METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE: WHAT WE ALL NEED TO KNOW

VCH Department of Family & Community Practice CME Rounds
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Disclosures (Past 24 months)

- Speaker: Abbvie, Advanz, Gilead, GSK, Neurocrine
- Consultant: Abbvie, Advanz, Gilead, GSK, Ipsen, Neurocrine

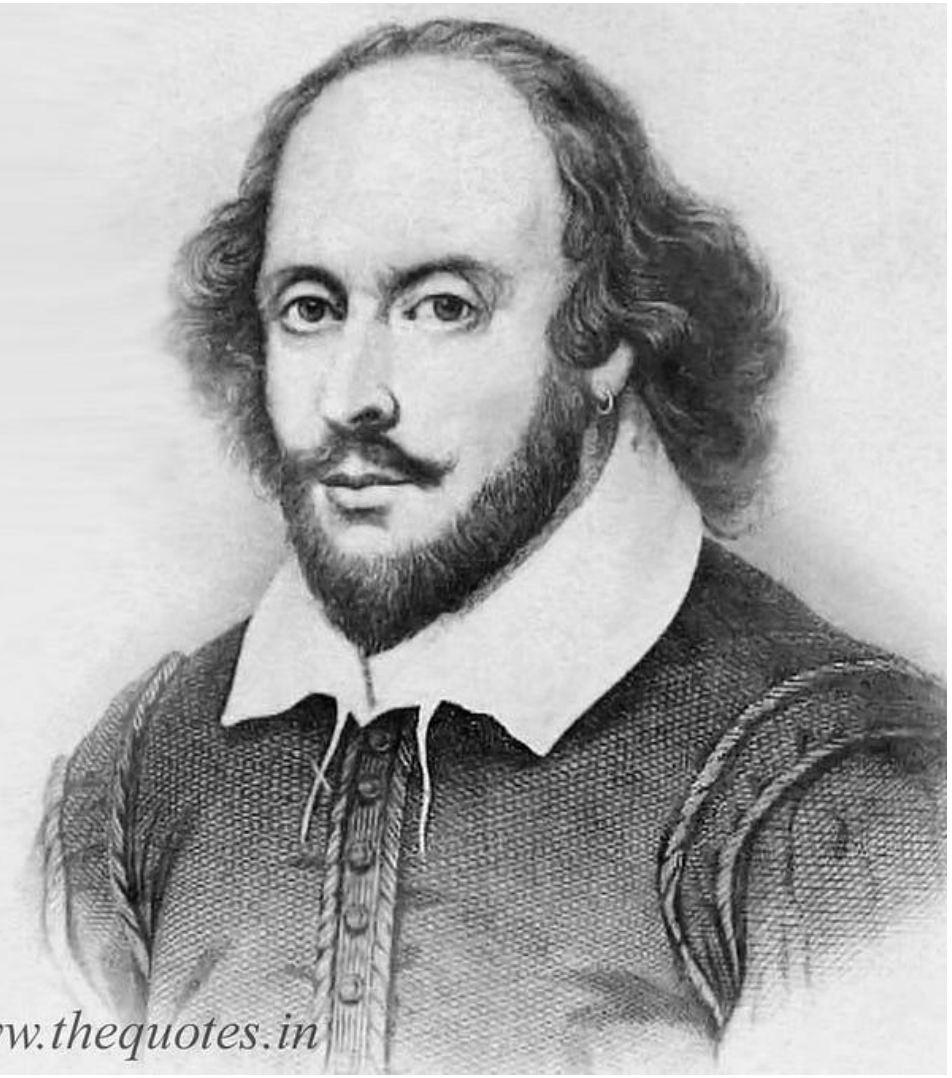
Objectives

- Review new nomenclature and classification in steatotic liver disease
- Discuss the evaluation, diagnosis and natural history of steatotic liver disease
- Explore treatment including lifestyle changes and pharmacologic interventions

NOMENCLATURE

What's in a name? That which we call a rose by any other name would smell as sweet.

William Shakespeare



NAFLD

Problems:	‘Non-alcoholic’ = exclusionary
	Individuals with NAFLD who also consume significant alcohol not clearly classified
	‘Non-alcoholic’ and ‘fatty’ are viewed by many as stigmatizing terms Younossi Z. EASL ILC 2023, THU-453

Special Article

JOURNAL
OF HEPATOLOGY

A multisociety Delphi consensus statement on new fatty liver disease nomenclature

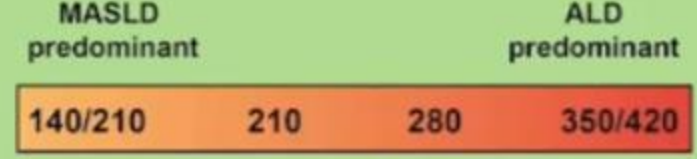
Mary E. Rinella[1,*], Jeffrey V. Lazarus[2,3], Vlad Ratziu[4], Sven M. Francque[5,6], Arun J. Sanyal[7], Fasiha Kanwal[8,9], Diana Romero[2], Manal F. Abdelmalek[10], Quentin M. Anstee[11,12], Juan Pablo Arab[13,14,15], Marco Arrese[15,16], Ramon Bataller[17], Ulrich Beuers[18], Jerome Boursier[19], Elisabetta Bugianesi[20], Christopher D. Byrne[21,22], Graciela E. Castro Narro[16,23,24], Abhijit Chowdhury[25,26], Helena Cortez-Pinto[27], Donna R. Cryer[28], Kenneth Cusi[29], Mohamed El-Kassas[30], Samuel Klein[31], Wayne Eskridge[32], Jiangao Fan[33], Samer Gawrieh[34], Cynthia D. Guy[35], Stephen A. Harrison[36], Seung Up Kim[37], Bart G. Koot[38], Marko Korenjak[39], Kris V. Kowdley[40], Florence Lacaille[41], Rohit Loomba[42], Robert Mitchell-Thain[43], Timothy R. Morgan[44,45], Elisabeth E. Powell[46,47,48], Michael Roden[49,50,51], Manuel Romero-Gómez[52], Marcelo Silva[53], Shivaram Prasad Singh[54], Silvia C. Sookoian[15,55,56], C. Wendy Spearman[57], Dina Tiniakos[11,58], Luca Valenti[59,60], Miriam B. Vos[61], Vincent Wai-Sun Wong[62], Stavra Xanthakos[63], Yusuf Yilmaz[64], Zobair Younossi[65,66,67], Ansley Hobbs[2], Marcela Villota-Rivas[68], Philip N. Newsome [69,70,*], on behalf of the NAFLD Nomenclature consensus group

MASLD
METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

MASH
METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS

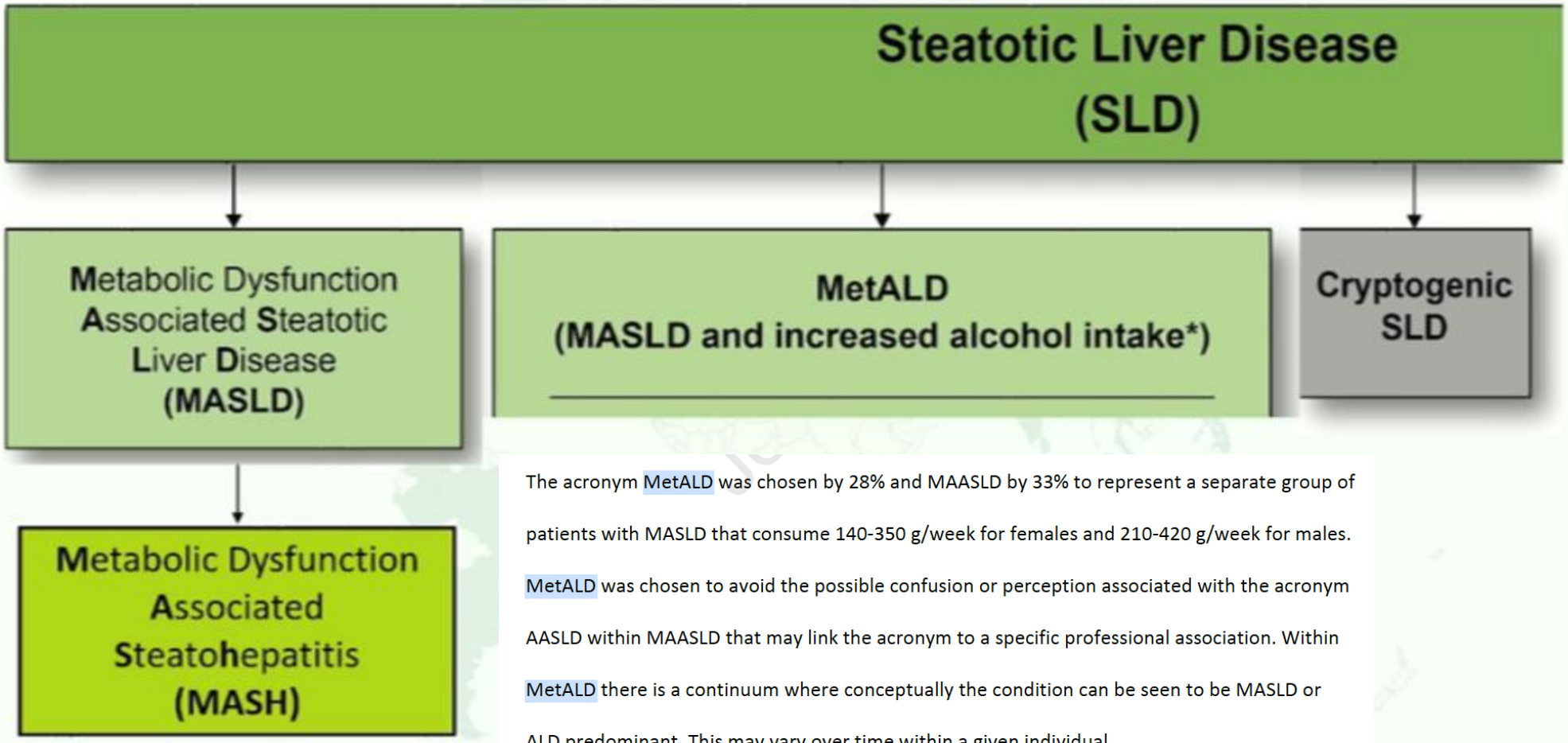
Steatotic Liver Disease (SLD)

- **Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)**
- **MetALD (MASLD and increased alcohol intake*)**



- **Alcohol-Associated (Alcohol-related) Liver Disease (ALD)**
- **Specific aetiology SLD**
  - **Drug-Induced Liver Injury (DILI)**
  - **Monogenic diseases****
  - **Miscellaneous*****
- **Cryptogenic SLD**

*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

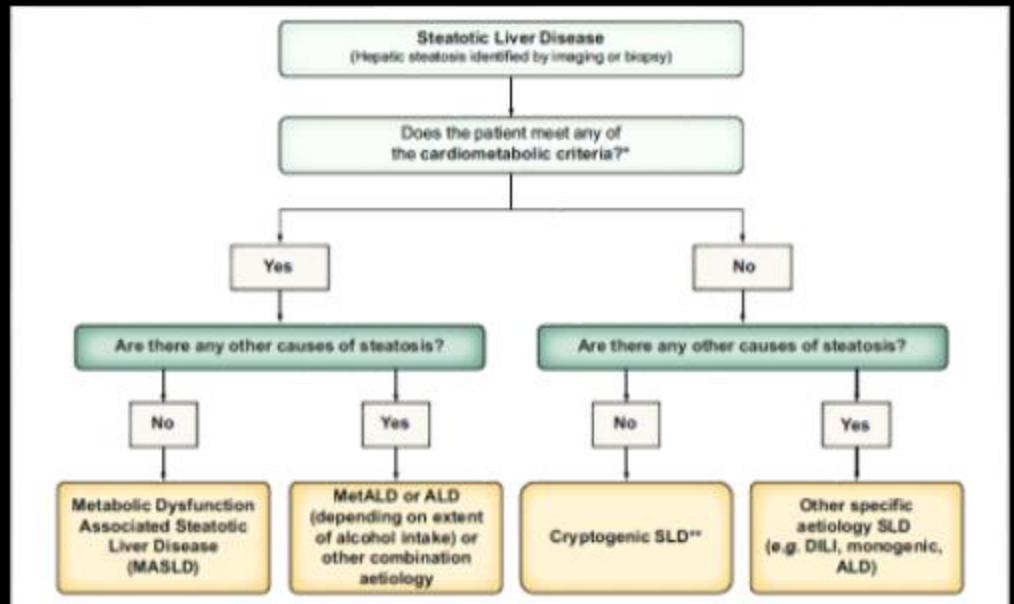


The acronym MetALD was chosen by 28% and MAASLD by 33% to represent a separate group of patients with MASLD that consume 140-350 g/week for females and 210-420 g/week for males. MetALD was chosen to avoid the possible confusion or perception associated with the acronym AASLD within MAASLD that may link the acronym to a specific professional association. Within MetALD there is a continuum where conceptually the condition can be seen to be MASLD or ALD predominant. This may vary over time within a given individual.

ALEH

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

EASL
The Home of Hepatology



*Cardiometabolic criteria

Adult criteria

At least 1 out of 5:

- ☐ BMI ≥25 kg/m² [23 Asia] OR WC >94 cm (M) 80 cm (F) 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
- ☐ Blood pressure ≥130/85 mmHg OR specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥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

Paediatric criteria

At least 1 out of 5:

- ☐ 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 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 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 age <10 yr, ≥1.15 mmol/L [≥100 mg/dl]; age ≥10 yr, ≥1.70 mmol/L [≥150 mg/dl] OR lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤1.0 mmol/L [≤40 mg/dl] OR lipid lowering treatment

New Nomenclature:

- **What this change hopes to achieve**:
  - Remove stigma
  - Provide a ‘neutral’ disease nomenclature that when communicated to patients, carries fewer preconceived notions
  - Provide a better defined clinical and future research classification for individuals previously considered to have NAFLD + a level of alcohol consumption that may be putting them at additional risk
  - All of the above without needing to ‘re-classify’ or ‘re-diagnose’ patients

- **What this change is unlikely to achieve**:
  - Make all stakeholders satisfied, comfortable, and/or happy

Table 1. Delphi Panel Characteristics (N=225)

