MASLD: Fisiopatología y rol del alcohol en la modulación del daño hepático

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16:30-16:50

SOCHIDIAB
SOCIEDAD CHILENA DE DIABETOLOGÍA

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Conflictos de interés

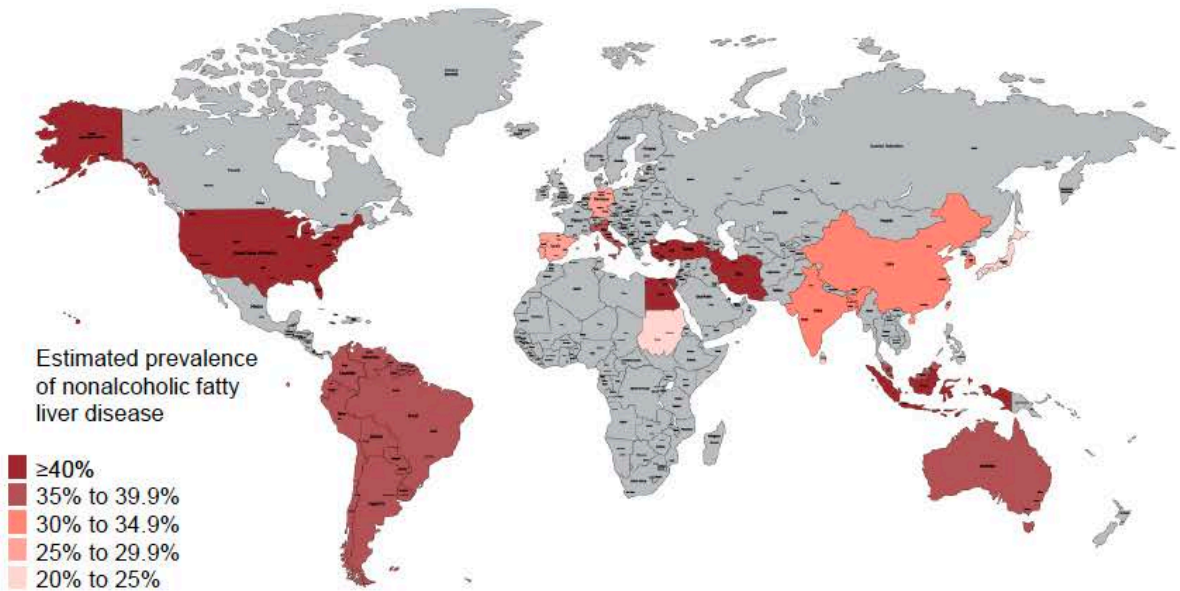
- Industria: Inventiva (lanifibranor), Astra Zeneca (Fortuna)
- Fuente de financiamiento: ANID (Fondecyt)

MASLD Epidemiology and Rising Prevalence

Globally, the overall prevalence of **MASLD is 32%**, while the prevalence of **MASH is between 12% and 14%**[1]

Geographical Differences in the Prevalence of MASLD Worldwide[2,3]

- Prevalence is significantly higher among those with T2D and visceral obesity[4-7]
- Among those with obesity, the prevalence of MASH is 25% to 30%, while ~30% to 40% of people with diabetes have MASH[4-7]

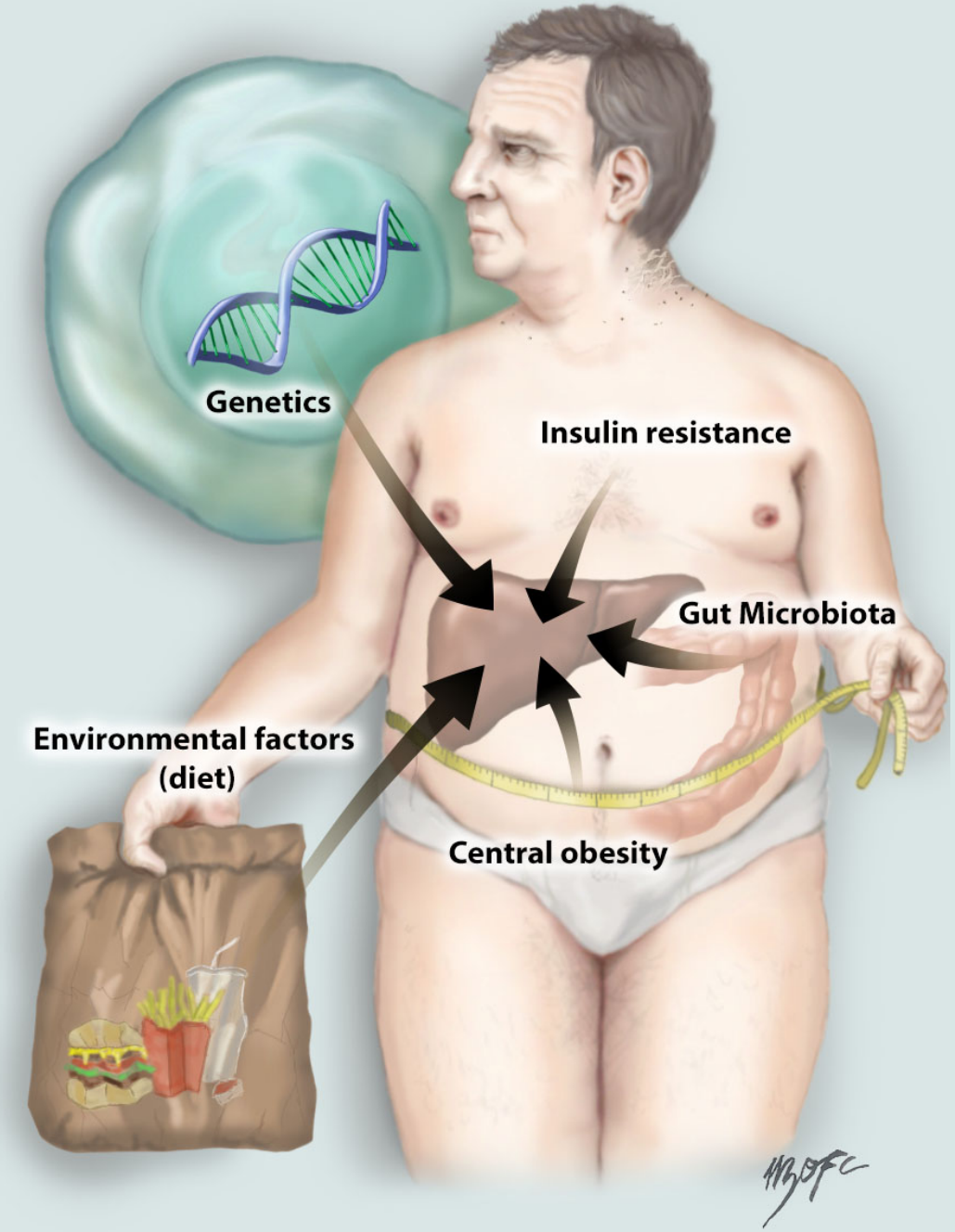


In one study, ~70% of patients with T2D have MASLD (steatosis) and ~15% have clinically significant liver fibrosis (stages ≥F2),[8] consistent with other recent population-based studies in the United States[9,10]

1. Harrison SA et al. J Hepatol. 2021;75:284-291. 2. Teng ML et al. Clin Mol Hepatol. 2023;29(suppl):S32-S42. 3. Riazi K et al. Lancet Gastroenterol Hepatol. 2022;7:851-861. 4. Younossi ZM et al. Hepatology. 2016;64:73-84. 5. Younossi ZM et al. J Hepatol. 2019;71:793-801. 6. Kim D et al. Hepatol Int. 2019;13:205-213. 7. Kanwal F et al. Clin Gastroenterol Hepatol. 2016;14:301-8.e1-2. 8. Lomonaco R et al. Diabetes Care. 2021;44:399-406. 9. Ciardullo S et al. Diabetes Care. 2021;44:519-525. 10. Barb D et al. Obesity (Silver Spring). 2021;29:1950-1960.

Tópicos

- ✓ Sinopsis fisiopatológica MASLD
- ✓ Papel del alcohol en la modulación del daño hepático
- ✓ Implicancias clínicas



✓ El desarrollo de **MASLD/MASH** involucra múltiples vías moleculares que complejas y que no han sido completamente dilucidadas

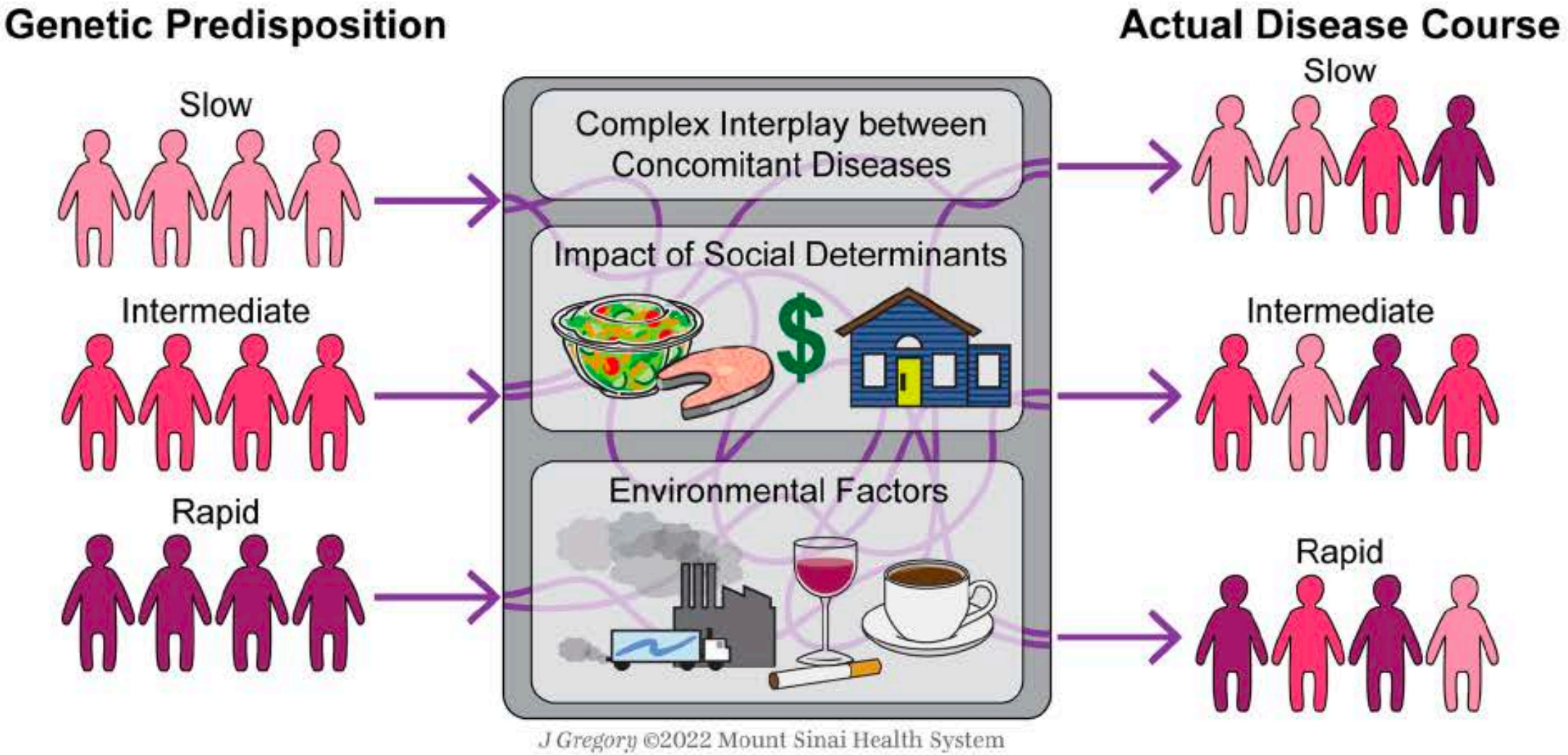
✓ Las alteraciones fisiopatológicas pueden ocurrir de forma **secuencial** o **paralela** y con diferentes jerarquías dentro del espectro de la enfermedad y a lo largo del tiempo

