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Canadian Association for the Study of the Liver | CASL ACEF | Association canadienne pour l'étude du foie

CanNASH

CAHN Canadian Association of Hepatology Nurses | Association Canadienne Des Infirmieres D'Hepatologie

CanHepC
Canadian Network on Hepatitis C
Réseau Canadien sur l'Hépatite C

Global epidemiology of NASH

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JOINT 2023 CDDW™-CLM CONFERENCE

Disclosures

- Speaker symposium and advisory board Sanofi, Pfizer and Boehringer Ingelheim.

Outline

- Current MAFLD prevalence
- Project trends in MAFLD
- Burden of MAFLD related complications:
  - ESLD
  - HCC
  - Transplantation
  - Extrahepatic associations: CVD/T2DM etc.
- Economic burden and quality of life

MAFLD

Hepatic steatosis in adults
(detected either by imaging techniques, blood biomarkers/scores or by liver histology)

Overweight or obesity
(defined as BMI ≥25 kg/m² in Caucasians or BMI ≥23 kg/m² in Asians)

Lean/normal weight
(defined as BMI <25 kg/m² in Caucasians or BMI <23 kg/m² in Asians)

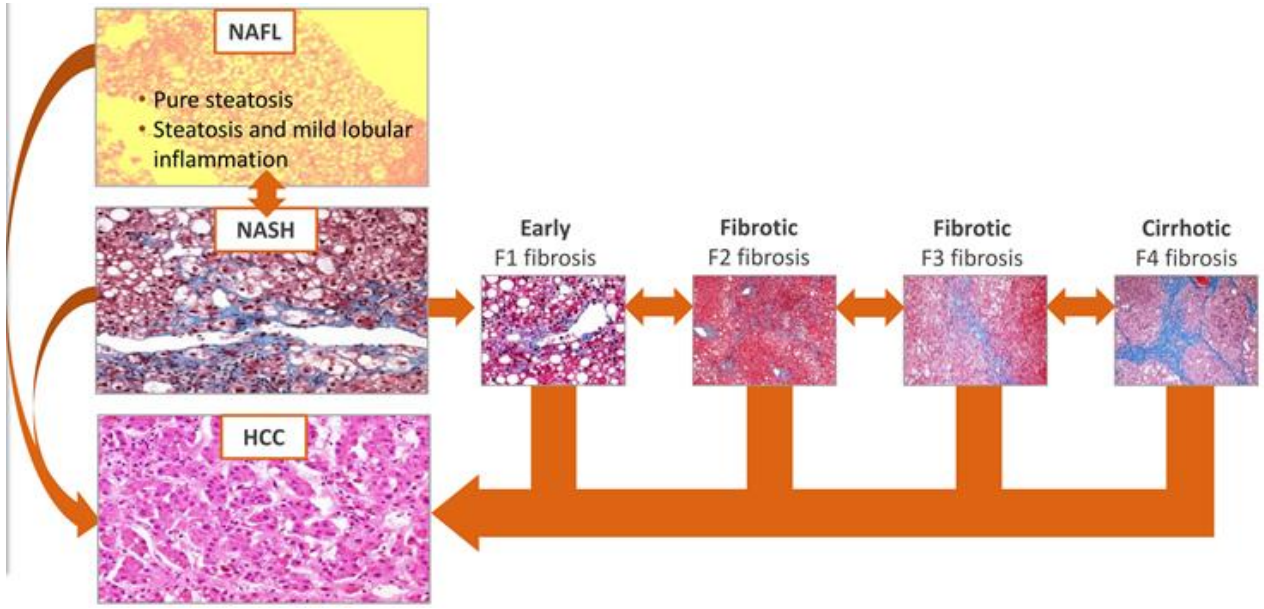
Type 2 diabetes mellitus
(According to widely accepted international criteria)

***If* presence of <u>at least</u> two metabolic risk abnormalities:**

- Waist circumference ≥102/88 cm in Caucasian men and women (or ≥90/80 cm in Asian men and women)
- Blood pressure ≥130/85 mmHg or specific drug treatment
- Plasma triglycerides ≥150 mg/dl (≥1.70 mmol/L) or specific drug treatment
- Plasma HDL-cholesterol <40 mg/dl (<1.0 mmol/L) for men and <50 mg/dl (<1.3 mmol/L) for women or specific drug treatment
- Prediabetes (*i.e.*, fasting glucose levels 100 to 125 mg/dl [5.6 to 6.9 mmol/L], or 2-hour post-load glucose levels 140 to 199 mg/dl [7.8 to 11.0 mmol] or HbA1c 5.7% to 6.4% [39 to 47 mmol/mol])
- Homeostasis model assessment of insulin resistance score ≥2.5
- Plasma high-sensitivity C-reactive protein level >2 mg/L

MAFLD
(Metabolic dysfunction-associated fatty liver disease)

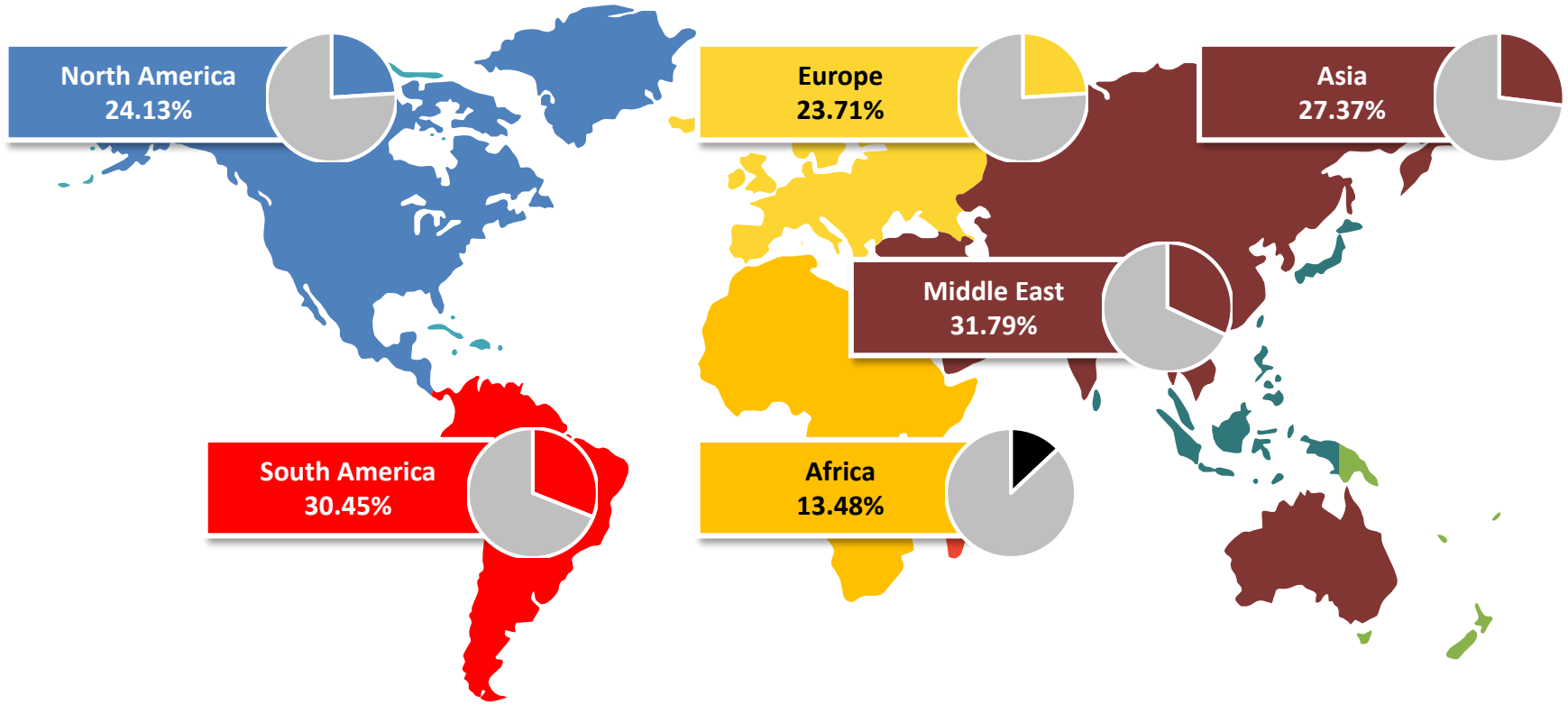
The spectrum of MAFLD



Eslam M, et al. J Hepatol. 2020 Jul;73(1):202-209.

MAFLD prevalence

Prevalence of MAFLD



Worldwide prevalence of MAFLD is 25%

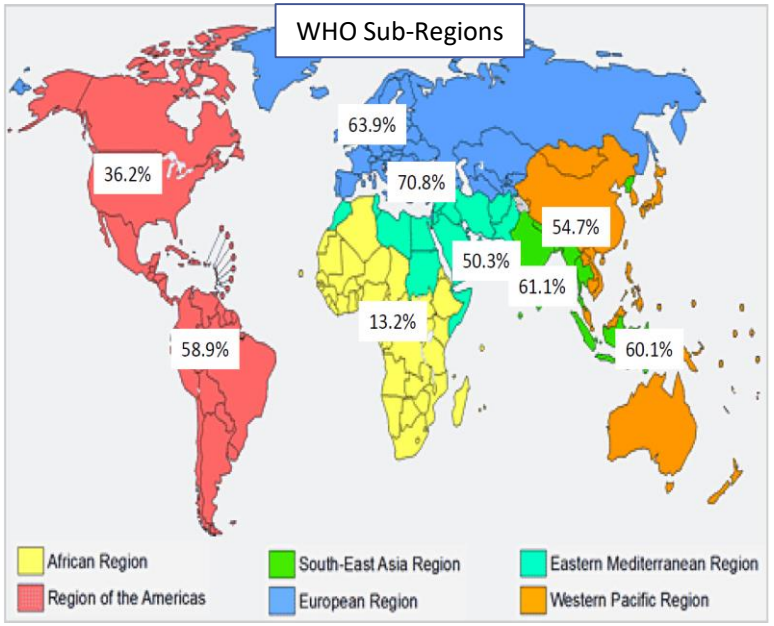
Worldwide prevalence of MAFLD among people with T2DM is 55.5%

Worldwide prevalence of MAFLD among children is 7.6%

Younossi Z et al., Nat Rev Gastroenterol Hepatol. 2018 Jan;15(1):11-20.Younossi ZM et al. Hepatology. 2016;64(1):73-84

The Global Prevalence of MAFLD in Diabetics

- Systematic review of 88,978 diabetics from 28 countries
  - Overall global MAFLD prevalence among diabetics was 57.80% (95% CI: 53.88% –61.62%)
  - Overall prevalence of NASH among biopsied diabetics was 65.26% (95% CI: 51.73-76.71)
  - Prevalence of NASH in the patient population with T2D is 36.16% (95% CI:28.03–44.29)
  - Overall prevalence of advanced fibrosis (fibrosis ≥ F3) 15.05% (95% CI: 8.17-26.08)

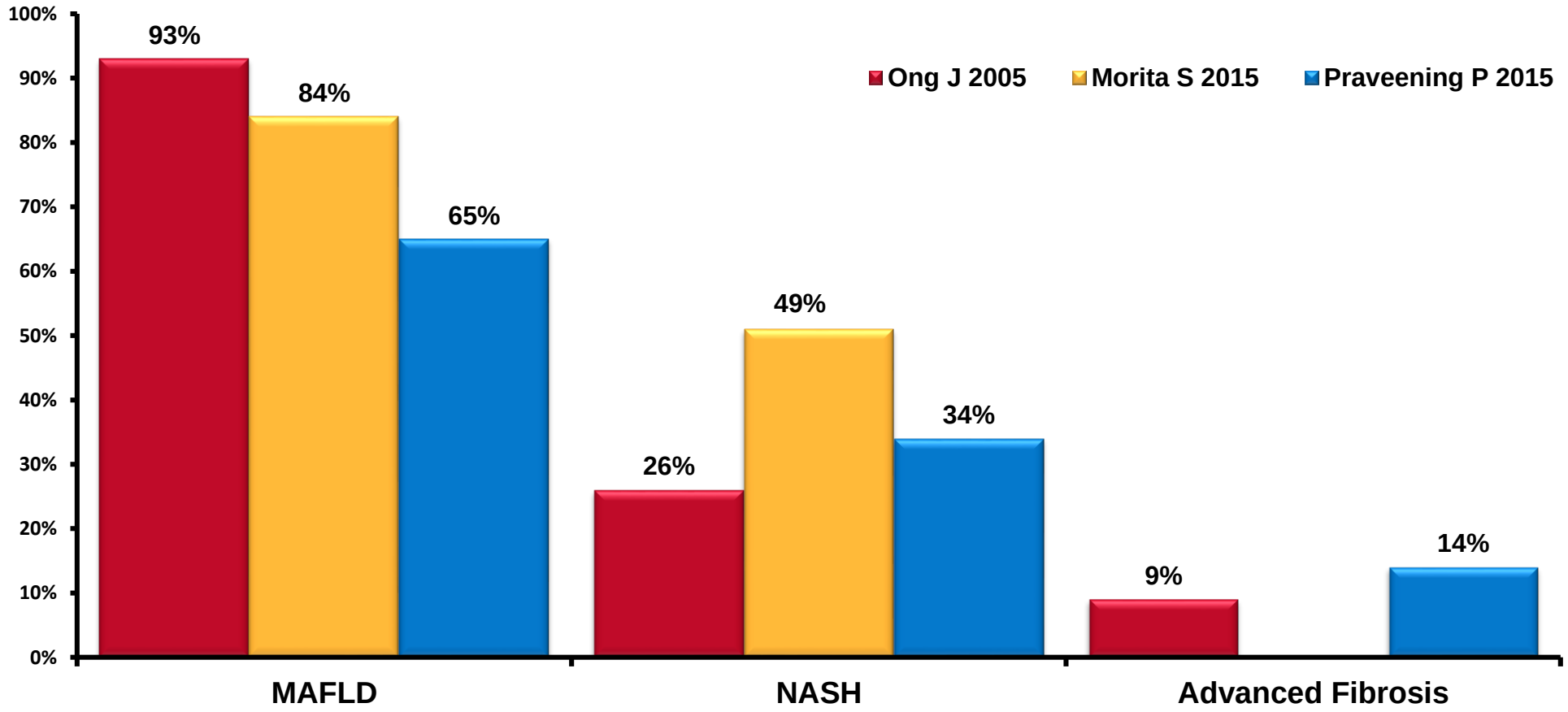


MAFLD Prevalence among T2DM Stratified by BMI		
Mean BMI	N	Prevalence (95% CI)
Overall	73	57.56 (53.03-61.96)
Lean, BMI ≤ 25 kg/m^2	9	53.88 (44.57-62.92)
Overweight, 25<BMI<30 kg/m^2	42	58.18 (53.36-62.84)
Obese, BMI ≥ 30 kg/m^2	22	57.86 (46.13-68.77)