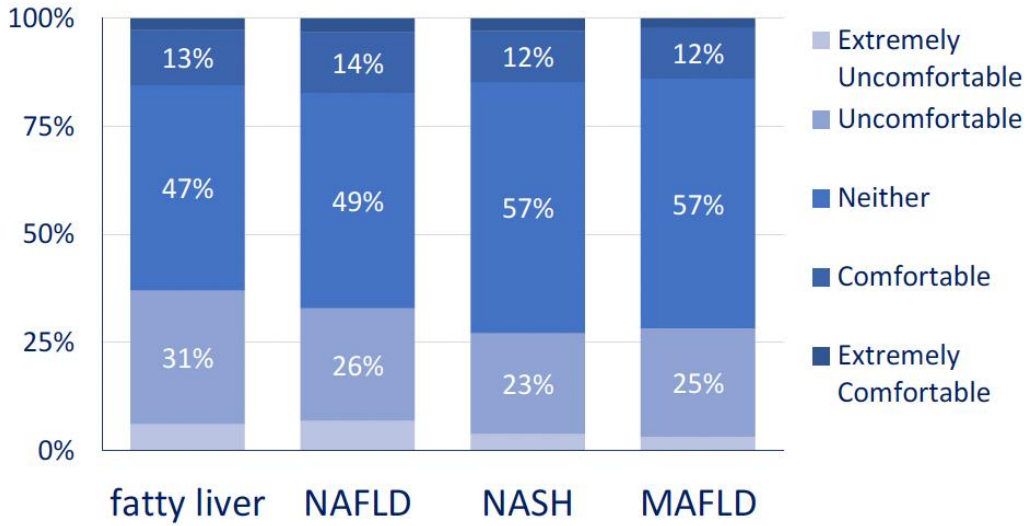
	N	%
Professional characteristics		
Primary sector of employment		
Civil society	7	3
Private	21	9
Public	34	15
Academic	158	70
Other	4	2
Primary field/area of work		
Clinical research	118	54
Healthcare provider	61	28
Non-clinical research	13	6
Patient/policy advocacy	18	9
Other	7	4
Primary area of specialty/expertise* (among healthcare providers, clinical and non-clinical researchers)		
Gastroenterology	7	4
Endocrinology	13	7
Hepatology	151	82
Other	13	8
Years working in the field post-training		
0-12	53	29
13-24	69	37
25-36	51	27
37-48	13	7
% of work in NAFLD-related clinical care, research or both		
0-25	26	12
26-50	61	27
51-75	68	30
76-100	44	19
Number of articles (co)authored on topic of NAFLD		
<6	32	17
6-20	42	22
21-50	39	21
>50	74	40
Liver organization associated with *(N invited)*		
AASLD *(72)*	60	27
ALEH *(30)*	27	12
APASL, AMAGE, INASL, SAASL, TASL *(41)*	29	13
EASL *(70)*	66	29
GI and endocrinological societies *(21)*	15	7
Pathology societies *(4)*	3	1
Patient organization *(29)*	24	11

Terms **'non-alcoholic'** and **'fatty'** were deemed stigmatising by 61% and 66% of respondents

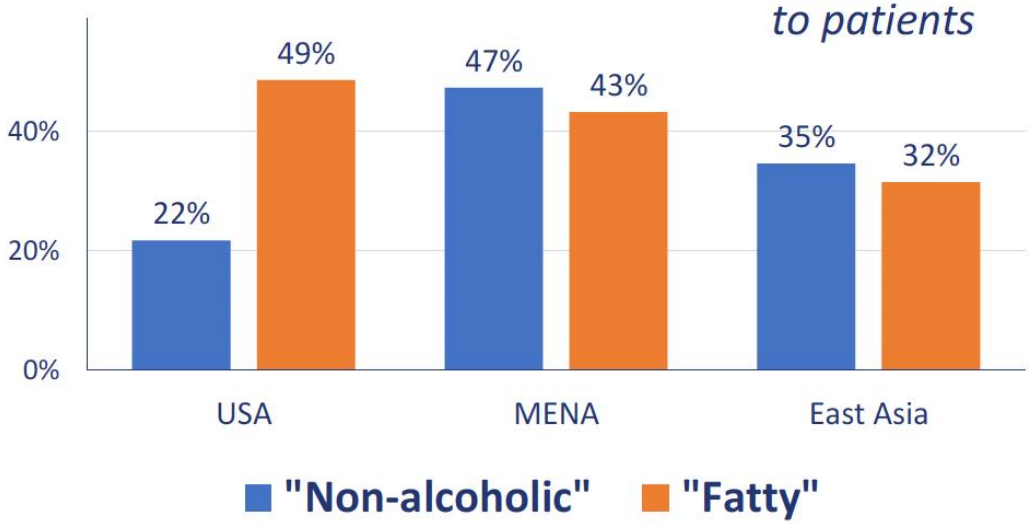
But 'stigmatising' from what perspective?

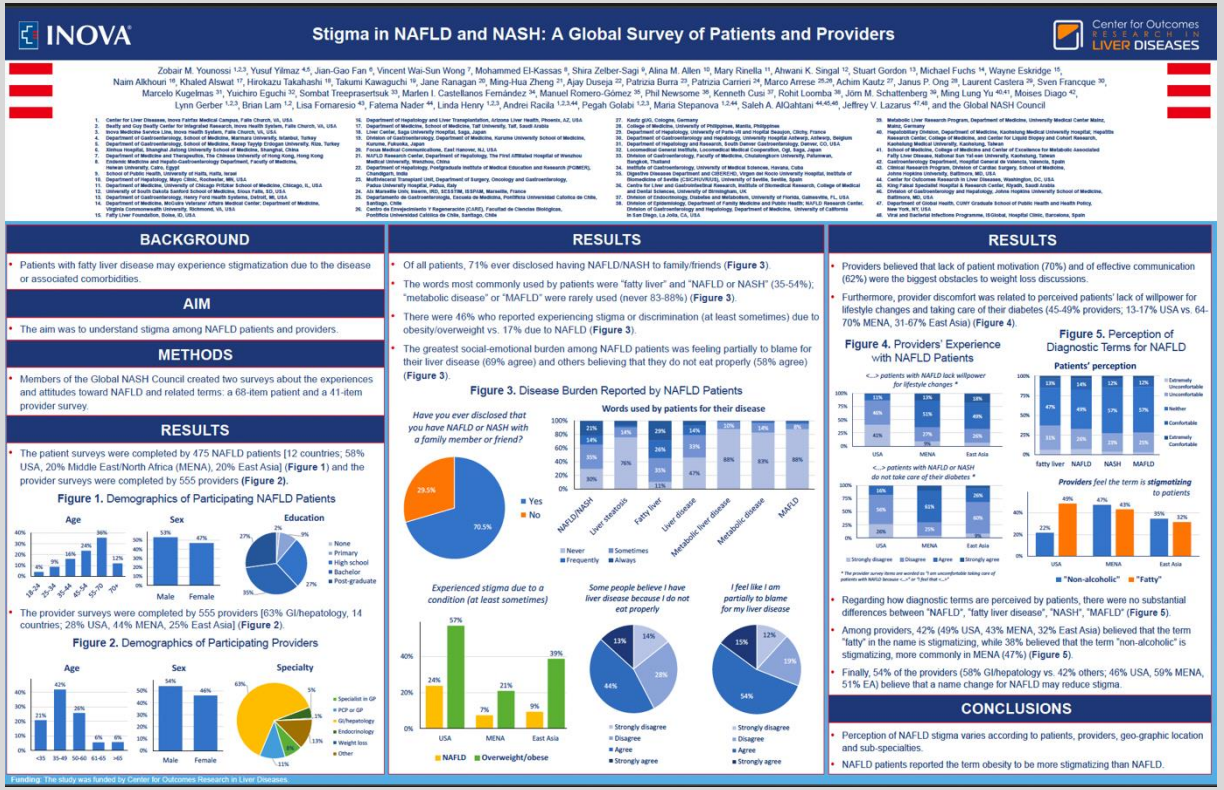
Figure 5. Perception of Diagnostic Terms for NAFLD

Patients' perception



Providers feel the term is *stigmatizing* to patients





INOVA

Stigma in NAFLD and NASH: A Global Survey of Patients and Providers

Center for Outcomes Research in Liver Diseases

Zobair M. Younossi [1,2,3], Yusuf Yilmaz [4,5], Jian-Gao Fan [6], Vincent Wai-Sun Wong [7], Mohammed El-Kassas [8], Shira Zelber-Sagi [9], Alina M. Allen [10], Mary Rinella [11], Ahwani K. Singal [12], Stuart Gordon [13], Michael Fuchs [14], Wayne Eskridge [15], Naim Alkhouri [16], Khaled Alswat [17], Hirokazu Takahashi [18], Takumi Kawaguchi [19], Jane Ranagan [20], Ming-Hua Zheng [21], Ajay Duseja [22], Patrizia Burra [23], Patrizia Carrieri [24], Marco Arrese [25,26], Achim Kautz [27], Janus P. Ong [28], Laurent Castera [29], Sven Francque [30], Marcelo Kugelmas [31], Yuichiro Eguchi [32], Sombat Treeprasertsuk [33], Marlen I. Castellanos Fernández [34], Manuel Romero-Gómez [35], Phil Newsome [36], Kenneth Cusi [37], Rohit Loomba [38], Jörn M. Schattenberg [39], Ming Lung Yu [40,41], Moises Diago [42], Lynn Gerber [1,2,3], Brian Lam [1,2], Lisa Fornaresio [43], Fatema Nader [44], Linda Henry [1,2,3], Andrei Racila [1,2,3,44], Pegah Golabi [1,2,3], Maria Stepanova [1,2,44], Saleh A. AlQahtani [44,45,46], Jeffrey V. Lazarus [47,48], and the Global NASH Council

BACKGROUND

- Patients with fatty liver disease may experience stigmatization due to the disease or associated comorbidities.

AIM

- The aim was to understand stigma among NAFLD patients and providers.

METHODS

- Members of the Global NASH Council created two surveys about the experiences and attitudes toward NAFLD and related terms: a 68-item patient and a 41-item provider survey.

RESULTS

- The patient surveys were completed by 475 NAFLD patients [12 countries; 58% USA, 20% Middle East/North Africa (MENA), 20% East Asia] (**Figure 1**) and the provider surveys were completed by 555 providers (**Figure 2**).

Figure 1. Demographics of Participating NAFLD Patients

- The provider surveys were completed by 555 providers [63% GI/hepatology, 14 countries; 28% USA, 44% MENA, 25% East Asia] (**Figure 2**).

Figure 2. Demographics of Participating Providers

RESULTS

- Of all patients, 71% ever disclosed having NAFLD/NASH to family/friends (**Figure 3**).
- The words most commonly used by patients were "fatty liver" and "NAFLD or NASH" (35-54%); "metabolic disease" or "MAFLD" were rarely used (never 83-88%) (**Figure 3**).
- There were 46% who reported experiencing stigma or discrimination (at least sometimes) due to obesity/overweight vs. 17% due to NAFLD (**Figure 3**).
- The greatest social-emotional burden among NAFLD patients was feeling partially to blame for their liver disease (69% agree) and others believing that they do not eat properly (58% agree) (**Figure 3**).

Figure 3. Disease Burden Reported by NAFLD Patients

RESULTS

- Providers believed that lack of patient motivation (70%) and of effective communication (62%) were the biggest obstacles to weight loss discussions.
- Furthermore, provider discomfort was related to perceived patients' lack of willpower for lifestyle changes and taking care of their diabetes (45-49% providers; 13-17% USA vs. 64-70% MENA, 31-67% East Asia) (**Figure 4**).

Figure 4. Providers' Experience with NAFLD Patients

Figure 5. Perception of Diagnostic Terms for NAFLD

- Regarding how diagnostic terms are perceived by patients, there were no substantial differences between "NAFLD", "fatty liver disease", "NASH", "MAFLD" (**Figure 5**).
- Among providers, 42% (49% USA, 43% MENA, 32% East Asia) believed that the term "fatty" in the name is stigmatizing, while 38% believed that the term "non-alcoholic" is stigmatizing, more commonly in MENA (47%) (**Figure 5**).
- Finally, 54% of the providers (58% GI/hepatology vs. 42% others; 46% USA, 59% MENA, 51% EA) believe that a name change for NAFLD may reduce stigma.

CONCLUSIONS

- Perception of NAFLD stigma varies according to patients, providers, geo-graphic location and sub-specialties.
- NAFLD patients reported the term obesity to be more stigmatizing than NAFLD.

Funding: The study was funded by Center for Outcomes Research in Liver Diseases.

CONCLUSIONS

- Perception of NAFLD stigma varies according to patients, providers, geo-graphic location and sub-specialties.
- NAFLD patients reported the term obesity to be more stigmatizing than NAFLD.

New Nomenclature: Potential Concerns

- **Unclear if prior nomenclature really was stigmatizing**
  - Data doesn't really support that it was, from a patient perspective
  - 'Patient advocates' and those likely to engage in advocacy activities are potentially quite a bit different that the 'typical' patients we see in clinic
- **If prior nomenclature was problematic, unclear if newer is better**
  - Delphi process drives change towards consensus but does that mean you end up in a better place than before?
- **When speaking to patients, if not the word 'fatty', are we OK to use 'fat'?**
  - Are we overestimating our patients' interest in semantics?

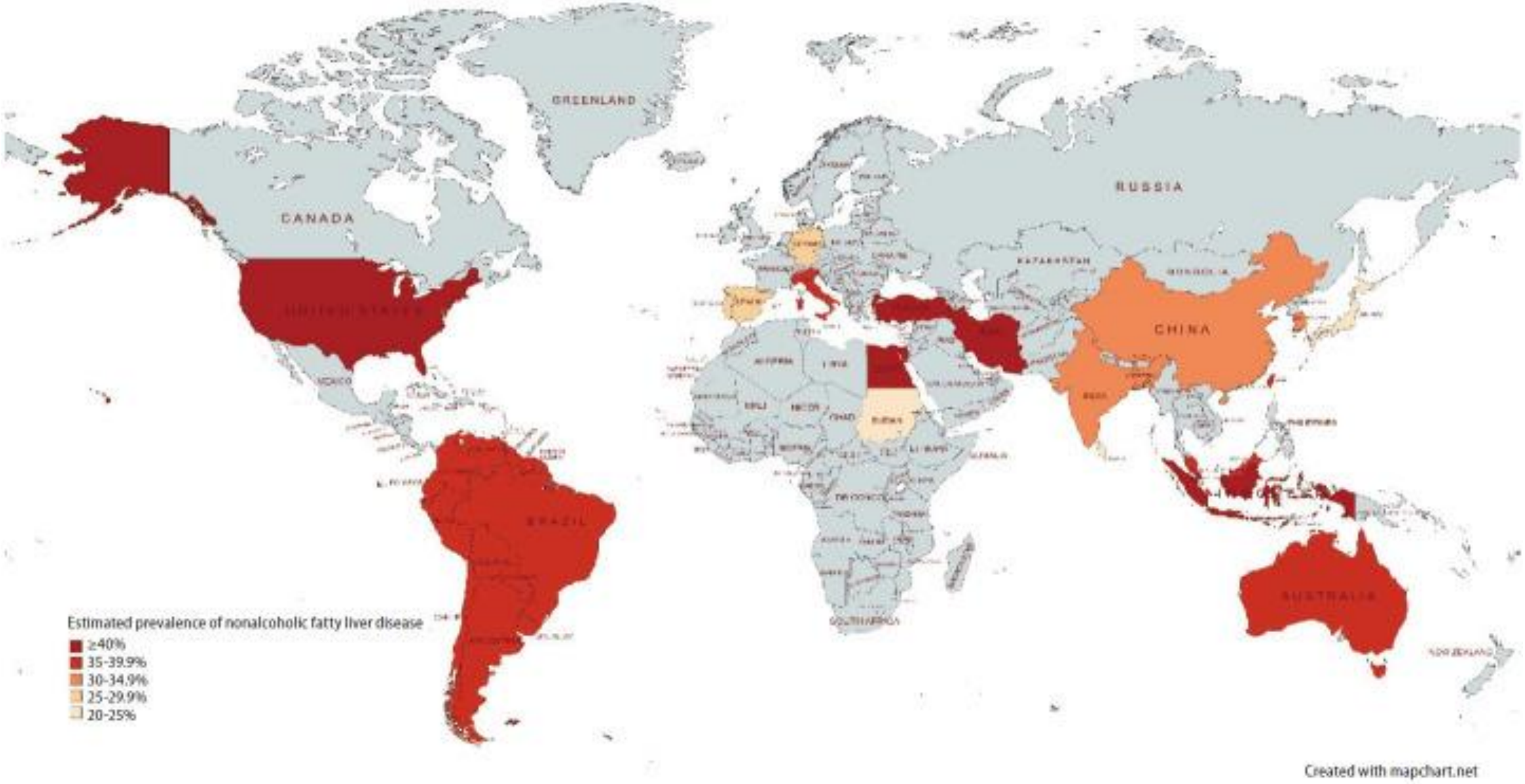
What's in a name? That which we call **NAFLD** by any other name would **STILL REFER TO FAT IN THE LIVER**

