Paris, January 14, 2020

Natural history of NAFLD, NASH and HCC

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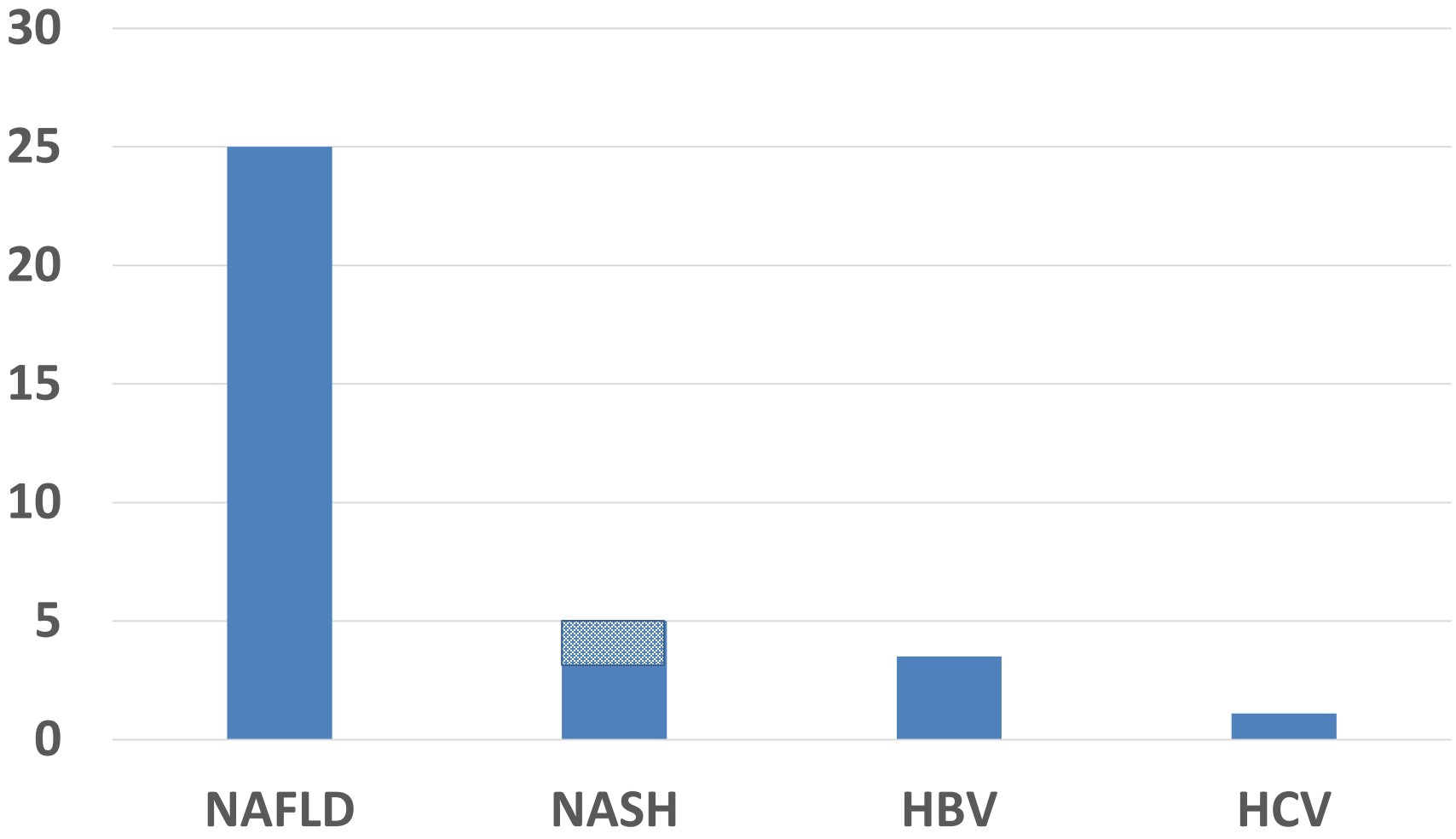
DISCLAIMER