For Asian, lean: BMI ≤ 23, overweight: 23< BMI< 27.4, and obese: BMI ≥ 27.5

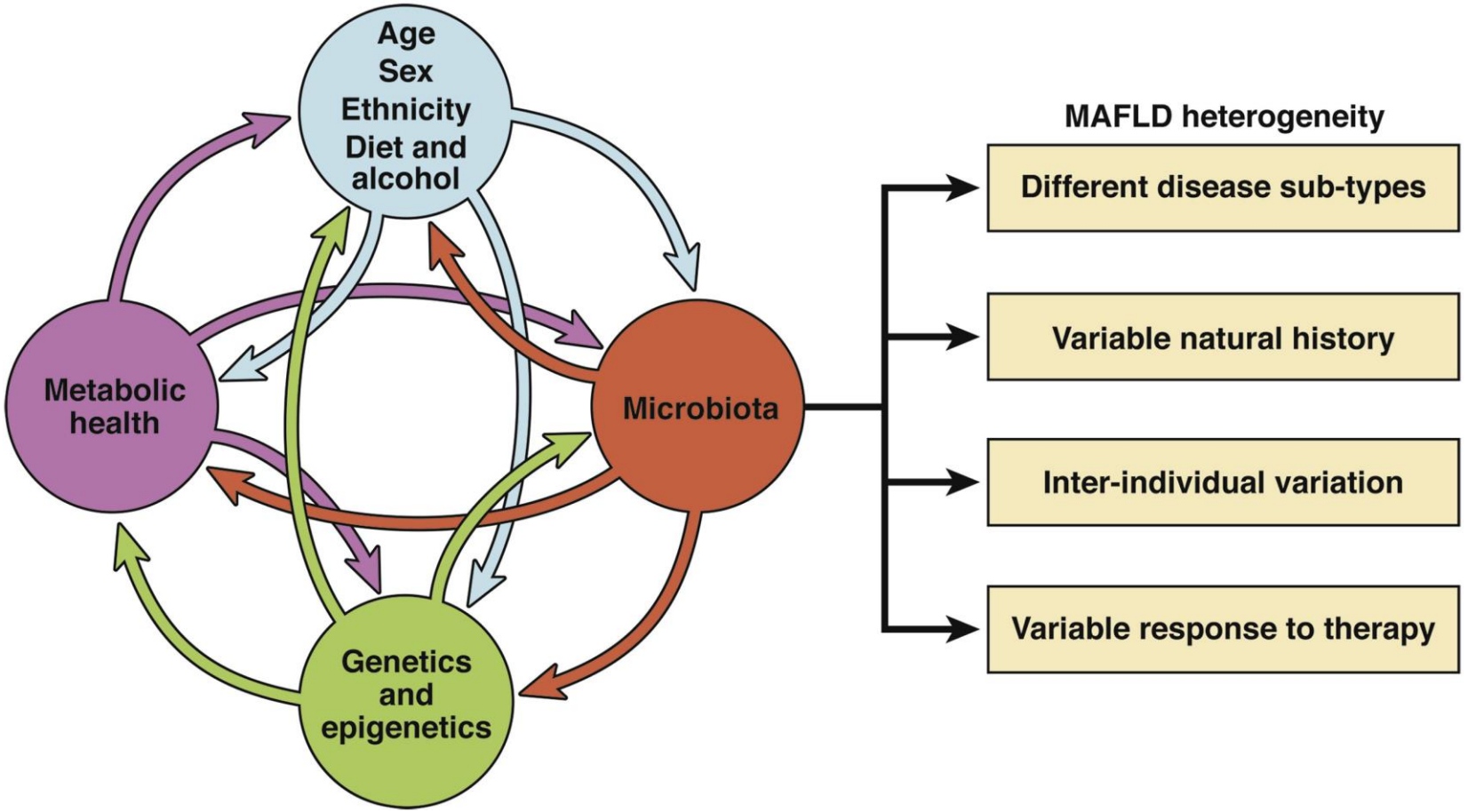
Golabi P, et al. AASLD 2017

Prevalence of MAFLD in Morbidly Obese Undergoing Bariatric Surgery



Younossi ZM, et al. Nat Rev Gastroenterol Hepatol. 2017; 2. Ong JP, et al. Obes Surg. 2005, 3. Morita S. Obes Surg. 2015; 4. Praveenraj P, et al. Obes Surg. 2015.

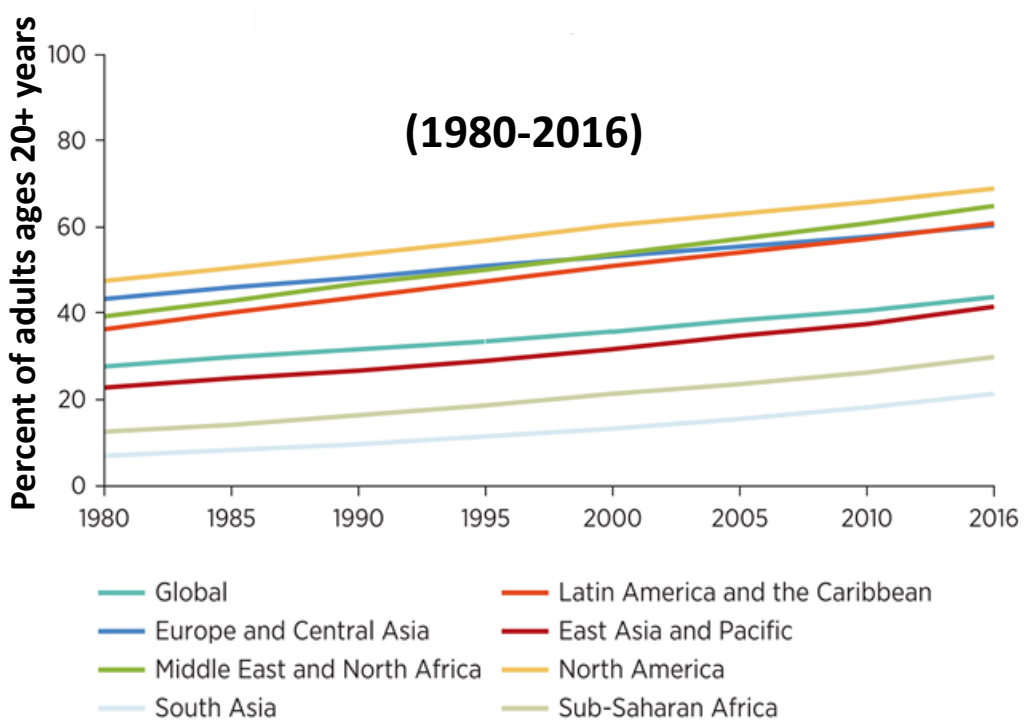
Why does MAFLD occur?



Eslam M, et al. Gastroenterology. 2020 May;158(7):1999-2014.e1.

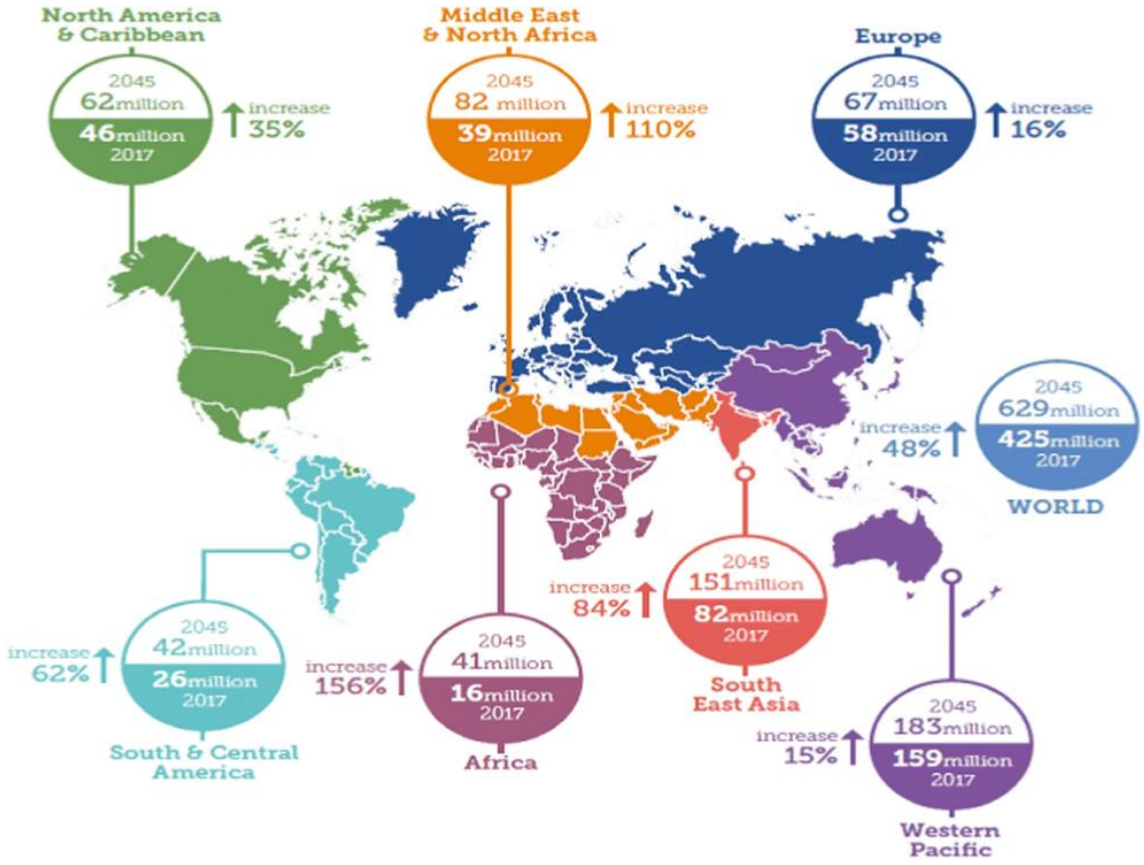
Burden of obesity and diabetes mellitus

Overweight/Obesity



- 1.9 Billion Adults Overweight
- Of these 600 Million Adults are Obese
- 42 Million Overweight Obese Infants & Young Children
- 70 Million Young Children Obese by 2025

