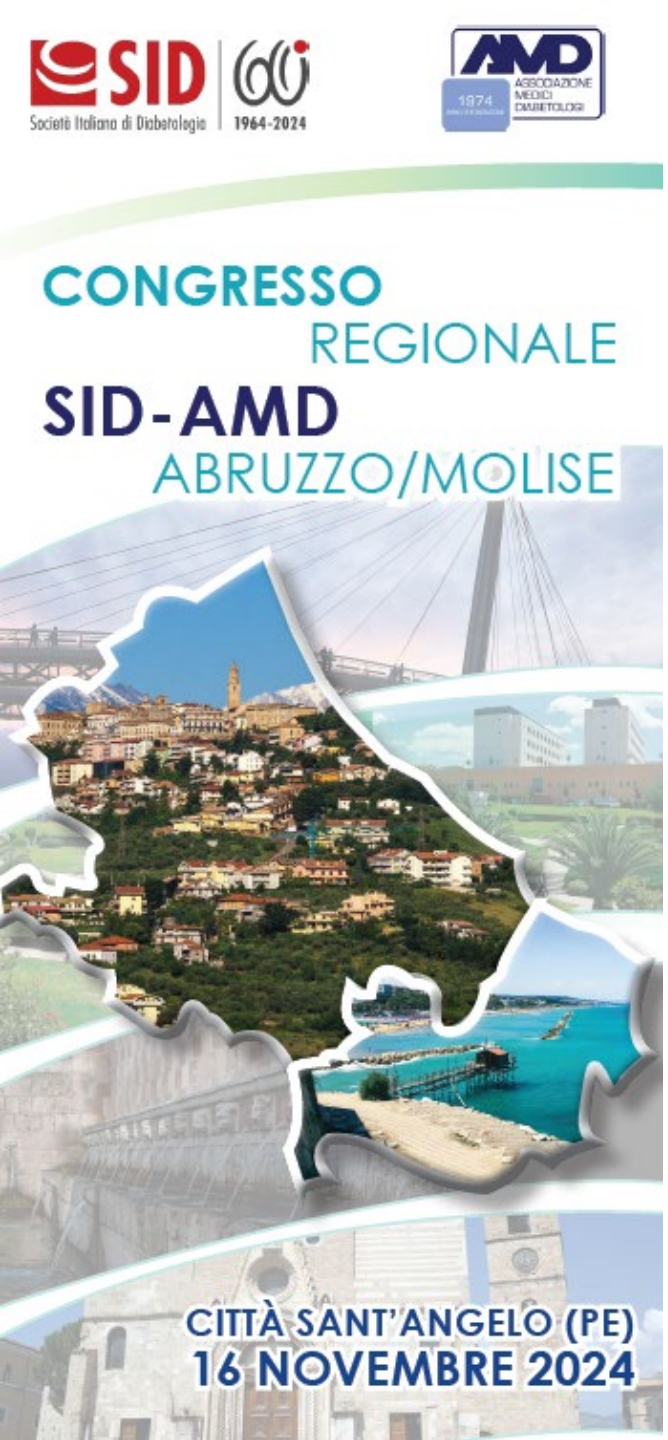


# Gestione della Obesità e Prevenzione/Trattamento di MASLD/MASH


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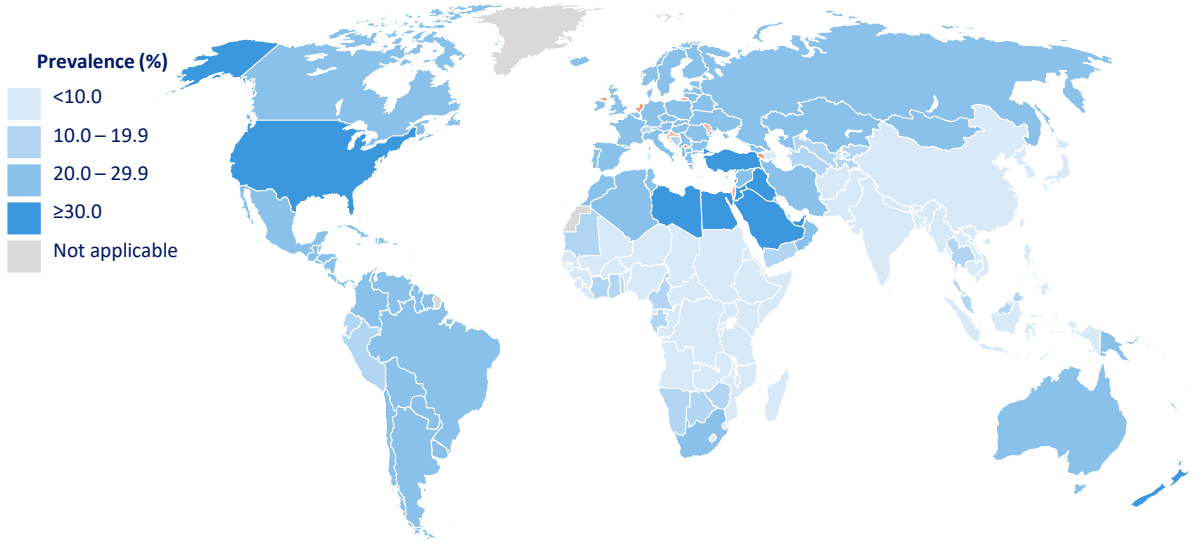
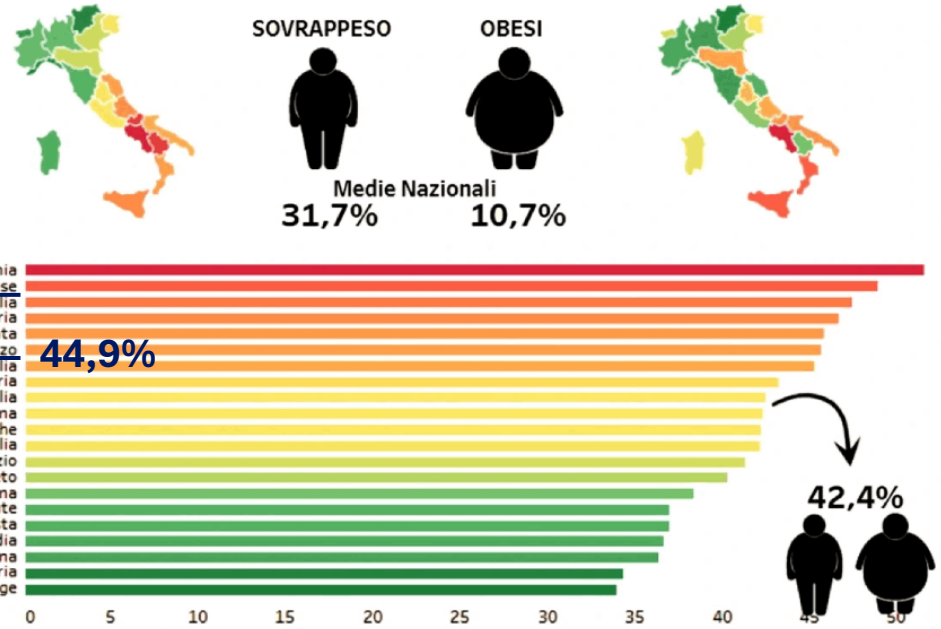
asl pescara