✓ La **heterogeneidad** de la enfermedad probablemente se deba a una contribución diferencial de las vías patogénicas

✓ El **alcohol** en incluso en dosis bajas ha sido un factor confundente en los estudios

Arab JP, Arrese M & Trauner M. Ann Rev Pathol 2018

MASLD/MASH: Complexity/heterogeneity



MASLD: Genetics

Table 2 | Genes involved in pathophysiology of overlap between NAFLD and ALD

Gene	Protein name	Variant	Cytogenetic location	Pathway	Outcomes in NAFLD and ALD
PNPLA3	Patatin-like phospholipase domain-containing 3	rs738409 C>G	22q13.31	Lipid metabolism	The risk variant modulates liver fat deposition, disease severity and progression in terms of inflammation and fibrosis in NAFLD and ALD[166,232]
TM6SF2	Transmembrane 6, superfamily member 2	rs58542926 C>T	19p13.3–p12	Miscellaneous	The polymorphism was associated with increased hepatic triglyceride content and advanced hepatic fibrosis or cirrhosis in NAFLD and ALD[233,234]
MBOAT7	Membrane-bound O-acyltransferase domain-containing 7	rs641738 C>T	19q13.42	Lipid composition of cell membranes	The variant was identified as a risk factor for ALD and promotes fat accumulation in the liver and development of NAFLD, inflammation, fibrosis and HCC due to reduced protein expression[166,234]
GCKR	Glucokinase regulator	rs1260326 T>C	2p23.3	Lipid synthesis	The variant decreases circulating fasting glucose and insulin levels but increases the production of malonyl-CoA, thereby promoting hepatic fat accumulation by serving as a substrate for lipogenesis and by blocking fatty acid oxidation[235]
HSD17B13	17β-hydroxysteroid dehydrogenase 13	rs72613567 T>TA rs62305723 G>A	4q22.1	Lipid metabolism	HSD17B13 protects against liver inflammation, cirrhosis and HCC due to both dysmetabolism and alcohol; the risk variants are related to the modulation of inflammation and fibrogenesis[170]
SOD2	Superoxide dismutase 2, mitochondrial	rs4880 C>T	6q25.3	Oxidative stress	The risk variant was associated with more advanced fibrosis in NASH[236] and may increase the susceptibility to alcohol-related cirrhosis[237]

Genes are ordered according to relevance to clinical practice. ALD, alcohol-related liver disease; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Diaz et al Nat Rev Gastroenterol Hepatol. 2023 Dec;20(12):764-783
Sookoian et al. Clin Gastro Hepatol 2024

Stressed Adipose Tissue

Normal adipose development

Normal nutrition
Normal microbiome
Adipocyte growth factors

Normal adipose development

Different adipocyte populations and other adipocyte precursors

Preadipocyte subtypes

Mature adipocyte subtypes

Lipodystrophic adipocytes

Resident macrophages (M2)

Proinflammatory macrophages (M1)

Distinct types of macrophages

Stromovascular cells

Insulin receptors

Kahn. J Clin Invest. 2019;129:3990. Reproduced in accordance with https://creativecommons.org/licenses/by/4.0/.

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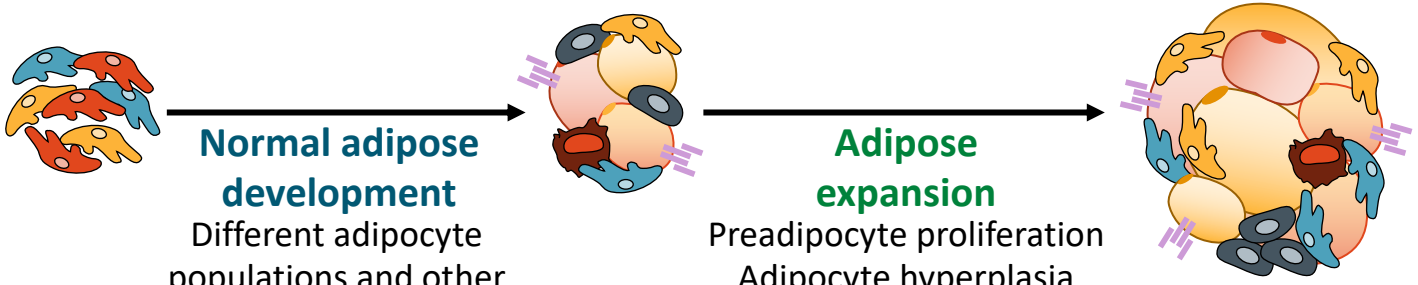
Stressed Adipose Tissue

Normal adipose development

Normal nutrition
Normal microbiome
Adipocyte growth factors

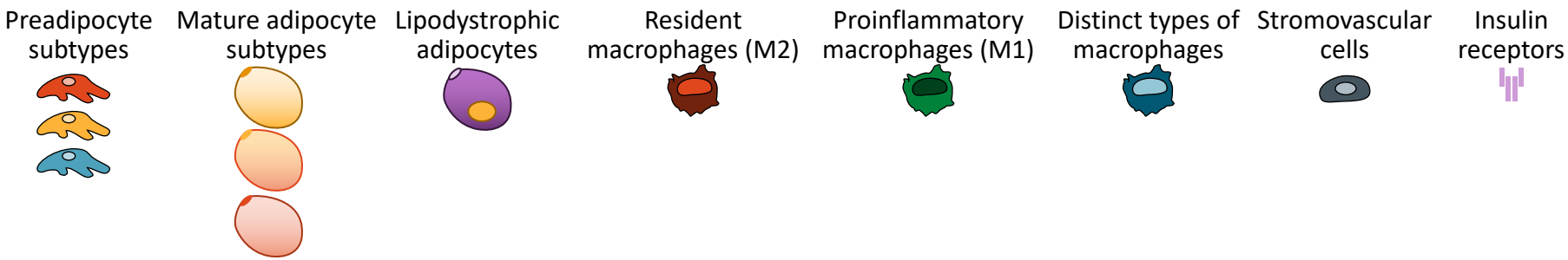
Healthy adipose expansion

Increased number of small adipocytes
Low inflammation



Normal adipose development
Different adipocyte populations and other adipocyte precursors

Adipose expansion
Preadipocyte proliferation
Adipocyte hyperplasia



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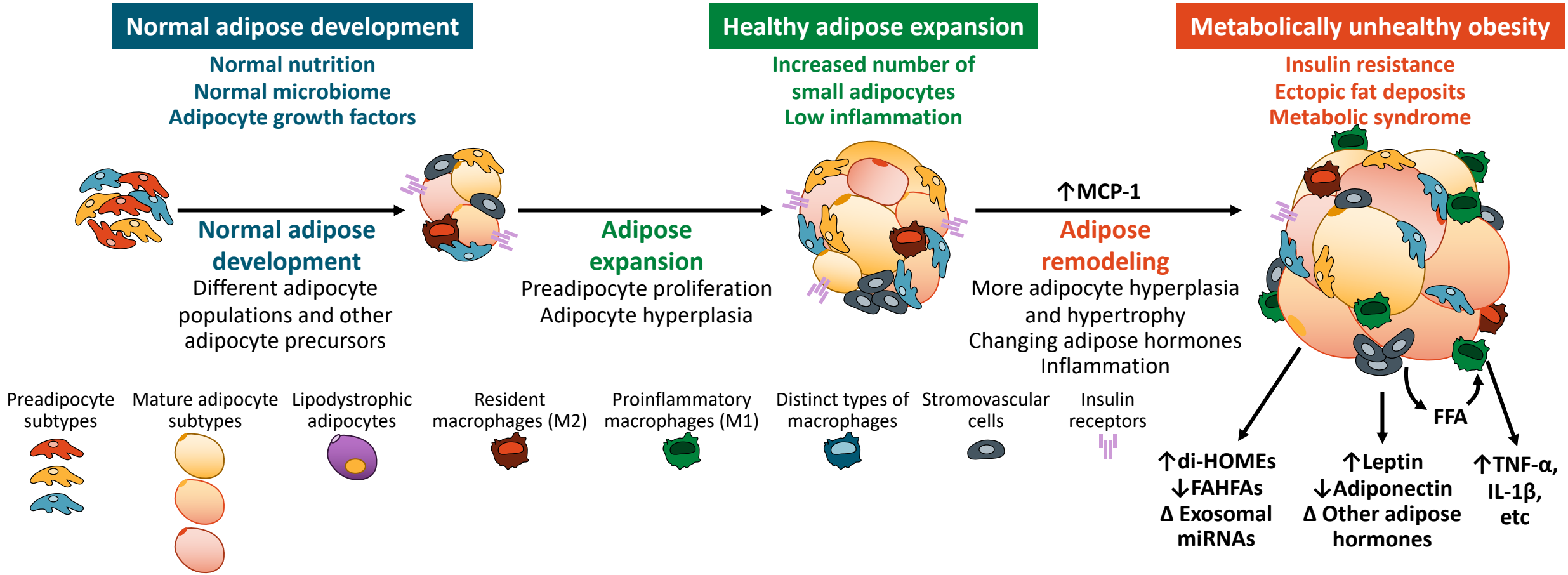
Stressed Adipose Tissue