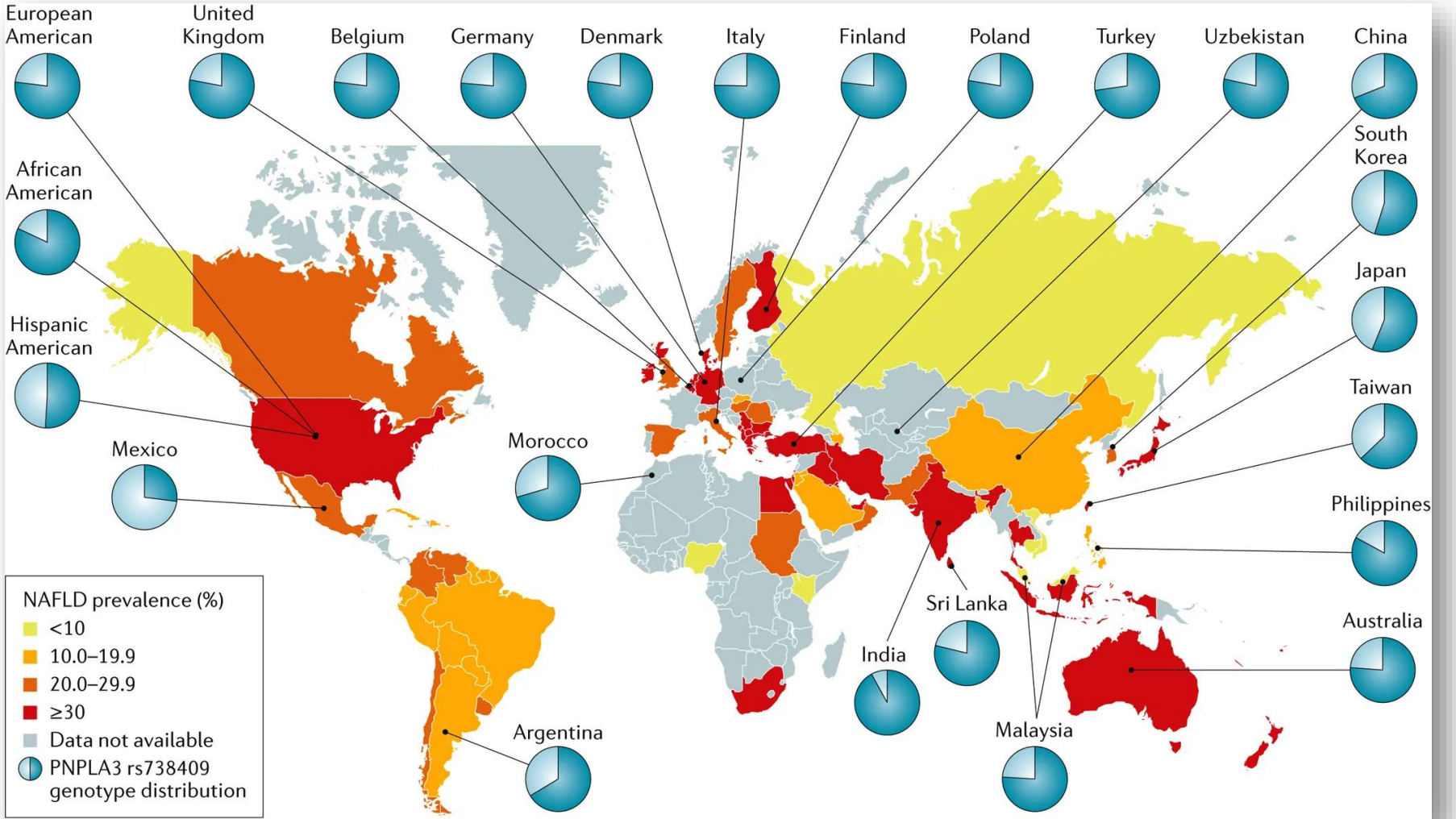
- Conflicts of interest: none

Global prevalence of major chronic liver disorders



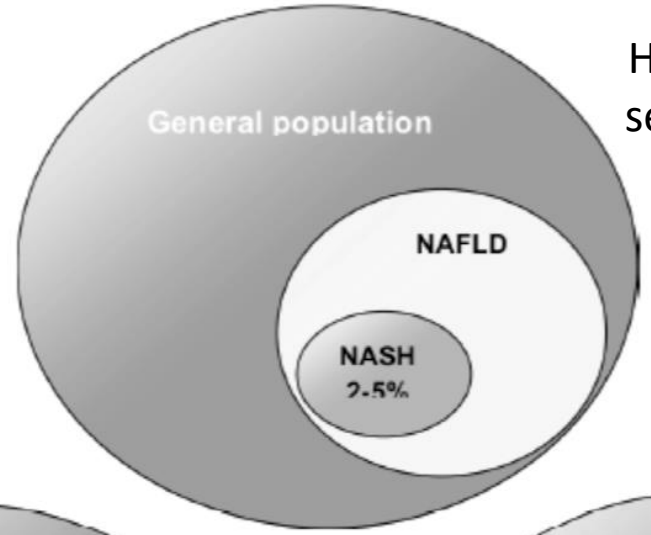
GROUND KE. Av Sp Environm Med 1982;53:14-8; GRANT LM & LISKER-MELMAN M. Ann Hepatol 2004;3:93-9; KLEINER DE, *et al.* Hepatology 2005;41:1313-21
WILLIAMS CD, *et al.* Gastroenterology 2011;140:124-31; VERNON G, *et al.* Aliment Pharmacol Ther 2011;34:274-85; RINELLA ME. Hepatology 2011;54:1118-20
CHALASANI N, *et al.* Gastroenterology 2012;142:1592-609; RINELLA ME. JAMA 2015;313:2263-73; ESTES C, *et al.* Hepatology 2018;67:123-133
YOUNOSSI Z, *et al.* Hepatology 2016;64:1577-86; WHO Global Hepatitis Report 2017