La dr.ssa Baldassarre MPA dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

*Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).*

# Obesity: a growing global (and local) challenge



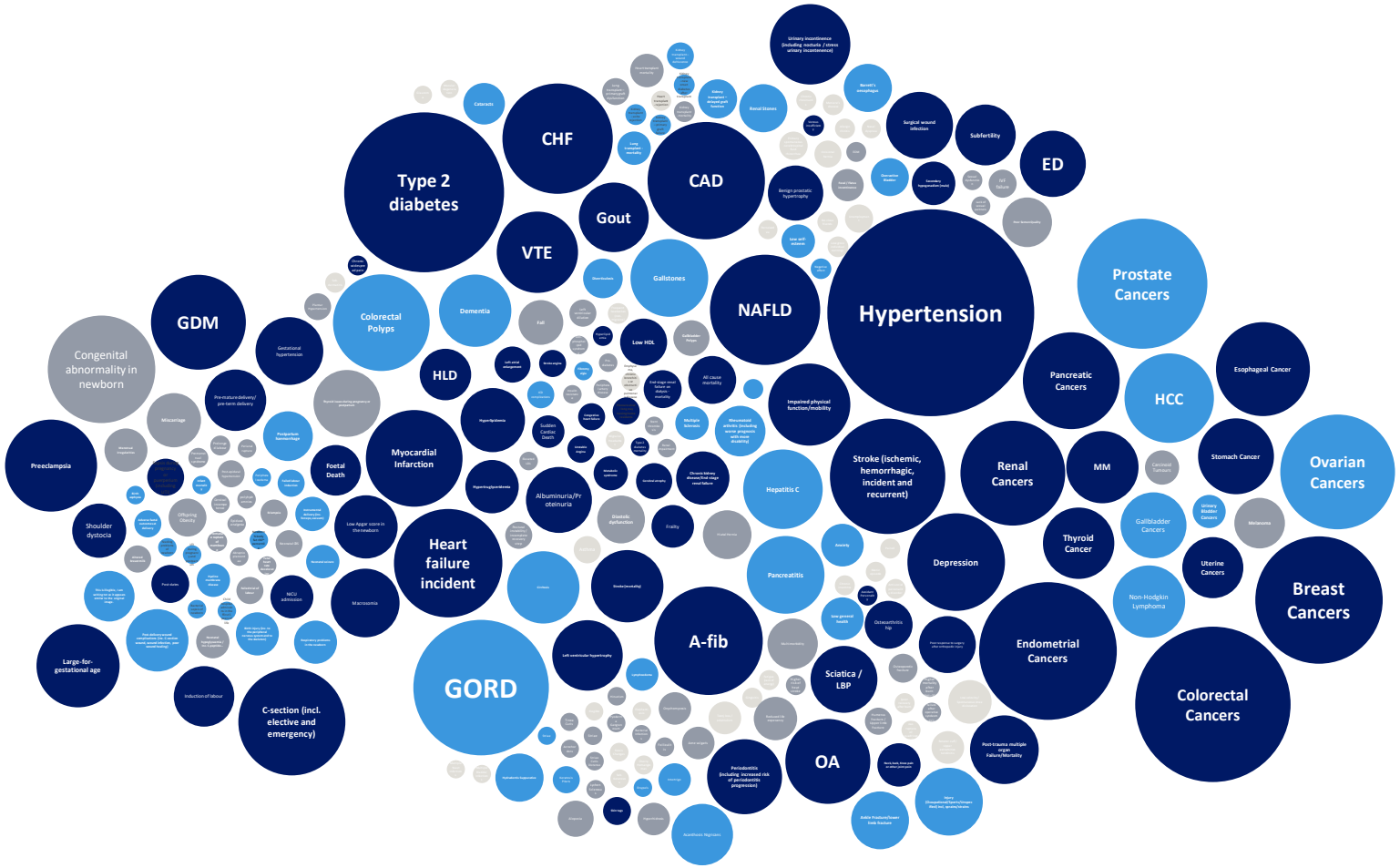


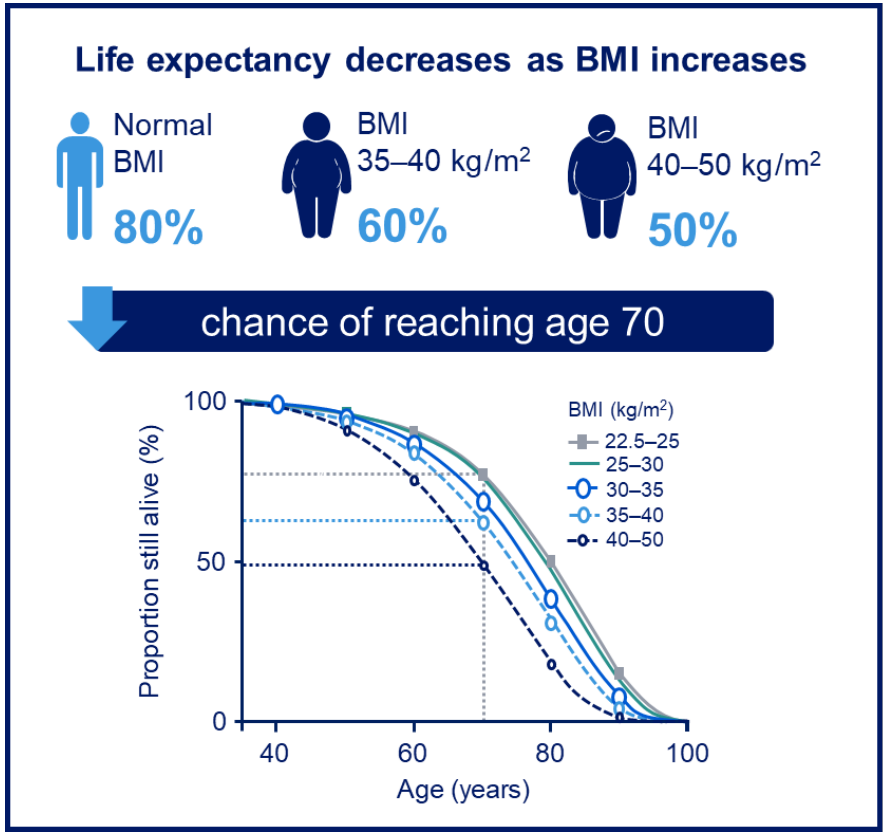
**34,4% Overweight**

**10,5% Obesity**

*World Obesity Atlas, 2022; D'Errico M, et al. Eur J Health Econ 2022; https://www.epicentro.iss.it/okkioallasalute/indagine-2023-report-Abruzzo*

# Obesity is associated with multiple complications




*Prospective Studies Collaboration. Lancet 2009;373:1083–96*

# Prevalence of complications in people with obesity

Body mass index ≥30

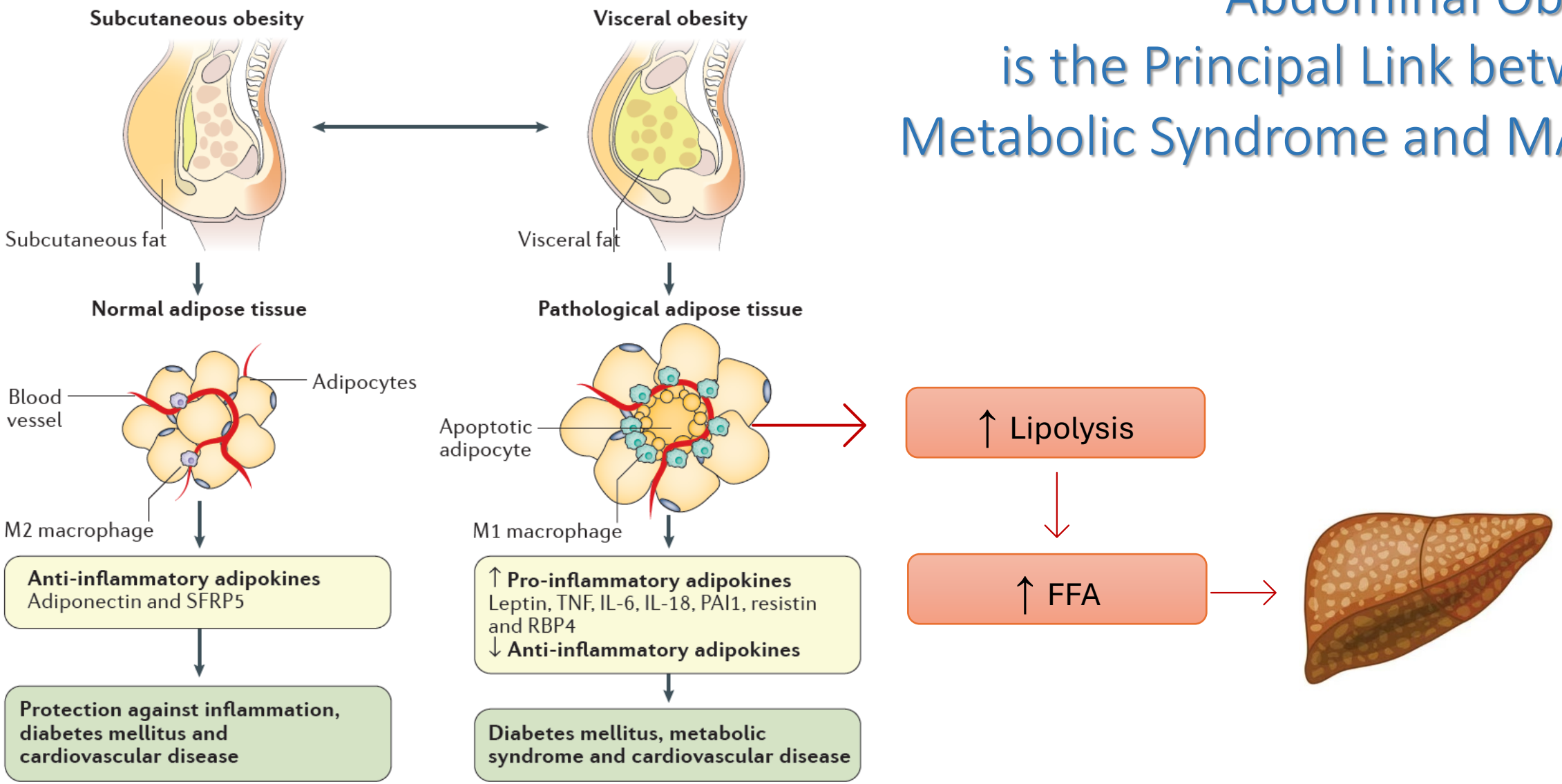
- **3%** Stroke
- **3.5%** Congestive heart failure
- **8%** Ischaemic heart disease
- **9%** PCOS
- **19%** Major depression
- **21%** Diabetes
- **21%** Myocardial infarction
- **80%** MASLD
- **35%** GERD symptoms*
- **~40%** OSAS
- **51%** Hypertension
- **60-70%** Dyslipidemia

**Weekly heartburn and regurgitation.*

*GERD, gastro-oesophageal reflux disease; NAFLD, nonalcoholic fatty liver disease; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome.*

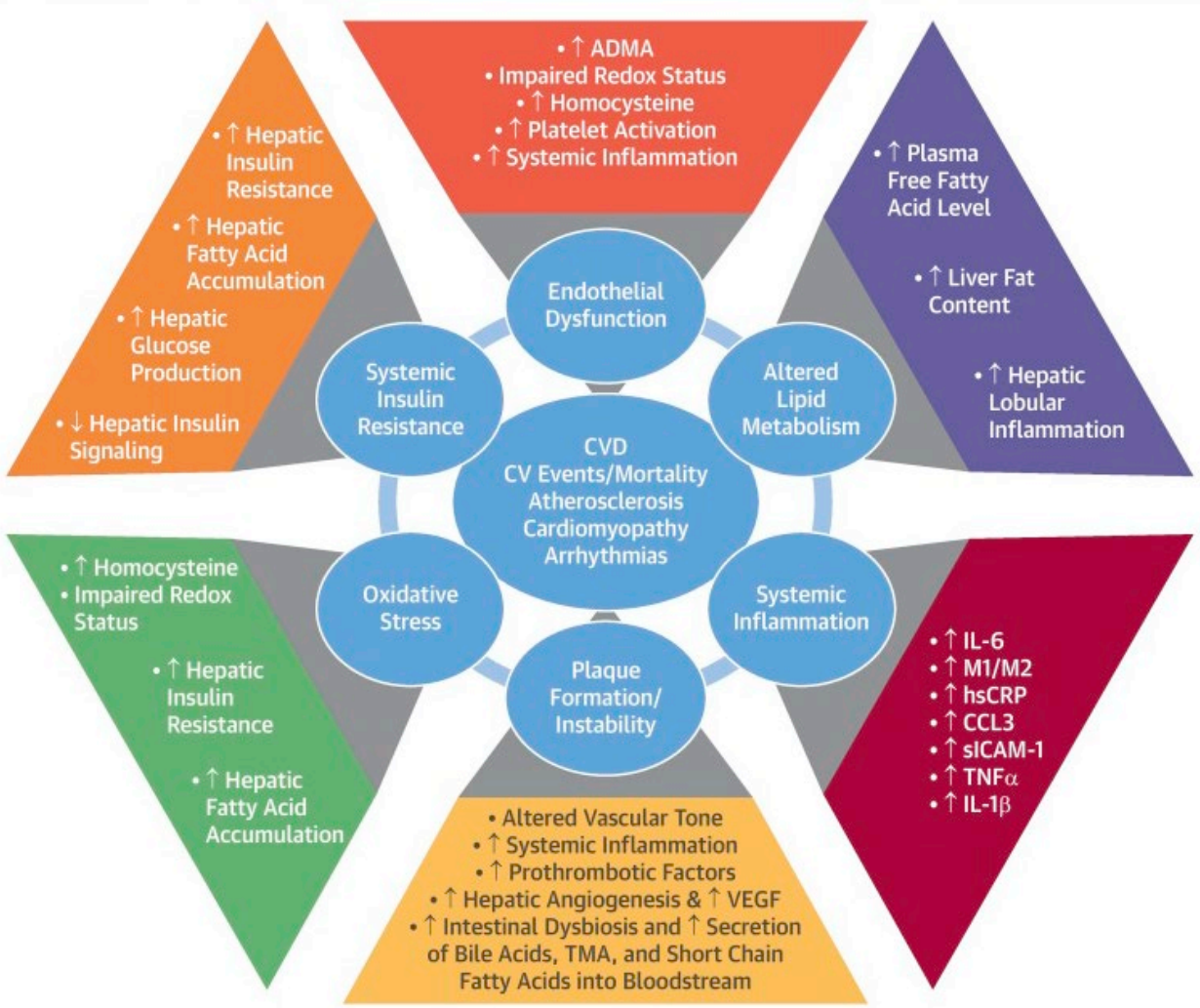
*Simon GE et al. Arch Gen Psychiatry 2006;63:824–30; Su W et al. J Med Economics 2015;18:886–97; López-Velázquez JA et al. Ann Hepatol 2014;13:166–78; Yildiz BO et al. J Clin Endocrinol Metab. 2008;93:162–68; El-Serag HB et al. Am J Gastroenterol. 2005;100:1243–50; Prieto-Alhambra D et al. Ann Rheum Dis 2014;73:1659–64; Modena DAO et al. Rev Assoc Med Bras 1992;63:852–8.*

# Abdominal Obesity is the Principal Link between Metabolic Syndrome and MASLD




*Mod from Gonzales-Muniesa et al. Nature Reviews Disease Primers volume 3, Article number: 17034 (2017)*