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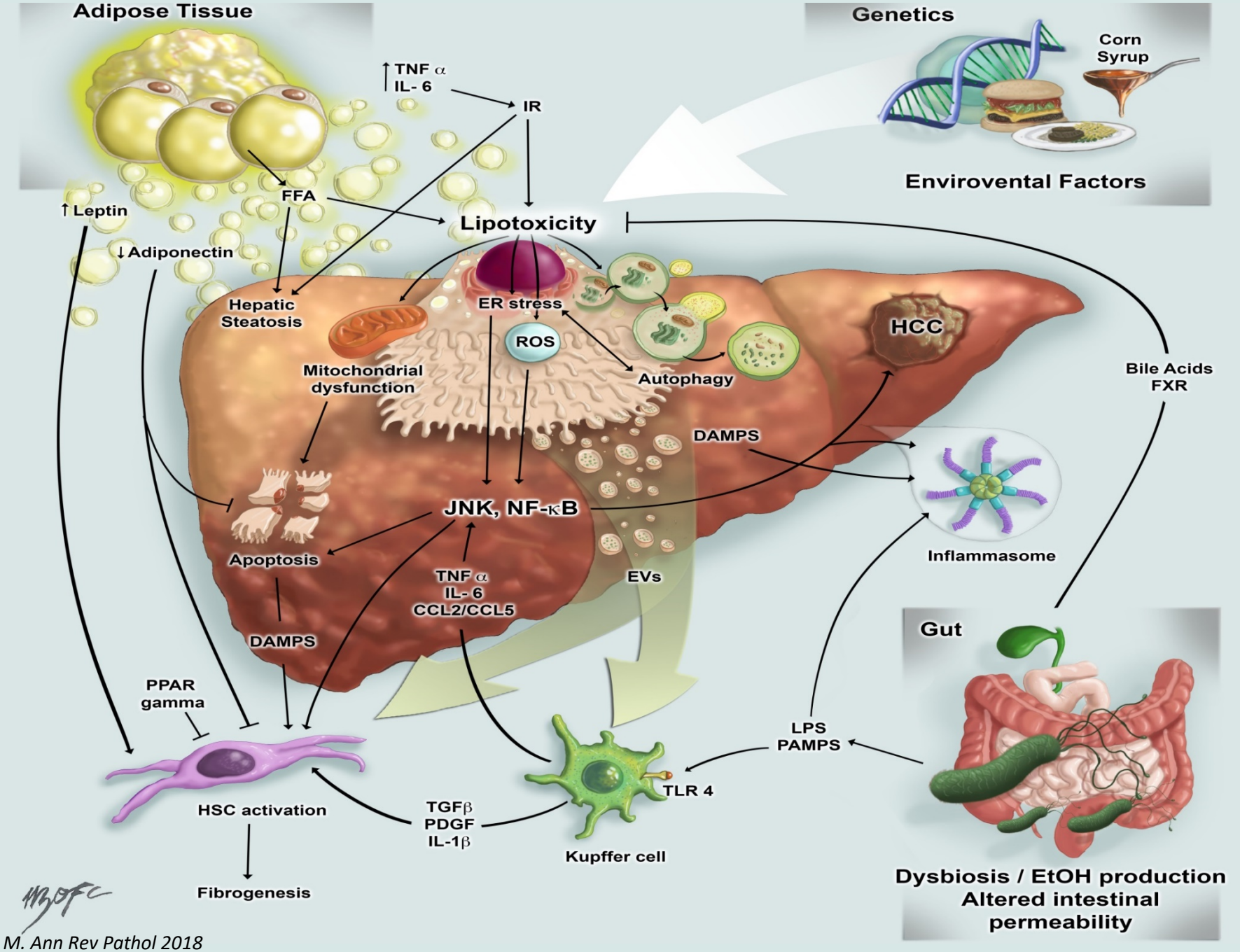
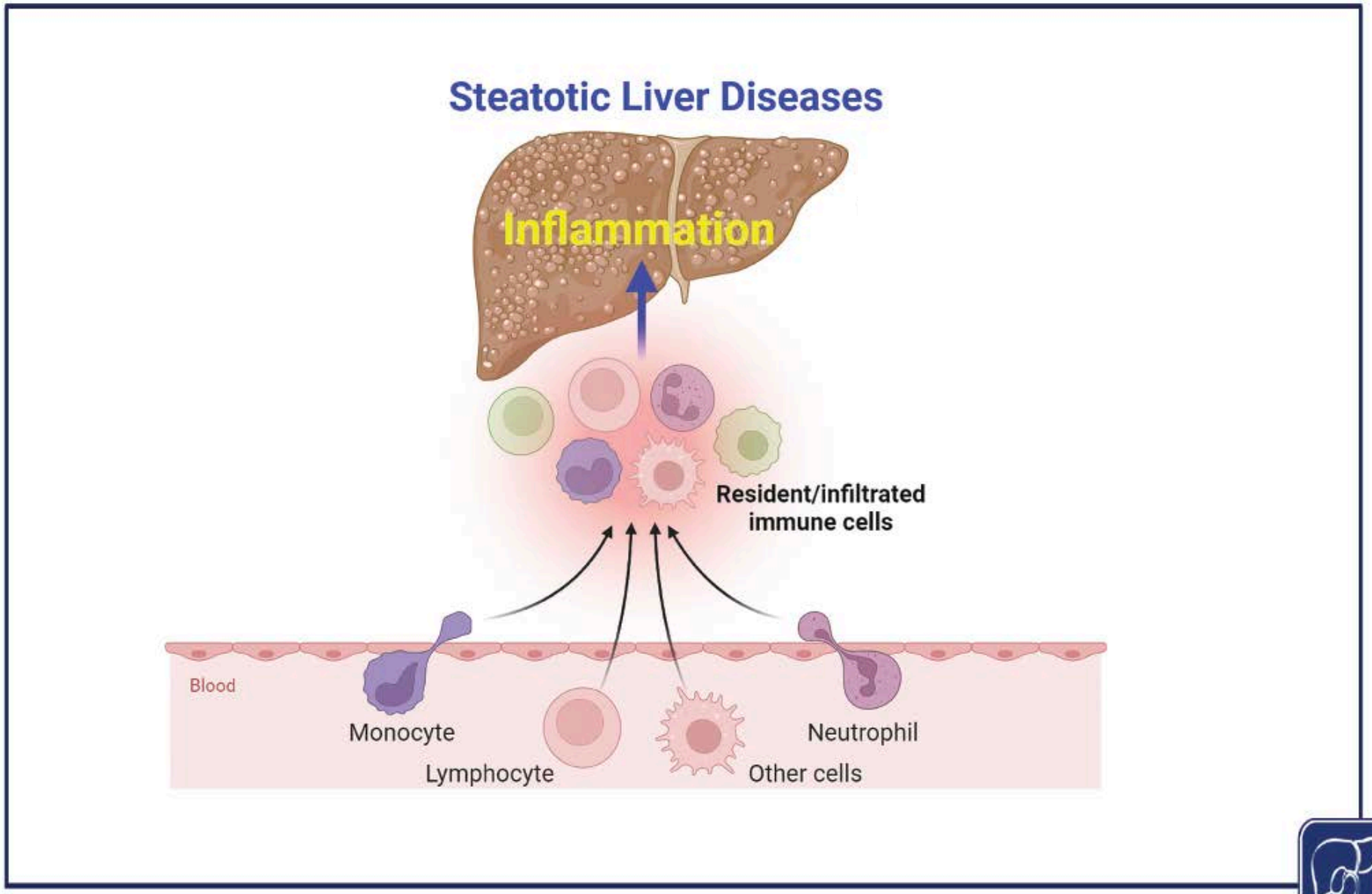
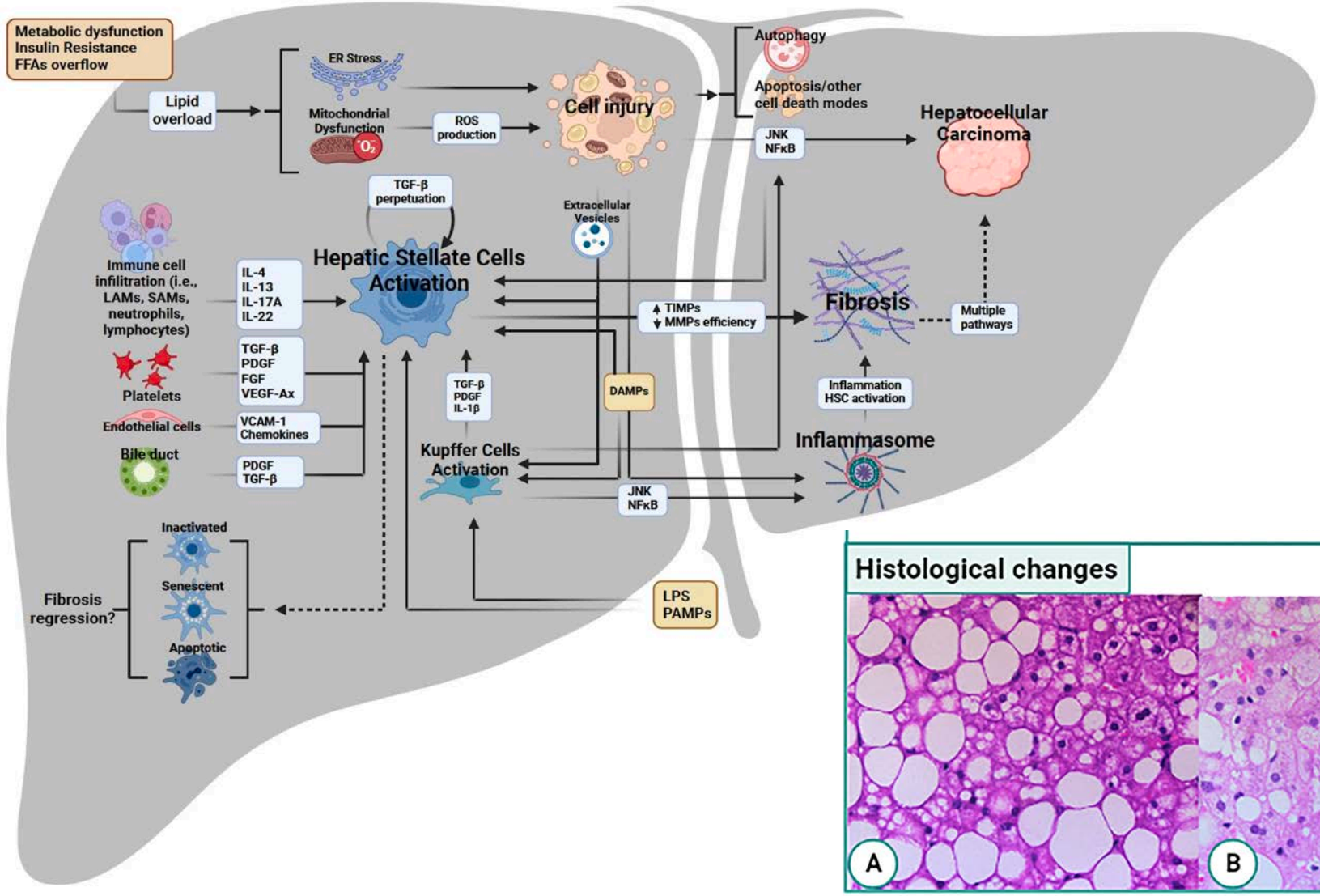


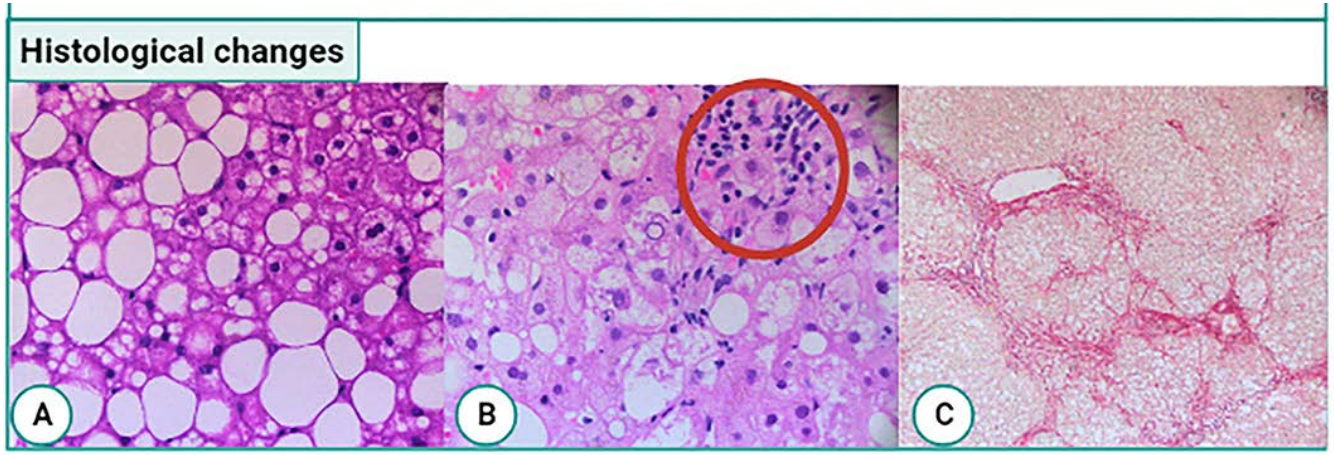
Arab JP, Arrese M & Trauner M. Ann Rev Pathol 2018