William Shakespeare


AFEF
SOCIÉTÉ FRANÇAISE D'HÉPATOLOGIE
ALEH
AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES
aga
American Gastroenterological Association
AMERICAN LIVER FOUNDATION
ASPC
The American Society for Preventive Cardiology
ASGE
American Society for Gastrointestinal Endoscopy
Asian Pan-Pacific Society
Asociación Colombiana de Hepatología
AEEH
Asociación Española para el Estudio del Hígado
APEH
APEF
ASSOCIAÇÃO PORTUGUESA PARA O ESTUDO DO FÍGADO
Asociación Puertorriqueña de Gastroenterología
ABGH
AQHİB
BASL
British Association for the Study of the Liver
BRITISH LIVER TRUST
Belgian Week of Gastroenterology
Canadian Association for the Study of the Liver
CASL ACEF
Association canadienne pour l'étude du foie
THE CROATIAN SOCIETY OF GASTROENTEROLOGY
DGH
Dansk Selskab for Gastroenterologi og Hepatologi
DGVS
Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten
EASL
The Home of Hepatology
ELPA
European Liver Patients' Association
ESPGHAN
FLF
Fatty Liver Foundation
THE FORUM
For Collaborative Research℠
Asociación de Especialistas en Gastroenterología y Endoscopía Digestiva de Costa Rica
GLI
GLOBAL LIVER INSTITUTE
HASL
Hellenic Association for the Study of Liver
Ελληνική Εταιρεία Μελέτης Ήπατος
INASL
JSH
一般社団法人 日本肝臓学会
The Japan Society of Hepatology
LEVERFORENINGEN DANMARK
NGF
ÖGGH
Österreichische Gesellschaft für Gastroenterologie und Hepatologie
SASL
SAHE
Sociedad Argentina de Hepatología
SGU
Sociedad de Gastroenterología del Uruguay
SEPD
SOLDA
SOCIETY ON LIVER DISEASE IN AFRICA
Sociedade Brasileira de Hepatologia
srgh
1958
ueg
UNITED EUROPEAN GASTROENTEROLOGY
UASLD
SOCIEDAD VENEZOLANA DE GASTROENTEROLOGÍA

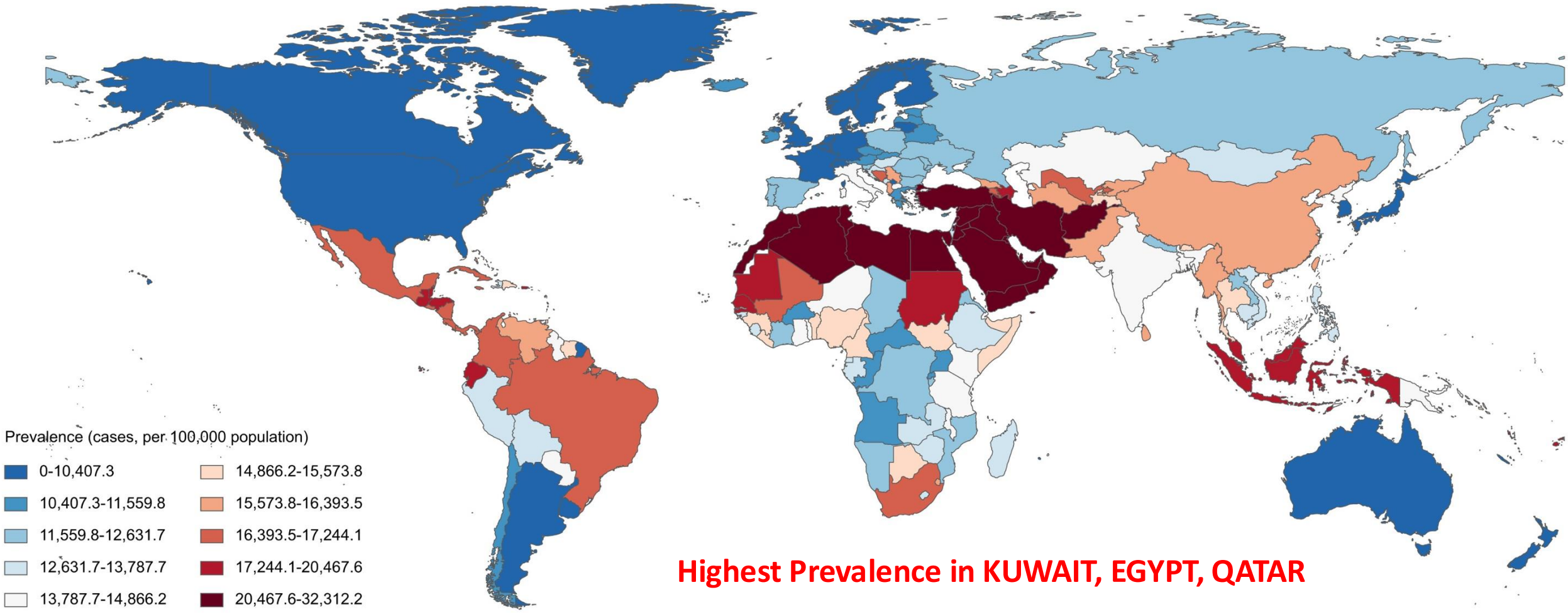
DISEASE BURDEN

Estimated Global Prevalence of MASLD: 25-40%



Adapted from: Teng ML. Clin Mol Hepatol. 2023 Feb;29(Suppl):S32-S42.;

Age-standardized point prevalence rates of MASLD per 100,000 in 2021



Highest Prevalence in KUWAIT, EGYPT, QATAR

Global Burden of MASLD, 2010-2021. JHEP Reports 2025. vol. 7 j 1–12

Burden of nonalcoholic fatty liver disease in Canada, 2019-2030: a modelling study

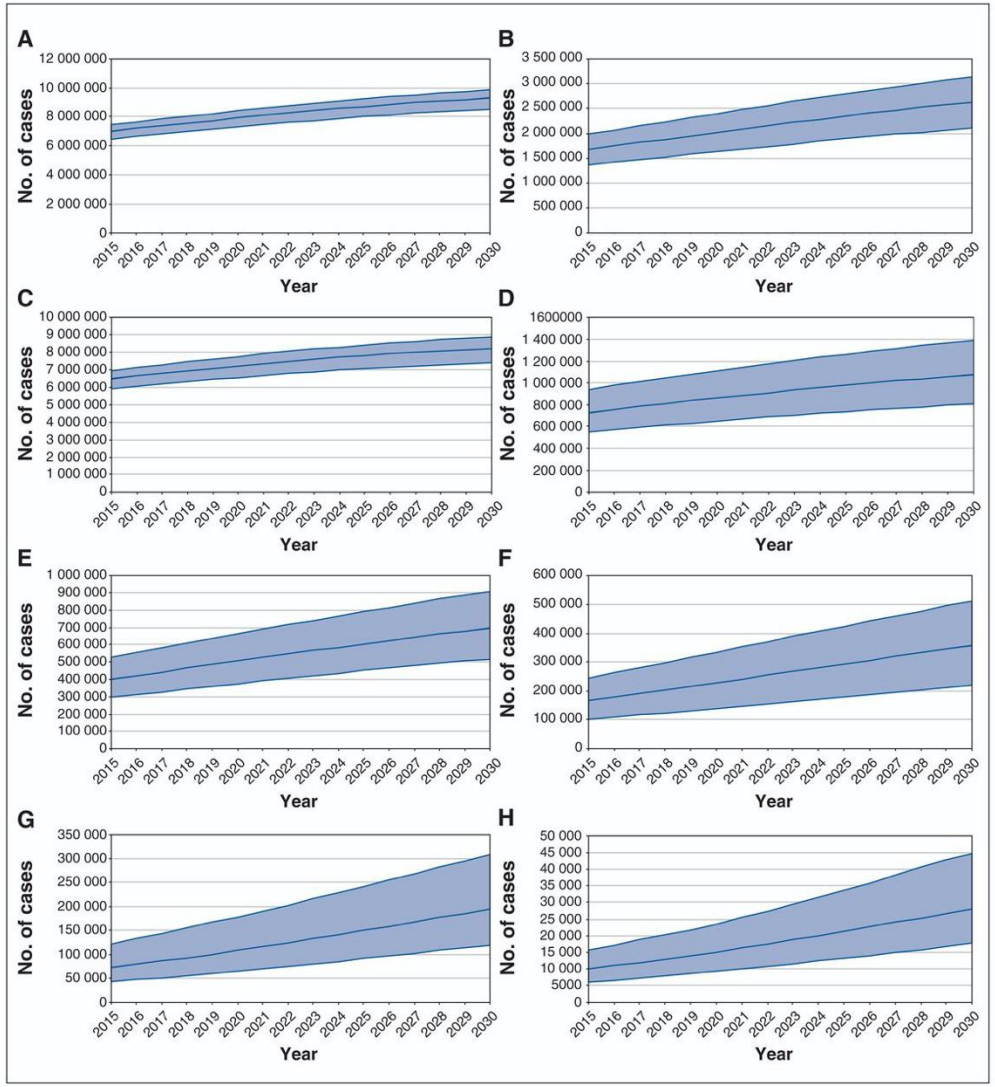


Figure 1: Model-estimated prevalent cases of:
nonalcoholic fatty liver disease (NAFLD) (A)
nonalcoholic steatohepatitis (B)
stage F0 NAFLD (C)
stage F1 NAFLD (D)
stage F2 NAFLD (E)
stage F3 NAFLD (F)
compensated cirrhosis NAFLD (G)
decompensated cirrhosis, hepatocellular carcinoma and liver transplantation related to NAFLD (H)
for Canada, 2015–2030. Shaded areas represent 95% uncertainty interval.

cmajo June 9, 2020 vol. 8 no. 2 E429-E436

Burden of nonalcoholic fatty liver disease in Canada, 2019-2030: a modelling study

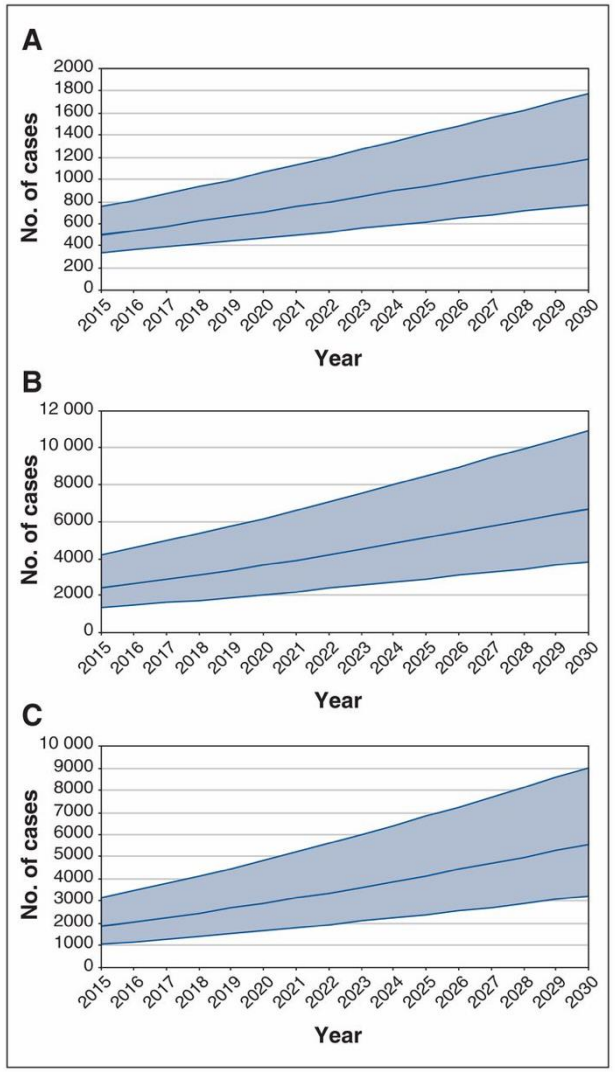
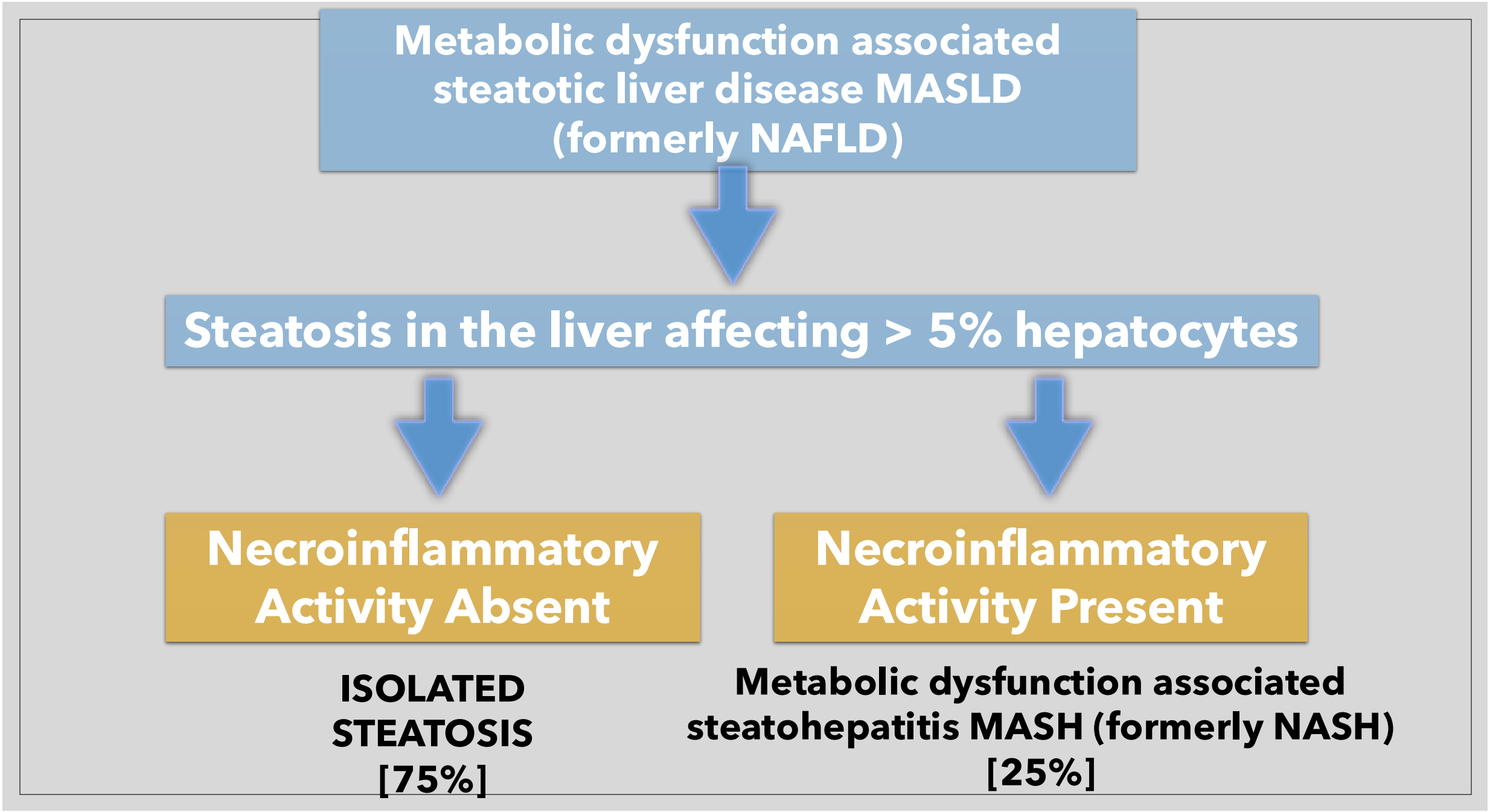