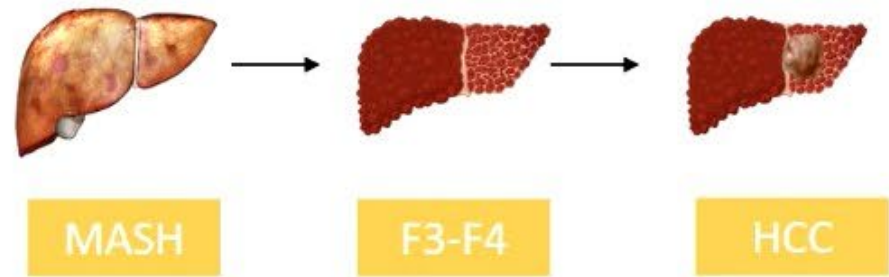
# Pathophysiological Mechanisms of Increasing Risk of Cardiovascular Disease in MASLD




*Stahl et al. JACC vol 73, no. 8, 2019; Zannad et al. J Intern Med. 2024; 296: 24–38.*

# Bidirectional relationship between MASLD and T2DM

Type 2 Diabetes




hampers **to maintain an optimal glycemic control**

Increase risk of

**macrovascular and microvascular complications**

*Cusi K. Diabetologia (2016) 59:1112–1120*
*Birkenfeld Al et al. Hepatology. 2014;59(2):713-23*
*Targher et al.Nat Rev Endocrinol. 2018 Feb;14(2):99-114*

Increased risk of progression towards:

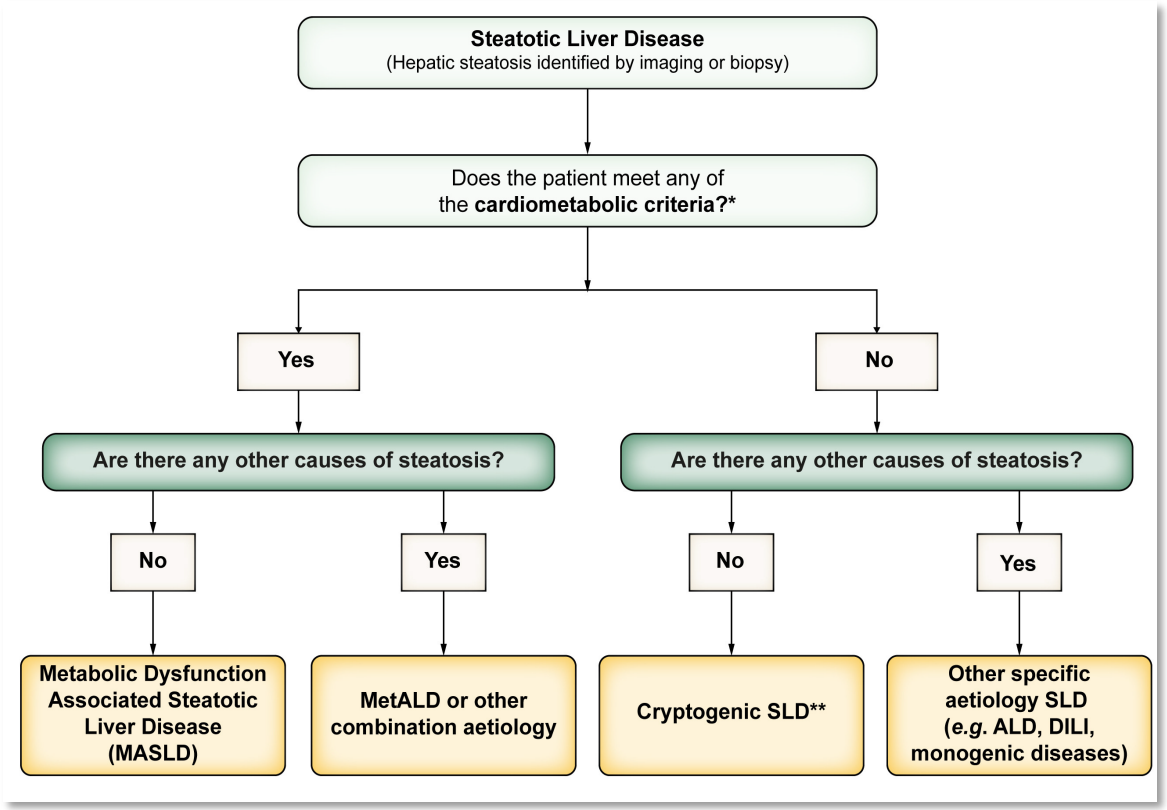
- ✓ **MASH**
- ✓ **Advanced fibrosis**
- ✓ **HCC**
- ✓ **Liver –related outcomes**

*McPherson S et al. J Hepatol. 2015;62(5):1148-55*
*Wang P et al. Diabetes Metab Res Rev. 2012;28(2):109-22*
*Huang et al Gastroenterology . 2023 Aug;165(2):463-472.e5.6*
*Huang et al. Lancet Gastroenterol Hepatol. 2023 Sep;8(9):829-836.*

# NAFLD is now MASLD (Metabolic dysfunction-Associated Steatotic Liver Disease)

Rinella ME et al. J Hepatol. 2023 Jun 20:S0168-8278(23)00418-X

# MASLD: Diagnostic Criteria



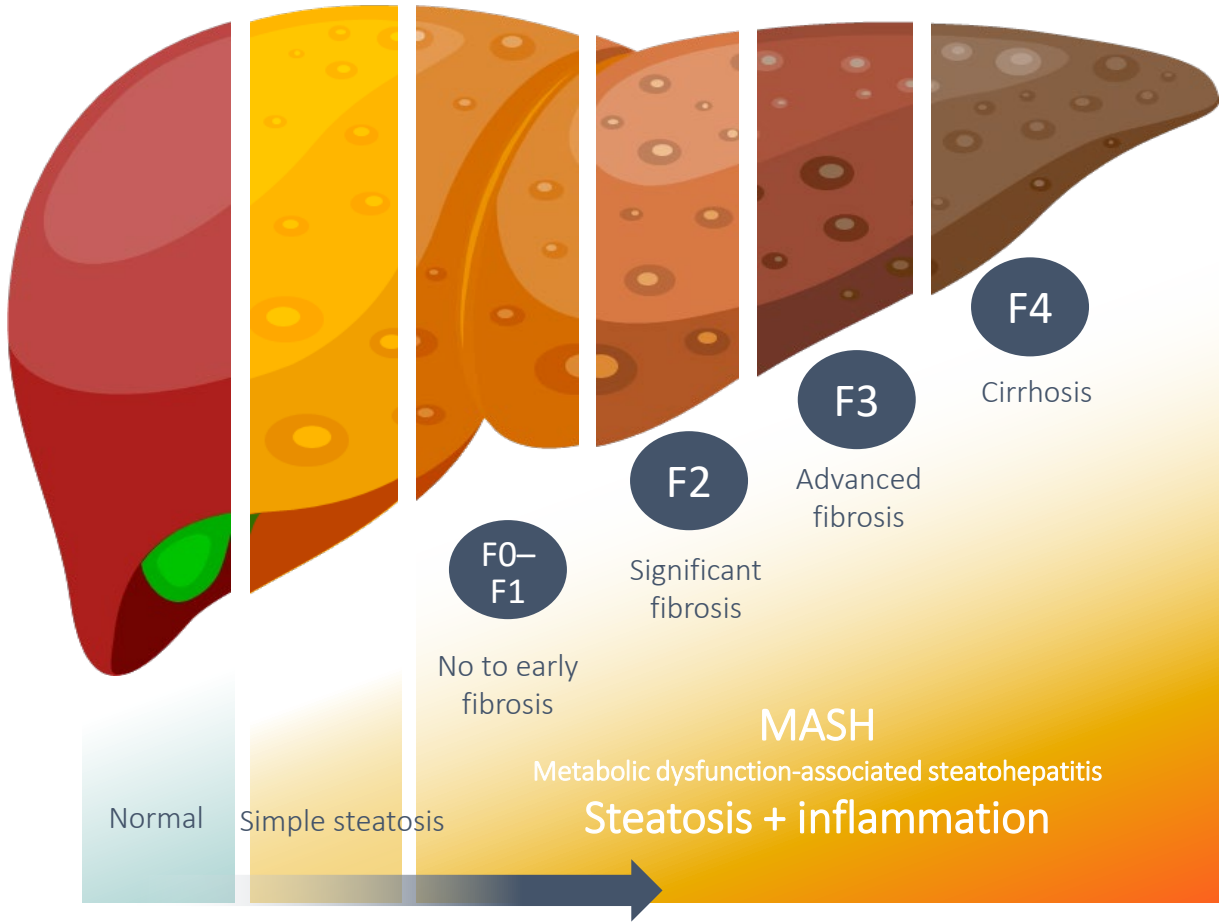

*Cardiometabolic criteria

| 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 ≥30/85 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 <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 |

Aligned with Alberti et al. Circulation 2009

Rinella ME et al. J Hepatol. 2023 Jun 20:S0168-8278(23)00418-X

# MASLD/MASH: Diagnosis in Clinical Practice




| Parameter |
|---|
| Age |
| AST |
| ALT |
| Platelet count |
| BMI |
| Albumin |
| Impaired fasting glucose/diabetes? |

NAFLD fibrosis score

| NAFLD fibrosis score[1] | Effect | NPV or PPV, % |
|---|---|---|
| <-1.455 | Rules out fibrosis | 88 to 93 |
| >0.676 | Predicts fibrosis | 82 to 90 |

FIB-4 Score

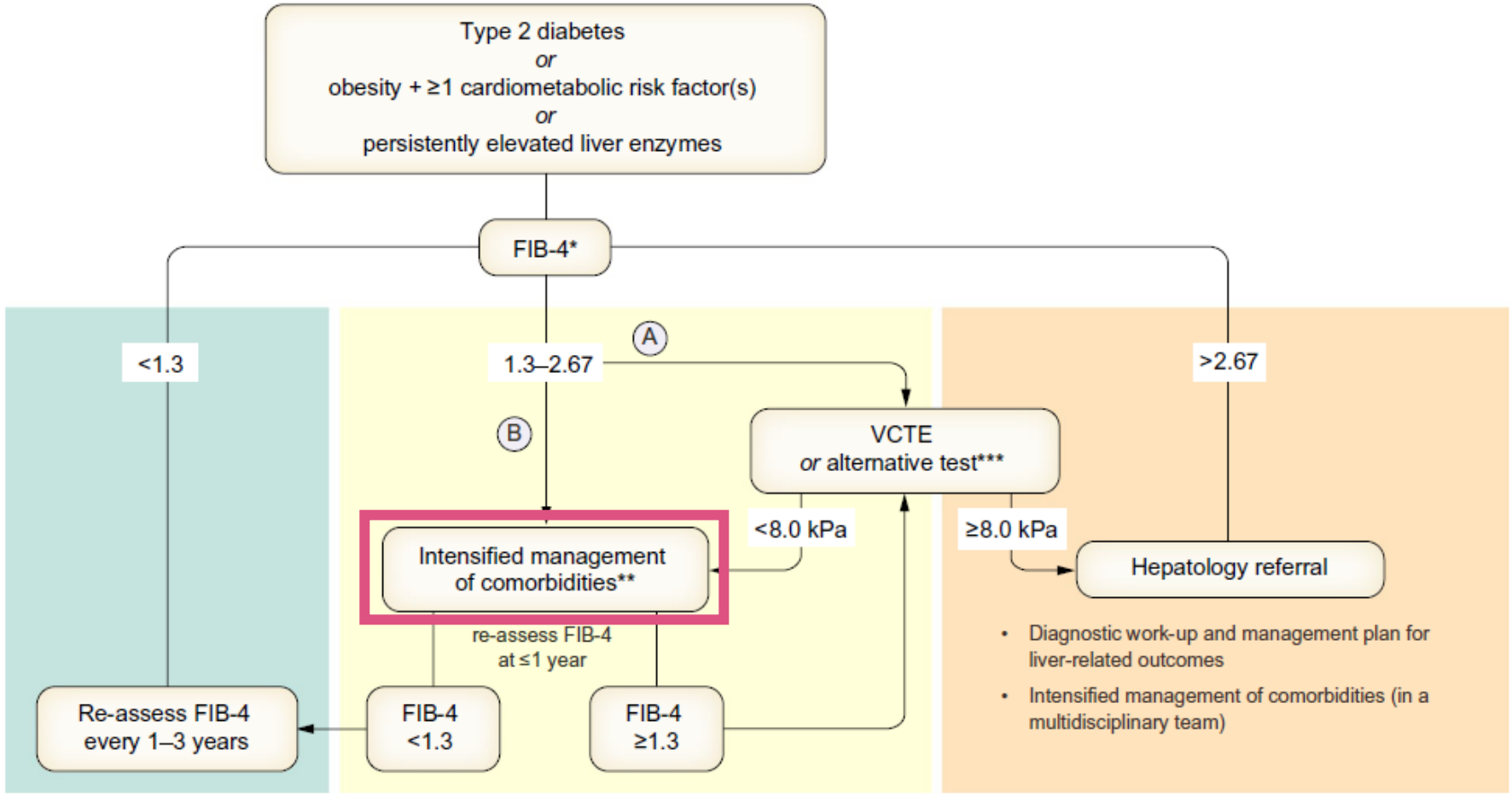
| FIB-4 Score [2,3] | Effect | NPV or PPV, % |
|---|---|---|
| <1.3 | Rules out fibrosis | 95 |
| >3.25 | Predicts fibrosis | 75 |