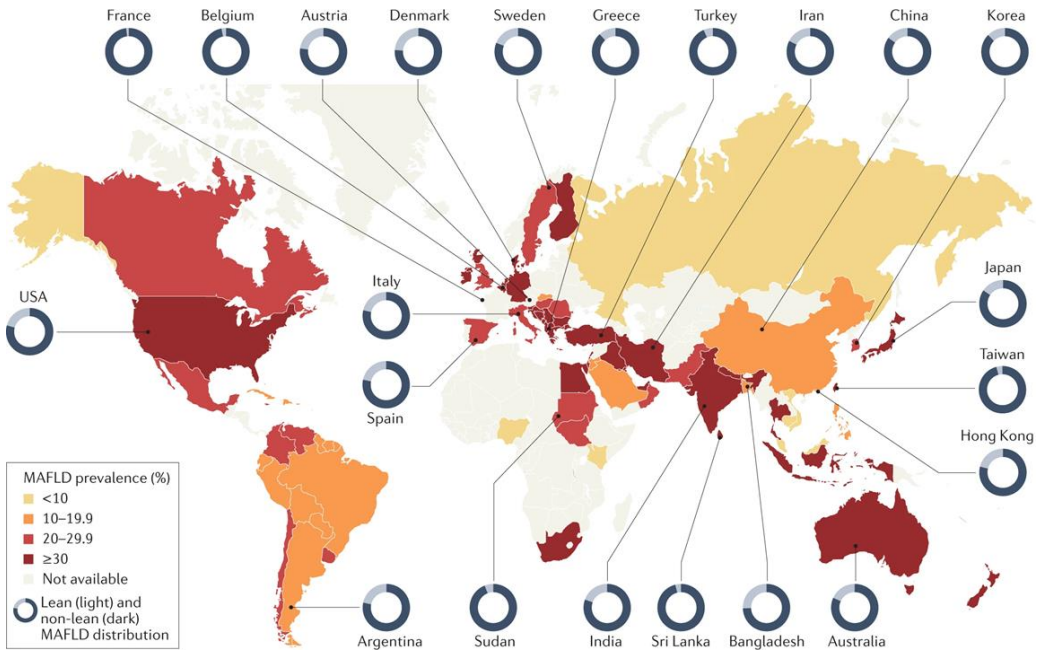
Diabetes mellitus



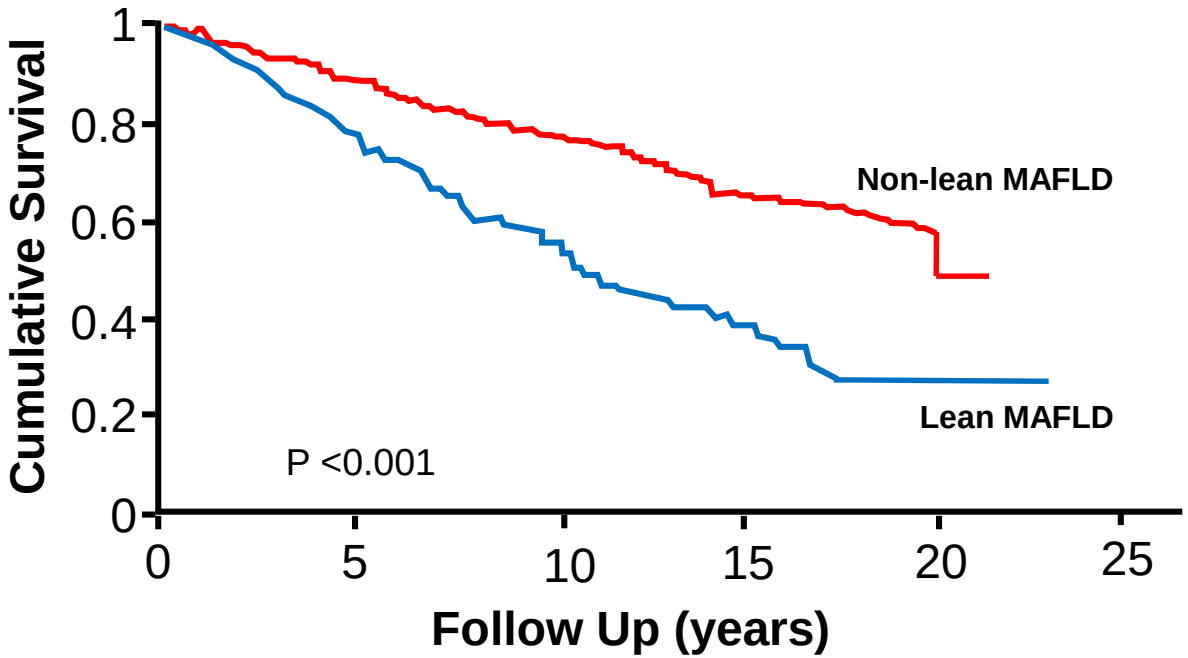
Shekar M, Popkin B. Obesity: health and economic consequences of an Impending global Challenge. 2020. DF Diabetes Atlas. IDF diabetes atlas, 9th edn. Brussels and Belgium; 2019.

Lean MAFLD

40% of the MAFLD population is not obese



Survival free of liver transplantation is lower in lean MAFLD



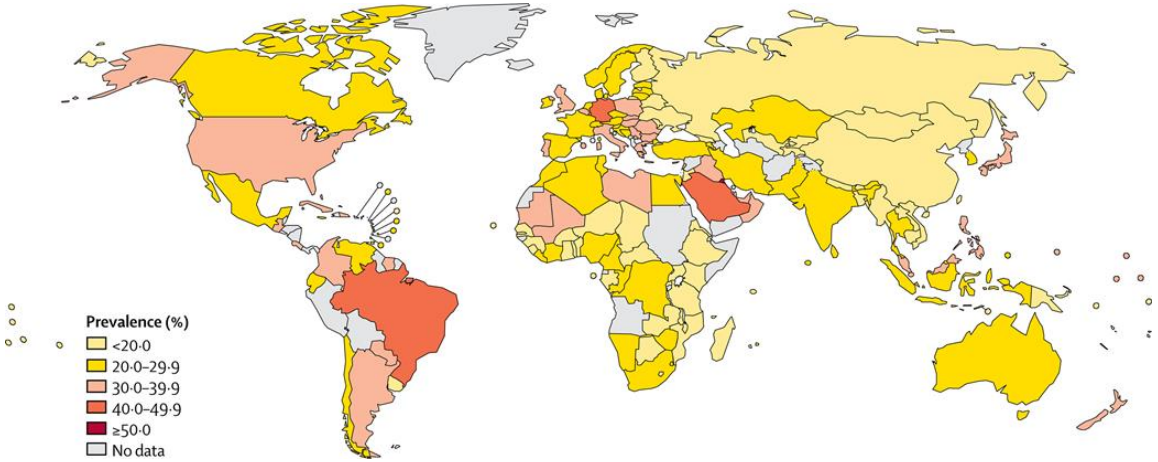
Eslam M, et al. Lancet Gastroenterol Hepatol. 2020.
Ye Q, et al.Lancet Gastroenterol Hepatol . 2020 May 12;S2468-1253(20)30077-7.

Dela Cruz AC, et al.Gastroenterology 2014;146:S-909.

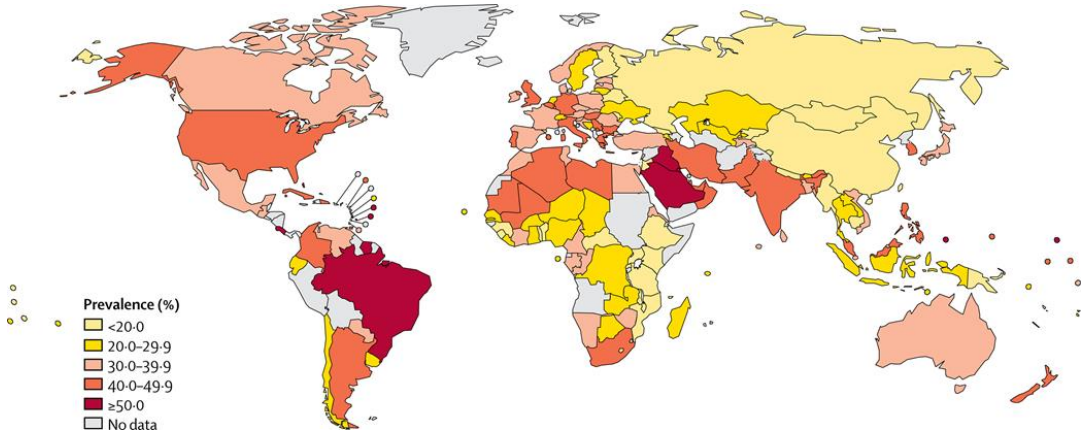
The insufficient physical activity

Not doing ≥150 min of moderate-intensity, or 75 min of vigorous-intensity PA/W, or any equivalent combination

Men



Women

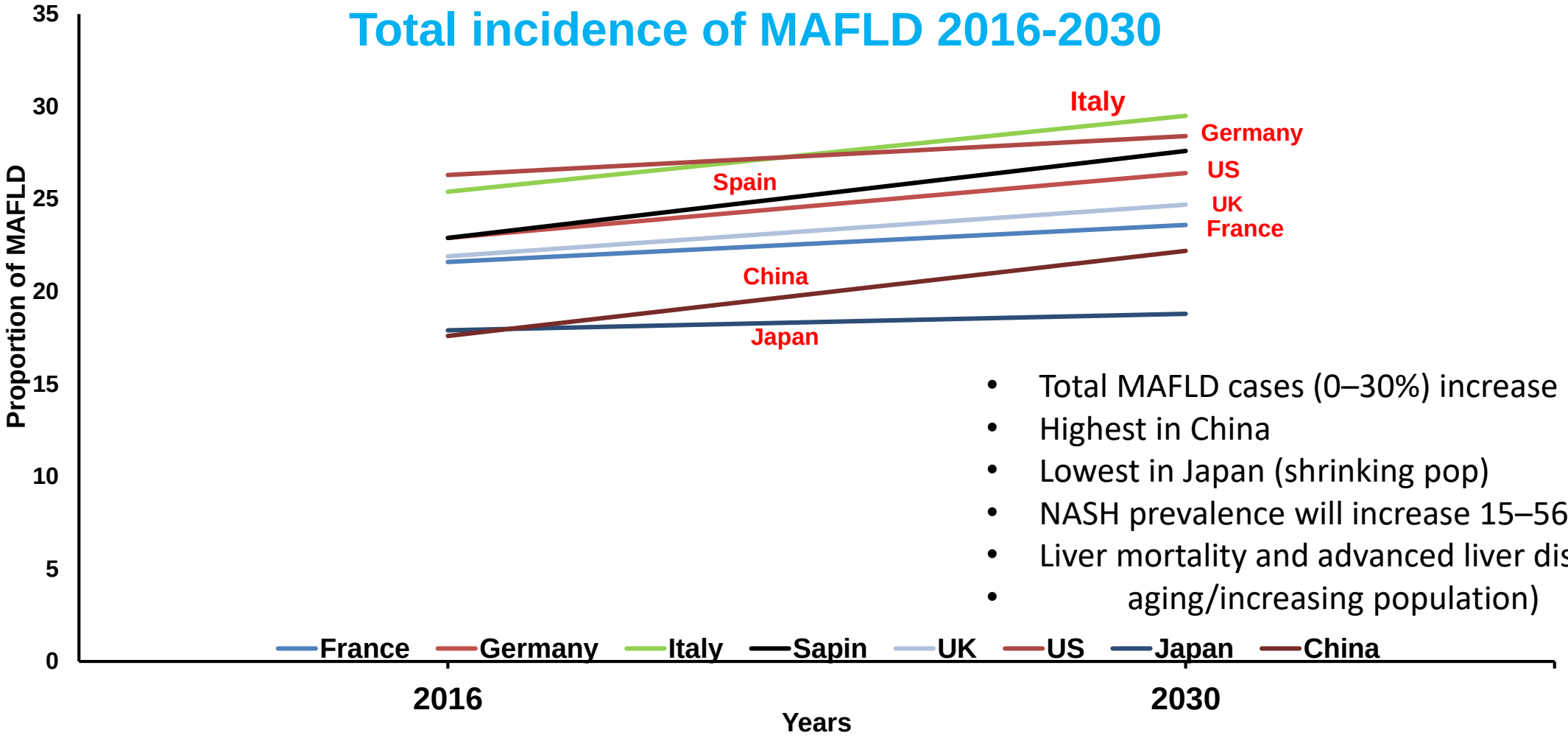


- Global age-standardised prevalence of insufficient physical activity was 27·5% in 2016, 23·4% in men vs 31·7% in women.
- The highest levels in 2016, were in women in Latin America and the Caribbean (43·7%), south Asia (43·0%), and high-income Western countries (42·3%).

Guthold R et al., Lancet Glob Health. 2018 Sep 4

Future burden of MAFLD incidence

Modeled Projection of MAFLD future



- Total MAFLD cases (0–30%) increase 2016–2030
- Highest in China
- Lowest in Japan (shrinking pop)
- NASH prevalence will increase 15–56%
- Liver mortality and advanced liver disease 2X
- aging/increasing population)

Estes C et al., J Hepatol. 2018 Jun 8

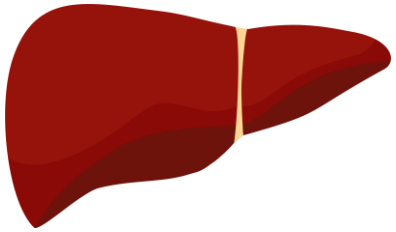
The burden of MAFLD: the health-economic impact

MAFLD and liver outcomes

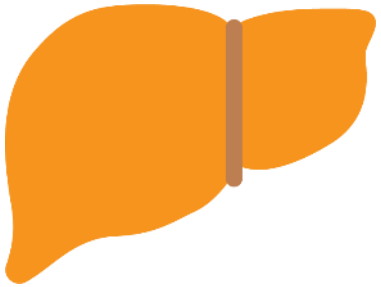
Natural history of MAFLD according to data from Asia

25% of the world's population have MAFLD

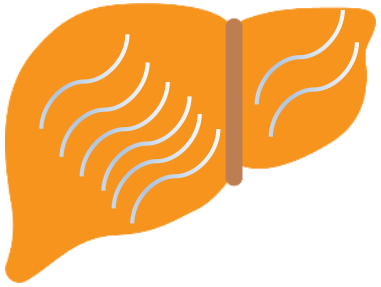
- **Annual incidence of MAFLD 3-4%**
- **25% progress from steatosis to steatohepatitis and have fibrosis progression in 3 years.**
- **Fibrosis progression 1 stage in 7 years in steatohepatitis; 1 stage in 14 years in steatosis.**



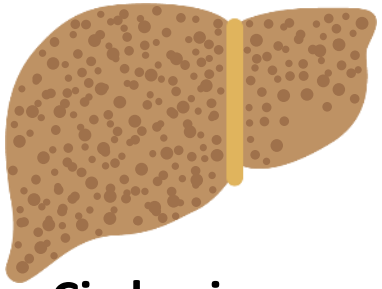
Normal Liver



Steatosis



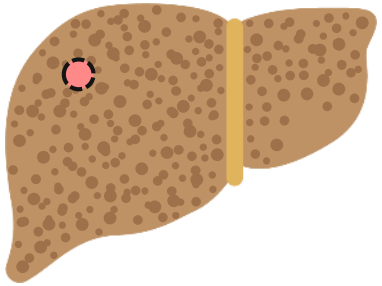
Steatohepatitis ± fibrosis



Cirrhosis

- **30-50% of MAFLD-related HCC in Asia are non-cirrhotic.**
- **<0.1% per year.**