NAFLD affects one quarter of the global population



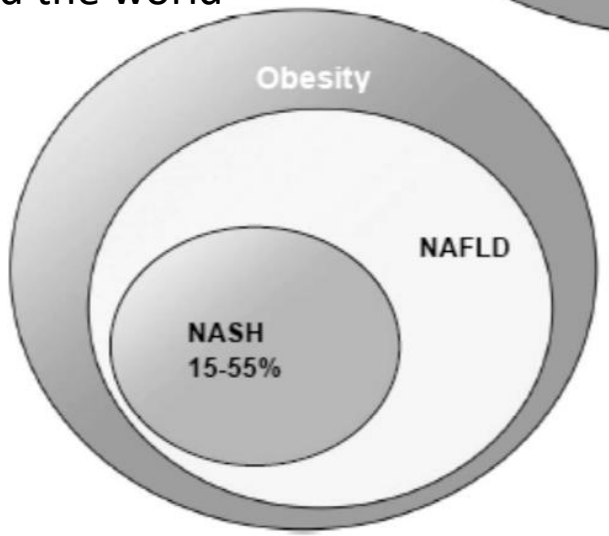
YOUNOSSI *et al,* Nat Rev Gastroenterol Hepatol 2017;15:11-20

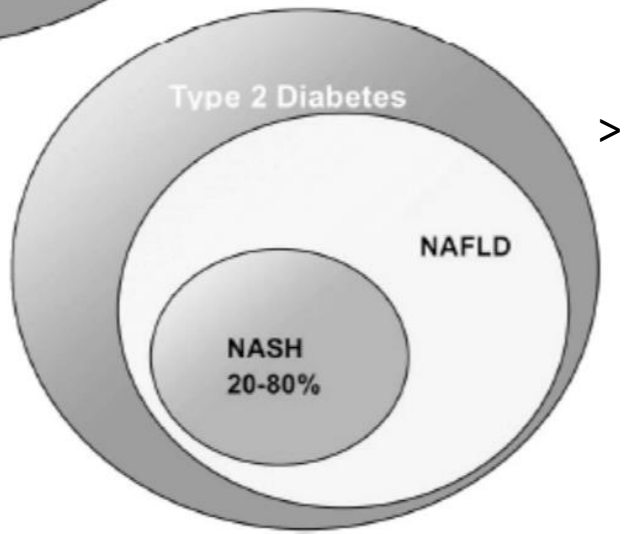
NAFLD - The dimension of the problem



Hepatologists only see the most severe cases (the tip of iceberg), and have a scarce idea of the global extent of disease