| | |
|---|---|
| Vit. D (Sie) [ng/ml] | 37,0 |
| Fibrosis-4 (FIB-4) | 1,03 |
| NAFLD fibrosis score (NFS) | -0,9665 |
| Piastrine [10^9/L] | 238,00 |
| Albumina (Sie) [g/dl] | 4,3 |
| Colesterolo non HDL (calc) [mg/dl] | 164 |

Gold Standard: Biopsia o Spettroscopia RMN
Pratica Clinica: Ecografia, CAP

Gold Standard: Biopsia
Imaging: VCTE, 2D-SWE
Marcatori Sierici: FIB-4, NFS

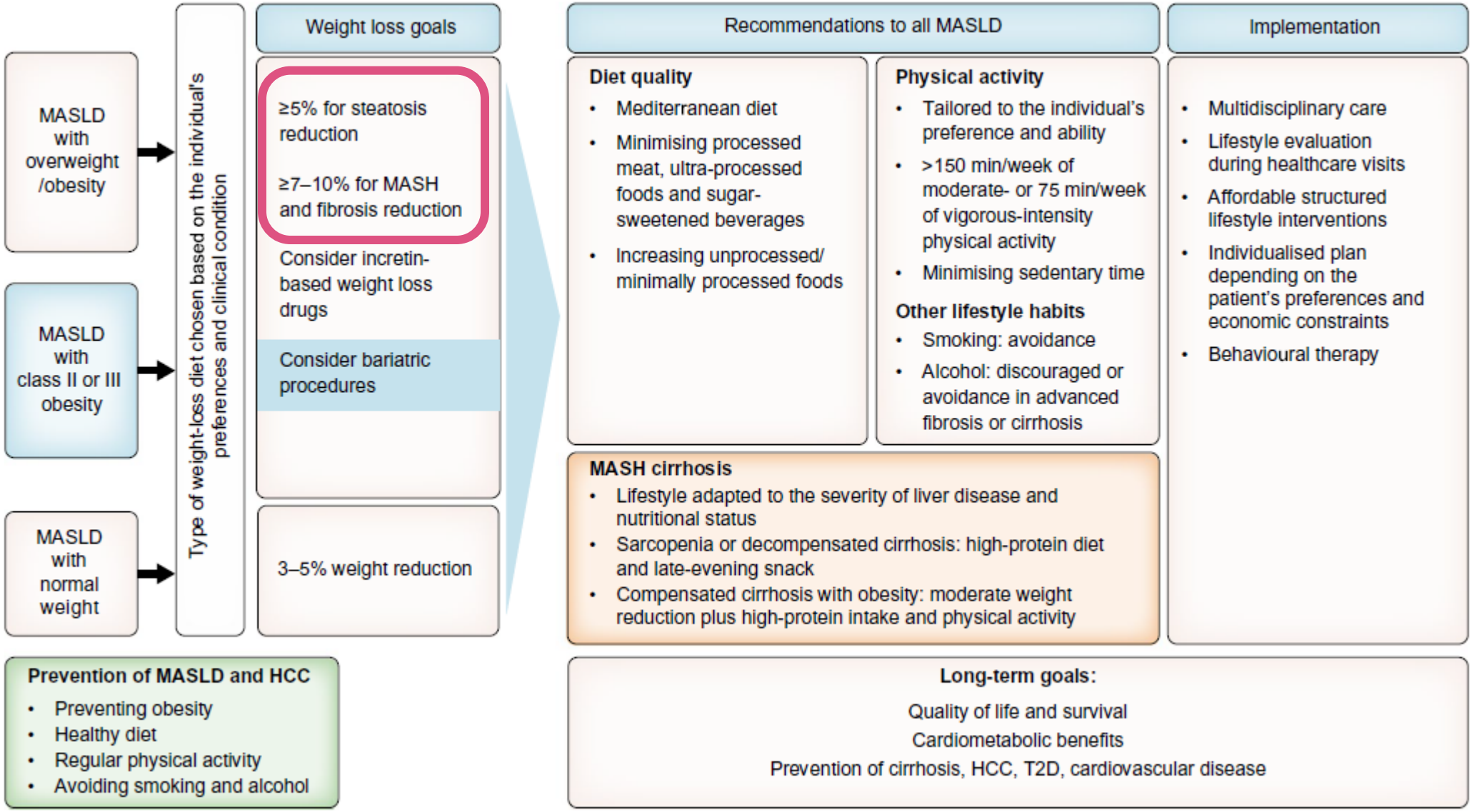
# Non-invasive assessment of the risk for advanced fibrosis




* FIB-4 thresholds valid for age ≤65 years (for age >65 years: lower FIB-4 cut-off is 2.0)
** e.g. lifestyle intervention, treatment of comorbidities (e.g. GLP1RA), bariatric procedures
*** e.g. MRE, SWE, ELF, with adapted thresholds
Ⓐ and Ⓑ are options, depending on medical history, clinical context and local resources