Figure 2: Model-estimated incident cases of: hepatocellular carcinoma (A) decompensated cirrhosis (B) incident liver-related death (C) related to nonalcoholic fatty liver disease for Canada, 2015–2030. Shaded areas represent 95% uncertainty interval.

cmajo June 9, 2020 vol. 8 no. 2 E429-E436

EVALUATION


Metabolic dysfunction associated steatotic liver disease MASLD (formerly NAFLD)
Steatosis in the liver affecting > 5% hepatocytes
Necroinflammatory Activity Absent
Necroinflammatory Activity Present
ISOLATED STEATOSIS [75%]
Metabolic dysfunction associated steatohepatitis MASH (formerly NASH) [25%]

Defining Steatosis

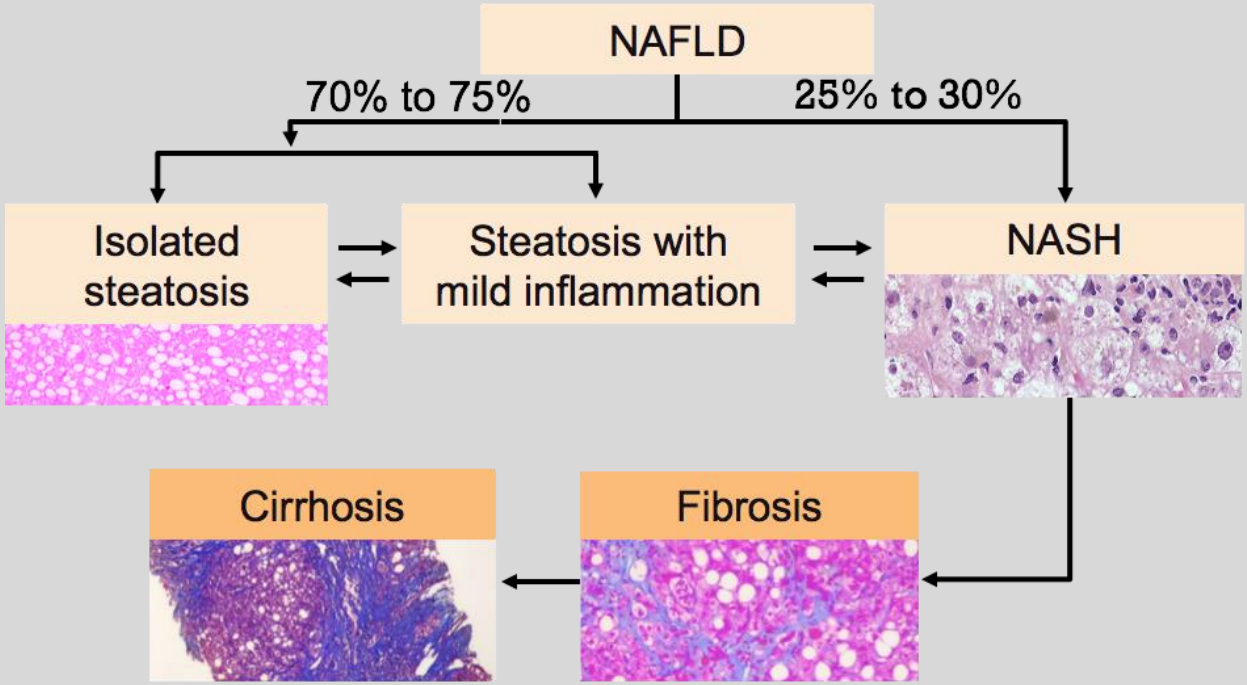
- HISTOLOGIC
  - Gold standard
  - > 5% of hepatocytes with steatosis
- SURROGATE
  - Imaging evidence of fatty infiltration of the liver
  - “Increased Echogenicity” on US
  - Decreased sensitivity if <20% of liver affected by fat; findings may be similar to those of early cirrhosis

Defining Necroinflammatory Activity

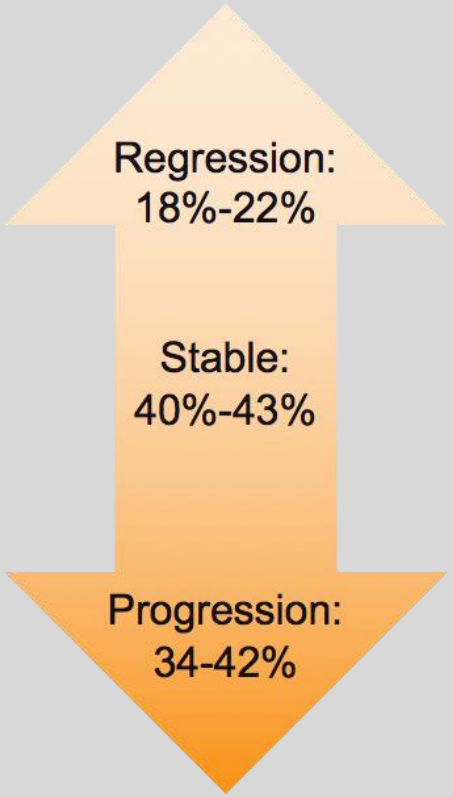
- HISTOLOGIC
  - Gold standard
  - Presence of hepatocellular ballooning; Mallory's hyaline; inflammatory cells
- SURROGATE
  - Elevated liver enzymes (ALT and AST)
  - *But normal ALT can still progress*

NAFLD Disease Progression

Histological Subtypes[1,2]



Change in Fibrosis*[3,4]



*N = 108 pts with NAFL/NASH and median 6.6 yrs follow-up (data from serial biopsies).

1. Ludwig J, et al. Mayo Clin Proc. 1980;55(7):434-438.
2. Kleiner DE, et al. Hepatology. 2005;41(6):1313-1321.
3. McPherson S, et al. J Hepatol. 2015;62:1148-1155.
4. Singh S, et al. Clin Gastroenterol Hepatol. 2015 Apr;13(4):643-54

Adapted from: clinicaloptions.com

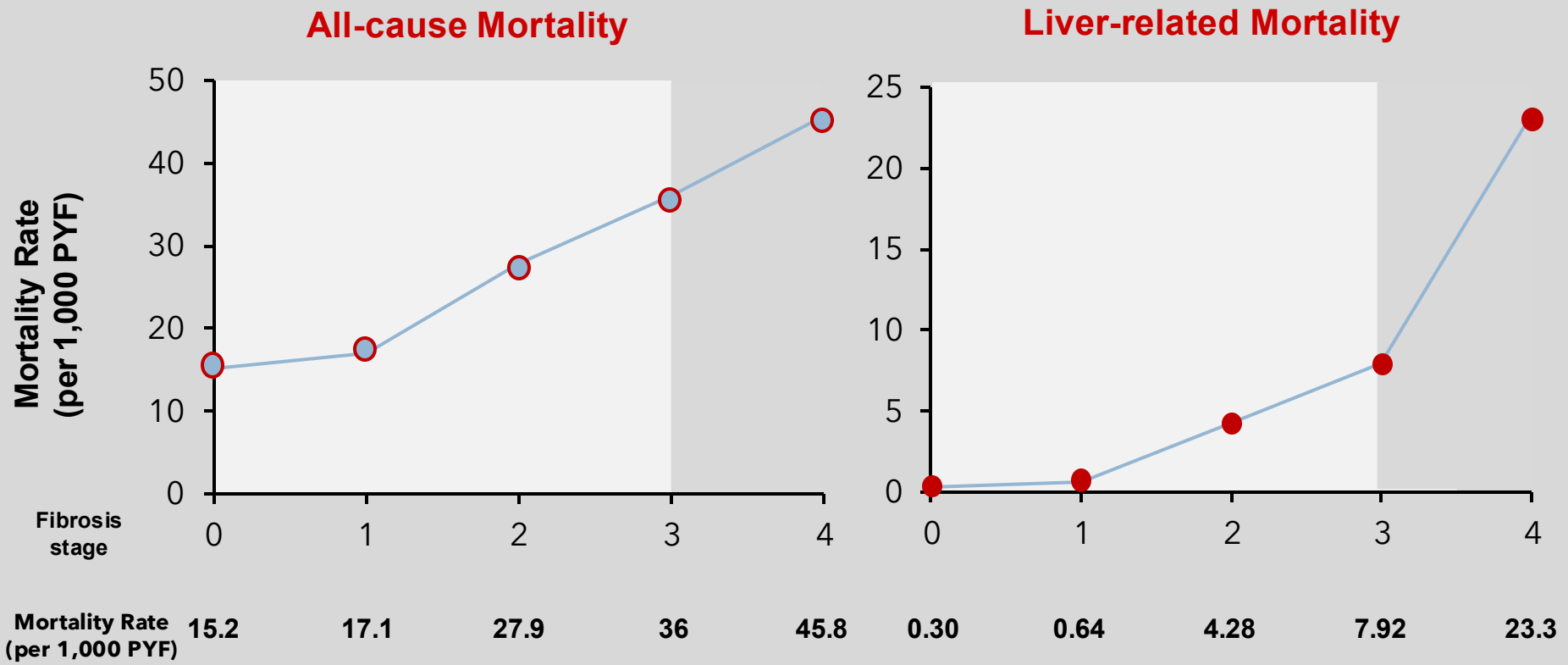
Recommended/Available Non-Invasive Risk Stratification Tools

- FIB-4
  - Age, AST, ALT, plts

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

  - Score ≤ 1.30 can rule out advanced fibrosis with 90% NPV
  - Score ≥ 2.67 identifies advanced fibrosis with 80% PPV
  - NB: Caution in those < 35 years old or > 65 years old
- Elastography
  - FibroScan (transient elastography) – point of care
  - US-based shear wave elastography – imaging facility

Mortality Risk Increases as Fibrosis Progresses



Systematic review and meta-analysis of 5 studies in 1495 NAFLD patients with 17,452 person-years follow-up

PYF = patient year of follow up.

Dulai P, et al. Hepatology. 2017;65(5):1557–1565.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prospective Study of Outcomes in Adults with Nonalcoholic Fatty Liver Disease

Arun J. Sanyal, M.D., Mark L. Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Brent A. Neuschwander-Tetri, M.D., AnnaMae Diehl, M.D., Srinivasan Dasarathy, M.D., Rohit Loomba, M.D., M.H.Sc., Naga Chalasani, M.D., Kris Kowdley, M.D., Bilal Hameed, M.D., Laura A. Wilson, Sc.M., Katherine P. Yates, Sc.M., Patricia Belt, B.S., Mariana Lazo, M.D., Ph.D., David E. Kleiner, M.D., Ph.D., Cynthia Behling, M.D., Ph.D., and James Tonascia, Ph.D., for the NASH Clinical Research Network (CRN)*

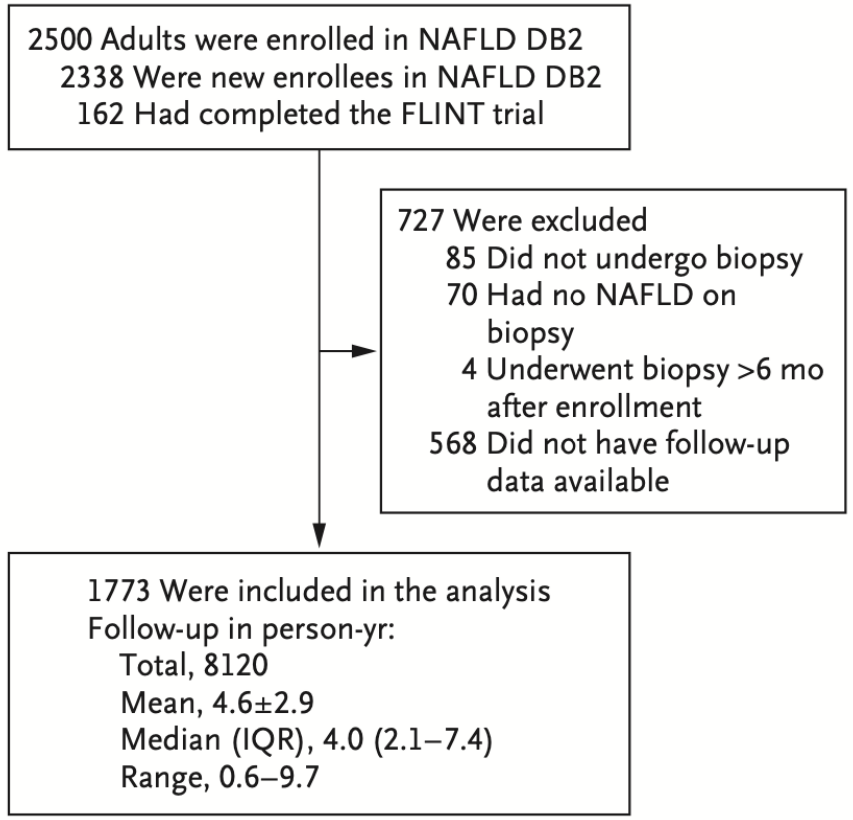
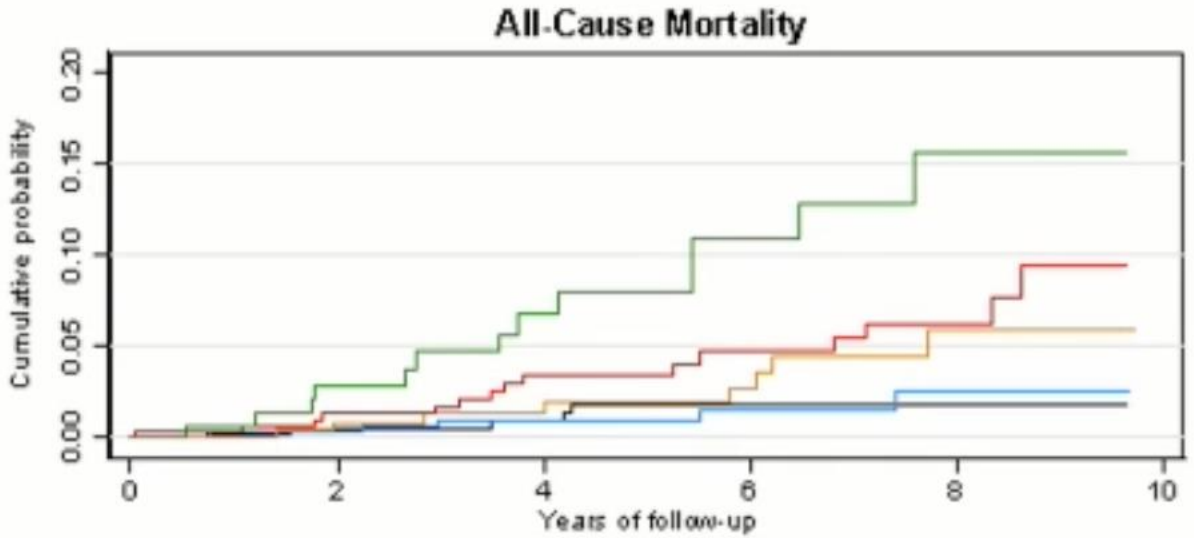


Figure 1. Selection Criteria for Analysis Database.