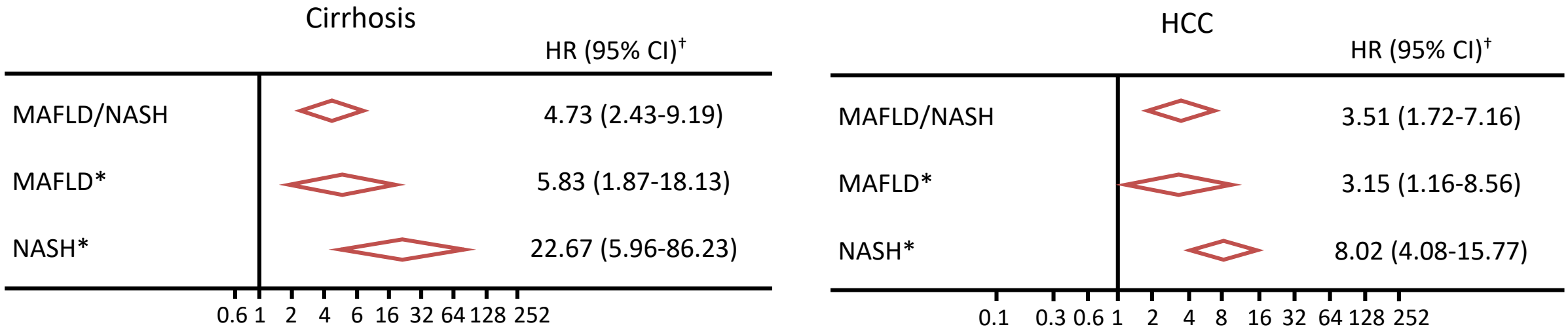
1-4% per year



Hepatocellular carcinoma

Fan JG, et al. J Hepatol. 2017 Oct;67(4):862-87

Associations between MAFLD/NASH and cirrhosis or HCC



- **18 million primary care records (UK, Netherlands, Spain, Italy); 136, 457 MAFLD/NASH; 2,674 (NASH only UK and Spain)**
- **Matched to 100 non MAFLD (gender, age, visit, practice)**
- **Incident cirrhosis or HCC**
- ***UK/Spain only.**
- **†Adjusted for age, smoking, BMI.**

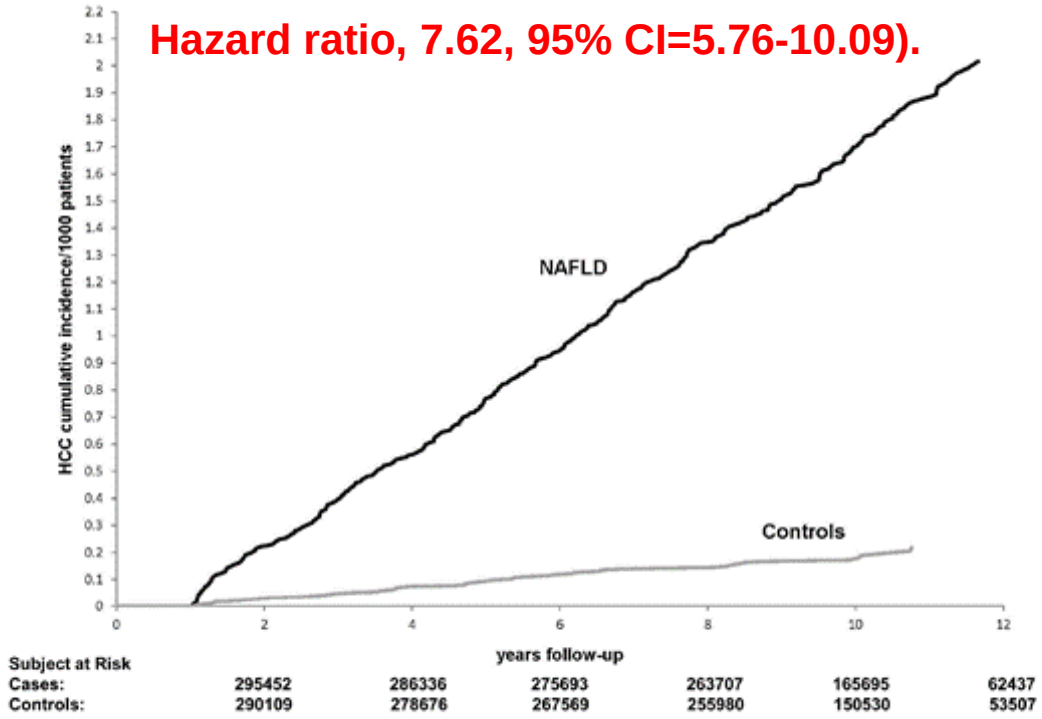
- Like MAFLD/NASH, diabetes also independently predicted cirrhosis or HCC outcome (HR: 2.66; 95% CI: 2.52-2.81)

Alexander M, et al. EASL 2018. Abstract PS-106.

Risk of HCC in Patients with MAFLD

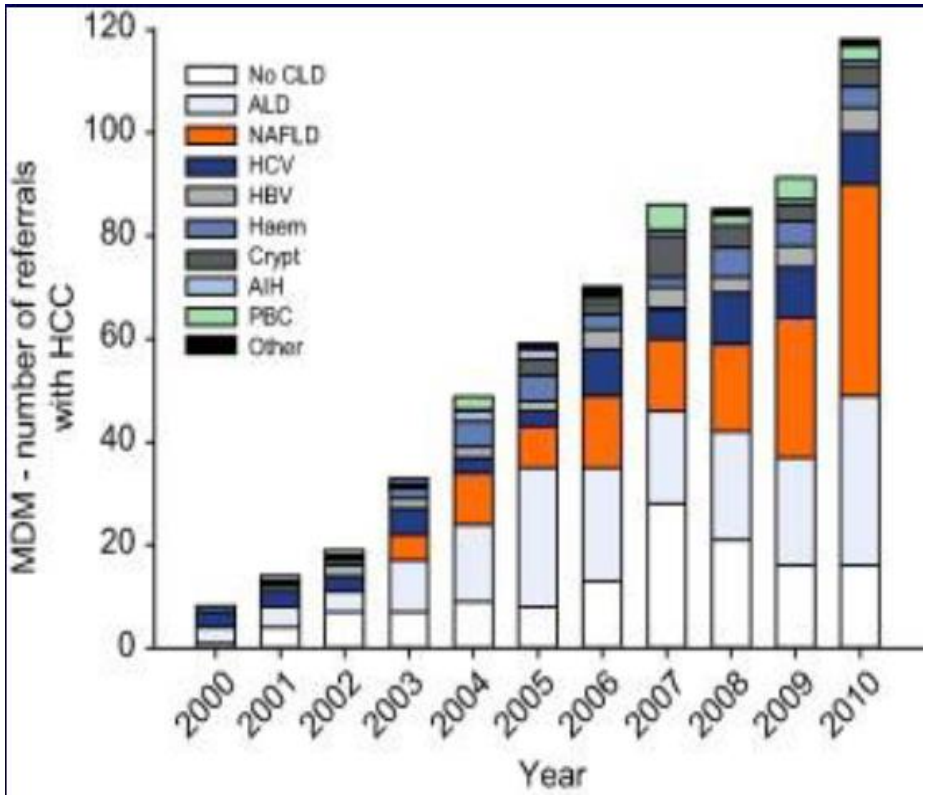
U.S. national Veterans Health Administration (VHA) system.
296,707 MAFLD patients with 296,707 matched controls.

Hazard ratio, 7.62, 95% CI=5.76-10.09).



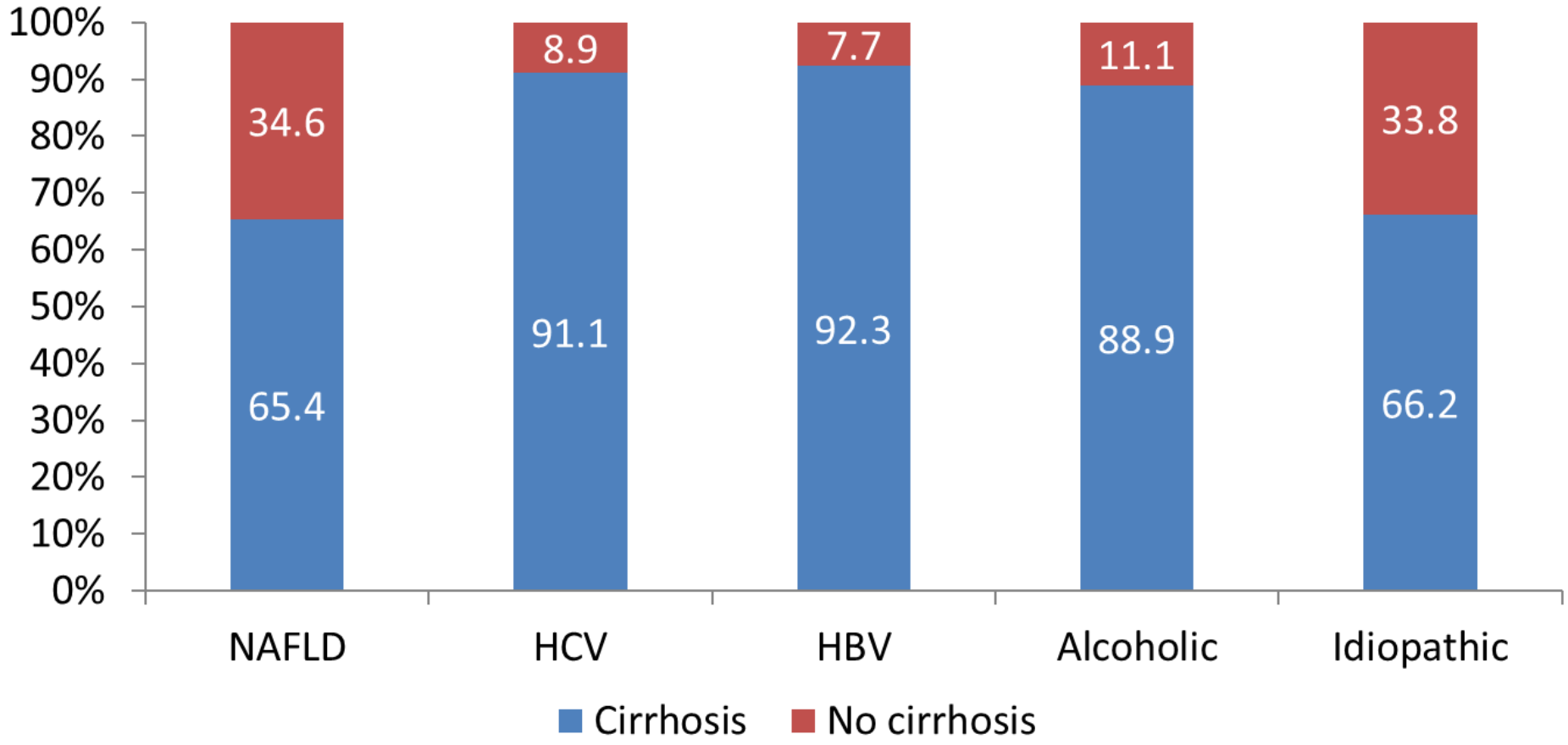
Kanwal F, et al.Gastroenterology. 2018 Aug 22

MAFLD is becoming the leading cause of HCC in UK



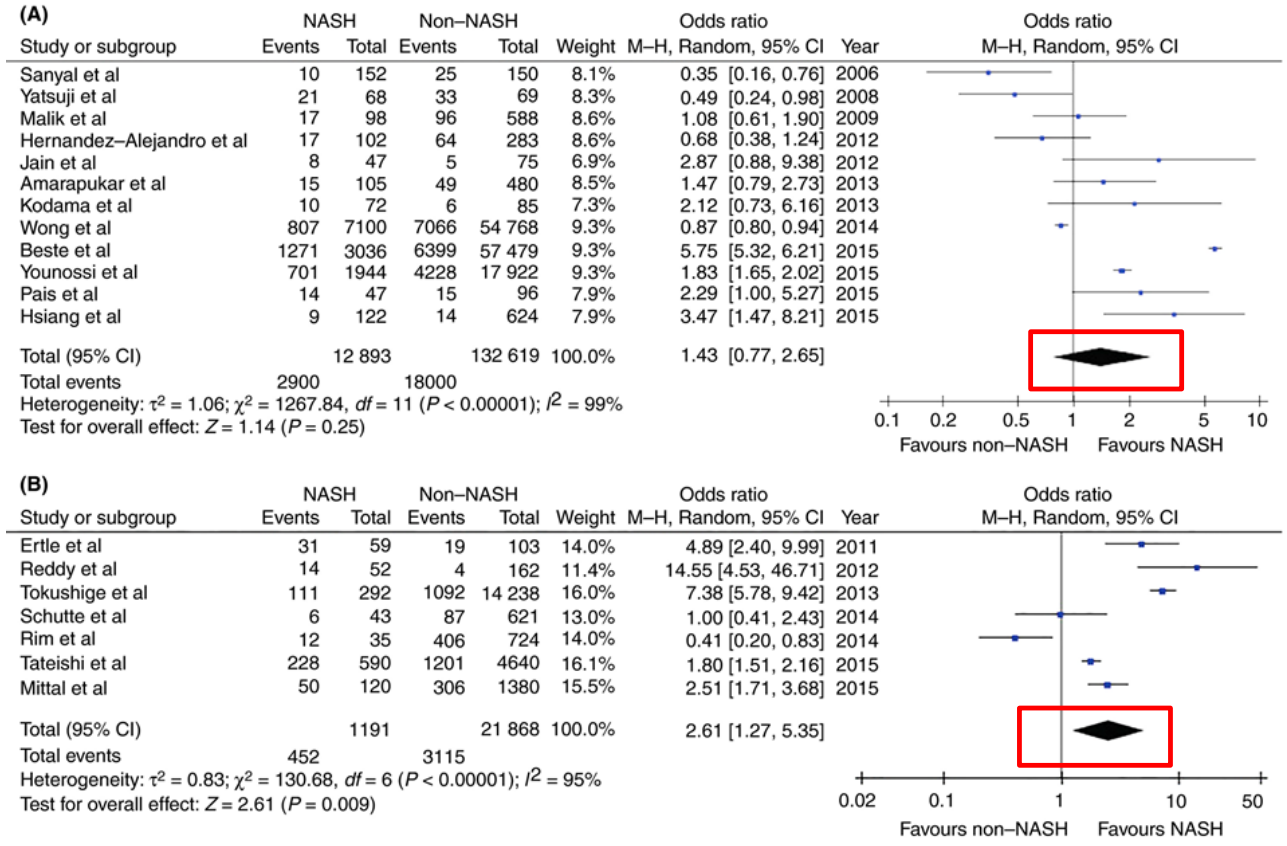
Dyson J et al, J hepatol 2015

Non-cirrhotic HCC in the VA cohort



Mittal et al. Clin Gastroenterol Hepatol 2016;14:124

Meta-analysis: risk of HCC in NASH without cirrhosis compared to other liver diseases