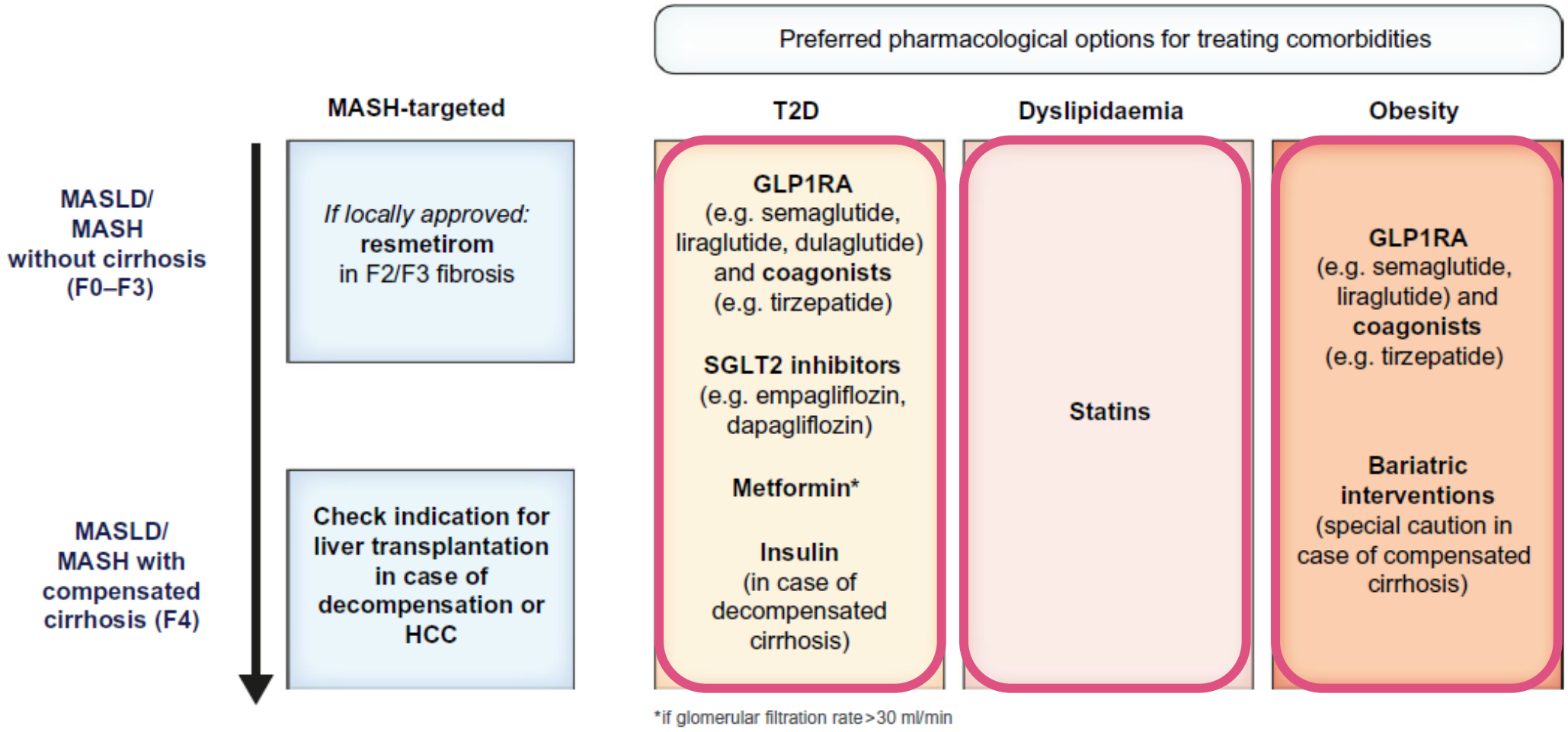
*Diabetologia (2024) 67:2375–2392*

# EASL–EASD–EASO Clinical Practice Guidelines on the management of MASLD




*Diabetologia (2024) 67:2375–2392*

# EASL–EASD–EASO Clinical Practice Guidelines on the management of MASLD



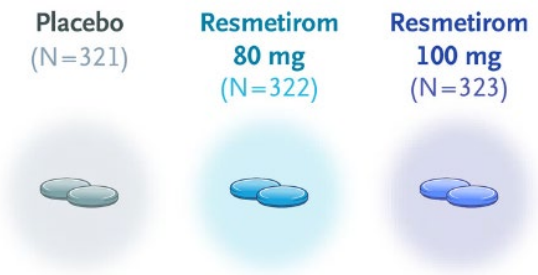

*Diabetologia (2024) 67:2375–2392*

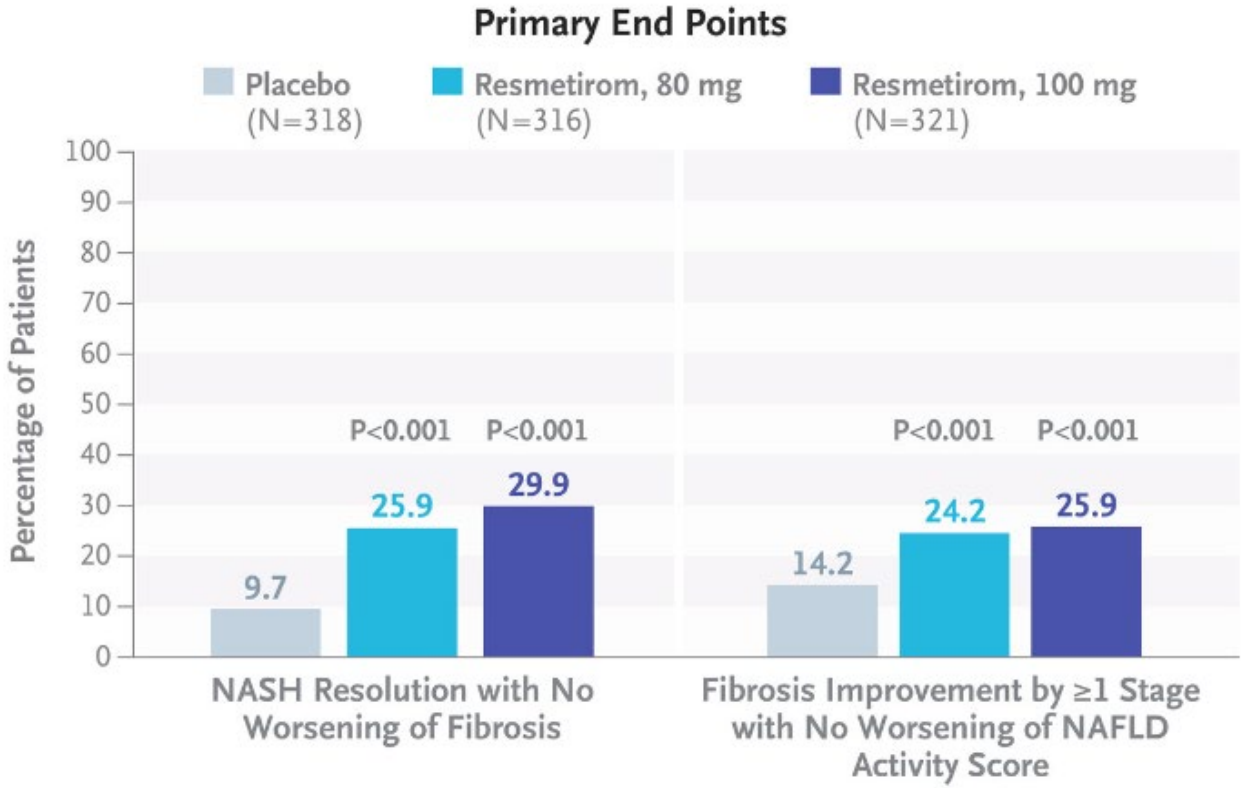
RESEARCH SUMMARY

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

Harrison SA et al. DOI: 10.1056/NEJMoa2309000

Agonista selettivo dell'isoforma beta del recettore degli ormoni tiroidei

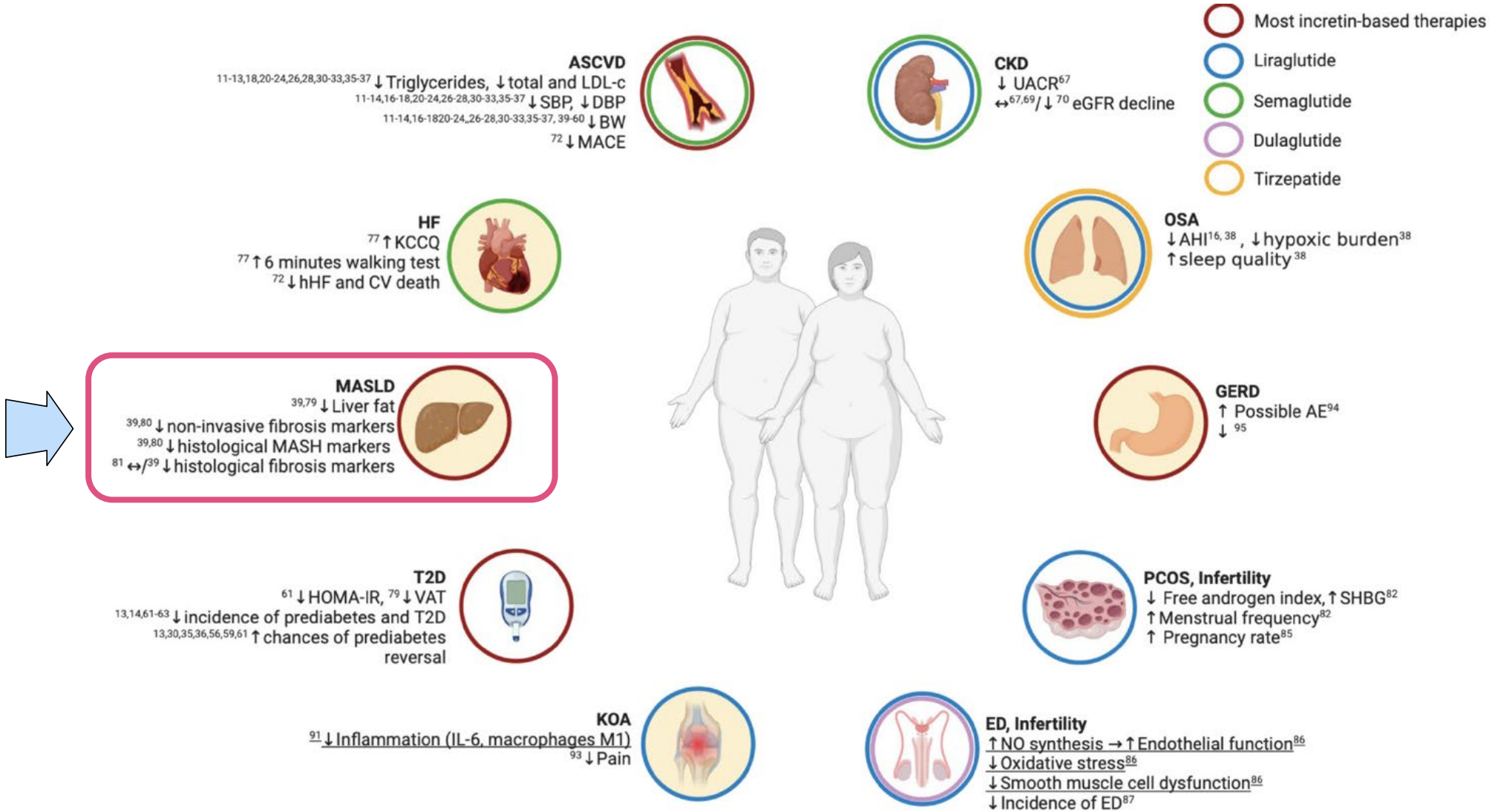



- aumento della SHBG con corrispettivo aumento dei livelli circolanti totali di estradiolo e testosterone
- ↓ funzionalità dell'asse ipofisario-tiroideo, con una riduzione dal 17 al 21% dei livelli di free T4 con parallela riduzione del TSH

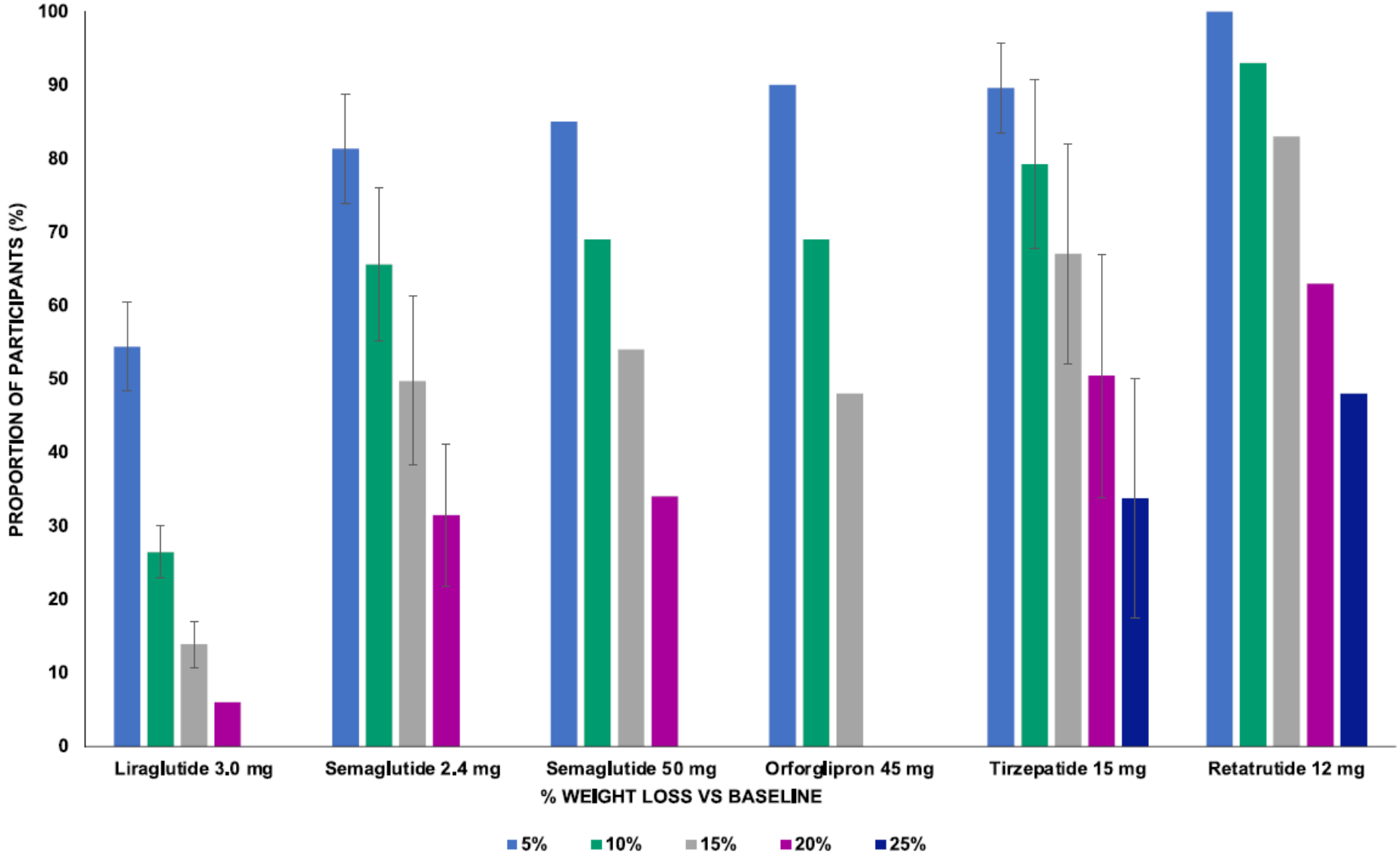
*Harrison SA et al. N Engl J Med 2024 Feb 8;390(6):497-509*