Patients from the Nonalcoholic Fatty Liver Disease (NAFLD) Database-2 noninterventional registry (DB2) were enrolled along with a subgroup of patients who had previously participated in and completed all study visits for the Farnesoid X Receptor Ligand Obeticholic Acid in Noncirrhotic Nonalcohlic Steatohepatitis (NASH) Treatment (FLINT) trial conducted by the NASH Clinical Research Network. IQR denotes interquartile range.

N Engl J Med 2021;385:1559-1569

All cause mortality



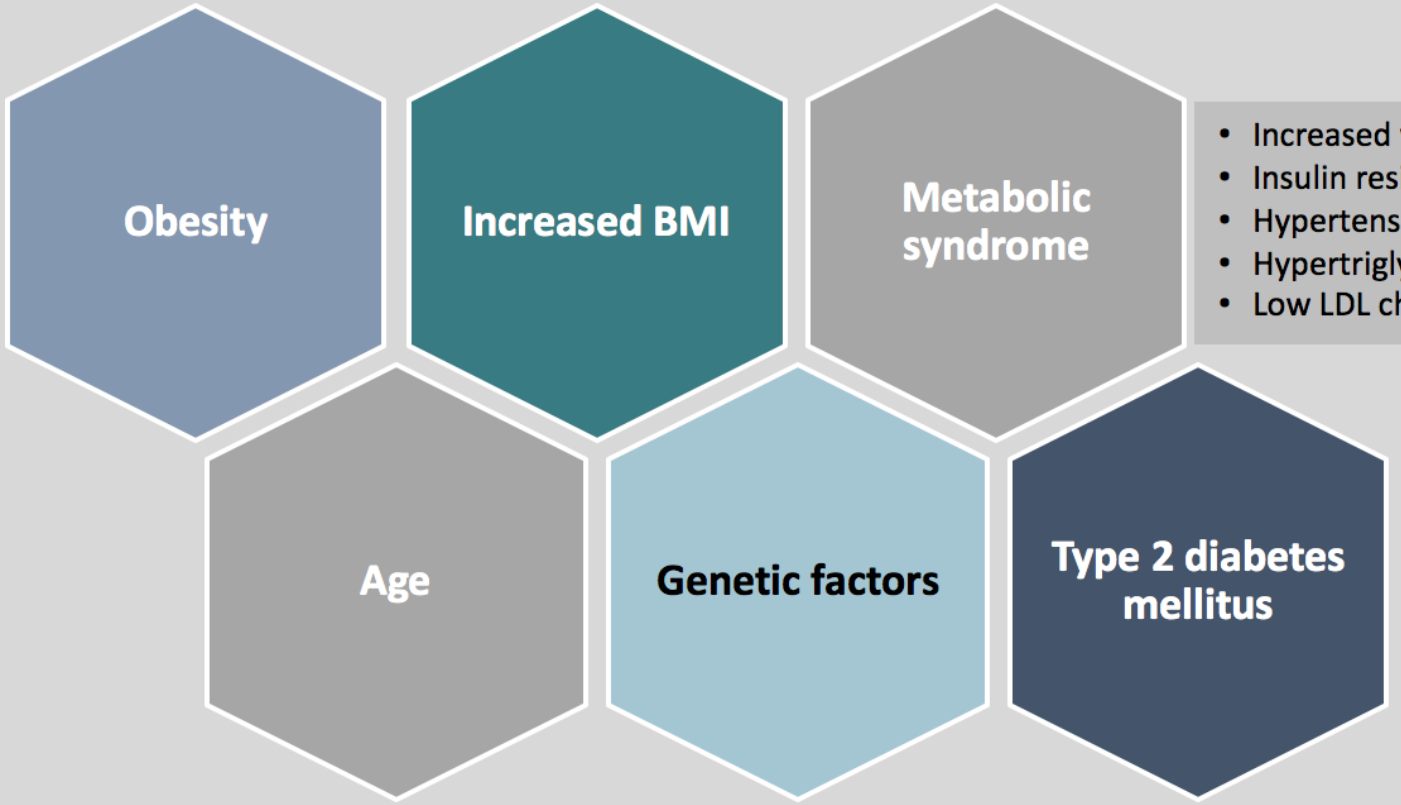
No. at risk (Events)

F4	167	(4)	125	(4)	85	(3)	51	(2)	26	(0)	0
F3	367	(4)	280	(5)	193	(2)	141	(2)	81	(2)	0
F2	320	(2)	244	(1)	162	(2)	115	(3)	50	(0)	0
F1	455	(1)	348	(2)	227	(1)	150	(1)	83	(0)	0
F0	461	(2)	352	(1)	225	(2)	157	(0)	100	(0)	0

F4 F3 F2 F1 F0

Crude RR(95% CI): F4 vs F0 = 7.6 (2.7, 21.6)
Crude RR(95% CI): F3 vs F0 = 3.6 (1.3, 9.8)
Crude RR(95% CI): F2 vs F0 = 2.3 (0.8, 7.0)
Crude RR(95% CI): F1 vs F0 = 1.0 (0.3, 3.6)

Risk Factors for Developing MASH May Also Contribute to Fibrosis Progression



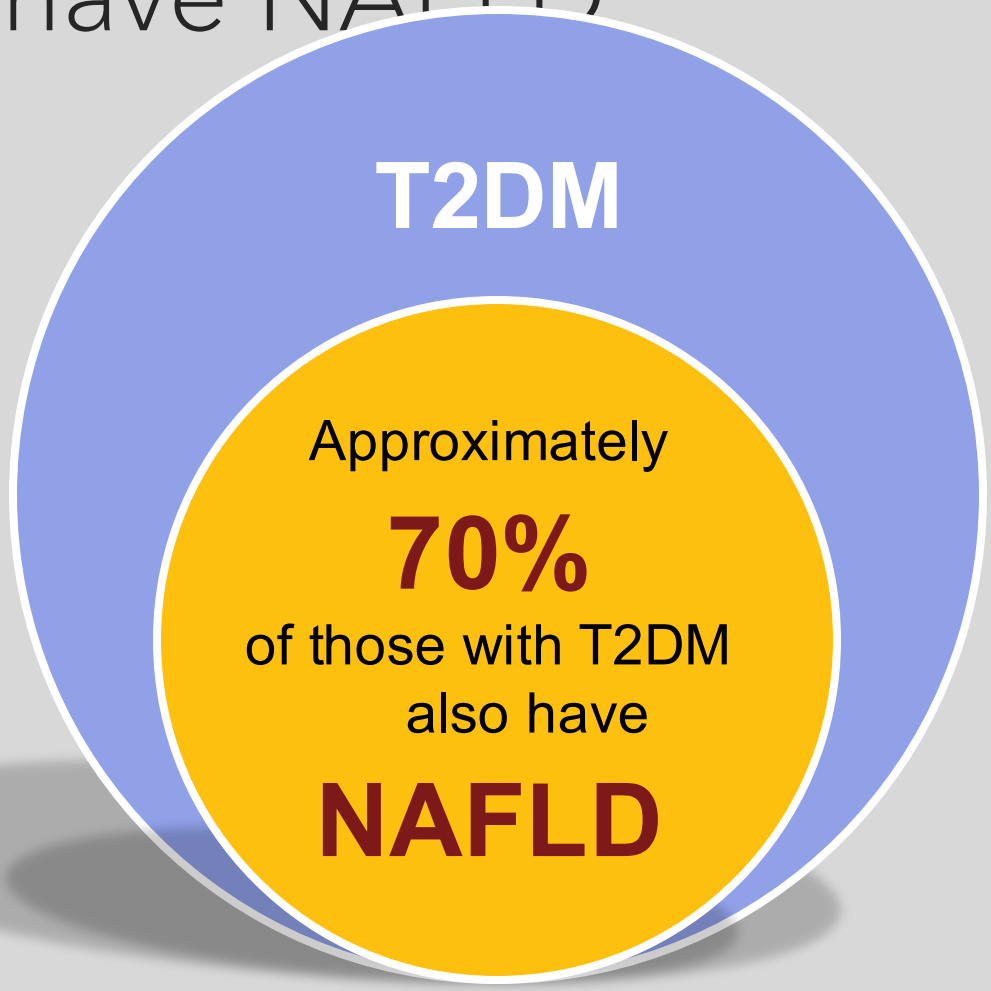
- Increased waist circumference
- Insulin resistance
- Hypertension
- Hypertriglyceridemia
- Low LDL cholesterol

- PNPLA3 gene variant I148M
- TM6SF2

BMI, body mass index; LDL, low-density lipoprotein.

1. Marengo A, et al. *Clin Liver Dis.* 2016;20(2):313-324. 2. Chalasani N, et al. *Hepatology.* 2018;67(1):328-357.

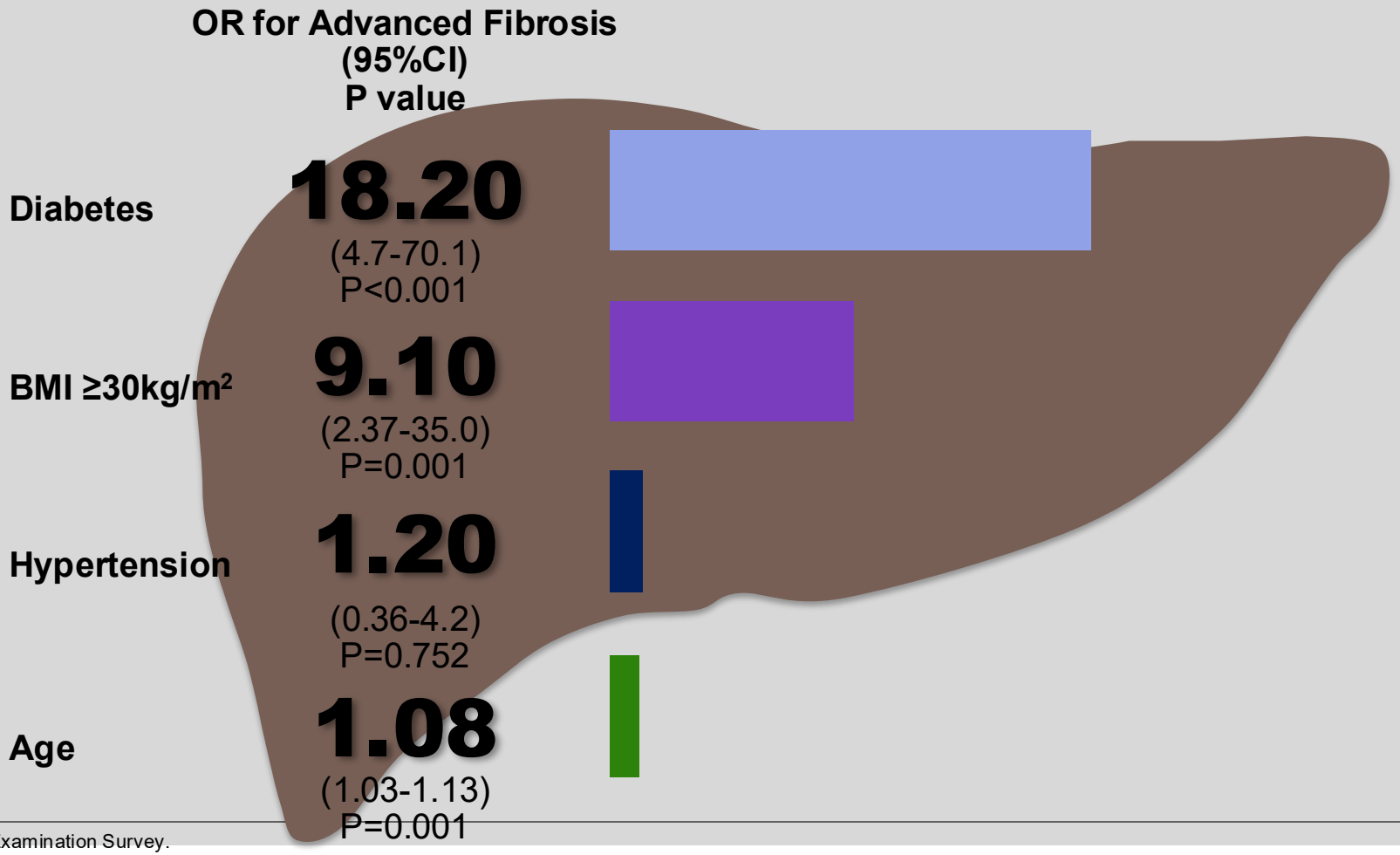
A Large Proportion of Patients with T2DM have NAFLD



- NAFLD is the most common liver disease in the US and Canada
- NAFLD is closely associated with T2DM, obesity, and insulin resistance
- NAFLD can be considered the hepatic manifestation of metabolic syndrome

1. Argo CK and Caldwell SH. Clin Liver Dis. 2009;13:511–531; 2. Fan JG, et al. J Hepatol. 2017;67:862–873; 3. Hunt CM, et al. Fed Pract. 2019;36:20–29; 4. Targher G, et al. Diabetes Care. 2007;30:1212–1218.

Diabetes is One of the Strongest Predictors of Advanced Fibrosis in Patients with NAFLD



NHANES = National Health and Nutrition Examination Survey.

Wong RJ, et al. Aliment Pharmacol Ther. 2017;46:974–980.

Clinical Presentation

- May often be asymptomatic
- Fatigue (up to 70%)
- Vague RUQ Pain
- Hepatomegaly
- Metabolic syndrome, Diabetes
- Exclude: alcohol (Hx); viral (HBsAg/HCV Ab); autoimmune (ANA; smooth muscle Ab; quantitative immunoglobulins)

Laboratory Abnormalities

- Transaminase elevation usually with ALT > AST, except when advanced fibrosis or component of alcohol-related liver disease present, when ratio may reverse
- Elevated GGT; elevated ALP in minority
- Hyperferritinemia very common, and not indicative of iron overload

When to Be Concerned?