Obesity
1 billion persons overweight or obese around the world

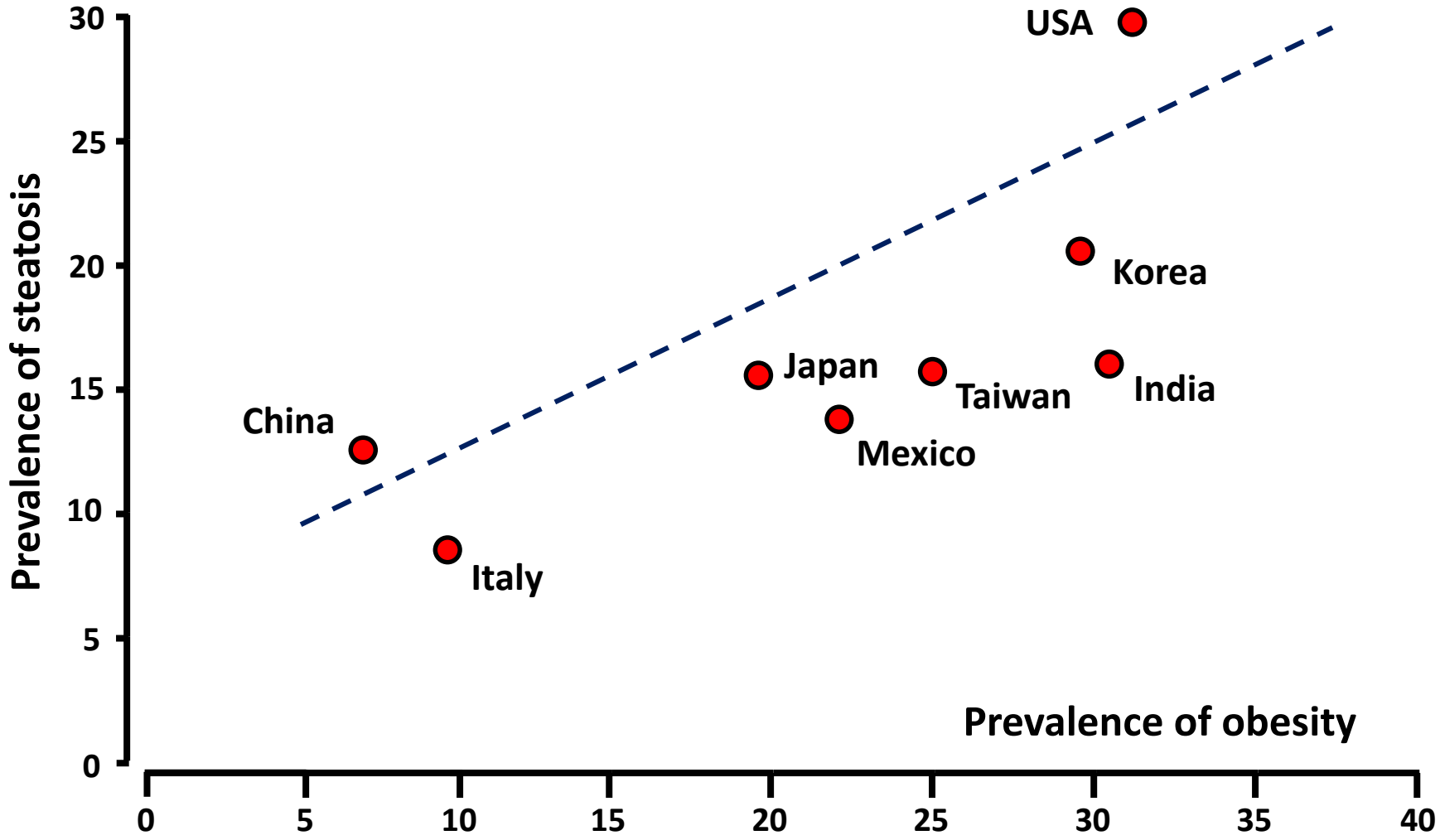




Diabetes
> 380 milion cases (550 in 2030)

BHALA *et al*, Curr Pharma Des 2013;19:5169-76

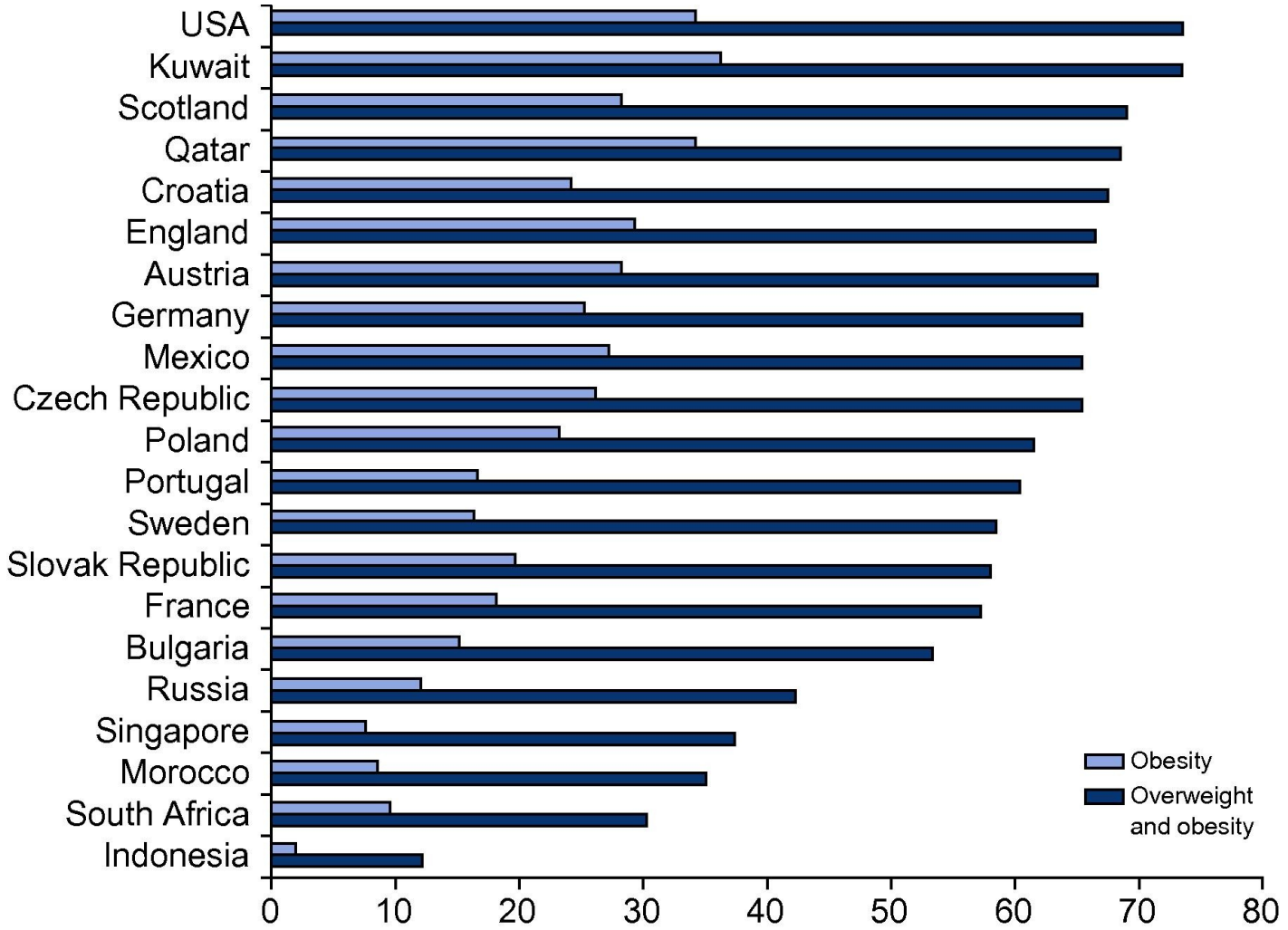
NAFLD prevalence correlates with obesity