# Effect of incretin-based therapies on obesity-related comorbidities



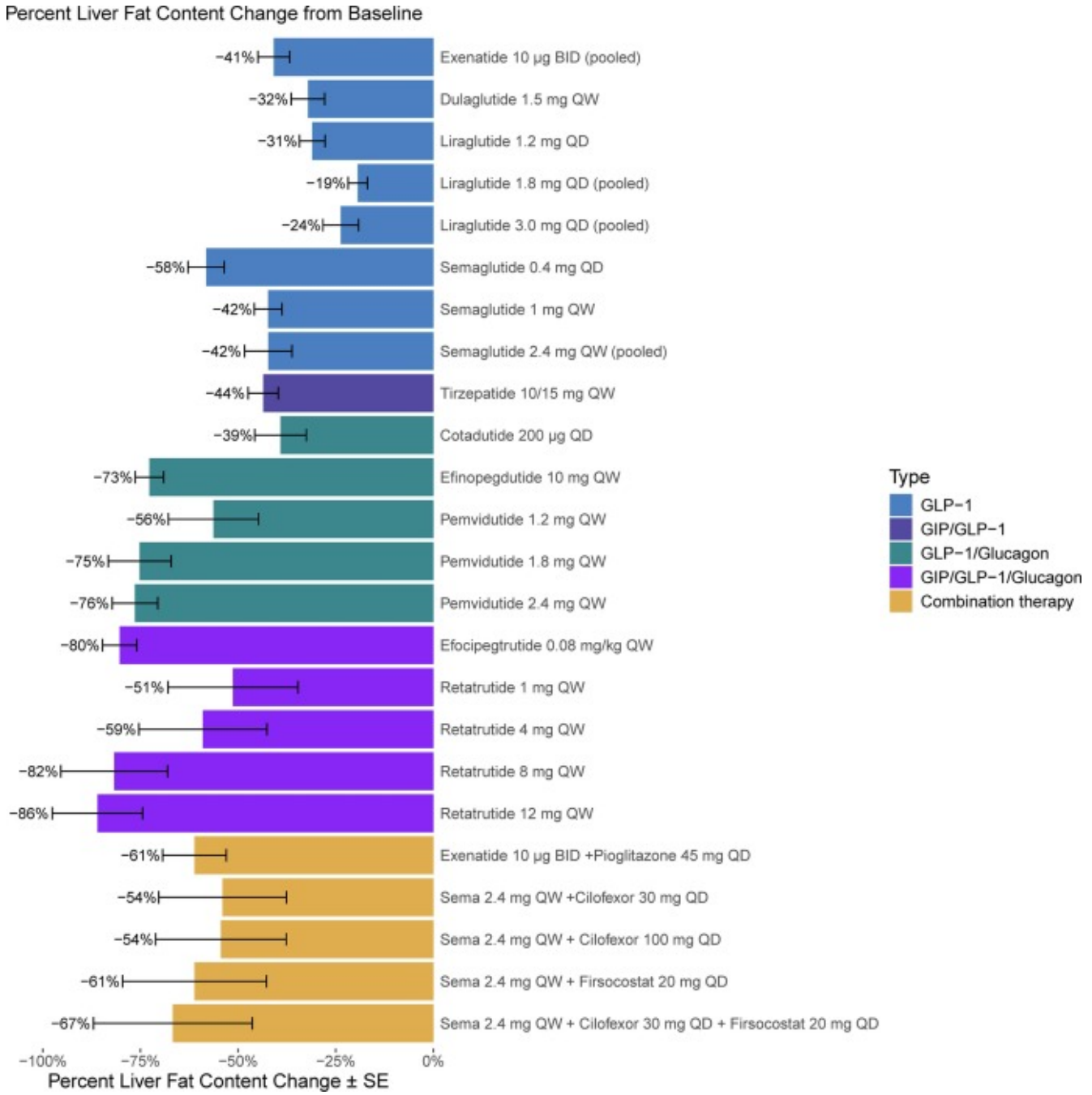

*Caruso et al. NPJ Metab health Dis. 2024*

# Body weight loss with incretin-based anti-obesity medications




*Caruso et al. NPJ Metab health Dis. 2024*

# Relative percent liver fat change with Incretin-based Therapies




*Brouwers et al. DRCP Volume 211, May 2024*

BREAKING NEWS

company announcement

# Semaglutide 2.4 mg demonstrates superior improvement in both liver fibrosis and MASH resolution in the ESSENCE trial

In 1,200 adults with metabolic dysfunction-associated steatohepatitis (MASH) and moderate to advanced liver fibrosis (stage 2 or 3)
At week 72, 37.0% of people treated with semaglutide 2.4 mg achieved improvement in liver fibrosis with no worsening of steatohepatitis compared to 22.5% on placebo. 62.9% of people treated with semaglutide 2.4 mg achieved resolution of steatohepatitis with no worsening of liver fibrosis compared to 34.1% on placebo.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 25, 2024 VOL. 391 NO. 4

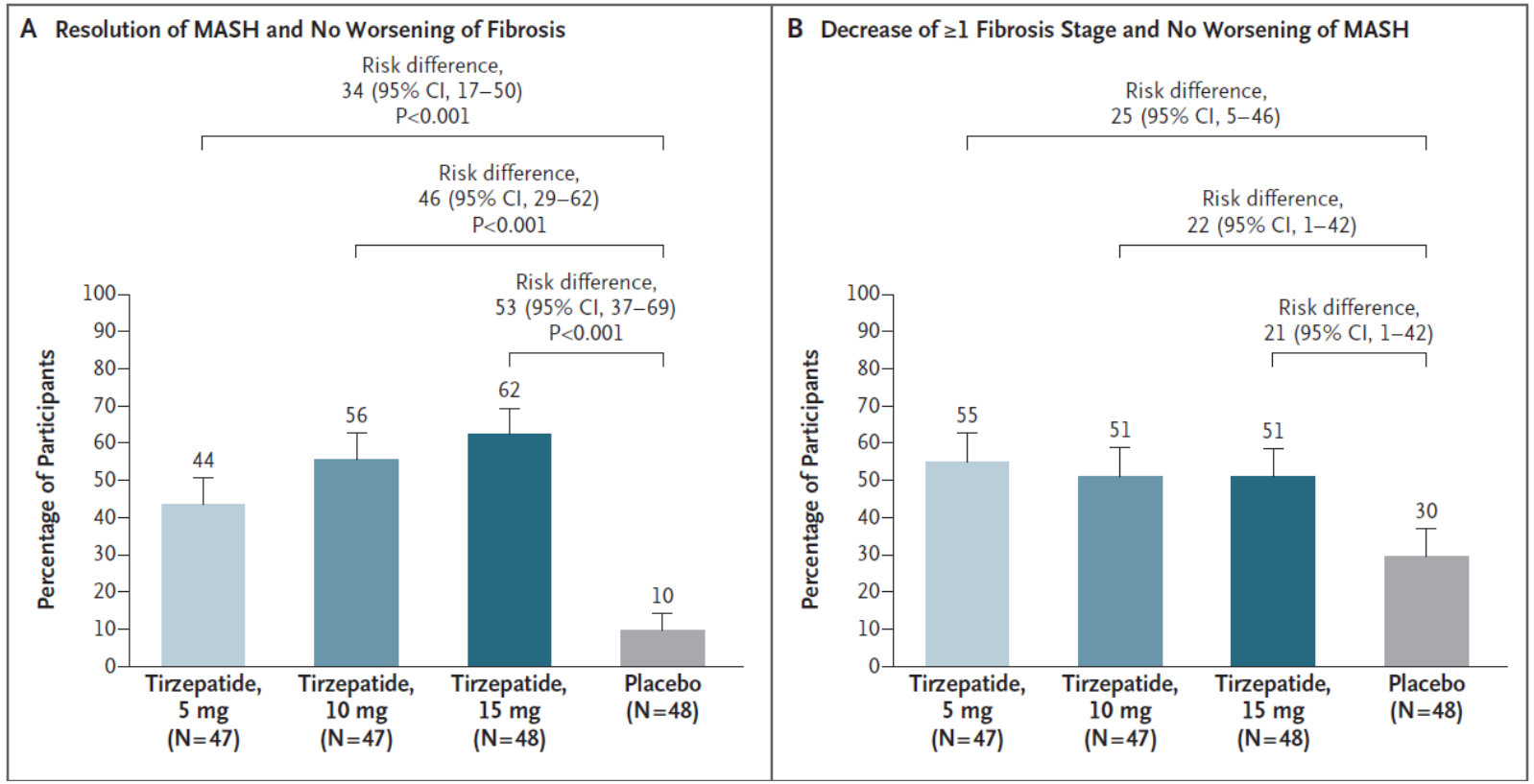
# Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

*«The small sample size did not provide adequate statistical power to evaluate the effect of tirze on fibrosis»*

**PARTICIPANTS** 52 Weeks

| | |
|---|---|
| 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 |



JAMA Internal Medicine | Original Investigation

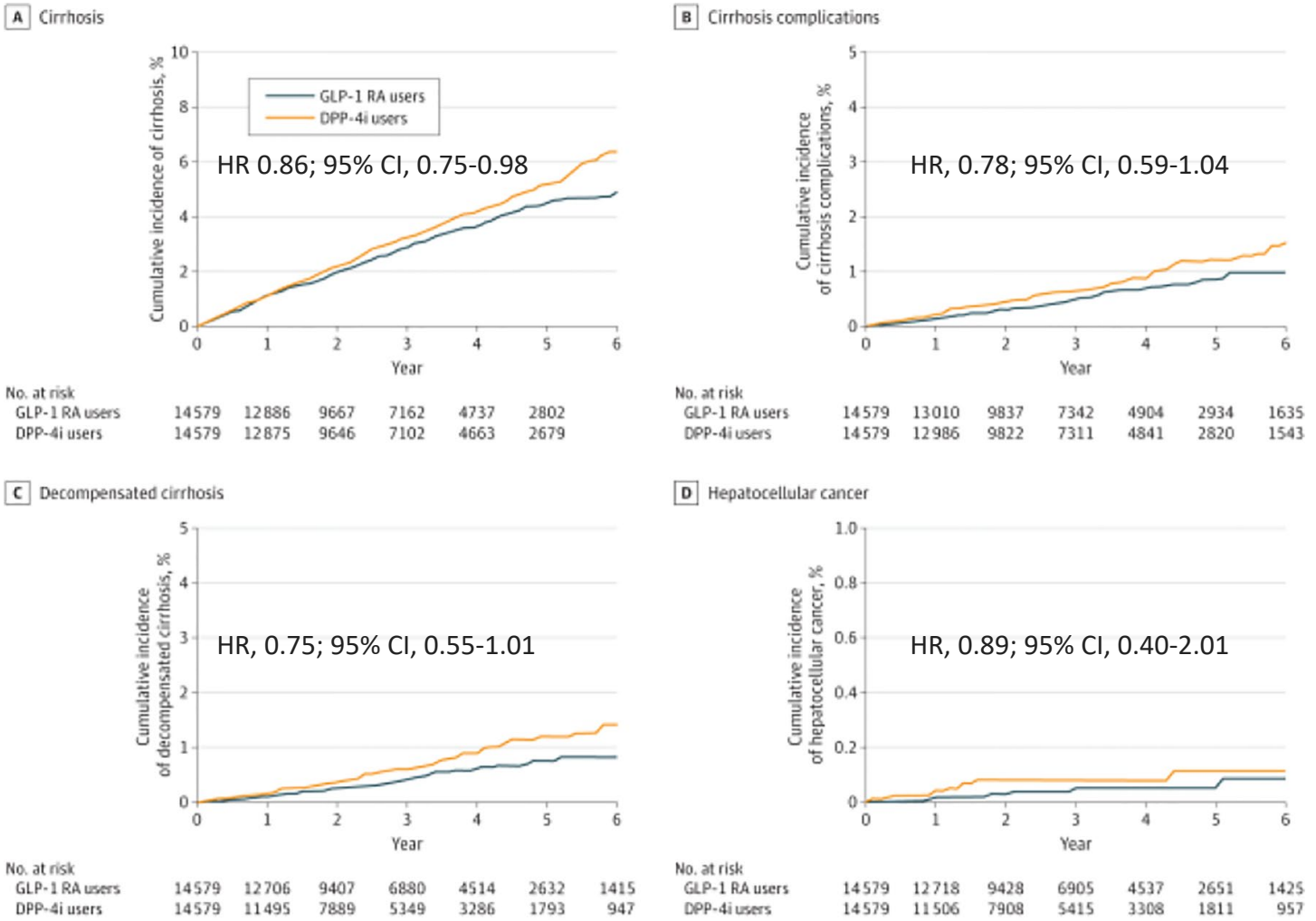
# GLP-1 Receptor Agonists and Risk for Cirrhosis and Related Complications in Patients With Metabolic Dysfunction-Associated Steatotic Liver Disease