- Steatotic liver disease is typically identified through imaging (incidentally or during investigation of abnormal liver tests)
- We should be most concerned with MASH and certainly MASH + hepatic fibrosis
- Clinical predictors of MASH:
  - **Elevated ALT**; **DM**; advanced age; hispanics and asians; central obesity; dyslipidemia
- Signs of advanced fibrosis: AST>ALT; low plts; splenomegaly

How to More Formally Risk Stratify? Liver elastography

- **FibroScan** (transient elastography)
  - Non-invasively measures liver fibrosis
  - May also quantify fat using CAP (controlled attenuation parameter)
- US-based Shear Wave Elastography (**US-SWE**)
  - Liver elastography measurements taken at same time as diagnostic US (available at certain centres)
- ** Those with stage 2 fibrosis or higher should be referred for further evaluation

Evaluation and Risk Stratification

- **FIB-4 first**, then elastography for those above threshold continues to be the consensus approach to risk stratification. For patients < 35, FIB-4 not well validated. For patients > 65, higher threshold is more appropriate.
- **Rule out other causes of liver disease**/refer for those with persistently abnormal liver enzymes
- A multitude of novel scoring systems have been and continue to be reported. FIB-4 currently retains its foothold due to simplicity and applicability across care settings

Evaluation and Risk Stratification

- **NB**: Current locations where **liver elastography** can be accessed:
  - MEDRAY Imaging
  - North Shore Medical Imaging
  - Vancouver General Hospital

- A multitude of novel scoring systems have been and continue to be reported. FIB-4 currently retains its foothold due to simplicity and applicability at the primary care level (and lack of additional cost to patient)

MANAGEMENT

Management

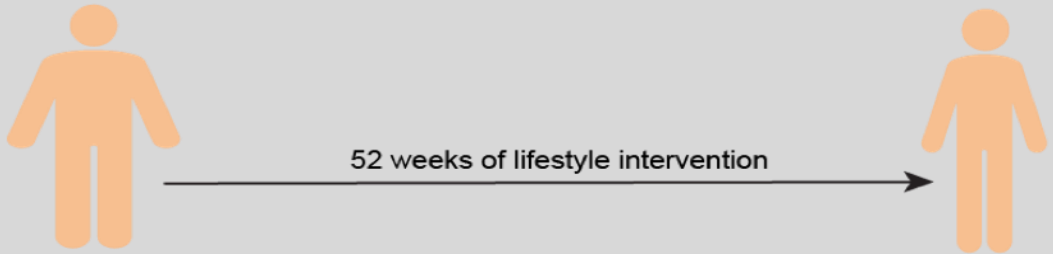
- Exercise and dietary modification
  - Improves liver enzymes
  - Decreases inflammatory activity
  - May result in fibrosis reversal
- In most studies, diet and exercise to result in 5-10% loss in TBW

How to Counsel Our Patients?

- Regular exercise – as much as possible
  - No firm conclusion yet on resistance vs aerobic
- Dietary advice (Most data is for Mediterranean Diet)
  - Step 1: Limit total caloric intake / achieve caloric deficit
  - Step 2: Limit carbohydrate intake
    - Bread, rice, potatoes, flour tortillas, fructose-containing soda and juices
- Goal is sustainable weight loss (not easy!)

Histologic Improvement in MASH (NASH) with Weight Loss

Increased likelihood of NASH resolution and fibrosis improvements were associated with higher degrees of weight loss



Weight loss, %	5%	7%	10%
NASH resolution, %	10%	26%	64%	90%
Fibrosis regression, %	16%	18%	16%	45%
Steatosis improvement, %	5%	65%	76%	100%
Patients achieving weight loss, %	70%	12%	9%	10%
Total N=293	n=205	n=34	n=25	n=29

In this study, only 1 in 5 patients may achieve weight loss sufficient to significantly improve liver histology

Benefits of weight-loss interventions are significantly decreased in those with more advanced NASH histological activity

Weight loss through lifestyle interventions is difficult to sustain

1. Vilar-Gomez E, et al. *Gastroenterology.* 2015;149(2):367-378. 2. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. National Institutes of Health; 1998. NIH publication 98-4083. https://www.nhlbi.nih.gov/files/docs/guidelines/ob_gdlns.pdf. Accessed August 15, 2018.

Future directions for dietary guidance?

- Ongoing studies looking at other dietary strategies such as time-restricted eating, LCHF; promising thus far
- Tools/apps being investigated as strategies for behavioural modification
- More data around lean-MASH (NASH) and how/if dietary guidance should differ in this population

November 12, 2023 02:45 pm EST - November 12, 2023 03:00 pm EST

156: MORTALITY, HEPATIC DECOMPENSATION, AND CARDIOVASCULAR OUTCOMES IN LEAN VS. NON-LEAN MASH CIRRHOSIS: A VETERANS AFFAIRS COHORT STUDY

Background: Studies on incident liver and cardiovascular outcomes in lean (body mass index: BMI <25 kg/m^2, or <23 kg/m^2 for Asians) vs. non-lean individuals with metabolic dysfunction-associated steatohepatitis (MASH) have reported mixed results. We aimed to compare incident clinical outcomes and mortality between lean and non-lean individuals with compensated MASH cirrhosis in a large national cohort.

Category: MASLD/NAFLD and MASH/NASH

Oral Abstract Presentation

Location: Grand Ballroom, Sheraton Boston Hotel

Presenting Author: Basile Njei*

Author: Catherine Mezzacappa, Binu V John, Marina Serper, David E. Kaplan, Tamar H. Taddei, Nadim Mahmud

Randomized Controlled Trial > Am J Clin Nutr. 2024 Mar;119(3):788-799.
doi: 10.1016/j.ajcnut.2023.11.013. Epub 2023 Nov 29.

Effect of an Asian-adapted Mediterranean diet and pentadecanoic acid on fatty liver disease: the TANGO randomized controlled trial

Yu Chung Chooi [1], Qinze Arthur Zhang [2], Faidon Magkos [3], Maisie Ng [4], Navin Michael [2], Xiaorong Wu [5], Vera Sergeyevna Brok Volchanskaya [5], Xianning Lai [5], Elvy Riani Wanjaya [5], Untzizu Elejalde [5], Chew Chan Goh [5], Clara Poh Lian Yap [5], Long Hui Wong [6], Kevin Junliang Lim [5], S Sendhil Velan [2], Jadegoud Yaligar [2], Mark Dhinesh Muthiah [7], Yap Seng Chong [8], Evelyn Xiu Ling Loo [9], Johan G Eriksson [10]; TANGO Study Group

Figure 1: Heart Healthy Asian Mediterranean Diet

Food Category	Heart Healthy Asian Mediterranean Recommended Amount	Examples of Asian Ingredients (or Alternatives)
Vegetables	✔ ≥400 g/day	Bok choy, cabbage, broccoli, bitter gourd, shiitake mushroom, oyster mushroom, black fungus, kelp, eggplant, kimchi, carrot
Fruits	✔ ≥3 servings/day	Watermelon, blueberries, apples, citrus, grapes
Legumes	✔ ≥3 servings/week (1 serving = 150g)	Tofu, soy milk, tempeh, natto, adzuki beans, mung beans, black beans, lentils
Nuts and seeds	✔ ≥3 servings/week (30 g/serving)	Peanuts, cashews, almonds, pistachios, walnuts, sesame seeds
Fish and seafood	✔ ≥3 servings/week (1 serving = 100–150 g fish, or 4–5 units or 200 g shellfish)	Salmon, mackerel, sardines, tuna, shrimp
Antioxidant-rich sauce (sofrito)	✔ ≥2 times/week OR 100 g/day red/orange vegetables	Sofrito or use of red/orange vegetables 100 g/day with use of garlic and onion ± Asian spices (e.g. ginger, cumin, turmeric)
Healthy oils	✔ Polyunsaturated fatty acid and mono-unsaturated fatty acid-rich oils	Corn, soybean, sunflower, canola, olive oil
	⛔ Limit saturated fat Butter/cream <1 serving/day (12 g) Avoid trans fats	Avoid ghee, lard, palm oil, coconut oil, trans fats (e.g. in deep-fried products)
Beverages	✔ Unsweetened drinks	Water, tea, coffee, herbal infusions. For tea, favour green tea
	⛔ Avoid alcohol Limit sweetened drinks <1/day	Limit drinks such as soda and fruit juice
Red/processed meat	⛔ Limit red/processed meat to <1 serving/day	
Sweets/bakery goods	⛔ Limit to <2 times/week	Limit commercially made pastries, cakes, biscuits

Source: Created in BioRender. Huang V (2025) https://BioRender.com/wy8te7u

What Else Should We Do?

Optimize therapy for MASLD risk factors:

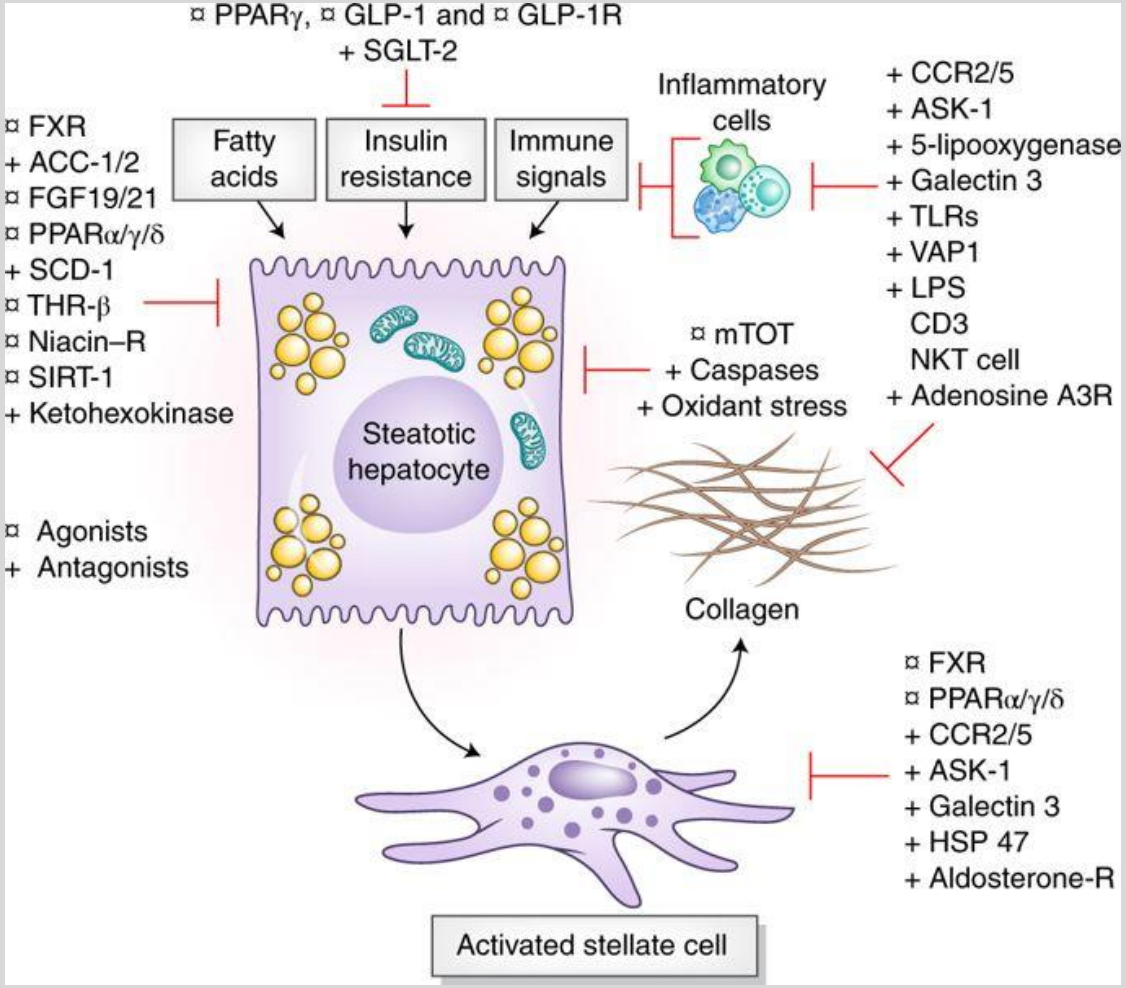
- Low threshold for escalation of pharmacotherapy in DM ‘optimize’
- Medications for weight loss?

Manage cardiovascular risk factors aggressively

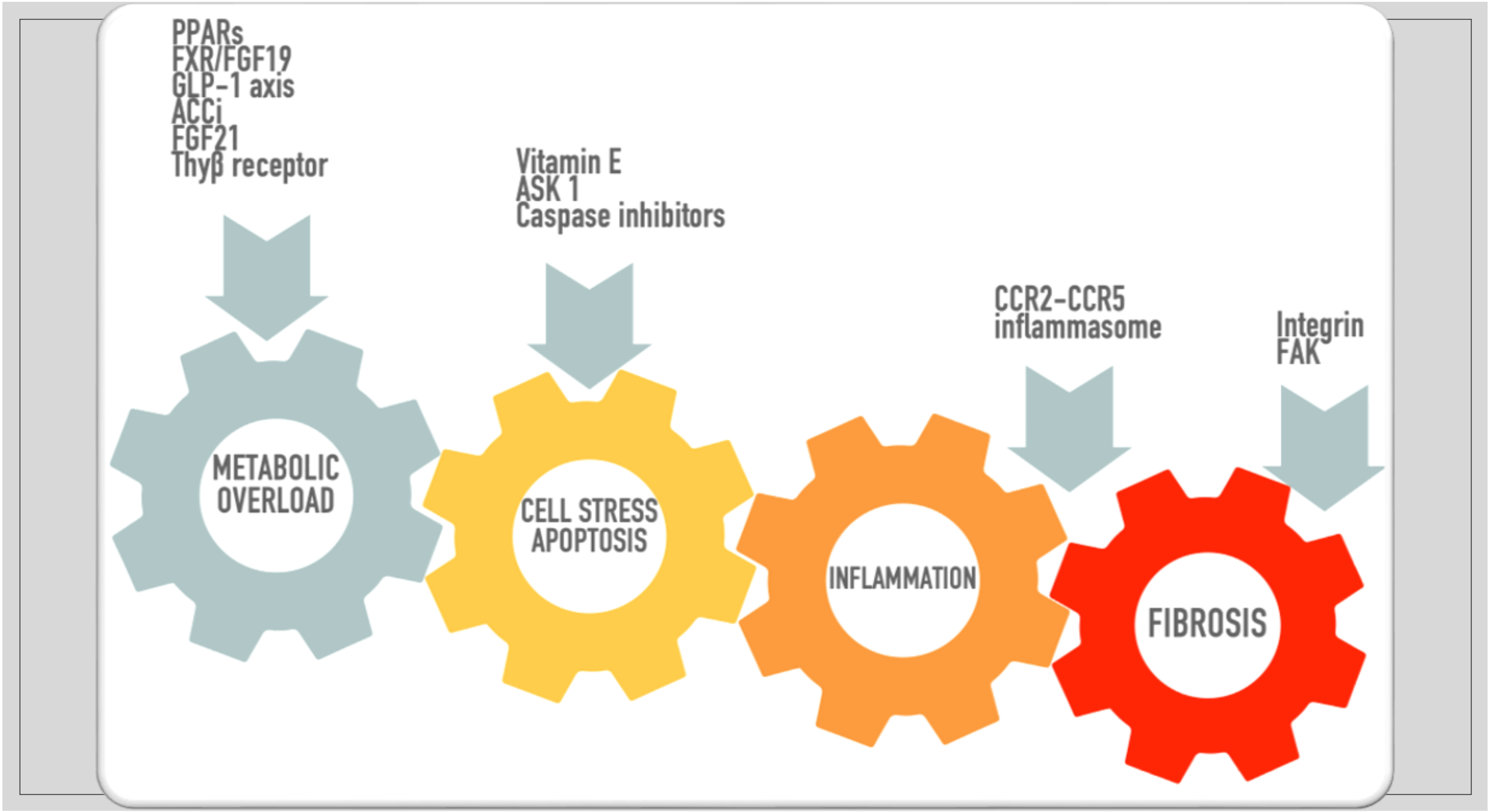
- Statins are SAFE!