Inflamación en MASLD



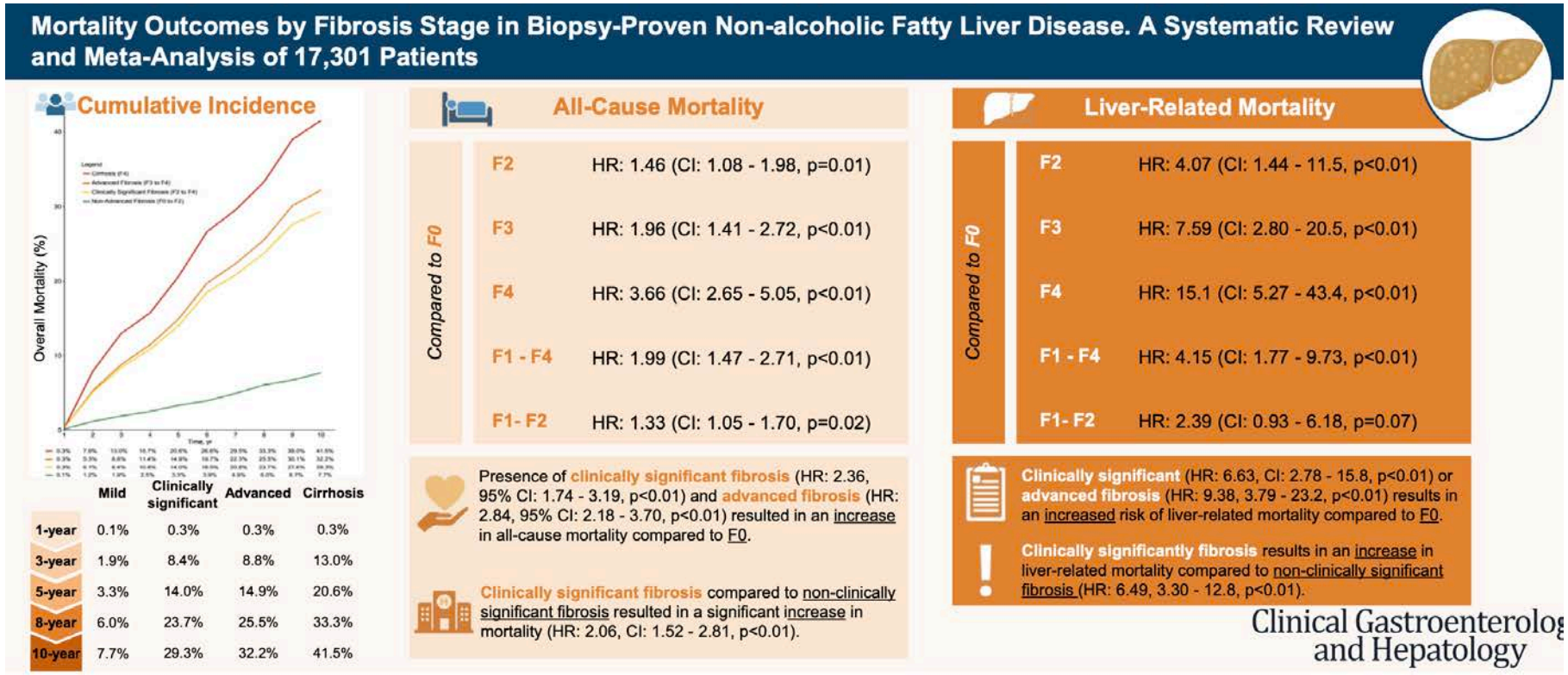
Fibrogenesis: Un proceso clave en la progresión de MASLD



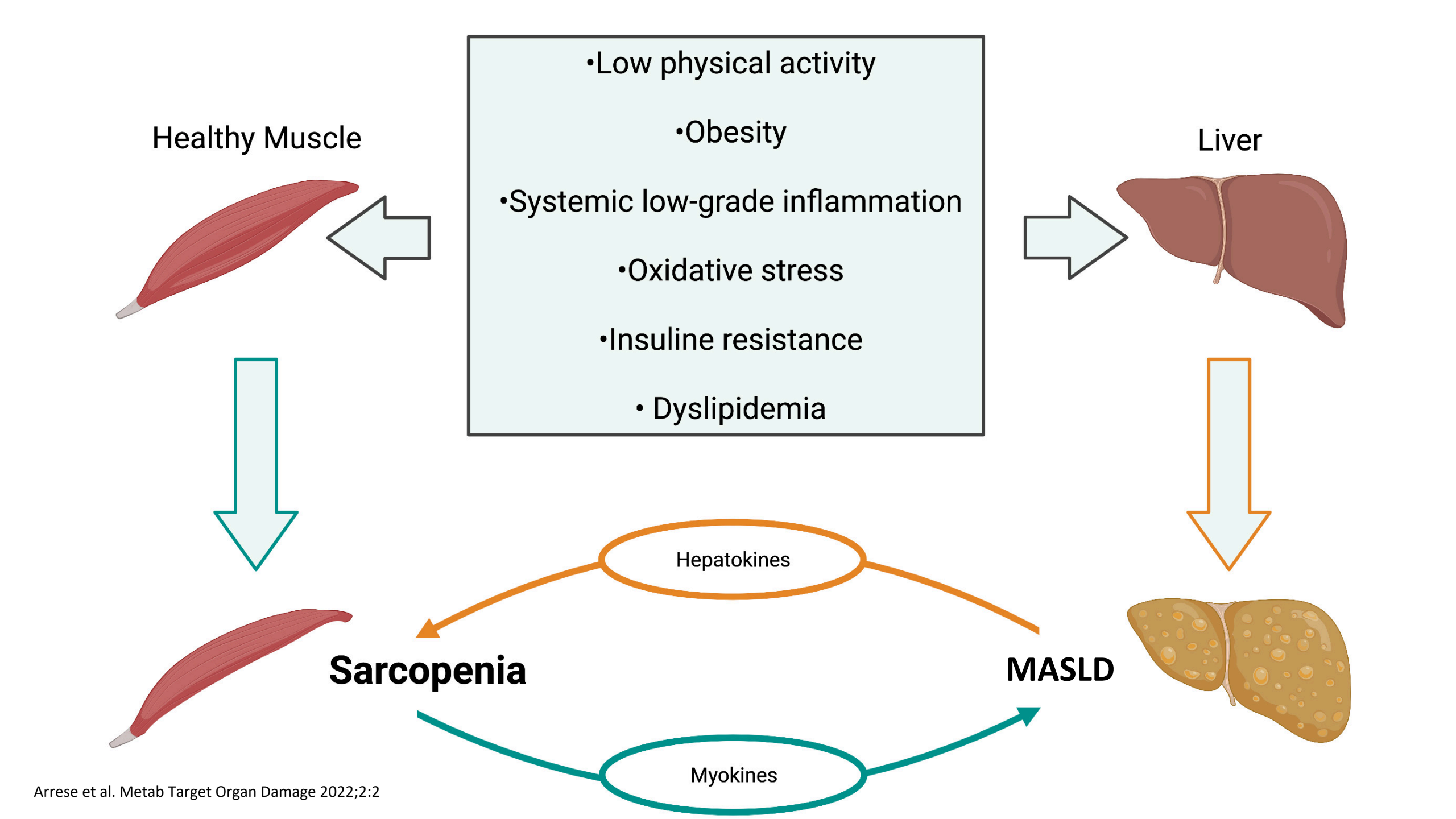


Arrese M, 2024

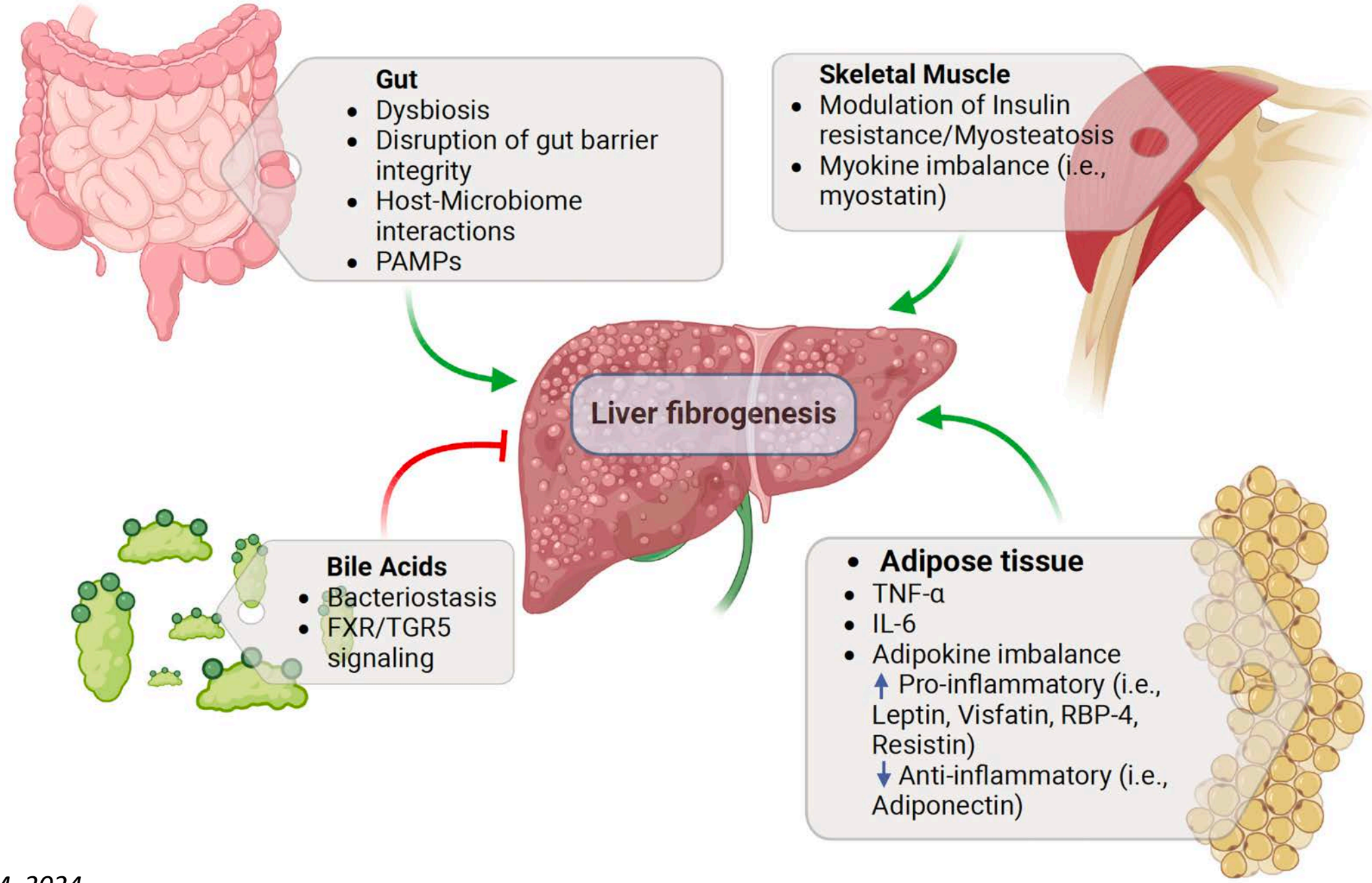
Fibrosis is the main determinant of clinical outcomes including mortality



Hagström. J Hepatology. 2017;67:1265.
Hang Ng et al. Clin Gastroenterol Hepatol. 2023 Apr;21(4):931-939.e5.

