)

Bariatric interventions
(special caution in case of compensated cirrhosis)

[a]If glomerular filtration rate is >30 mL/min.

EASL: European Association for the Study of the Liver; EASD: European Association for the Study of Diabetes; EASO: European Association for the Study of Obesity; GLP-1RA: glucagon-like peptide-1 receptor agonist; HCC: hepatocellular carcinoma; MASH: metabolic dysfunction-associated steatohepatitis; SGLT2: sodium-glucose cotransporter-2.

EASL-EASD-EASO Clinical Practice Guideline Panel. *J Hepatol.* 2024;81:492-542. Reproduced for educational purposes only.

Záver pre MASLD

- najčastejšie ochorenie pečene (cca 35% populácie)
  - nárast hepatálnych dôsledkov: ↑ podielu oLTx a HCC
- včasná detekcia a následne včasná intervencia
- NIT na identifikáciu rizikového pac a monitoring liečby
- nefarmakologická liečba fundamentom
- farmakologická liečba (holistická)
  - metabolické modulárory/metabol. dysfunkcia
  - liečba zameraná na hepar/hepatocyt