PHARMACOTHERAPY

Lots of Candidate Drug Targets in NASH



Friedman et al. Nature Medicine 24, 908-922. 2018


PPARs
FXR/FGF19
GLP-1 axis
ACCi
FGF21
Thyβ receptor
Vitamin E
ASK 1
Caspase inhibitors
CCR2-CCR5
inflammasome
Integrin
FAK
METABOLIC OVERLOAD
CELL STRESS APOPTOSIS
INFLAMMATION
FIBROSIS

Drug	Exciting trial name	Target	Primary Endpoint	Timeframe
Obeticholic acid	REGENERATE REVERSE N=540	FXR	Improvement in fibrosis **AND** no worsening of NASH	72 weeks
Elafibranor				weeks
Selonsertib	STELLA N=800/N=	inhibitor	worsening of NASH	48 weeks
Cenicriviroc	AURORA N=2000	antagonist	worsening of NASH	52 weeks
MGL-3196 (resmetiron)	MAESTRO-NASH N=2000 M	THR-β	NASH resolution or related events	52 weeks
Semaglutide	ESSENCE N=1200	GLP-1 agonist	Part 1: NASH resolution **AND** no worsening of fibrosis OR worsening of NASH	Part 1: 72 weeks Part 2: 240 weeks

FDA Complete Response Letter June 29, 2020 – insufficient for approval
Resubmit December 2022; FDA CRL June 22, 2023 – insufficient for approval

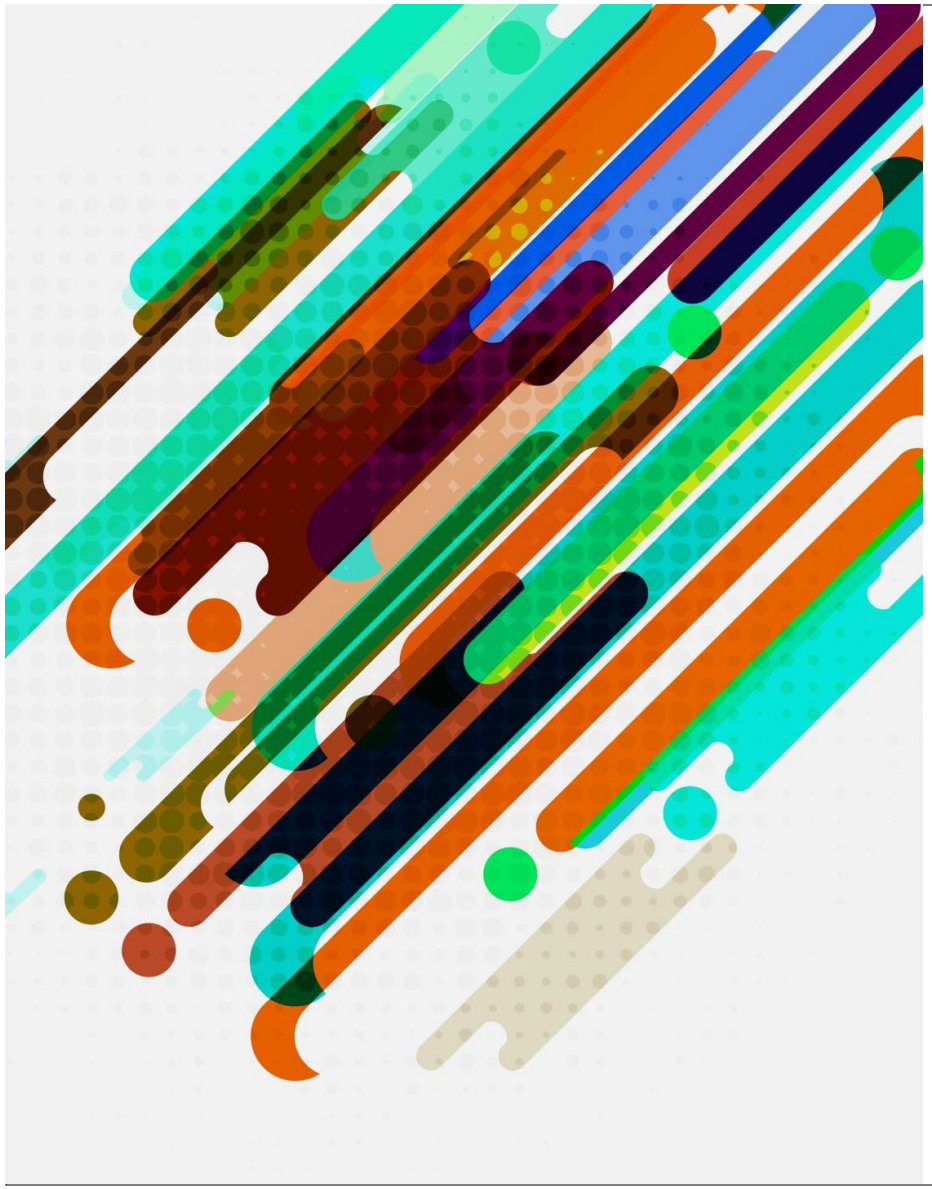
May 2020 – Negative interim results; program terminated July 22, 2020

February 2019 – program terminated due to lack of efficacy

April 2021– program terminated due to lack of efficacy

** FDA APPROVED March 14, 2024 **

** FDA APPROVED August 15, 2025**



PRIMARY RESULTS FROM MAESTRO-NASH:

A PIVOTAL PHASE 3 52-WEEK SERIAL LIVER BIOPSY STUDY IN 966 PATIENTS WITH NASH & FIBROSIS

S. Harrison. GS-001. 22 June 2023, 10:30

EASL ILC 2023

MAESTRO-NASH Trial Design

KEY ELIGIBILITY CRITERIA

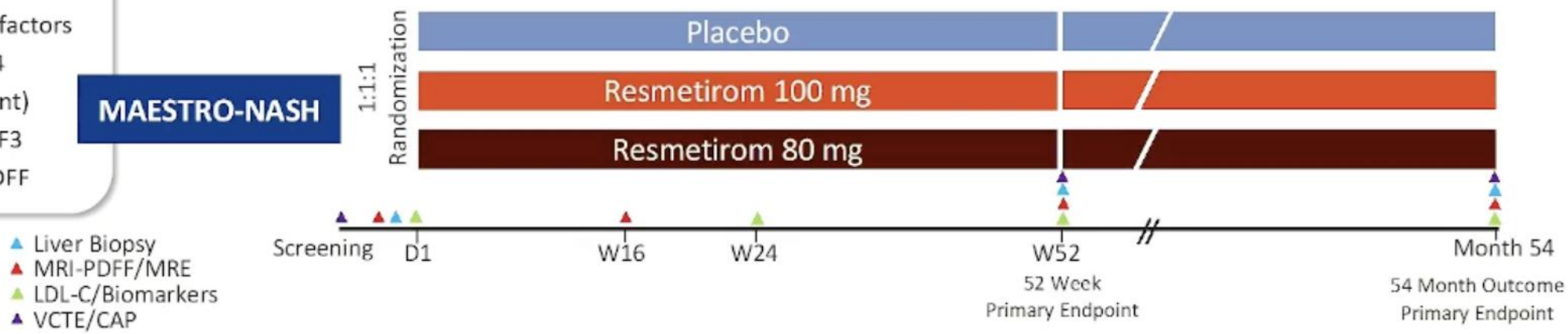
Presence of ≥3 metabolic risk factors

NASH on biopsy: NAS ≥4
(with ≥1 in each component)

Fibrosis stage F1B, F2, or F3

≥8% hepatic fat by MRI-PDFF

MAESTRO-NASH



DUAL PRIMARY ENDPOINT AT WEEK 52

NASH resolution (ballooning score=0, inflammation score=0/1, & ≥2-point reduction in NAS) with no worsening of fibrosis

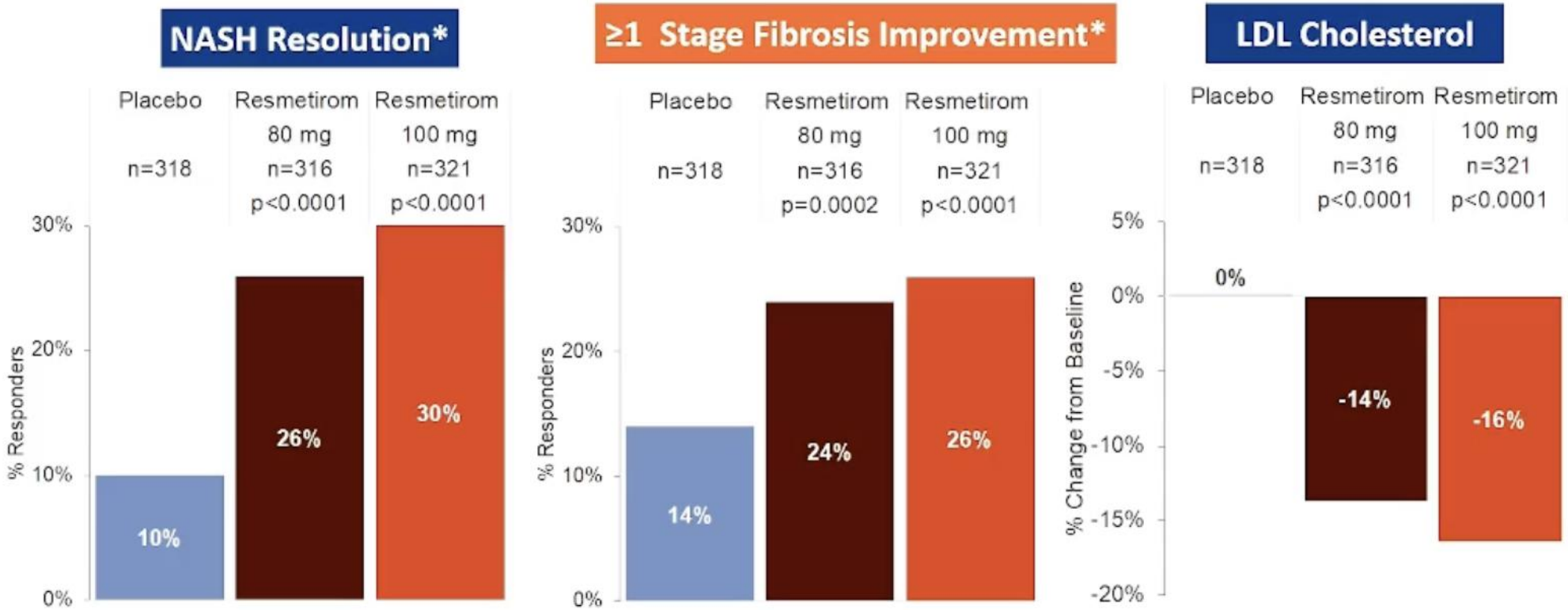
≥1-stage improvement in fibrosis with no worsening of NAS

Madrigal

LDL-C, low-density lipoprotein cholesterol; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis.

S. Harrison. GS-001

Dual Primary Endpoints (Week 52): Primary Analysis



Both primary liver biopsy endpoints and the key secondary endpoint of LDL cholesterol lowering were met

*NASH Resolution with no worsening of fibrosis; ≥1 Stage Fibrosis Improvement with no worsening of NAS

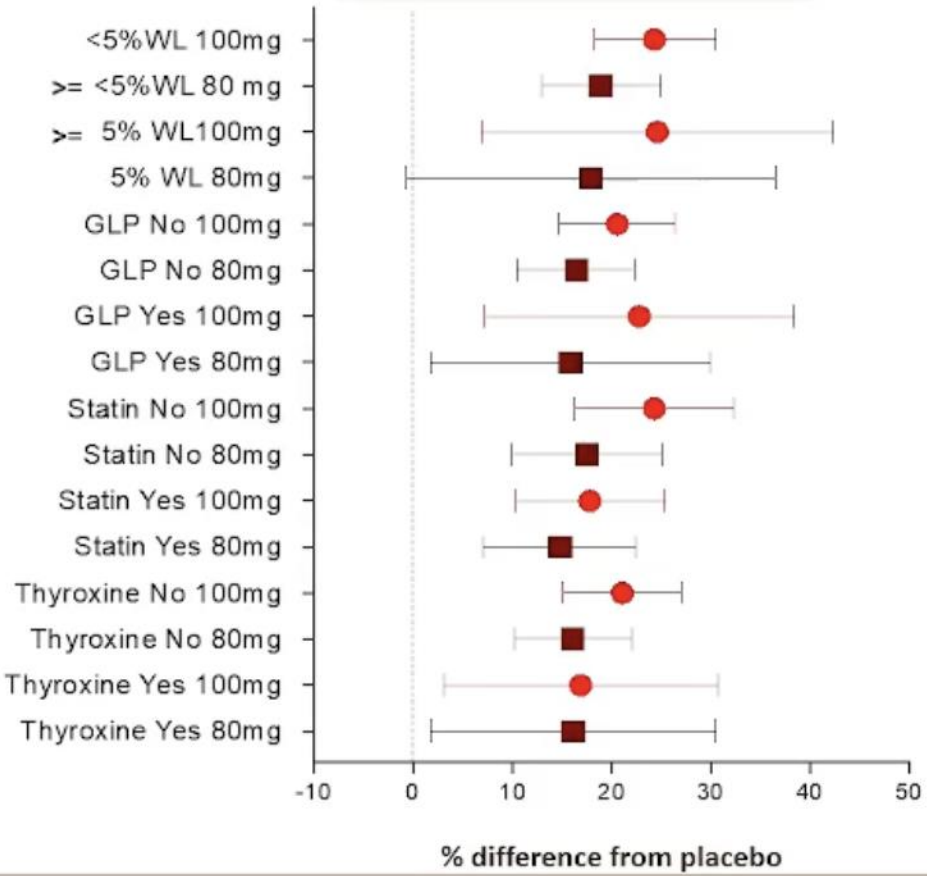
NASH, nonalcoholic steatohepatitis.