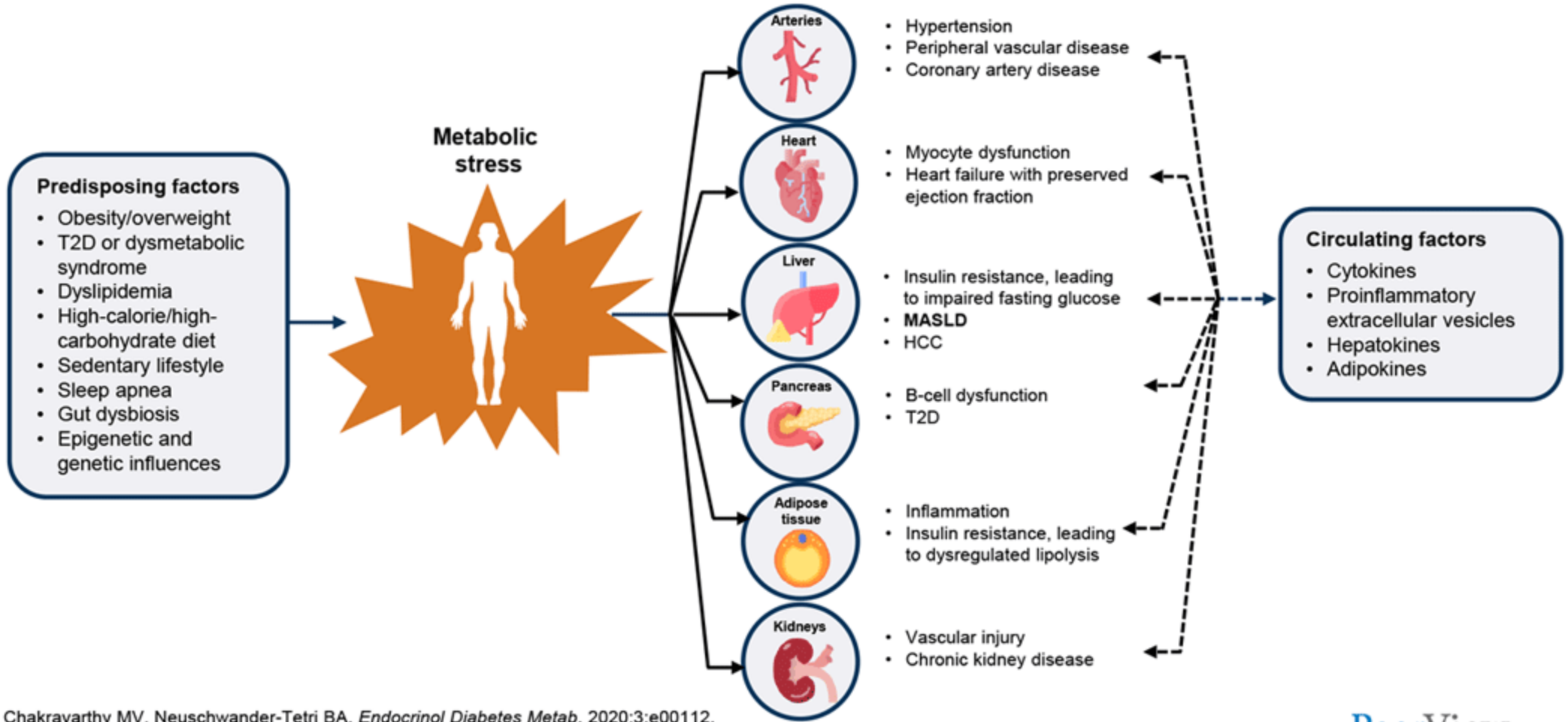


Arrese et al. Metab Target Organ Damage 2022;2:2



Arrese M, 2024

MASLD Is Part of a Systemic Disease With Strong Associations With Components of Metabolic Syndrome[1,2]



1. Chakravarthy MV, Neuschwander-Tetri BA. *Endocrinol Diabetes Metab*. 2020;3:e00112.
2. https://liverfoundation.org/liver-diseases/fatty-liver-disease/nonalcoholic-steatohepatitis-MASH/MASH-causes-risk-factors.

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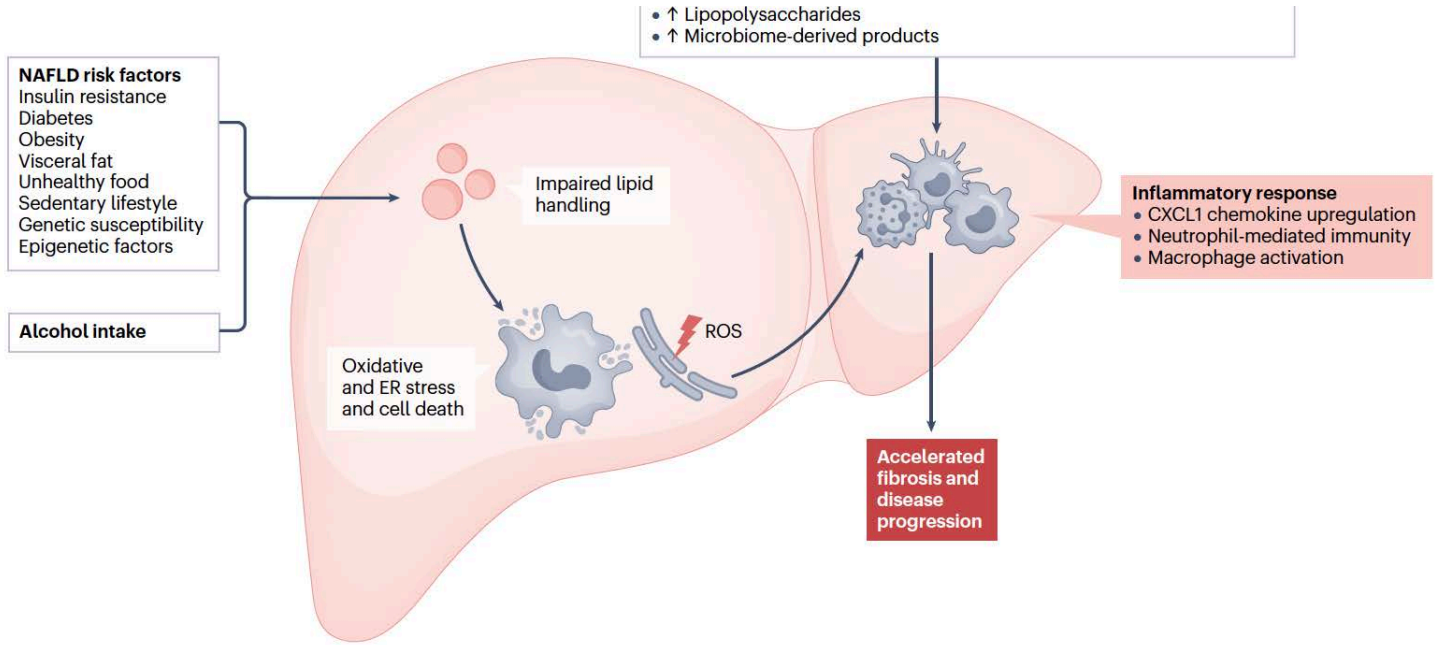
nature reviews gastroenterology & hepatology https://doi.org/10.1038/s41575-023-00822-y

Review article

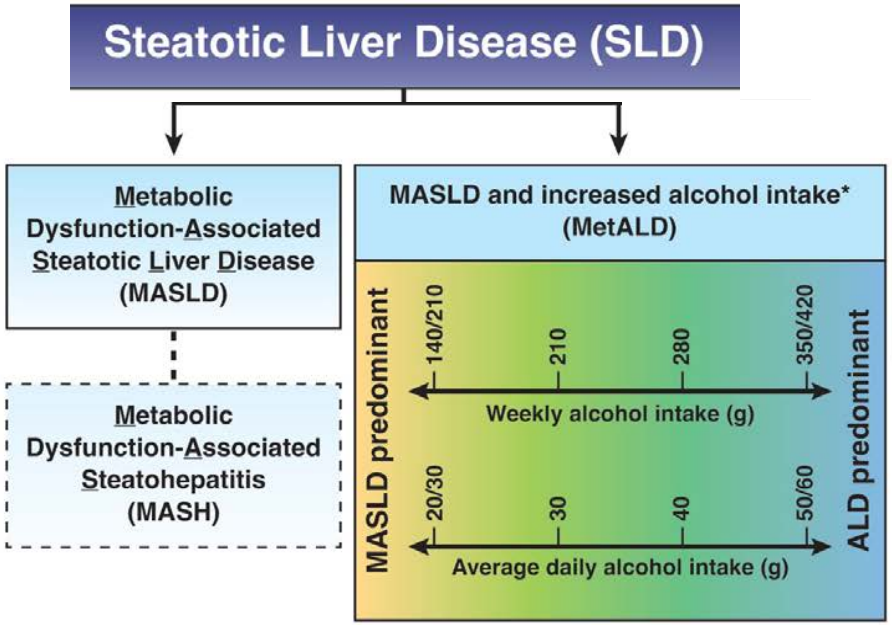
Check for updates

The intersection between alcohol-related liver disease and nonalcoholic fatty liver disease

Luis Antonio Díaz[1], Juan Pablo Arab[1,2,3], Alexandre Louvet[4,5,6], Ramón Bataller[7] & Marco Arrese[1]



MetALD: new opportunities to understand the role of alcohol in steatotic liver disease