(A)

Study or subgroup	NASH Events	NASH Total	Non–NASH Events	Non–NASH Total	Weight	Odds ratio M–H, Random, 95% CI	Year
Sanyal et al	10	152	25	150	8.1%	0.35 [0.16, 0.76]	2006
Yatsuji et al	21	68	33	69	8.3%	0.49 [0.24, 0.98]	2008
Malik et al	17	98	96	588	8.6%	1.08 [0.61, 1.90]	2009
Hernandez–Alejandro et al	17	102	64	283	8.6%	0.68 [0.38, 1.24]	2012
Jain et al	8	47	5	75	6.9%	2.87 [0.88, 9.38]	2012
Amarapukar et al	15	105	49	480	8.5%	1.47 [0.79, 2.73]	2013
Kodama et al	10	72	6	85	7.3%	2.12 [0.73, 6.16]	2013
Wong et al	807	7100	7066	54 768	9.3%	0.87 [0.80, 0.94]	2014
Beste et al	1271	3036	6399	57 479	9.3%	5.75 [5.32, 6.21]	2015
Younossi et al	701	1944	4228	17 922	9.3%	1.83 [1.65, 2.02]	2015
Pais et al	14	47	15	96	7.9%	2.29 [1.00, 5.27]	2015
Hsiang et al	9	122	14	624	7.9%	3.47 [1.47, 8.21]	2015
Total (95% CI)		12 893		132 619	100.0%	1.43 [0.77, 2.65]	
Total events	2900		18000				

Heterogeneity: $\tau^2 = 1.06$; $\chi^2 = 1267.84$, $df = 11$ ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 1.14$ ($P = 0.25$)

Odds ratio M–H, Random, 95% CI

0.1 0.2 0.5 1 2 5 10
Favours non–NASH Favours NASH

(B)

Study or subgroup	NASH Events	NASH Total	Non–NASH Events	Non–NASH Total	Weight	Odds ratio M–H, Random, 95% CI	Year
Ertle et al	31	59	19	103	14.0%	4.89 [2.40, 9.99]	2011
Reddy et al	14	52	4	162	11.4%	14.55 [4.53, 46.71]	2012
Tokushige et al	111	292	1092	14 238	16.0%	7.38 [5.78, 9.42]	2013
Schutte et al	6	43	87	621	13.0%	1.00 [0.41, 2.43]	2014
Rim et al	12	35	406	724	14.0%	0.41 [0.20, 0.83]	2014
Tateishi et al	228	590	1201	4640	16.1%	1.80 [1.51, 2.16]	2015
Mittal et al	50	120	306	1380	15.5%	2.51 [1.71, 3.68]	2015
Total (95% CI)		1191		21 868	100.0%	2.61 [1.27, 5.35]	
Total events	452		3115				

Heterogeneity: $\tau^2 = 0.83$; $\chi^2 = 130.68$, $df = 6$ ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 2.61$ ($P = 0.009$)

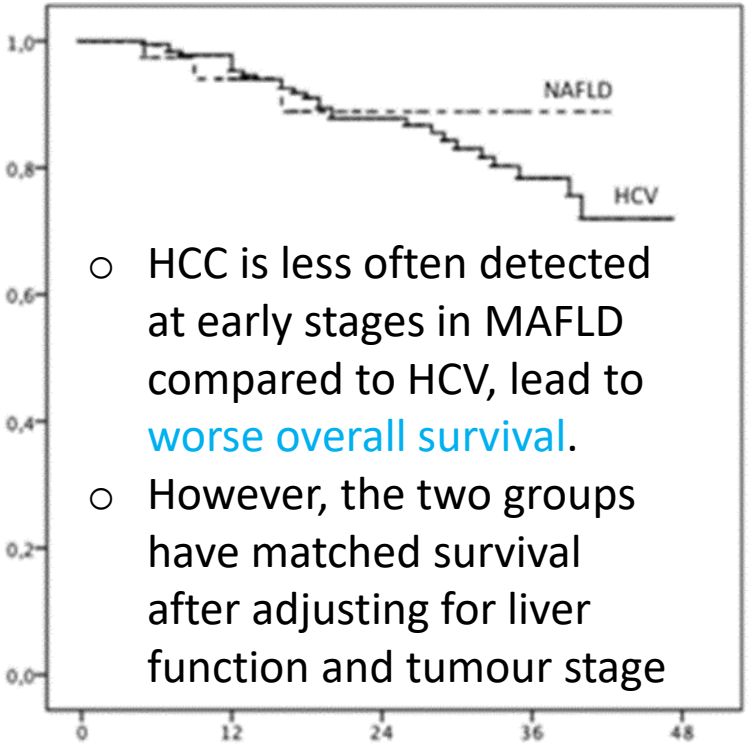
Odds ratio M–H, Random, 95% CI

0.02 0.1 1 10 50
Favours non–NASH Favours NASH

A, Pooled measure of effects for NASH and HCC in all patients (either with or without cirrhosis).
B, Pooled measure of effects of NASH and HCC in patients without cirrhosis.
The overall pooled estimate from the seven studies indicates that patients with NASH **have a 261% increased risk of HCC** when compared to all other aetiologies of liver disease.

Stine JG. Aliment Pharmacol Ther. 2018 Aug 22.

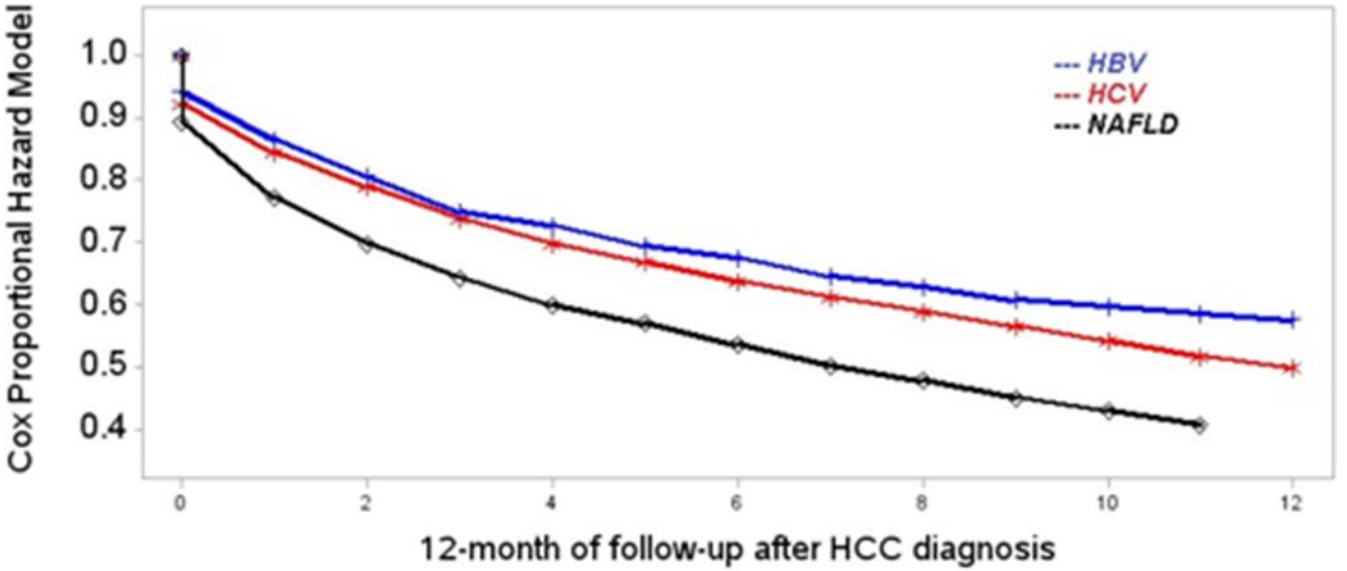
HCC in MAFLD have worse survival



- HCC is less often detected at early stages in MAFLD compared to HCV, lead to worse overall survival.
- However, the two groups have matched survival after adjusting for liver function and tumour stage

Patients at risk

Months	0	12	24	36	48
NAFLD	49	25	6	2	0
HCV	217	145	86	38	0



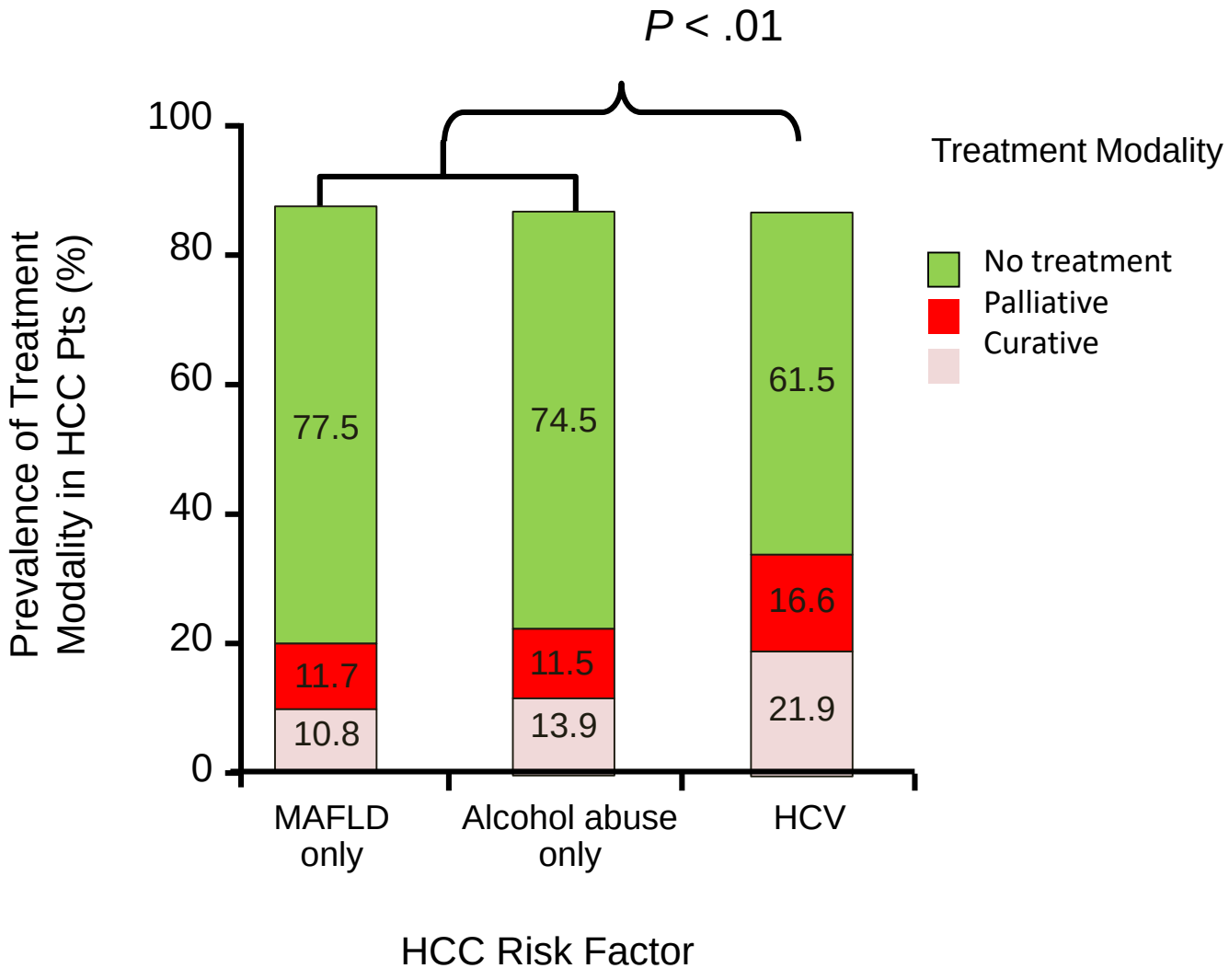
** Adjusted for age (years) at HCC diagnosis and tumor stage;*
Source: SEER-MEdicare, 2004 - 2009

In the HCV/HBV group with HCC, approximately 50% died within 1 year whereas in the MAFLD-related HCC cohort approximately 61% died within 1 year of diagnosis ($P < 0.0001$).
MAFLD patients with HCC had approximately 5 months shorter survival time than HCC related to viral hepatitis (HCV/HBV; all $P < 0.05$).

Piscaglia F, et al. Hepatology. 2016 Mar;63(3):827-38.

Younossi ZM, et al. Hepatology. 2015 Dec;62(6):1723-30.