S. Harrison. GS-001

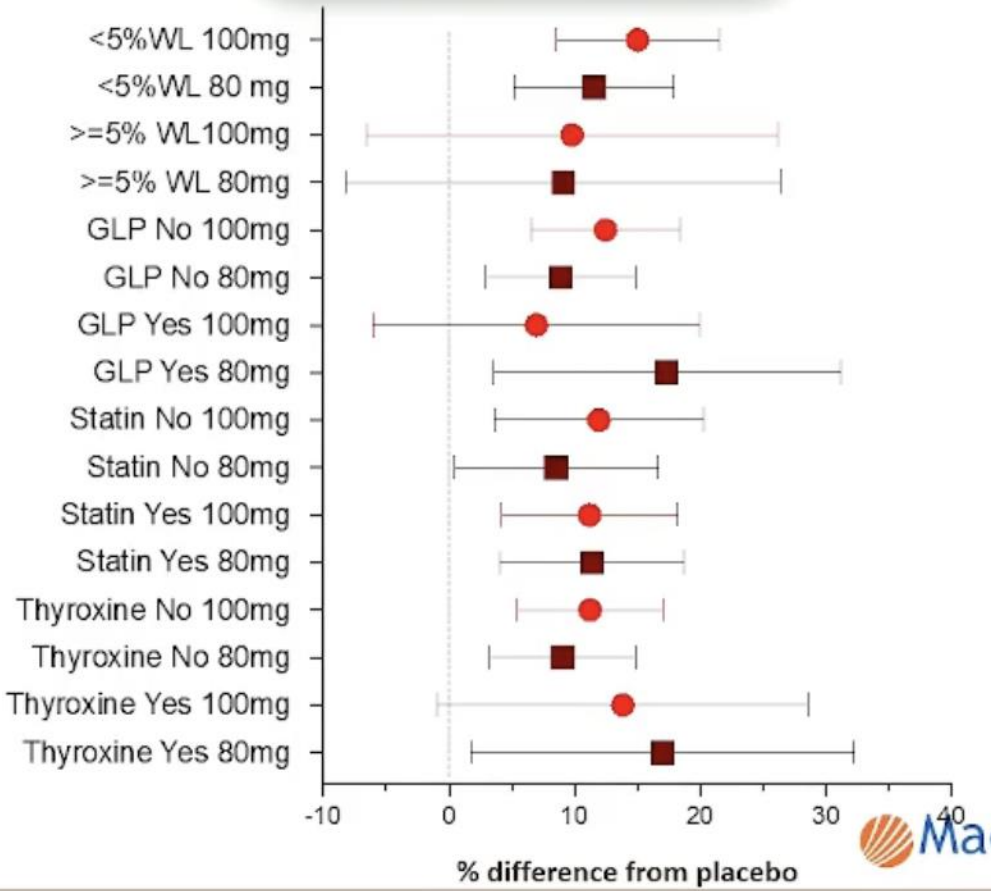
Weight Loss or Concomitant Drug Therapies

- GLP therapy, 14%; thyroxine, 13%; and statins, ~50% of patients in each arm; small differences relate to the small size of subgroups (>=5% weight loss n=47, 80 mg; n=57, 100mg; n=36, placebo)

NASH Resolution



Fibrosis Improvement



WL, weight loss; GLP, Glucagon-like peptide-1 receptor agonist

S. Harrison. GS-001

TEAEs Reported in >5% of Patients Overall

n (%)	Resmetirom 80mg (n=322)	Resmetirom 100mg (n=323)	Placebo (n=321)
Diarrhea	89 (27.6)	109 (33.7)	50 (15.6)
COVID-19	78 (24.2)	56 (17.3)	68 (21.2)
Nausea	70 (21.7)	62 (19.2)	40 (12.5)
Arthralgia	46 (14.3)	34 (10.5)	40 (12.5)
Back pain	36 (11.2)	27 (8.4)	38 (11.8)
Urinary tract infection	33 (10.2)	26 (8.0)	29 (9.0)
Fatigue	32 (9.9)	26 (8.0)	27 (8.4)
Pruritus	26 (8.1)	37 (11.5)	22 (6.9)
Abdominal pain upper	25 (7.8)	27 (8.4)	29 (9.0)
Headache	30 (9.3)	24 (7.4)	27 (8.4)
Vomiting	28 (8.7)	35 (10.8)	17 (5.3)
Type 2 diabetes	25 (7.8)	27 (8.4)	25 (7.8)
Abdominal pain	27 (8.4)	30 (9.3)	18 (5.6)
Constipation	21 (6.5)	27 (8.4)	18 (5.6)
Muscle spasms	14 (4.3)	22 (6.8)	21 (6.5)
Hypertension	16 (5.0)	13 (4.0)	25 (7.8)
Dizziness	21 (6.5)	19 (5.9)	11 (3.4)

Madrigal

S. Harrison. GS-001

MAESTRO-NASH Phase III Conclusions

Resmetirom achieved both co- primary liver biopsy endpoints of NASH resolution (without worsening of fibrosis) and fibrosis improvement

Both 80 and 100 mg doses were effective cf placebo (and not statistically different from each other)

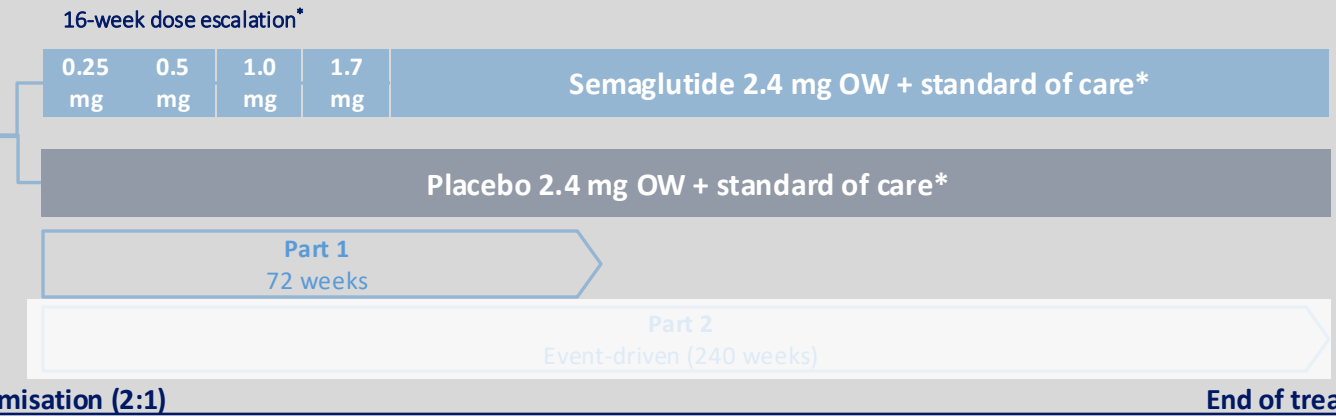
Safety profile is good overall (diarrhea and nausea), with more treatment-related study discontinuations at higher dosing

FDA approved as of March 14, 2024

ESSENCE: Semaglutide 2.4 mg in patients with MASH F2–F3, Trial design

Part 1: 800 participants

- Histological evidence of MASH
- NAS ≥4
- Histological evidence of fibrosis stage 2 or 3
- Score ≥1 for steatosis, lobular inflammation and hepatocyte ballooning



Part 1 Key endpoints

- **Primary endpoints**
  - Steatohepatitis resolution† and no worsening of liver fibrosis at Week 72
  - Improvement in liver fibrosis and no worsening of steatohepatitis‡ at Week 72
- **Confirmatory secondary endpoints**
  - Resolution of steatohepatitis and improvement in liver fibrosis
  - Change in body weight
  - Change in SF-36 Bodily Pain

Metabolic dysfunction-associated steatohepatitis (MASH) was previously known as nonalcoholic steatohepatitis (NASH).
*NAS, nonalcoholic fatty liver disease activity score. *Up titration every 4 weeks. One or more dose steps can be prolonged, or the dose lowered if the actual dose is not tolerated. If the designated target dose of once-weekly subcutaneous semaglutide 2.4 mg is not tolerated, patients may stay at a lower dose level. †Resolution of steatohepatitis is defined as a NAS score of 0-1 for inflammation, 0 for ballooning and any value for steatosis; ‡No worsening of steatohepatitis is defined as no increase from baseline in score for inflammation, ballooning and steatosis. Newsome PN et al. Aliment Pharmacol Ther. 2024. https://doi.org/10.1111/apt.18331.*

Newsome P. et al Abs. 5018 AASLD 2024 Late breaker, slide credit Novo Nordisc

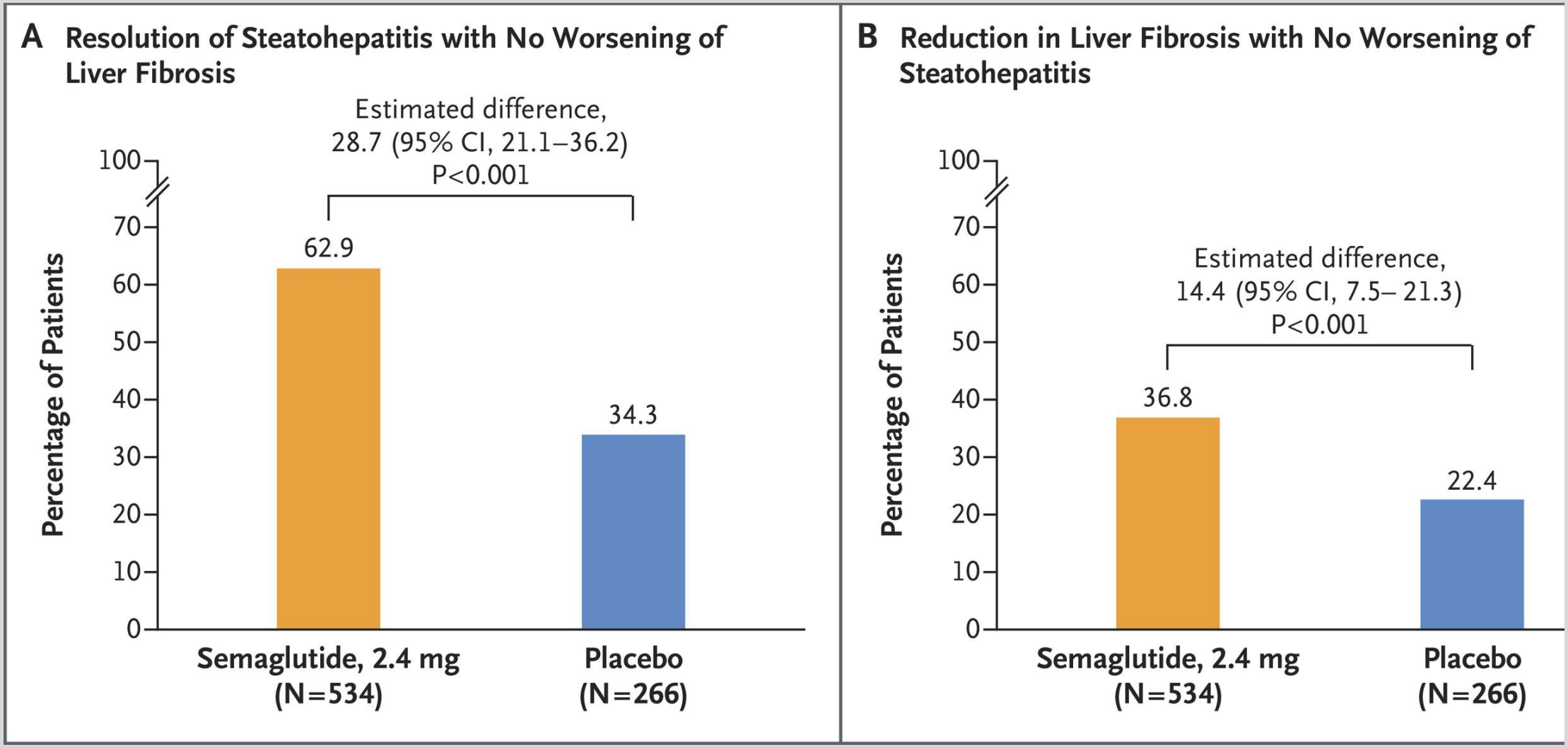
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis

Arun J. Sanyal, M.D.,[1] Philip N. Newsome, M.B., Ch.B., Ph.D.,[2,3] Iris Kliers, M.D.,[4] Laura Harms Østergaard, M.Sc.,[4] Michelle T. Long, M.D.,[4] Mette Skalshøi Kjær, M.D., Ph.D.,[4] Anna M.G. Cali, M.D.,[4] Elisabetta Bugianesi, M.D., Ph.D.,[5] Mary E. Rinella, M.D.,[6] Michael Roden, M.D.,[7-9] and Vlad Ratziu, M.D., Ph.D.,[10] for the ESSENCE Study Group*

ABSTRACT



Sanyal et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. NEJM>org. April 30, 2025.

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

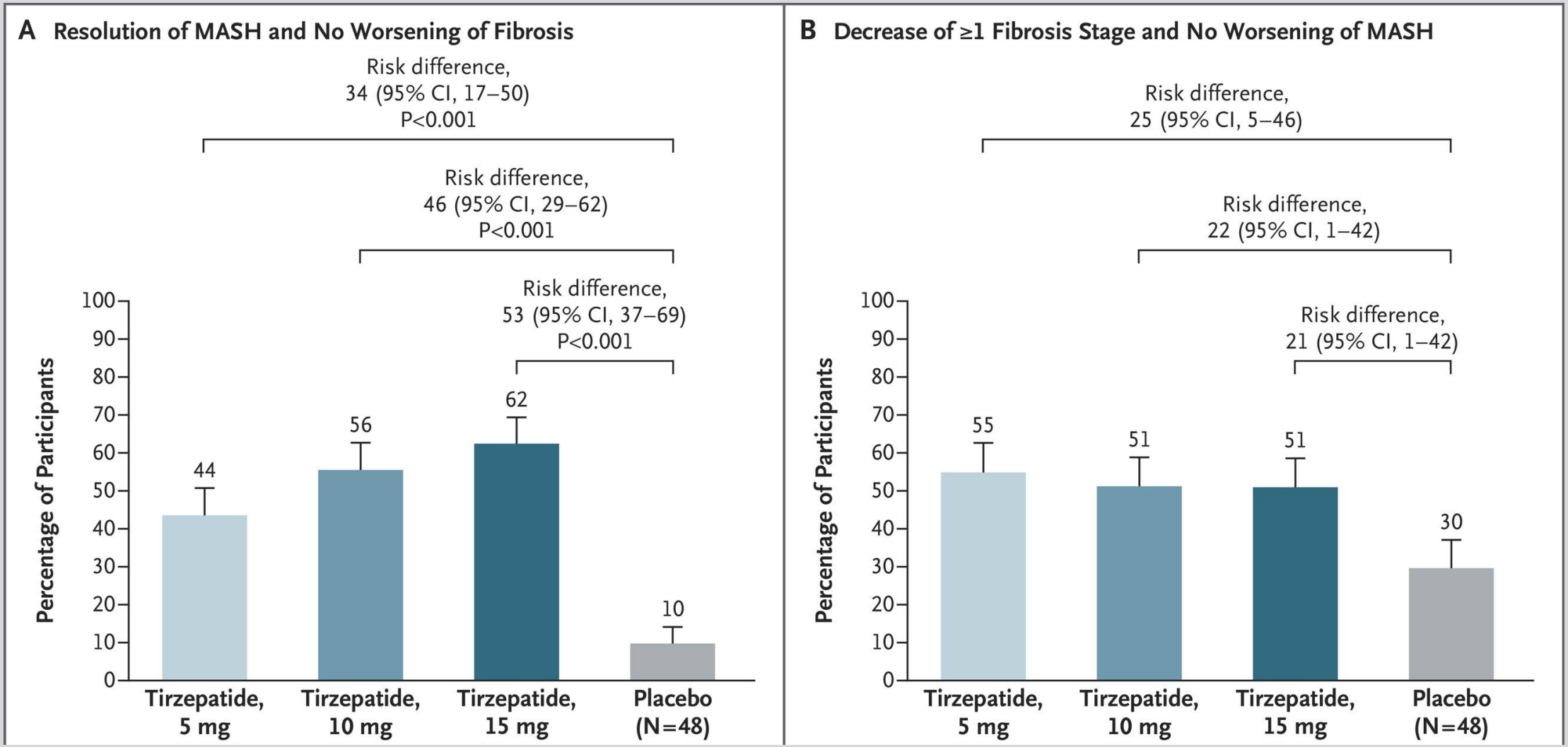
R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

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



Loomba et al. NEJM 2024;391:299-310

MASLD/MASH – Take Home Messages

- MASLD is **common**, especially in context of DM and obesity
- **Liver fibrosis** is linked to increased **mortality**
- **Fibrosis assessment** for risk stratification is essential
- **Treatment** currently focuses on lifestyle modification
- Those eligible for medical weight loss management with pharmacotherapy may also experience MASH-specific benefits. Currently not on-label for MASH – but soon!

Thank you!

Edward Tam

tam.edward@gmail.com