Fasiha Kanwal, MD, MSHS; Jennifer R. Kramer, MPH, PhD; Liang Li, PhD; Yu-Xiao Yang, MD, MSCE; Yumei Cao, MS; Xian Yu, PhD; Ronald Samuel, MD; Basim Ali, MD; Roxanne Desiderio, BS; George Cholankeril, MD, MSc; Mandeep Bajaj, MD; Hashem B. El-Serag, MD, MPH; Steven M. Asch, MD, MPH

**16 058 patients**
**(14 606 without and 1452 with cirrhosis)**
**Treated with GLP1RA**

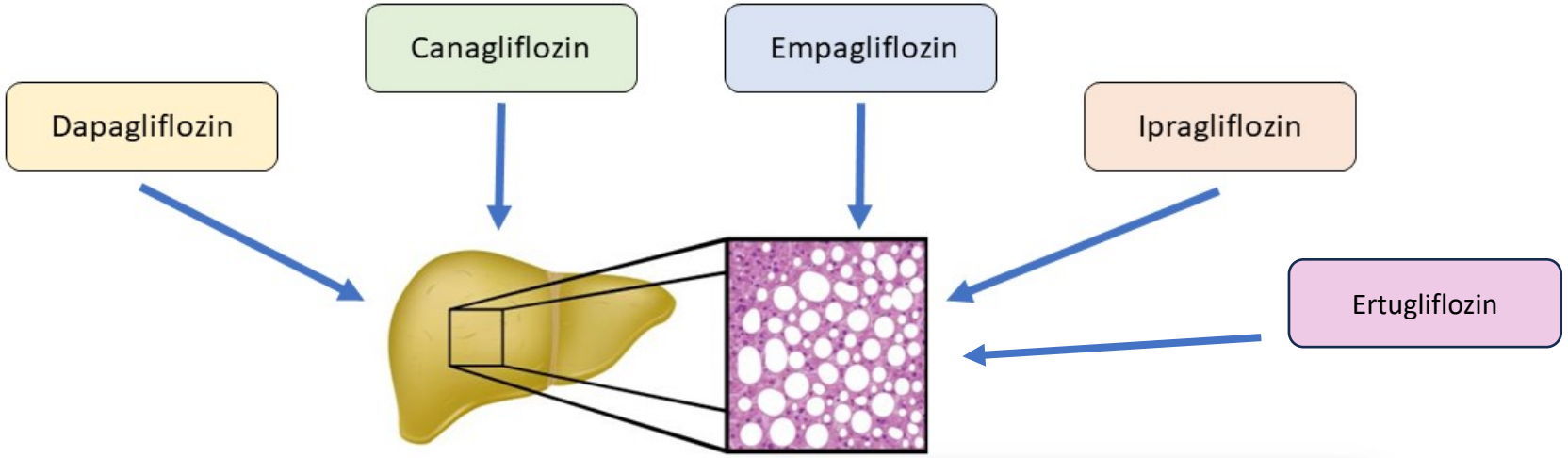
GLP-1 RA use was associated **with a lower risk of progression to cirrhosis** and mortality among patients with MASLD and diabetes.

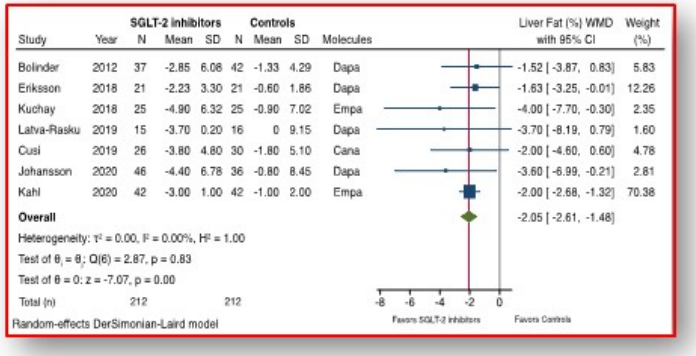
The protective association **was not seen in patients with existing cirrhosis**, underscoring the importance of treatment earlier in the disease course.




*Kanwal et al. JAMA Intern Med . 2024 Nov 1;184(11):1314-1323*

# SGLT-2i on MASLD-MASH



| Study | Year | SGLT-2 inhibitors N | Mean | SD | Controls N | Mean | SD | Molecules | Liver Fat (%) WMD with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Bolinder | 2012 | 37 | -2.85 | 6.06 | 42 | -1.33 | 4.29 | Dapa | -1.52 [ -3.87, 0.83] | 5.83 |
| Eriksson | 2018 | 21 | -2.23 | 3.30 | 21 | -0.60 | 1.86 | Dapa | -1.63 [ -3.25, -0.01] | 12.26 |
| Kuchay | 2018 | 25 | -4.90 | 6.32 | 25 | -0.90 | 7.02 | Empa | -4.00 [ -7.70, -0.30] | 2.35 |
| Latva-Rasku | 2019 | 15 | -3.70 | 0.20 | 16 | 0 | 9.15 | Dapa | -3.70 [ -8.19, 0.79] | 1.60 |
| Cusi | 2019 | 26 | -3.80 | 4.80 | 30 | -1.80 | 5.10 | Cana | -2.00 [ -4.60, 0.60] | 4.78 |
| Johansson | 2020 | 46 | -4.40 | 6.78 | 36 | -0.80 | 8.45 | Dapa | -3.60 [ -6.99, -0.21] | 2.81 |
| Kahl | 2020 | 42 | -3.00 | 1.00 | 42 | -1.00 | 2.00 | Empa | -2.00 [ -2.68, -1.32] | 70.38 |
| **Overall** | | | | | | | | | -2.05 [ -2.61, -1.48] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta_i = \theta_j$: $Q(6) = 2.87$, $p = 0.83$
Test of $\theta = 0$: $z = -7.07$, $p = 0.00$
Total (n) 212 212
Random-effects DerSimonian-Laird model

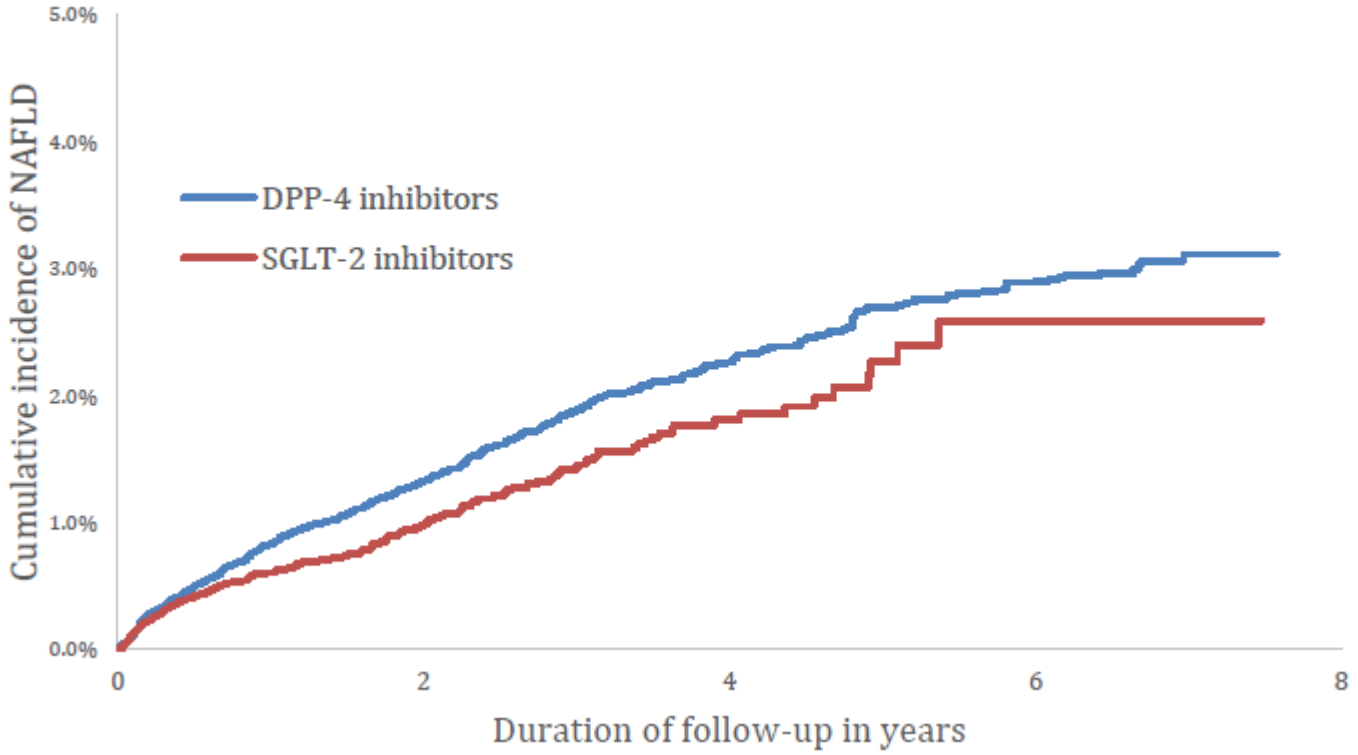
-8 -6 -4 -2 0
Favors SGLT-2 inhibitors
Favors Controls

Significant improvements in liver fat content (as assessed by magnetic resonance-based techniques) and serum liver enzyme levels

*Mantovani et Al, Metabolites 2021; Adil Khaliq et al.Medicine (Baltimore) 2024 Nov 8;103(45)*