HILDEN *et al,* 1977; GROUND *et al,* 1982; BELLENTANI *et al,* 2000; CLARK *et al,* 2001; RUHL *et al,* 2004
BROWNING *et al,* 2004; ANGELICO *et al,* 2005; HAMAGUSHI *et al,* 2005; JIMBA *et al,* 2005; LIN *et al,* 2005
FAN *et al,* 2005; ZELBER *et al,* 2006; ZHOU *et al,* 2007; FAN *et al,* 2007; TARGHER *et al,* 2007; LAZO *et al,* 2008

Countries with the highest adult prevalence of overweight and obesity

World Population: 7,505,257,673 and World Obesity Population: 774,000,000

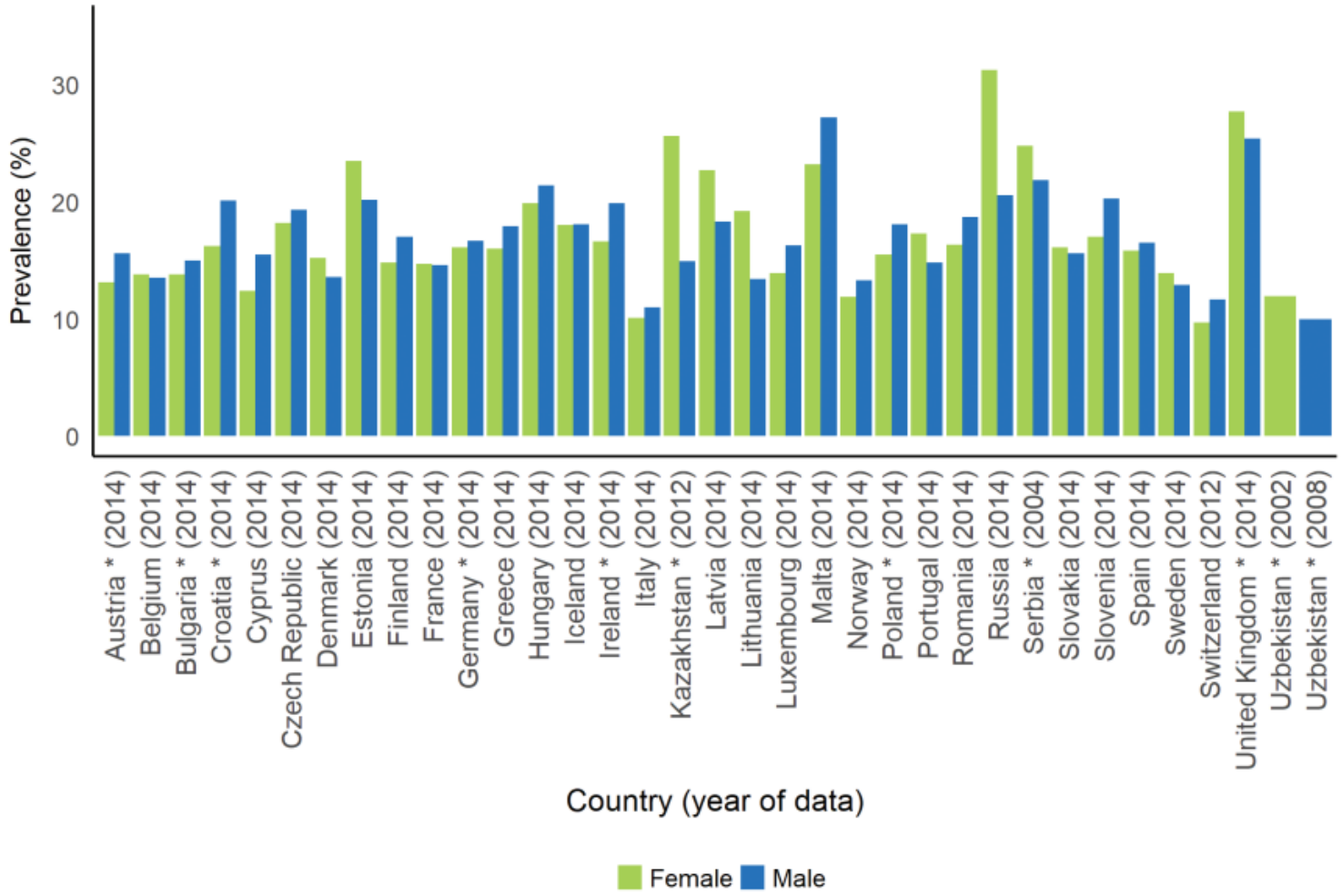


YOUNOSSI Z. J Hepatol 2019;70:531-44

https://renewbariatrics.com/obesity-rank-by-countries

Prevalence of obesity in Europe

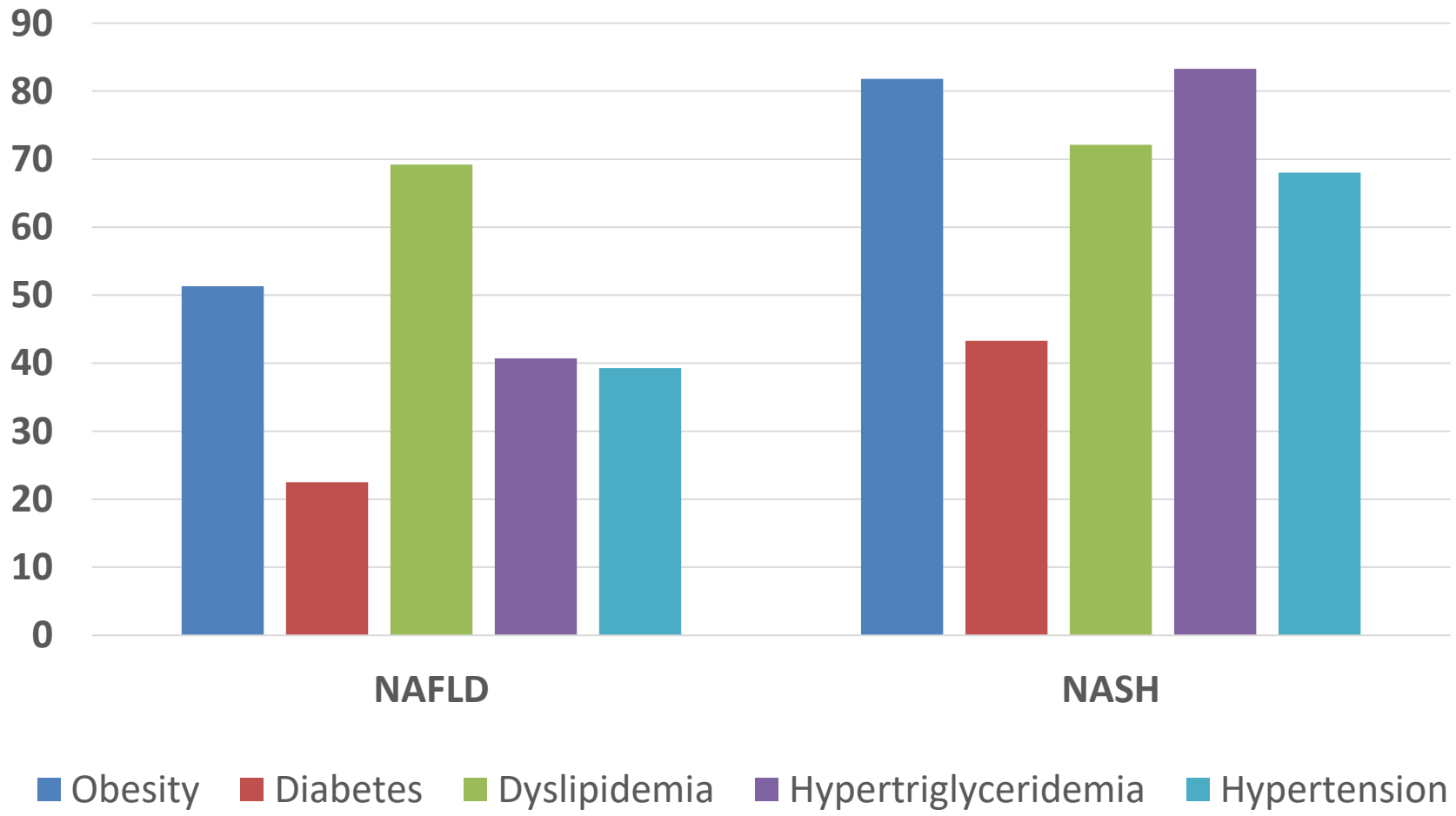
(most recent available data, The HEPAHEALTH I Project)