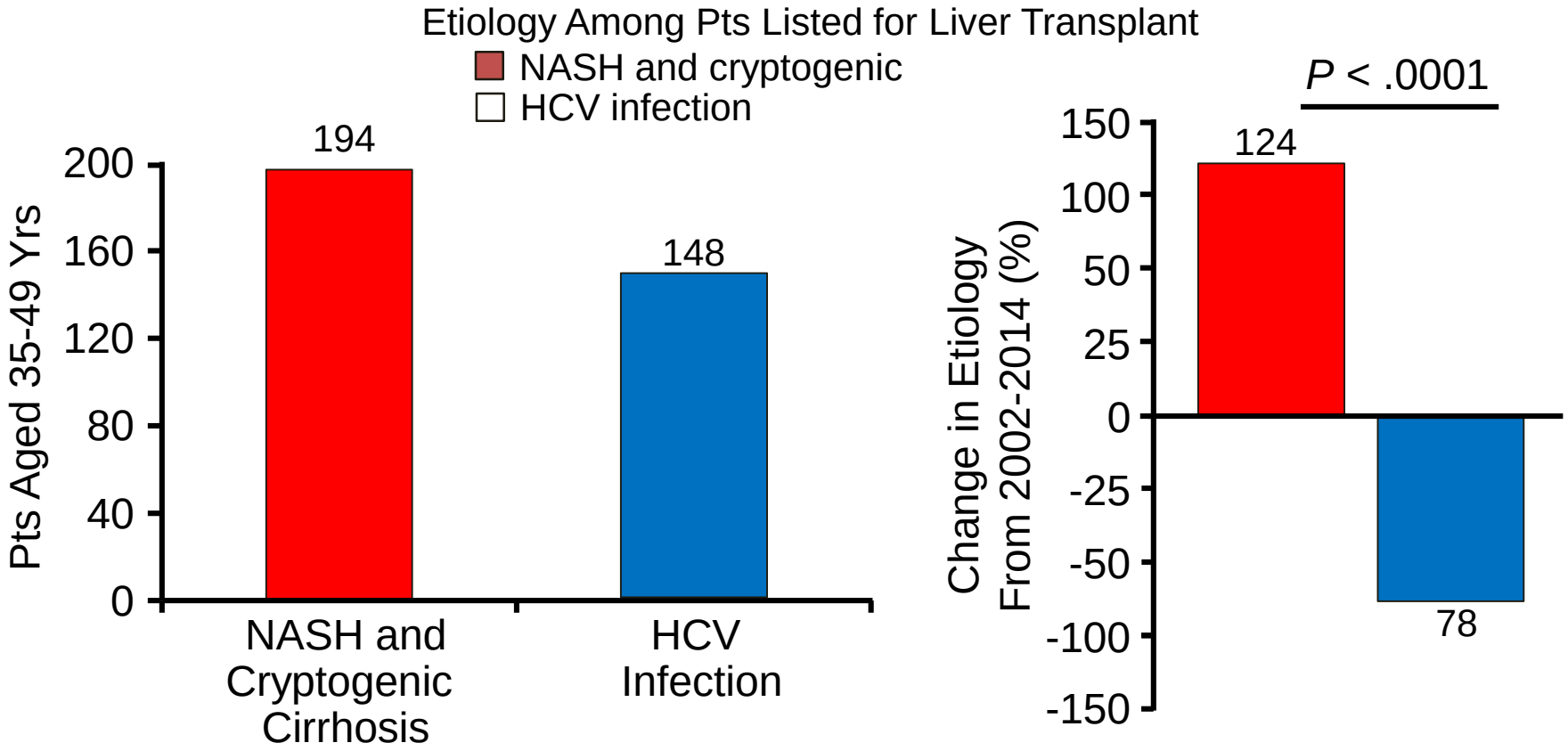
HCC in MAFLD are less likely to have curative Tx



Mittal S, et al. Clin Gastroenterol Hepatol. 2015;13:594-601.

NASH: Number One Indication for Liver Transplant in Pts Aged < 50 Yrs

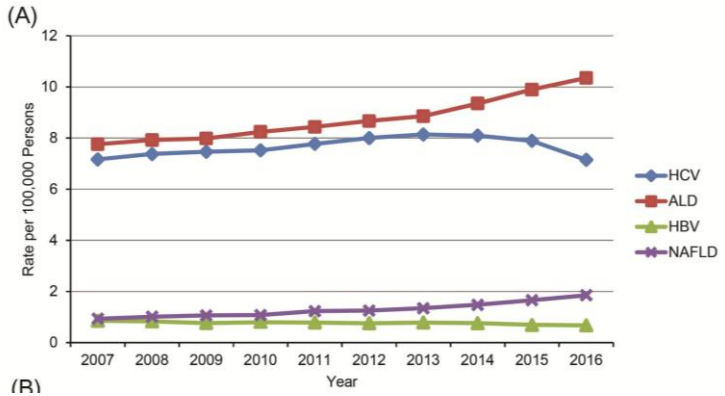
- In 2015 registry of pts listed for liver transplant, NASH surpassed HCV infection



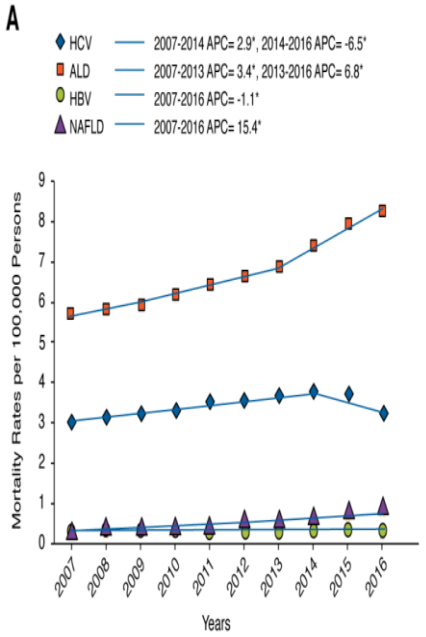
Banini BA, et al. ACG 2016. Abstract 46.

Changing Trends in Annual Mortality Rates of Cirrhosis and HCC in the United States

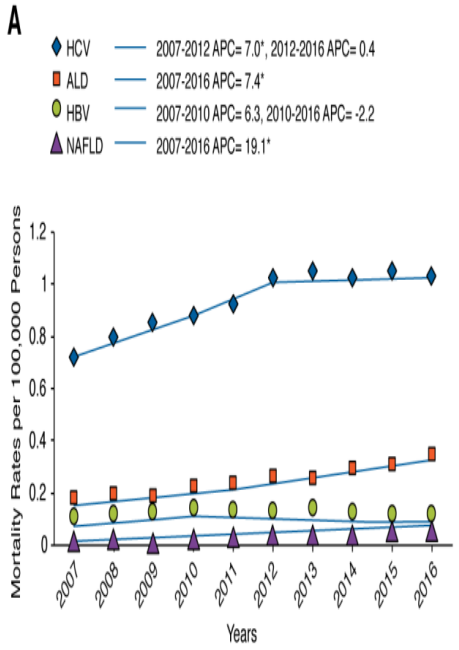
All-cause mortality



Age-Standardized Mortality Rates for Cirrhosis



Age-Standardized Mortality Rates for HCC

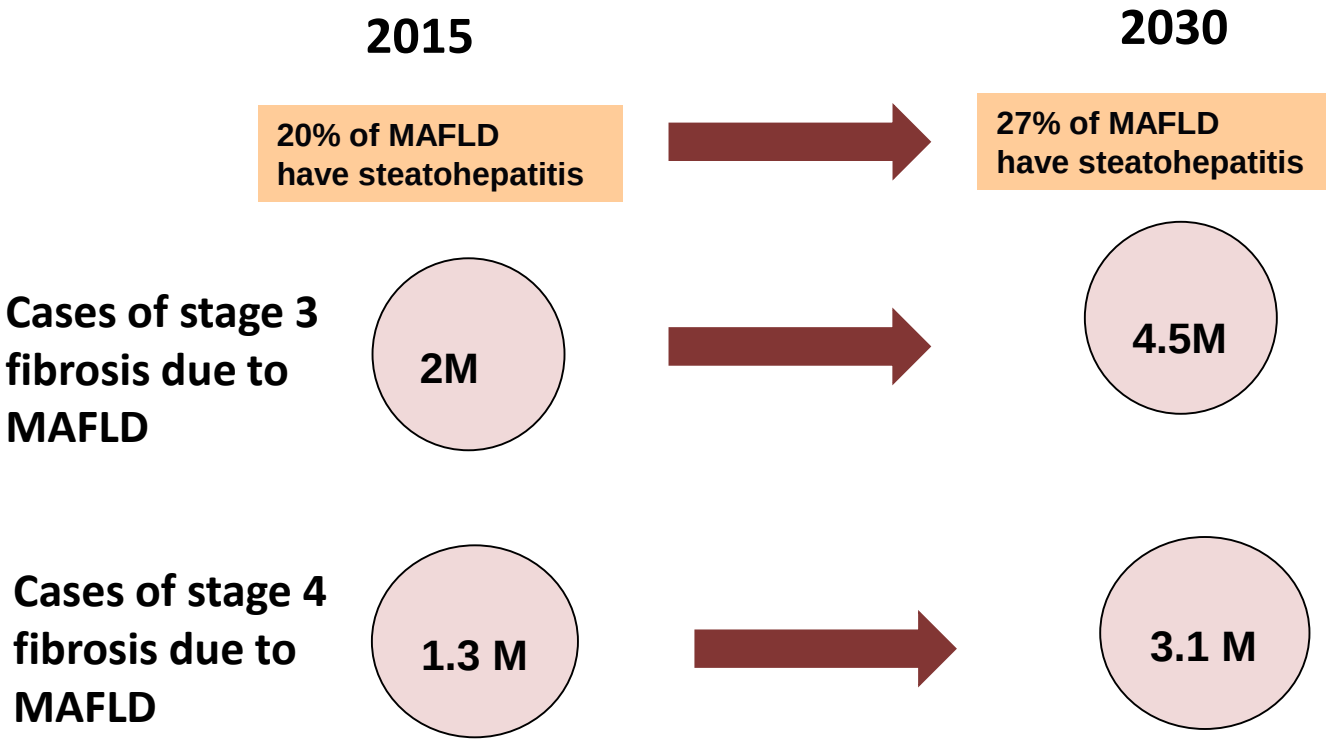


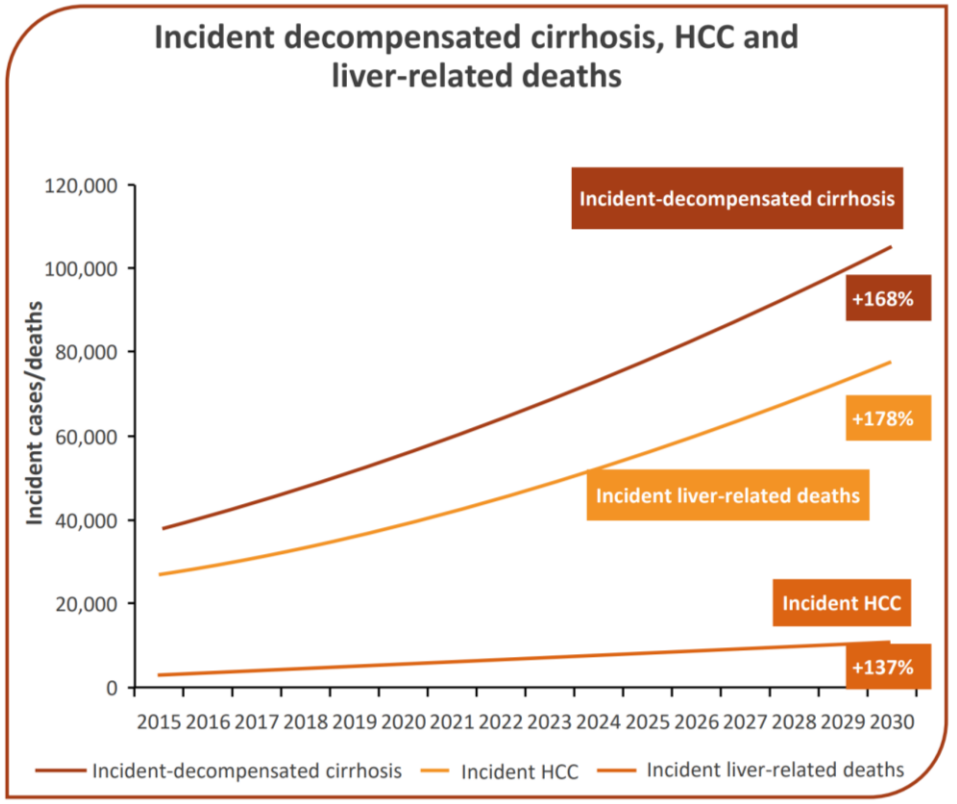
All cause mortality, Cirrhosis- and HCC-related mortality rates increased between 2007 and 2016 in the US.
However, mortality rates in HCV-cirrhosis demonstrated a significant decline from 2014-2016, during the direct-acting antiviral era.
Mortality rates for ALD/MAFLD-cirrhosis and HCC have continued to increase.
While HBV-cirrhosis-related mortality declined during the 10-year period.

Kim D, et al.Hepatology. 2018 Jul 16.