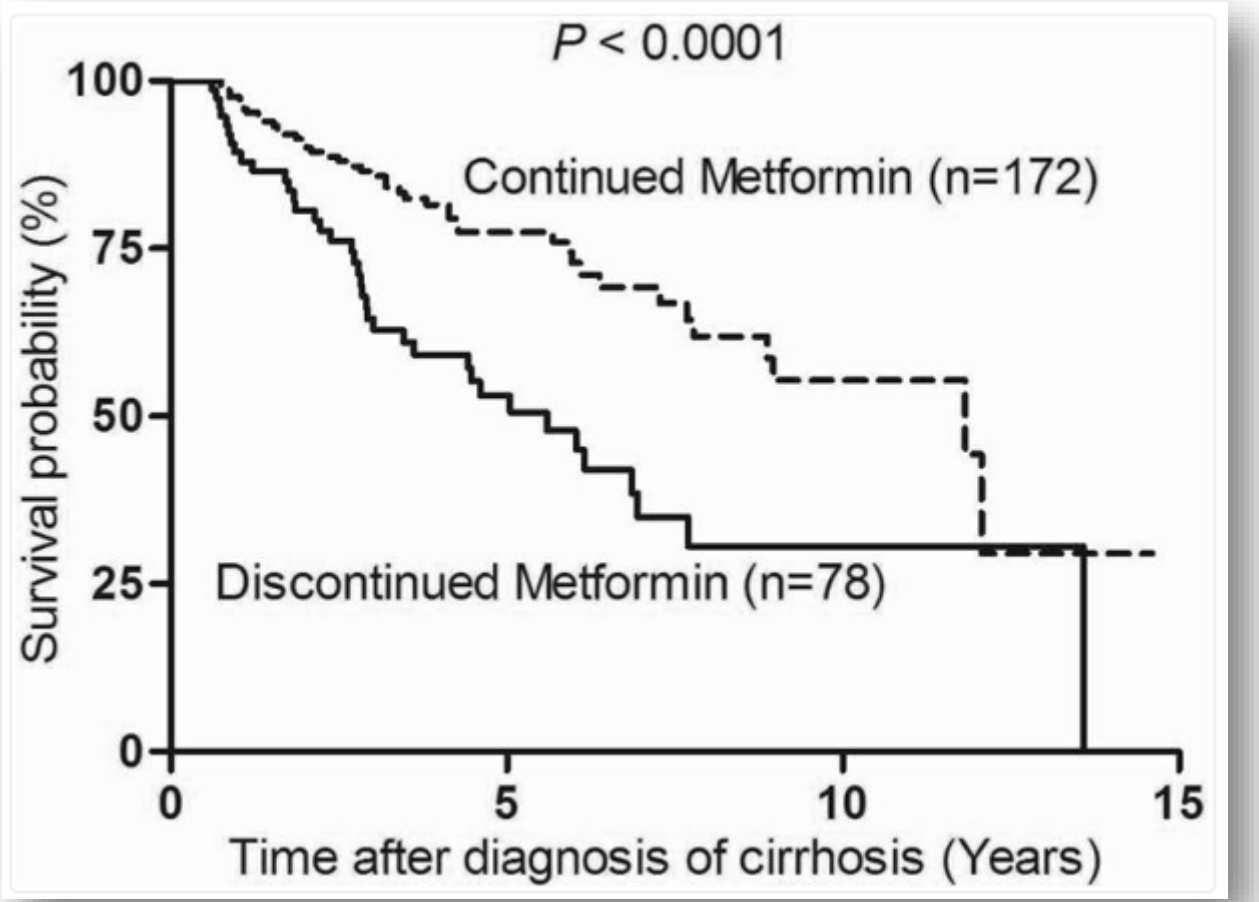
# Treatment with SGLT-2i vs. DPP-4i is Associated with Reduced Incidence of MASLD

- UK Clinical Practice Research Datalink
- 41184 and 148421 new users of SGLT-2i and DPP-4i
- SGLT-2i were associated with a decreased risk of MAFLD (HR 0.78, 95% CI 0.68-0.89)




*Pradhan R et al, Diabetes Care 2022*

# Metformin and Survival in Cirrhosis




After adjusting for other variables, continuation of metformin remained an independent predictor of better survival with a HR of 0.43 (95%CI: 0.24-0.78, *P* = 0.005). No patients developed metformin-associated lactic acidosis during follow-up.

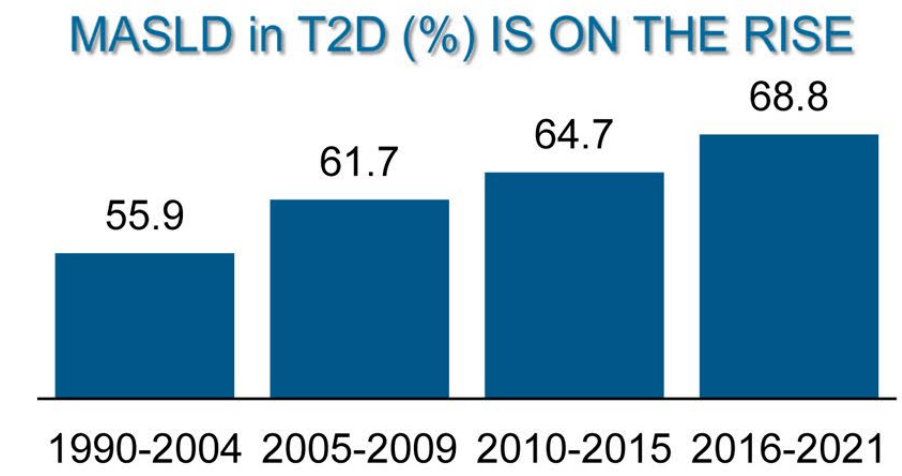
*Zhang et al. Hepatology. 2014 Jul 31;60(6)*

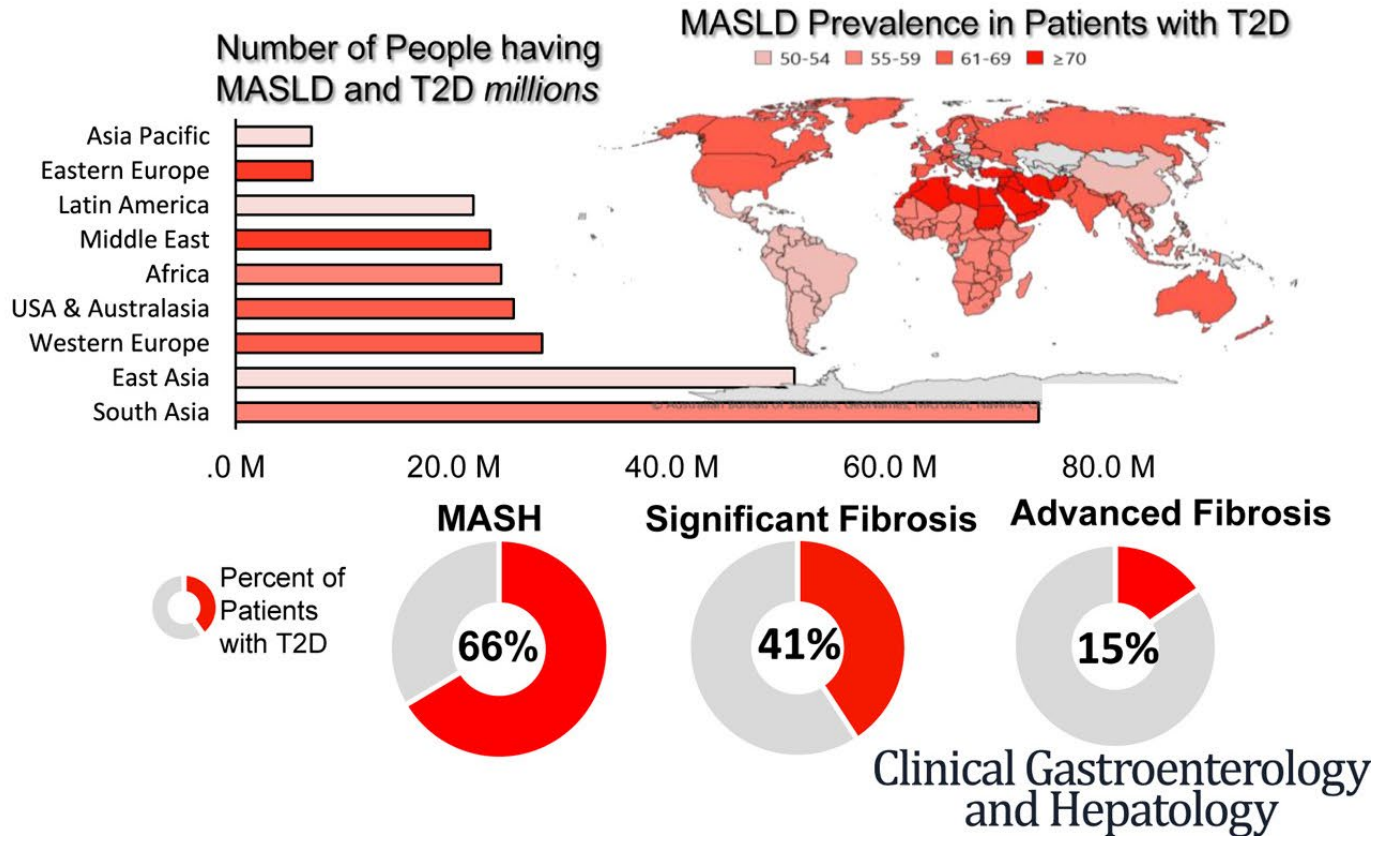
# The Global Epidemiology of MASLD/MASH Among Patients With T2D

**Globally**

**436 Million** Adults with T2D

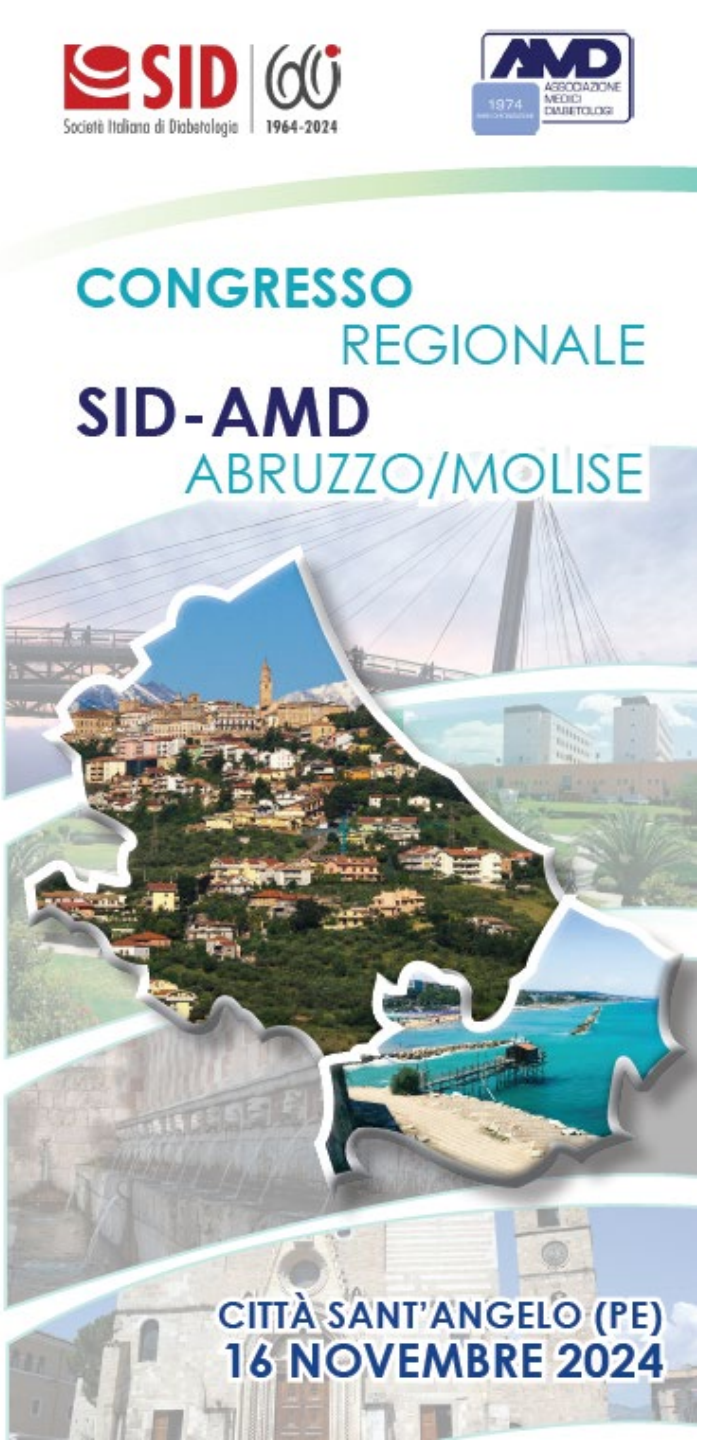
**65%** of T2D with MASLD




The highest MASLD prevalence among T2D patients was observed in Eastern Europe (80.62%, 75.72%–84.73%), followed by the Middle East (71.24%, 62.22%–78.84%)

*Younossi et al. Clinical Gastroenterology and Hepatology Volume 22, Issue 10, October 2024*




«Un'oncia di azione vale quanto una tonnellata di teoria»
*Friedrich Engels*

Grazie