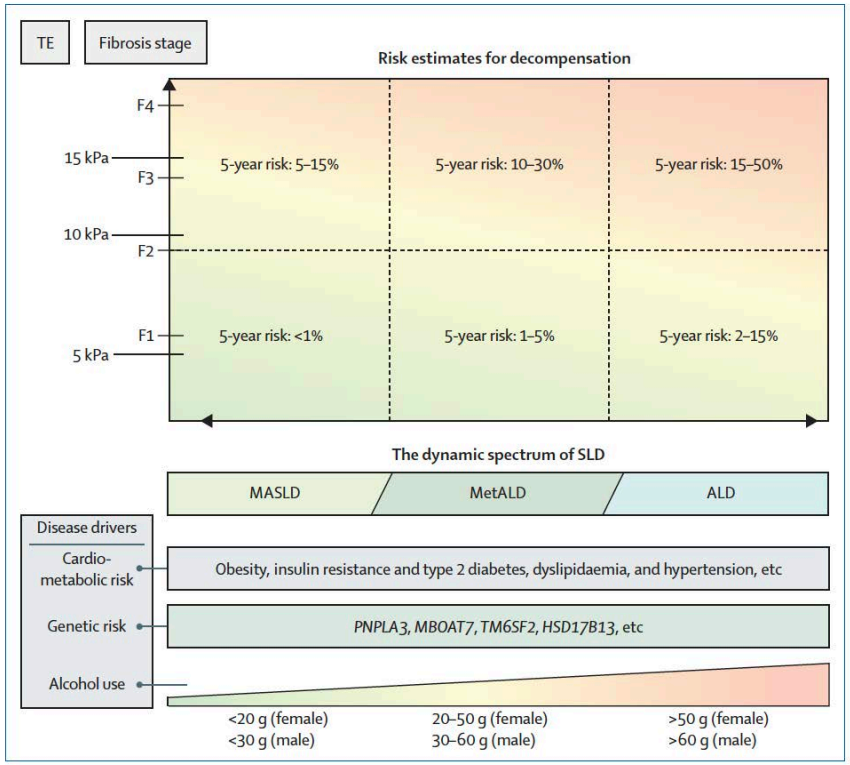
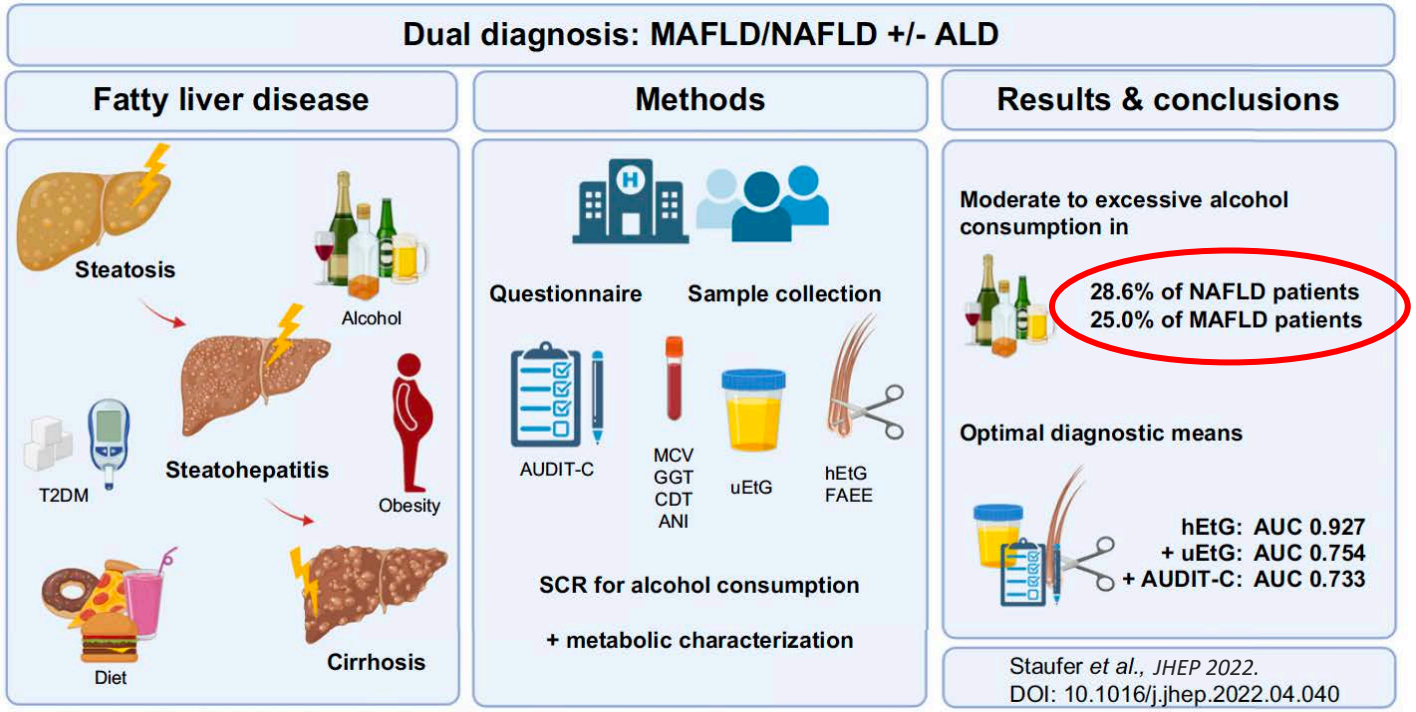


Figure: **The dynamic spectrum of steatotic liver disease**
The graph shows how the disease drivers of SLD (x-axis) and the severity of liver disease (y-axis) determine the risk of developing decompensated liver disease within 5 years. Risk estimates derived from observational studies.[8,11–13] ALD=alcohol-related liver disease. F1=fibrosis stage 1. F2=fibrosis stage 2. F3=fibrosis stage 3. F4=fibrosis stage 4. MASLD=metabolic dysfunction-associated steatotic liver disease. SLD=steatotic liver disease. TE=transient elastography.

Israelsen et al. Lancet Gastroenterol Hepatol 2023
Wei et al Clinical Gastroenterology and Hepatology 2023

Ethyl glucuronide in hair detects a high rate of harmful alcohol consumption in presumed non-alcoholic fatty liver disease

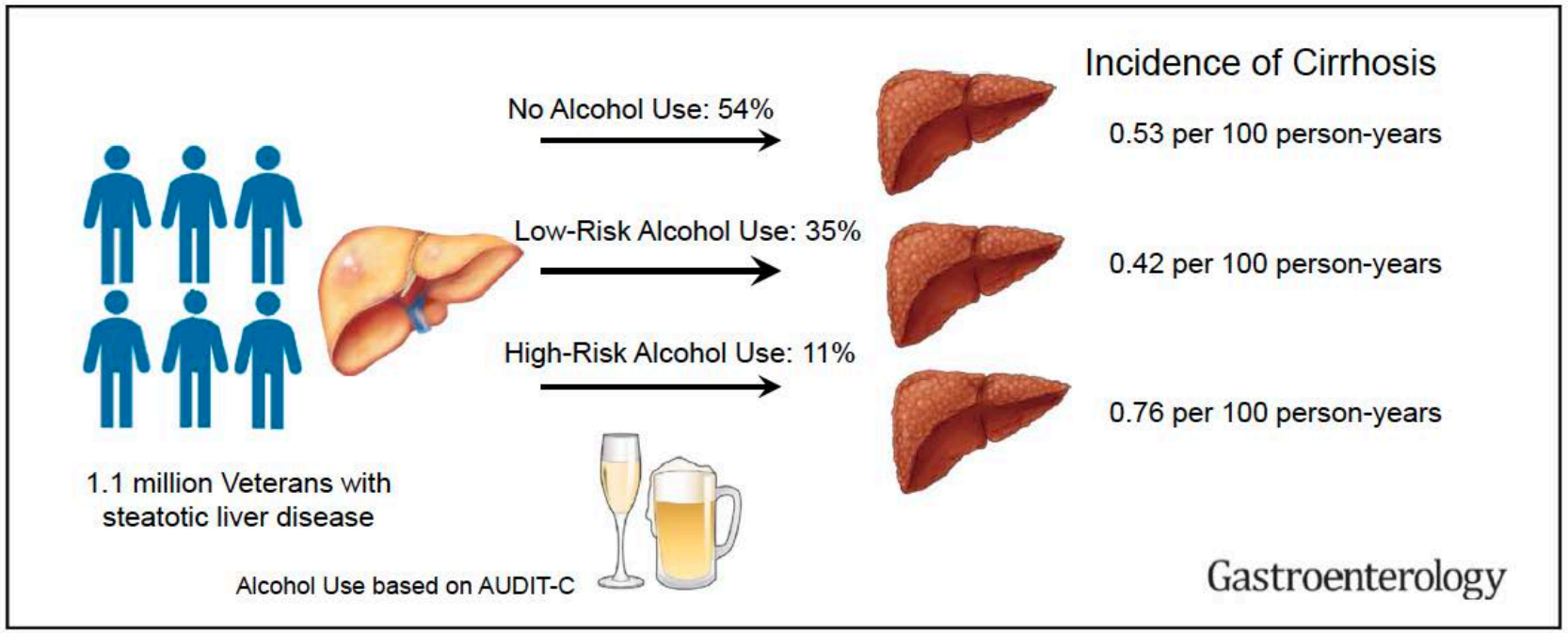


Staufer K et al. J Hepatol. 2022 May 20:S0168-8278(22)00316-6.

Impact of Longitudinal Alcohol Use Patterns on Long-Term Risk of Cirrhosis Among US Veterans With Steatotic Liver Disease

Robert J. Wong,[1,2] Zeyuan Yang,[2] Ramsey Cheung,[1,2] Ashwani K. Singal,[3] Albert Do,[4] Aijaz Ahmed,[1] and Aaron Yeoh[1]

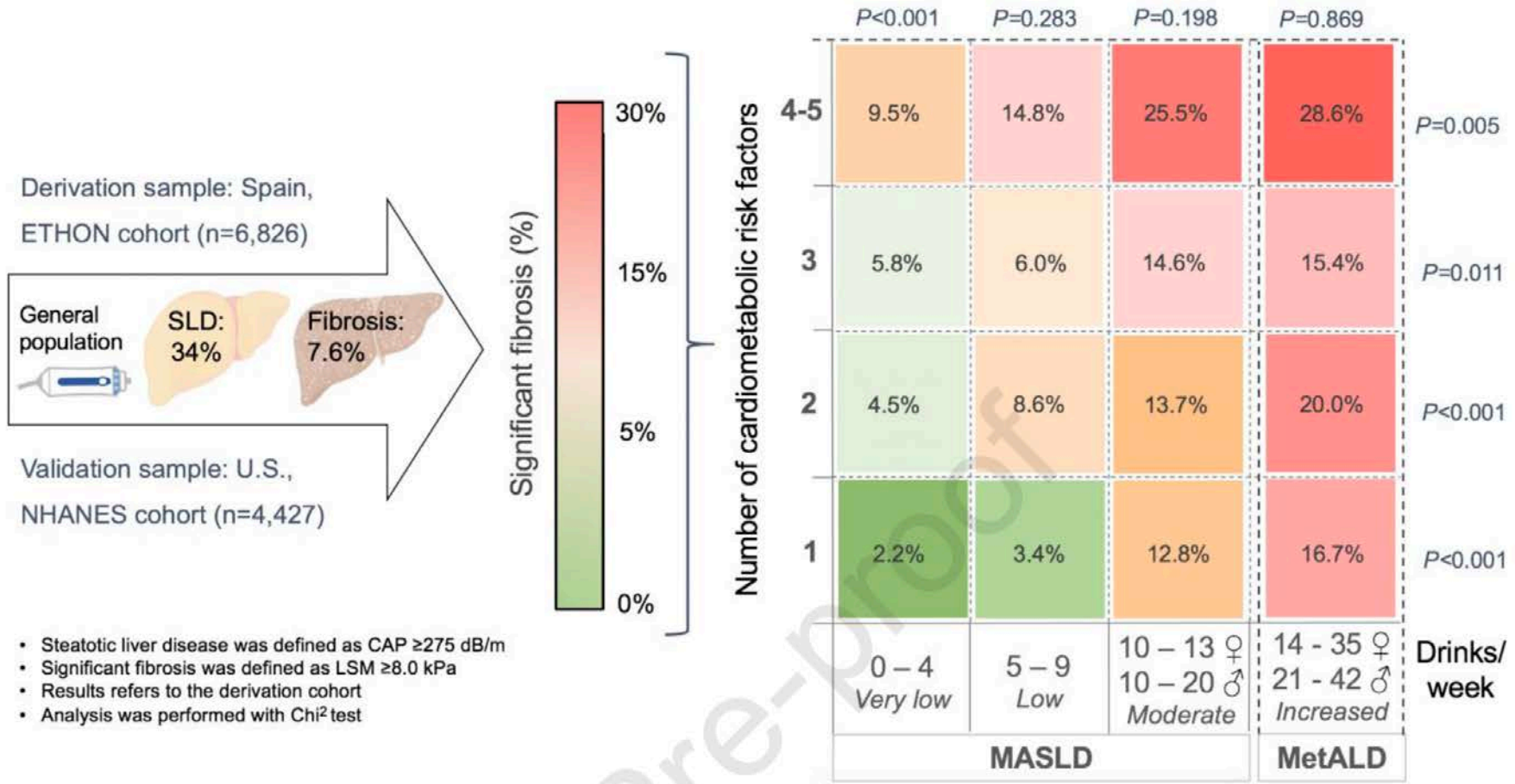
[1]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Palo Alto, California; [2]Gastroenterology Section, Veterans Affairs Palo Alto Healthcare System, Palo Alto, California; [3]University of Louisville School of Medicine; Jewish Transplant Hospital, Louisville, Kentucky; and [4]Division of Gastroenterology and Hepatology, University of California San Francisco School of Medicine, San Francisco, California



CLINICAL RESEARCH RELEVANCE

These data provide important data on the harmful effects of high-risk alcohol use in patients with steatotic liver disease, and future studies are needed to evaluate novel interventions for systematic and timely assessment of alcohol use with linkage to addiction services for those with identified high-risk alcohol use.