https://easl.eu/wp-content/uploads/2018/09/EASL-HEPAHEALTH-Report.pdf

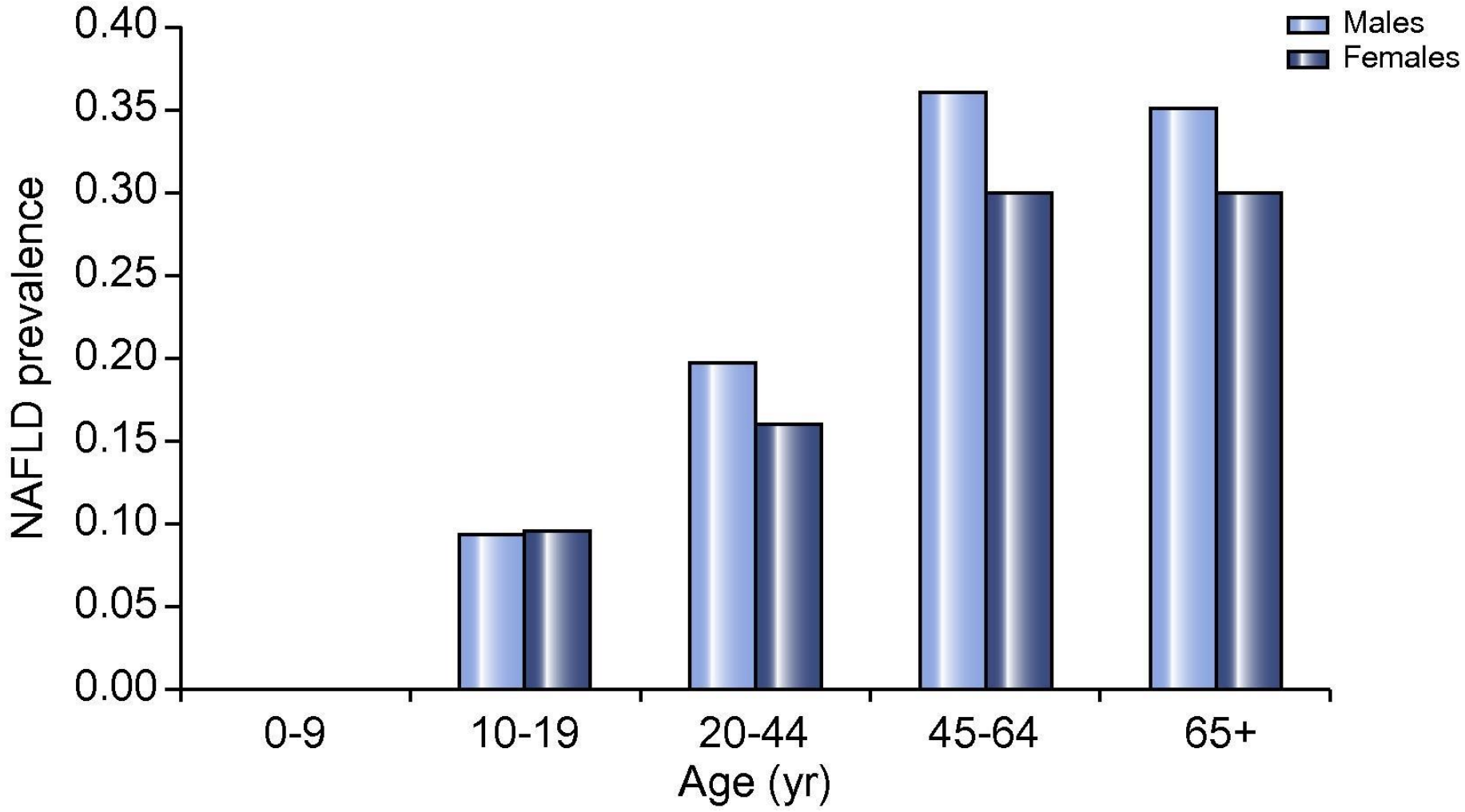
Proportion of patients with features of the metabolic syndrome among NAFLD *vs.* NASH cases

A meta-analytic assessment of prevalence, incidence, and outcomes



YOUNOSSI *et al,* Hepatology 2016;64:73-84

Trends in the prevalence of NAFLD by age



YOUNOSSI Z. J Hepatol 2019;70:531-44
https://www.who.int

Prevalence of NAFLD by age, ethnicity and sex in the US

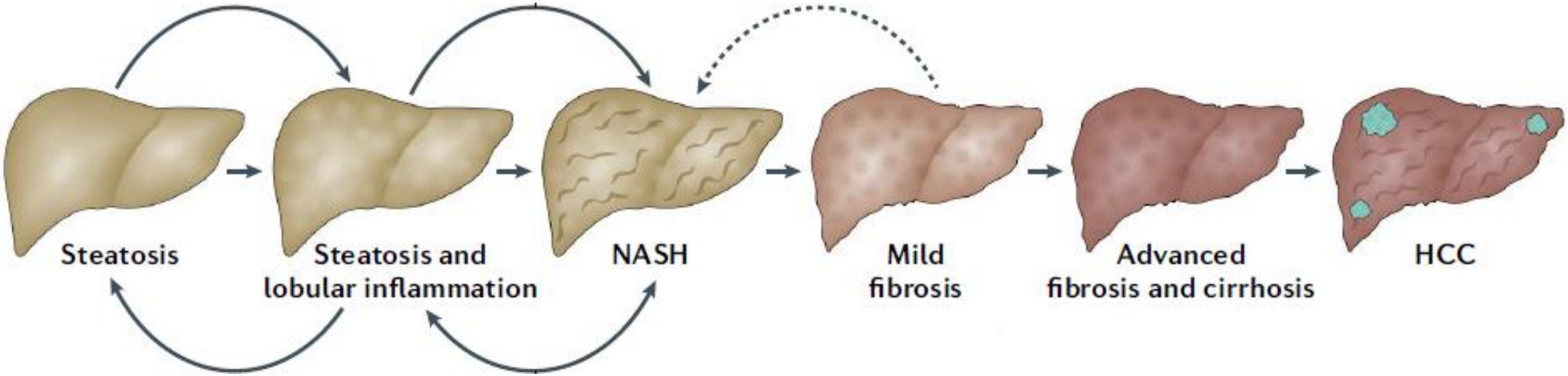
(NHANES III, 1988-1994)