Kim D, et al.Gastroenterology. 2018 Jul 12

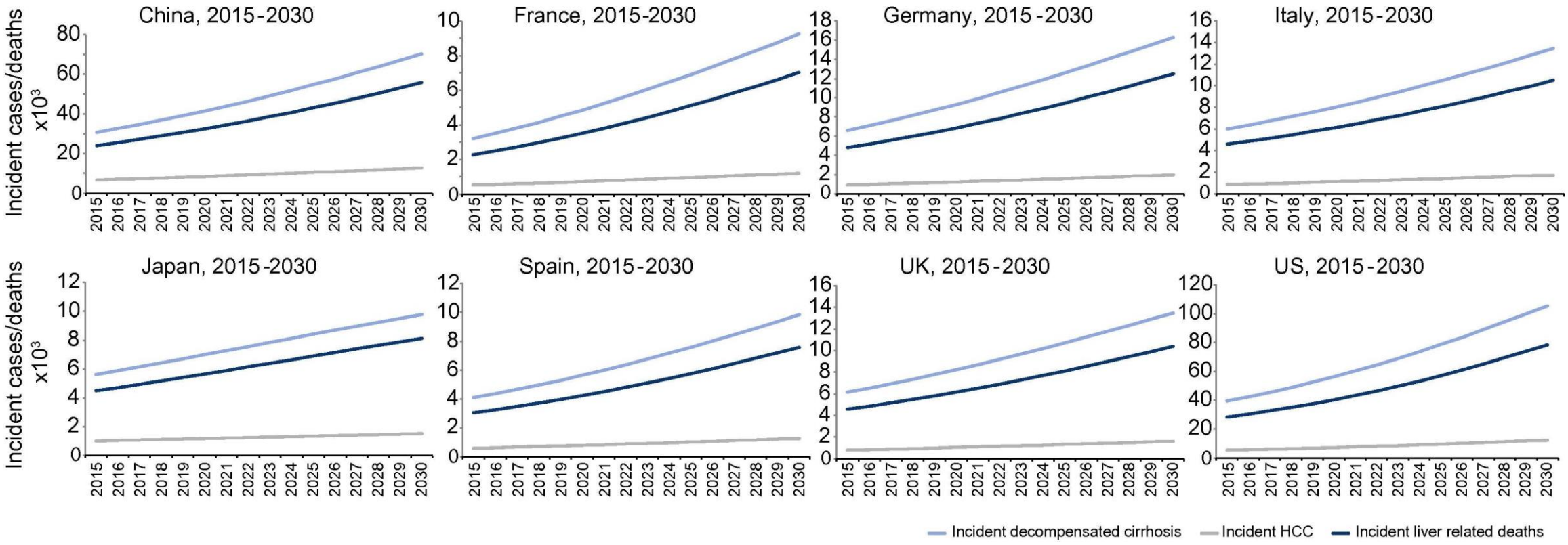
Evidence supporting the burden of MAFLD: The modelling data





Estes C et al. Hepatology. 2018;67:123–33

Incident decompensated cirrhosis, HCC and liver-related deaths among prevalent MAFLD population – 2015–2030

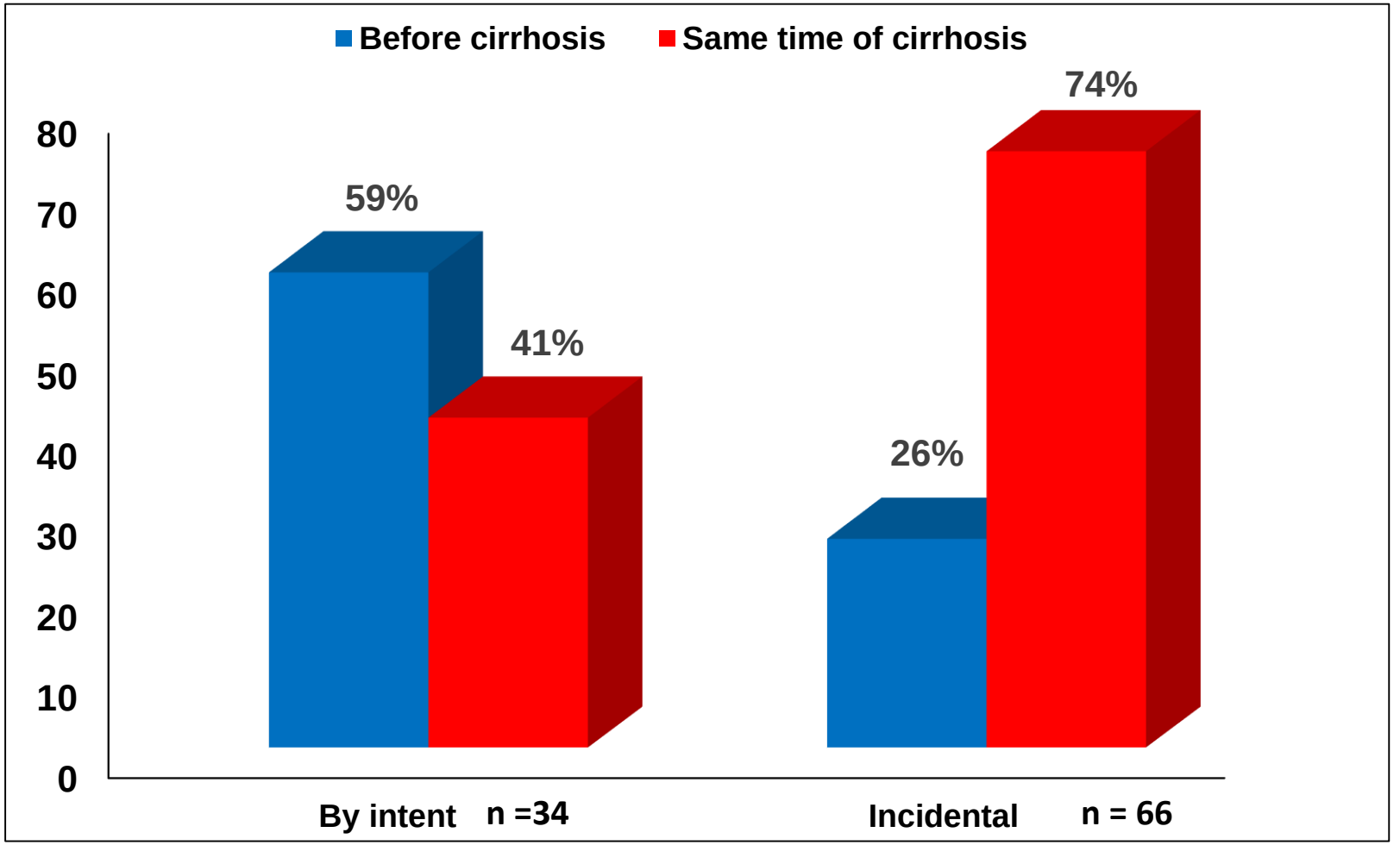


In all countries, prevalent HCC cases related to MAFLD are estimated to increase, ranging from increases of 47% in Japan to 130% in the US

Estes C, et al. J Hep. 2018 Jan;67(1):123-133

The majority of patients with MAFLD cirrhosis are diagnosed incidentally

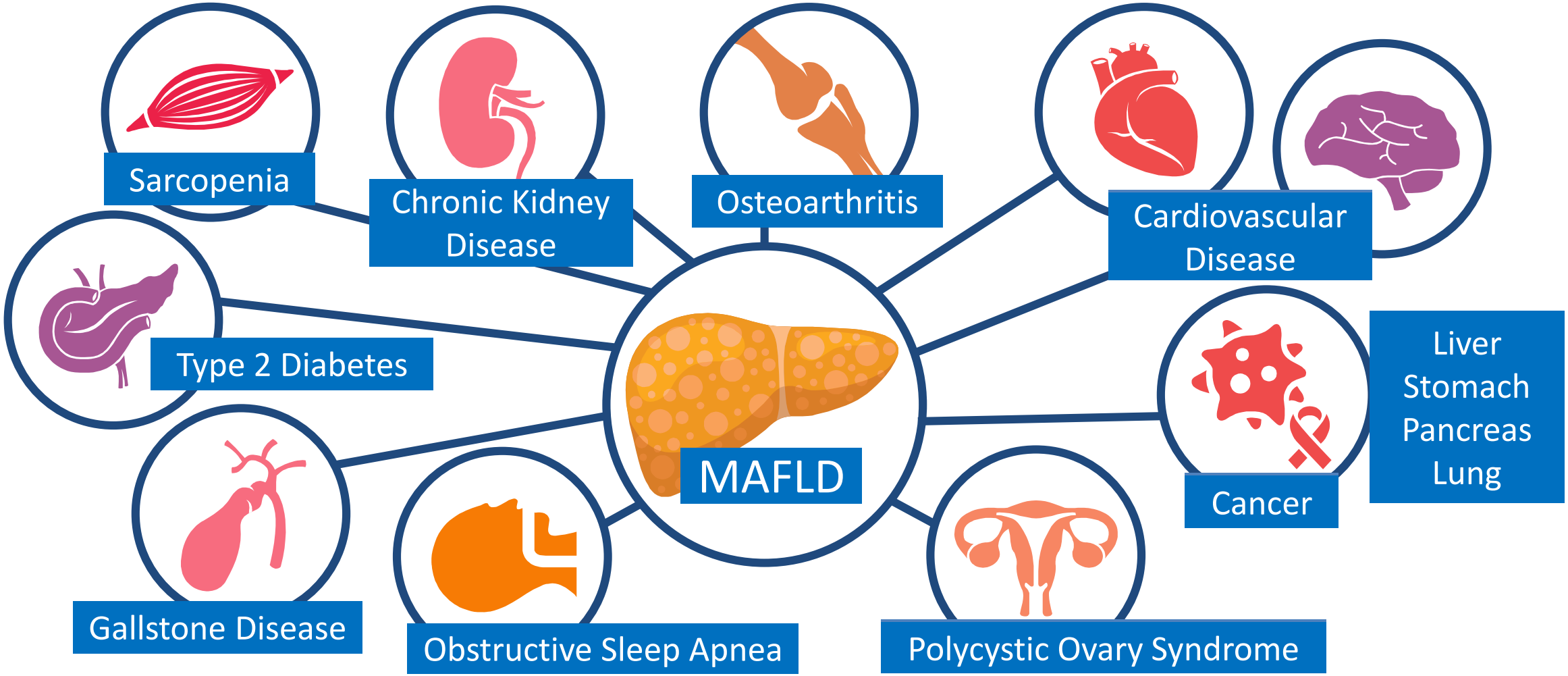
Study from Australia 100 patients with MAFLD cirrhosis to determine mode of cirrhosis diagnosis (incidental or by intent)



Bertot LC , et al. Commun. 2017 Feb 27;1(1):53-60

MAFLD and non-liver outcomes

MAFLD: A Systemic Disease With Comorbidities

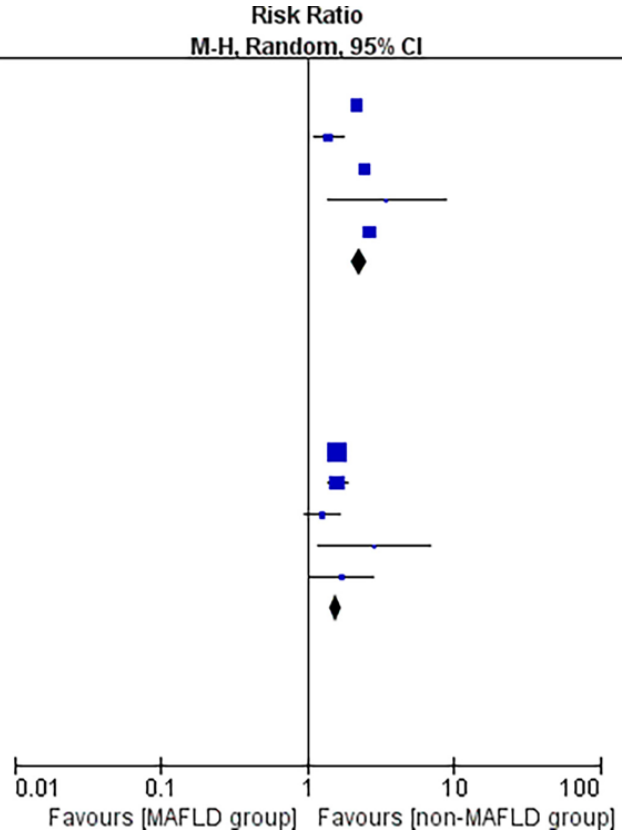


Younossi. Hepatology. 2019;69:2672.