Low-to-moderate alcohol consumption is associated with increased fibrosis in individuals with metabolic dysfunction-associated steatotic liver disease



- Steatotic liver disease was defined as CAP ≥275 dB/m
- Significant fibrosis was defined as LSM ≥8.0 kPa
- Results refers to the derivation cohort
- Analysis was performed with Chi^2 test

Pre-proof

Marti-Aguado et al. J HEP 2024 (IN PRESS)

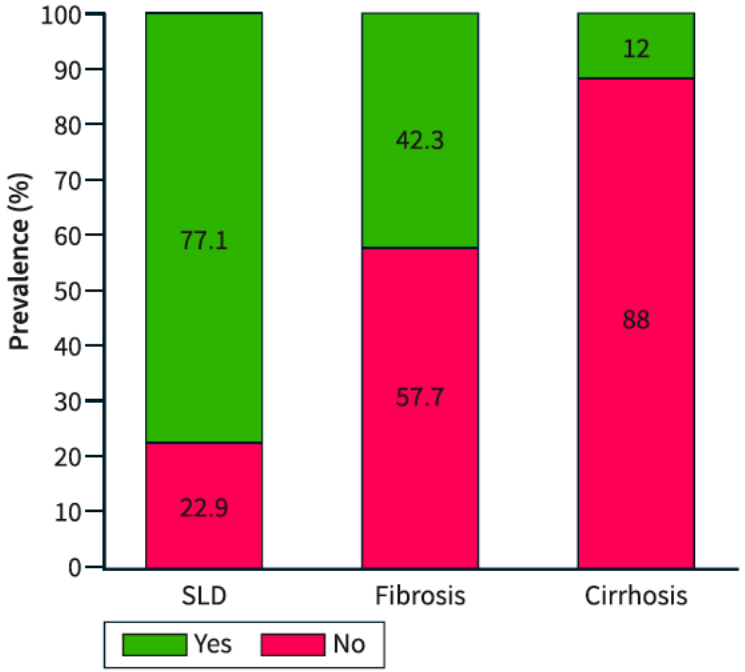
DOI: 10.1002/ueg2.12511

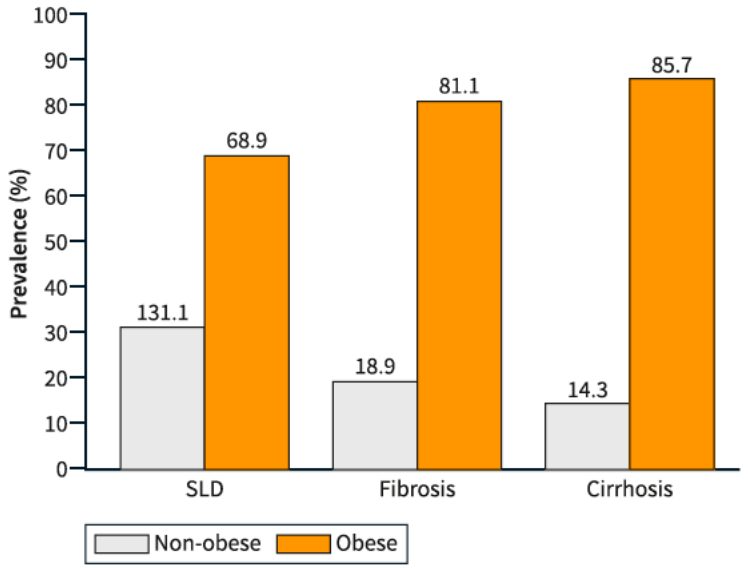
ORIGINAL ARTICLE

ueg journal WILEY

Obesity and harmful alcohol consumption are predictors for advanced liver disease in the disease management program for type 2 diabetes

Maurice Michel[1,2] | Michelle Doll[1,2] | Nastasia Albert[1,2] | Marc Morgenstern[3] | Andreas Behr[4] | Stefan Maxeiner[4] | Christian Labenz[1,2] | Peter R. Galle[1,2] | Jörn M. Schattenberg[1,2,5,6]

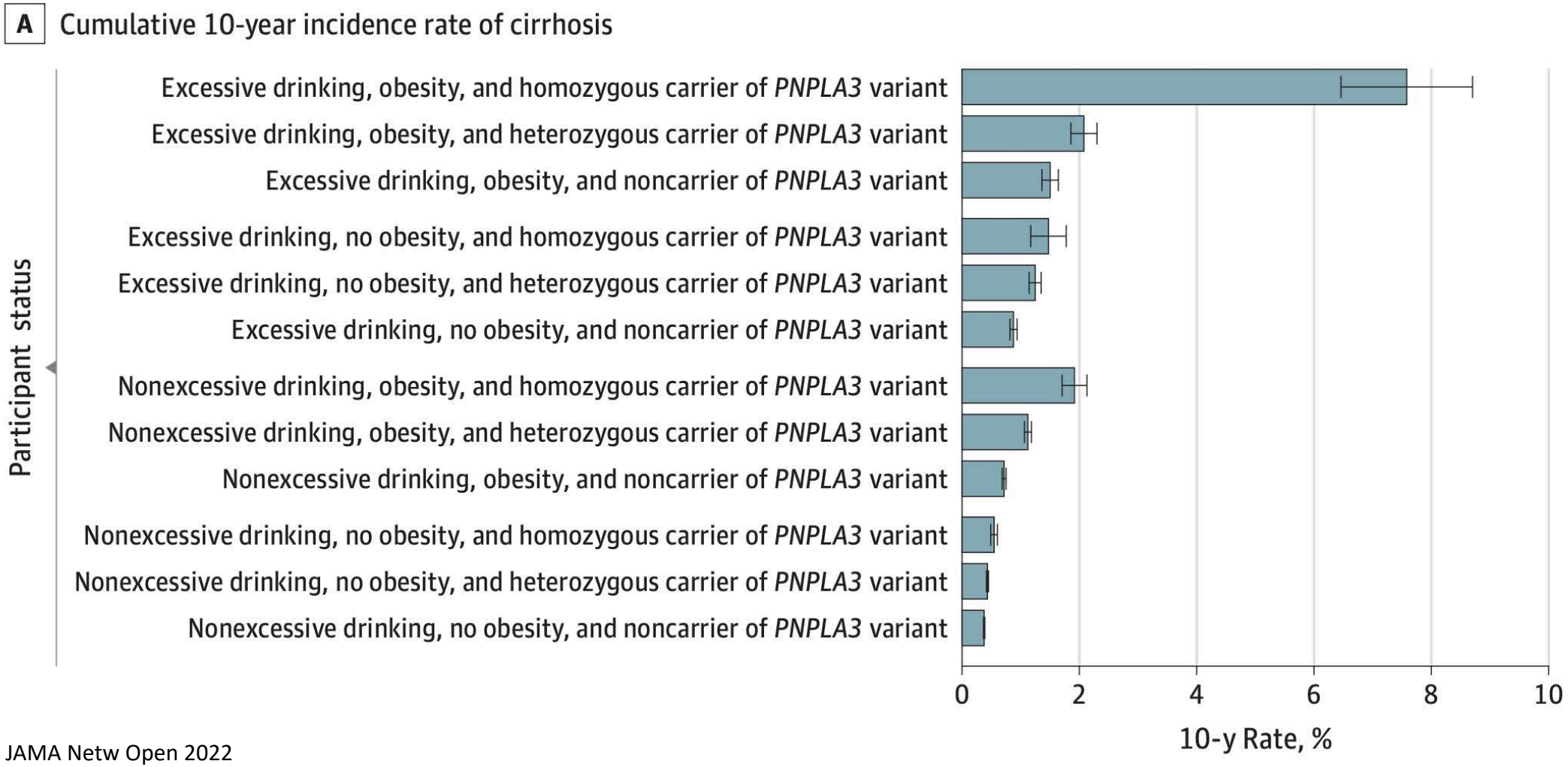




Results: The majority of participants were male (62%), and the median age was 66 years (interquartile range 59; 71). The median body mass index was 31.1 kg/m^2, with 58.9% of the participants being obese. Harmful alcohol consumption was prevalent in 8.0% and 20.0% of the entire cohort and in those with cirrhosis, respectively. The prevalence of SLD, fibrosis, and cirrhosis was 77.1%, 42.3%, and 12.0%, respectively. In multivariable logistic regression analysis, obesity, and harmful alcohol consumption were associated with the highest odds of fibrosis (odds ratio [OR] 5.198, 95% confidence interval [CI] 2.269–11.908) and cirrhosis (OR 5.615, 95% CI 1.274–24.756), respectively.

medicina.uc.cl

Individual susceptibility: Cirrhosis



Kim HS, et al. JAMA Netw Open 2022

Implicancias Clínicas patogenia: medicina de precisión

A Precision Medicine Guided Approach to the Utilization of Biomarkers in MASLD

Nimish Thakral, MD[1] Hailemichael Desalegn, MD, PhD[2] Luis Antonio Diaz, MD[3]
Daniel Cabrera, MD, PhD[4,5] Rohit Loomba, MD[6] Marco Arrese, MD[3] Juan Pablo Arab, MD[3,7]

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[2] Division of Gastroenterology, Department of Medicine, Schulich School of Medicine, Western University, London, Ontario, Canada
[3] Departamento de Gastroenterología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[4] Centro de Investigación e Innovación Biomédica (CiiB), Universidad de los Andes, Santiago, Chile
[5] Escuela de Medicina, Facultad de Ciencias Medicas, Universidad Bernardo O'Higgins, Santiago, Chile

Address for correspondence Juan Pablo Arab, MD, Division of Gastroenterology, Hepatology, and Nutrition, Department of Internal Medicine, Stravitz-Sanyal Institute of Liver Disease and Metabolic Health, Virginia Commonwealth University School of Medicine, 1201 E. Broad St., P. O. Box 980341, Richmond, VA 23284 (e-mail: juanpablo.arab@vcuhealth.org).

[6] Division of Gastroenterology and Hepatology, MASLD Research Center, University of California San Diego, San Diego, California
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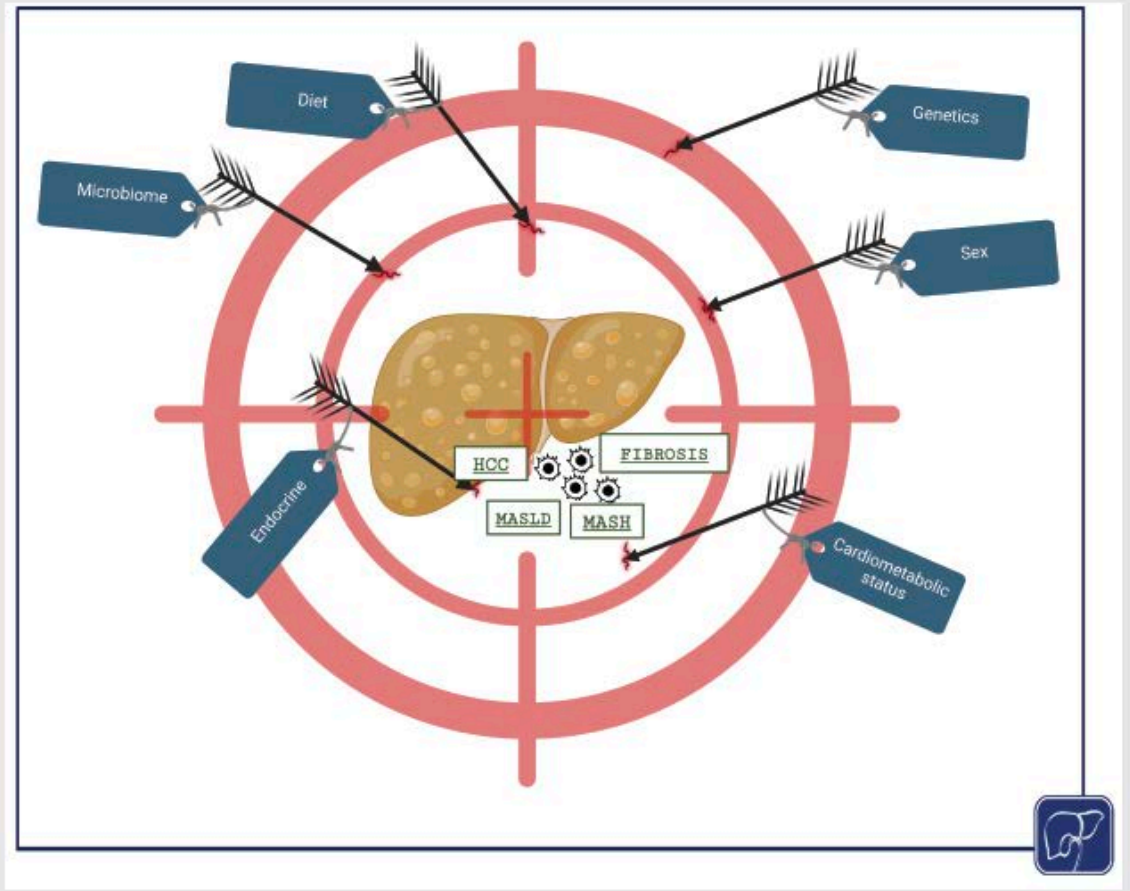
Semin Liver Dis

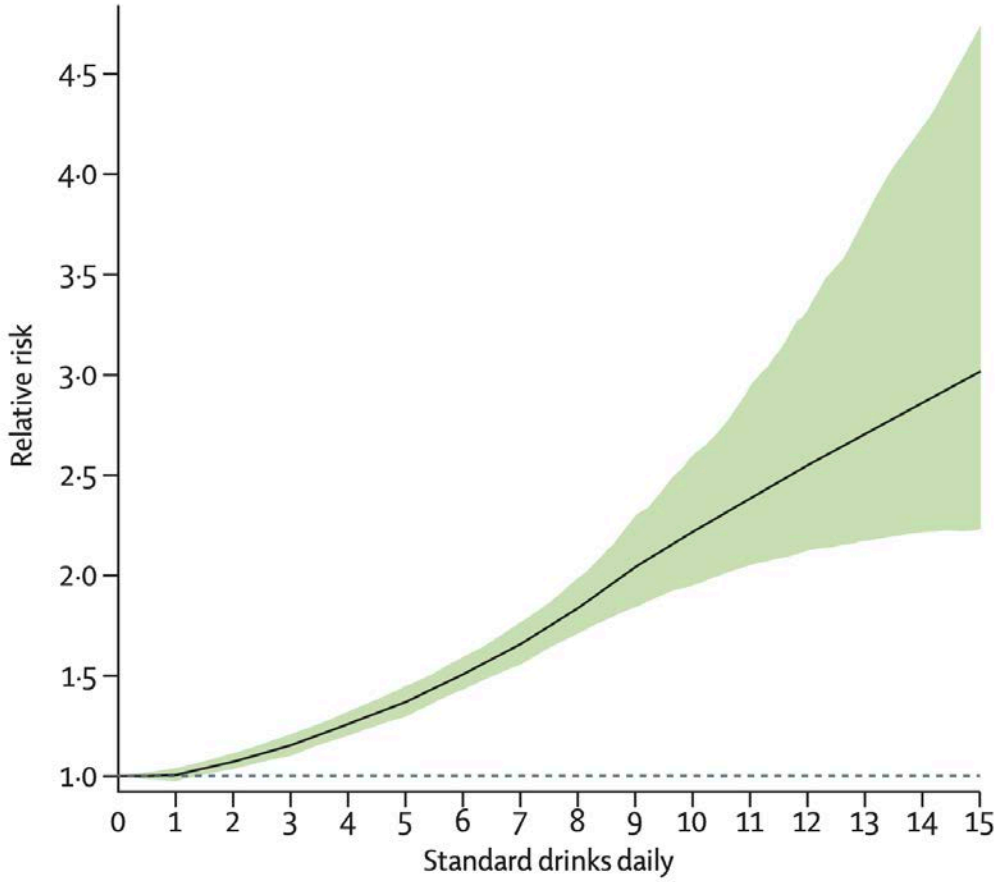
Graphical Abstract



How much alcohol can my patient <u>without</u> liver disease drink?

The level of consumption that minimises health loss due to alcohol use is **zero**

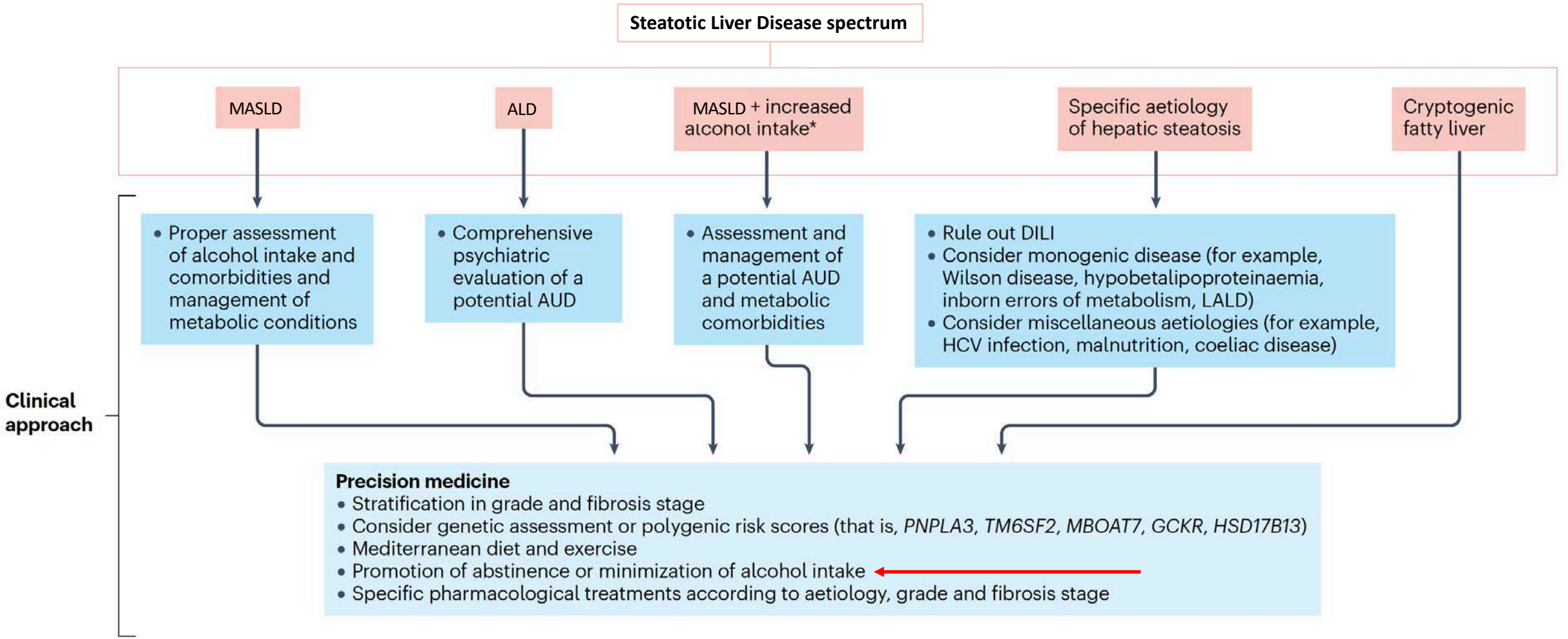
Weighted relative risk of alcohol for all attributable causes, by standard drinks consumed per day



na.uc.cl

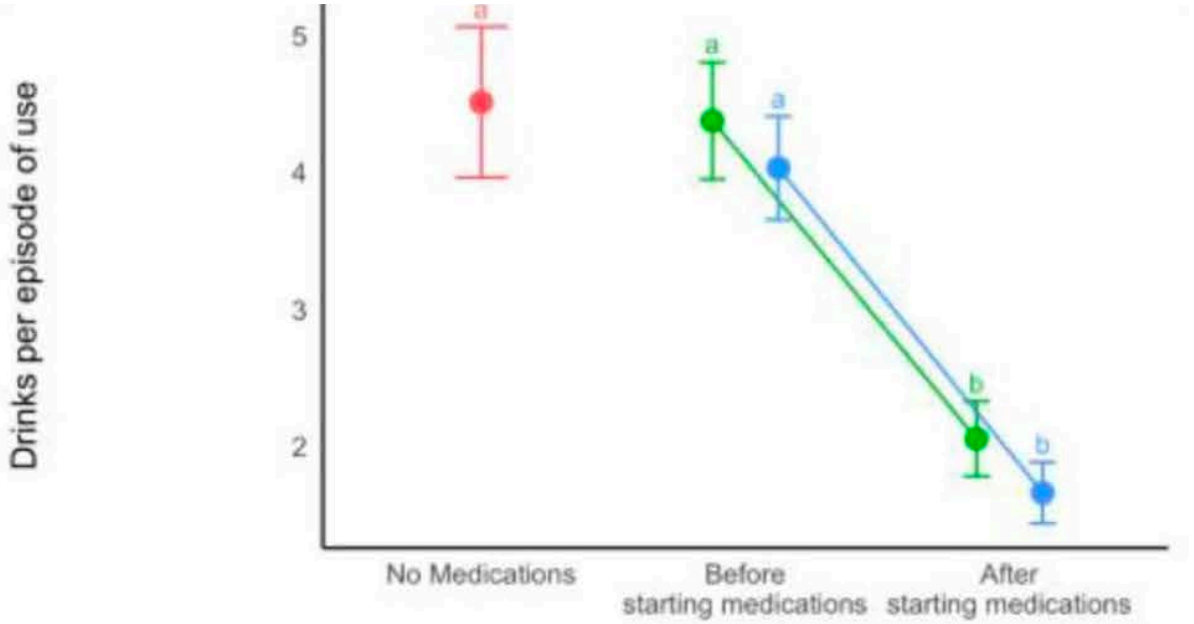
GBD Alcohol Collaborators. Lancet 2018

Implicancias Clínicas: MASLD & OH



Semaglutide and Tirzepatide reduce EtOH in obesity

- 1st: A machine-learning based attribution mapping of ~ 68,250 posts related to GLP-1 or GLP-1/GIP agonists on the Reddit platform
- 2nd: 153 participants; current alcohol drinkers; BMI ≥ 30
- Real-world evidence of reduced alcohol consumption in people with obesity taking Semaglutide or Tirzepatide medications, suggesting potential efficacy for treatment in AUD comorbid with obesity



Quddos F, et al. Sci Rep 2023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