MAFLD and cardiovascular diseases

MAFLD and risk of CVD incidence and CVD mortality

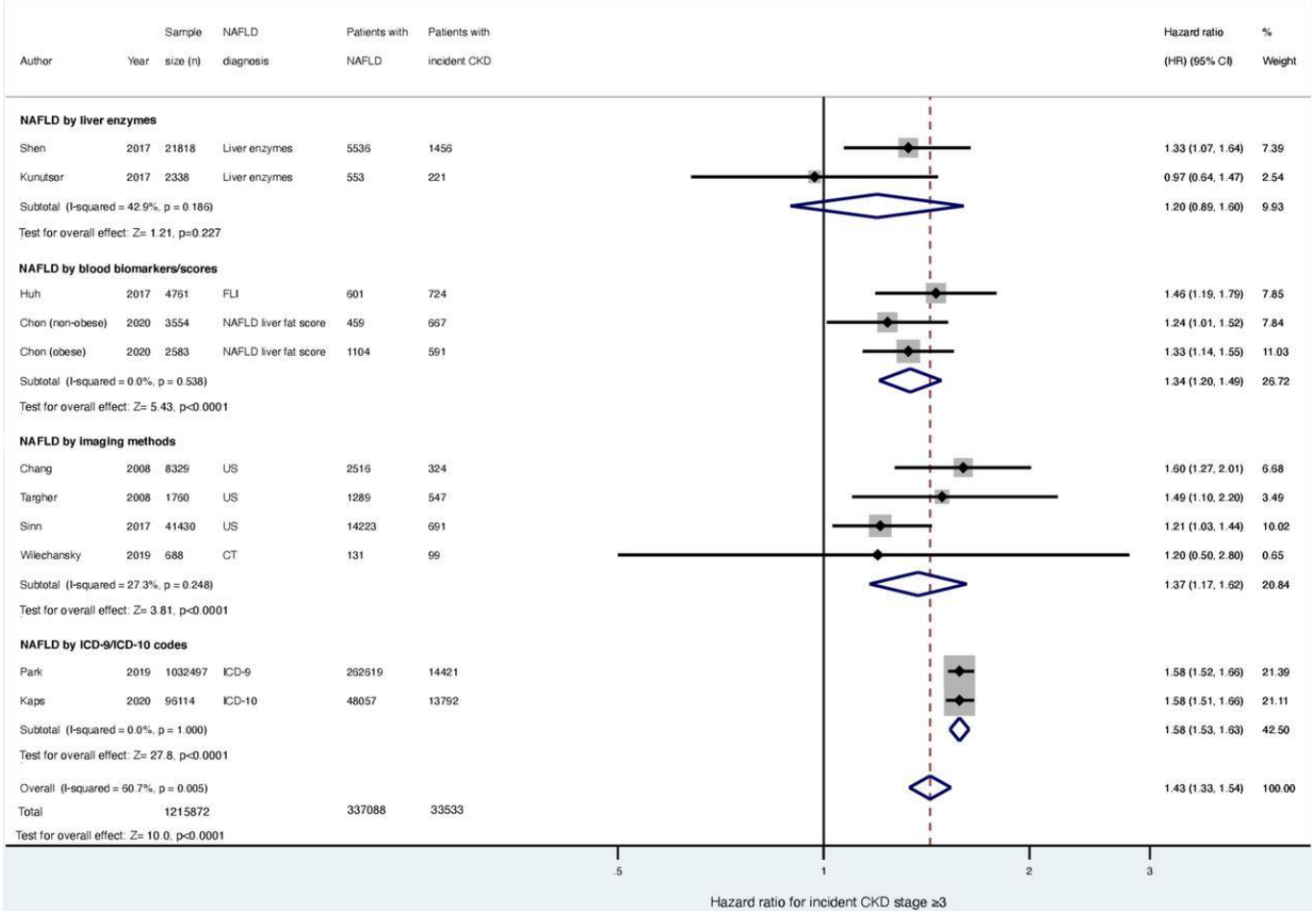
Study or Subgroup	MAFLD group Events	Total	non-MAFLD group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 CVDs						
Lee 2021	101188	31810967	81235	55715210	28.5%	2.18 [2.16, 2.20]
Liang 2022	162	2950	134	3417	14.3%	1.40 [1.12, 1.75]
Liu 2020	9181	160979	6105	262273	28.0%	2.45 [2.37, 2.53]
Niriella 2021	43	692	5	282	1.6%	3.50 [1.40, 8.76]
Yoneda 2021	3002	237242	10455	2215707	27.6%	2.68 [2.58, 2.79]
Subtotal (95% CI)		**32212830**		**58196889**	**100.0%**	**2.26 [2.00, 2.54]**
Total events	113576		97934			
Heterogeneity: Tau² = 0.01; Chi² = 152.52, df = 4 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 13.32 (P < 0.00001)						
1.2.2 CVD mortality						
Huang 2021	409	3909	566	8571	51.6%	1.58 [1.40, 1.79]
Kim 2021	228	2256	348	5505	32.2%	1.60 [1.36, 1.88]
Liu 2021	108	3306	85	3306	11.3%	1.27 [0.96, 1.68]
Nguyen 2021	155	2739	5	254	1.2%	2.87 [1.19, 6.94]
Semmler 2021	39	2189	26	2529	3.7%	1.73 [1.06, 2.84]
Subtotal (95% CI)		**14399**		**20165**	**100.0%**	**1.57 [1.42, 1.72]**
Total events	939		1030			
Heterogeneity: Tau² = 0.00; Chi² = 4.23, df = 4 (P = 0.38); I² = 5%						
Test for overall effect: Z = 9.17 (P < 0.00001)						



Wen W, et al. Front Endocrinol (Lausanne). 2022 Sep 16;13:934225

MAFLD increase risk of Chronic Kidney Disease

N=1 222 032 individuals



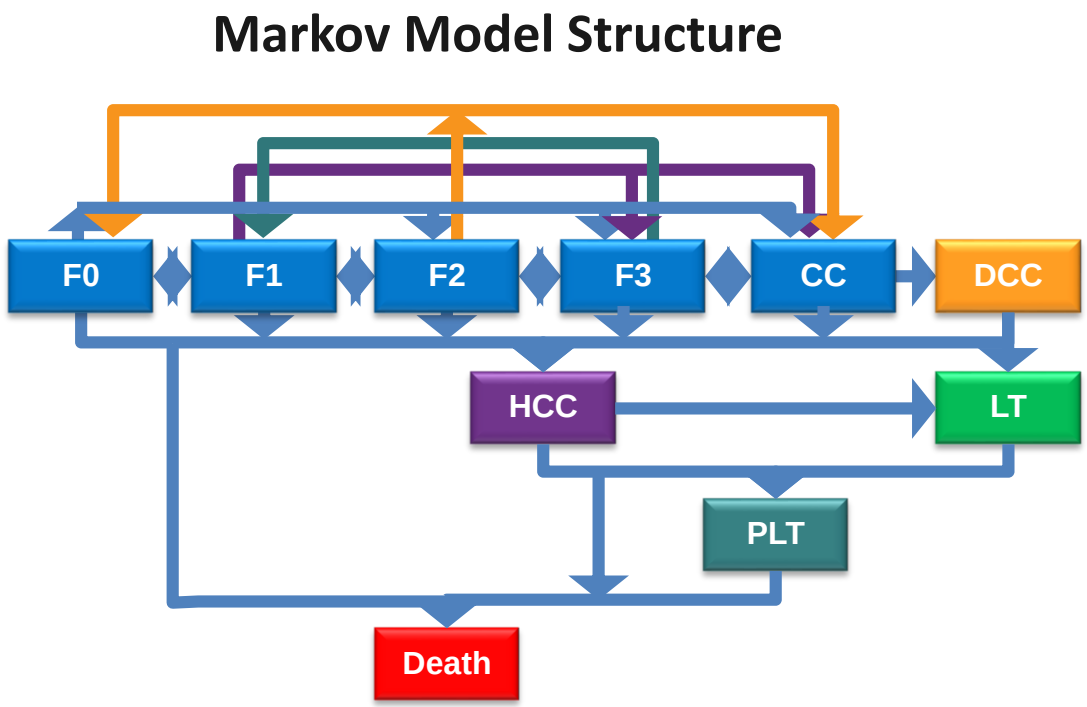
NAFLD is significantly associated with a~1.45-fold increased long-term risk of incident CKD stage ≥3 compared to matched controls

Mantovani A, et al. Gut. 2022 Jan;71(1):156-162.

MAFLD and economic and quality of life burden

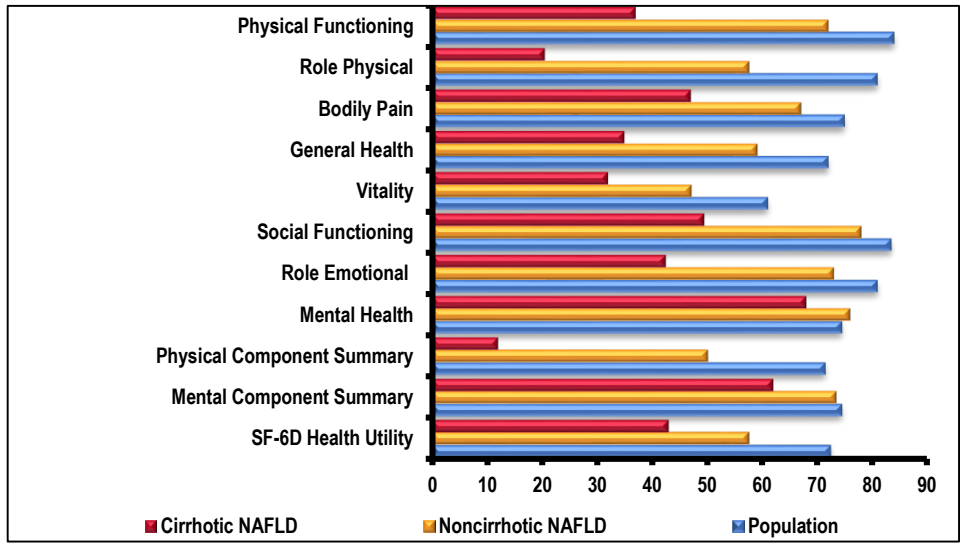
The Economic Burden of MAFLD and NASH: modeling

- **Economic models to assess burden of MAFLD** using interlinked Markov chains
  - US: Over 64 million people with MAFLD, with annual direct medical costs of about $103 billion ($1,613 per patient).
  - In EU-4 Germany/France/UK/Italy ~ 52 million people with MAFLD with annual direct medical costs of about €35 billion e354 to e1,163 per patient
  - Costs are high in patients aged 45-65.
  - Burden is higher when societal costs are included.
  - The projections of costs for each age-specific NASH cohort could increase ~400% in the next 5 years

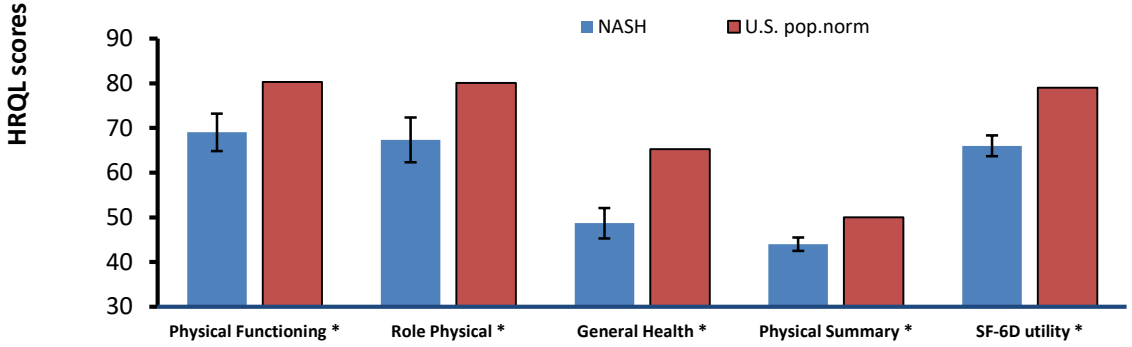


Younossi ZM, et al. Hepatology 2016;64(5):1577-1586, Younossi ZM, et al. Hepatology. 2018 Sep 4.

PROs in MAFLD

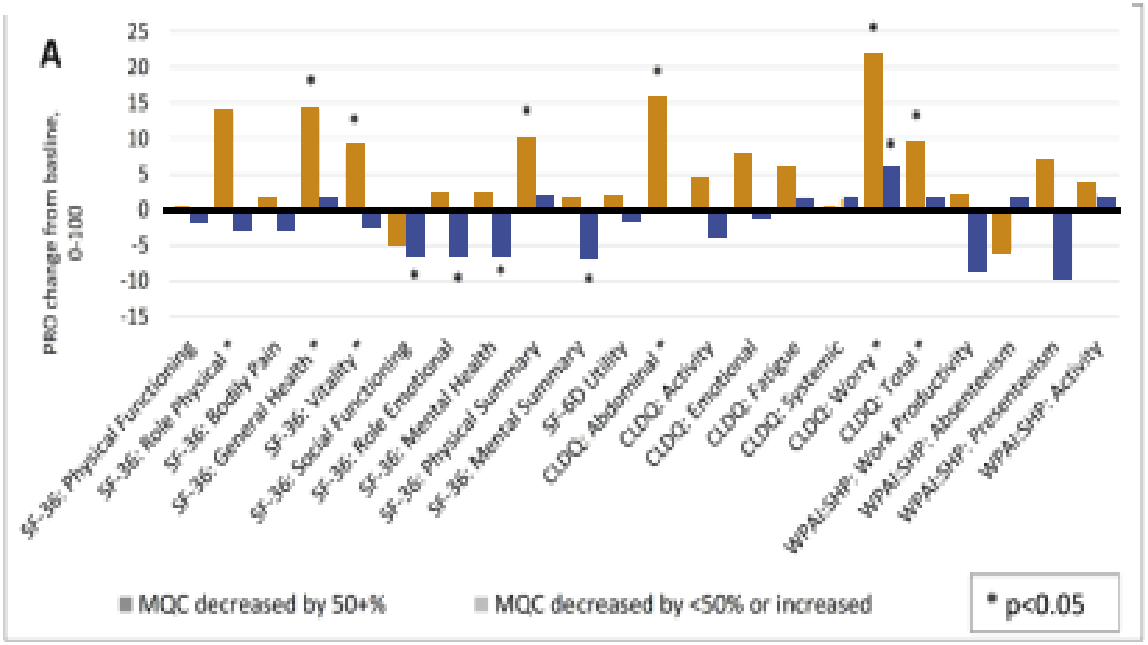


- NASH with Stage 2–3 fibrosis (N=72):
- Baseline PROs of physical health and general health



Disease-Specific CLDQ MAFLD-NASH

Domain	Cronbach-α	Item-to-own-dimension correlations	Cronbach-α with one item removed
Abdominal symptoms	0.90	0.78-0.84	0.83-0.88
Activity	0.74	0.27-0.67	0.63-0.78
Emotional	0.88	0.44-0.77	0.86-0.89
Fatigue	0.86	0.48-0.82	0.80-0.86
Systemic symptoms	0.75	0.34-0.59	0.69-0.75
Worry	0.89	0.49-0.82	0.86-0.90



Sayiner M, et al. *BMJ Open Gastro*. 2016; Younossi ZM et al. *Liver Int.* 2017; 37(8):1209-1218, Younossi Z et al Liver Int 2018

Summary

Health care burden of MAFLD/NASH

- MAFLD prevalence: High ~25%
- Project trends: Increase by 0-30% MAFLD; 15-56% NASH; Mort, ESLD X2 (by 2030)
  - Aging, increasing population
- MAFLD related complications:
  - Liver related (ESLD, HCC, OLT)
  - CVD/T2DM burden will kill the majority
- Health care, economic burden and quality of life: Significant
- At a population level:
  - Tackle obesity and insufficient PA
  - Precision pharmacotherapy for progressive disease

Thank you!!!

Down-under: Sydney