Increasing prevalence with age, 1.28 male to female ratio, increased prevalence in Mexican American

Sex by Age	Non-Hispanic White		Non-Hispanic Black		Mexican American		Total	
	Prevalence	95% CI	Prevalence	95% CI	Prevalence	95% CI	Prevalence	95% CI
Men								
<30 years	8.3	5.4, 12.7	10.9	7.5, 15.8	15.6	10.9, 21.8	9.9	7.4, 13.2
30–<40 years	15.9	12.5, 20.0	12.5	10.0, 15.6	25.7	21.6, 30.4	16.1	13.3, 19.4
40–<50 years	22.2	17.5, 27.7	17.1	12.7, 22.5	36.2	31.1, 41.6	22.3	18.2, 27.0
50–<60 years	28.0	21.5, 35.6	17.4	10.9, 26.6	41.4	31.3, 52.2	29.3	23.9, 35.4
≥60 years	28.1	24.4, 32.2	22.6	18.9, 26.8	33.4	27.6, 39.7	27.6	24.3, 31.3
Women								
<30 years	9.5	6.2, 14.2	12.0	8.7, 16.3	16.5	12.2, 22.0	10.6	7.9, 13.9
30–<40 years	11.1	8.4, 14.5	10.4	7.5, 14.1	23.2	18.6, 28.6	12.5	10.0, 15.6
40–<50 years	15.0	11.9, 18.7	14.3	9.8, 20.5	34.7	27.6, 42.6	16.1	13.4, 19.1
50–<60 years	20.5	16.7, 24.8	21.9	15.9, 29.4	35.7	25.6, 47.4	21.6	18.3, 25.3
≥60 years	25.7	22.3, 29.5	23.9	19.7, 28.8	34.4	28.8, 40.4	25.4	22.4, 28.6

LAZO M, *et al.* Am J Epidemiol 2013;178:38-45

Natural history of NAFLD



Adapted from ANSTEE Q, et al. Nat Rev Gastroenterol Hepatol 2019;16:411-428

Prevalence and factors of significant liver stiffness likely associated with NAFLD in the general population

(n=3076, age 18-75, Barcelona metropolitan area)

After excluding HCV, HBV and alcohol, 3.3% of 2710 persons had TE values ≥ 9.0 kPa

	6.8 kPa				8.0 kPa				9.0 kPa			
	OR	95% CI		*P* value	OR	95% CI		*P* value	OR	95% CI		*P* value
Male sex	2.86	2.08	4.05	.000	2.74	1.87	4.03	.000	3.49	2.12	5.72	.000
AST and/or ALT >ULN[a]	2.18	1.44	3.29	.000	1.91	1.16	3.14	.011	3.27	1.87	5.72	.000
Abdominal obesity[b]	4.06	2.81	5.88	.000	4.95	3.02	8.11	.000	5.12	2.71	9.66	.000
Glucose ≥100 mg/dL	1.63	1.15	2.32	.030	2.02	1.30	3.15	.002	2.35	1.30	4.25	.004
Low HDL level[c]	1.46	1.04	2.05	.030	1.77	1.18	2.60	.006	1.66	1.00	2.77	.052
Triglyceride level ≥150 mg/dL	1.60	1.15	2.22	.005	1.75	1.18	2.60	.006	1.29	0.78	2.13	.329
Type 2 diabetes	2.41	1.63	3.55	.000	2.07	1.32	3.25	.001	2.30	1.33	3.98	.003

NOTE. Logistic multivariate regression using dichotomized liver stiffness as a dependent variable. All variables mutually adjusted for age and sex.
AST, aspartate aminotransferase; HDL, high-density lipoprotein; OR, odds ratio; ULN, upper limit of normal.
[a]ULN was 40 U/L.
[b]Waist circumference ≥102 cm in men or ≥88 cm in women.
[c]HDL<40 mg/dL in men or <50 mg/dL in women.

CABALLERIA L, *et al,* Clin Gastroenterol Hepatol 2018;16:1138-1145

Disease activity and fibrosis progression of NAFLD

Prospective longitudinal hospital-based cohort study (n=52, biopsies at baseline and after 36 months)

NAFLD activity score at month 36	<3	3–4	≥5	Total
NAFLD activity score at baseline				
<3	12	16	1	29
3–4	5	10	3	18
≥5	0	5	0	5
Total	17	31	4	52

38%

Month 36	F0	F1	F2	F3	F4	Total
Baseline						
F0	17	7	0	1	1	26
F1	7	7	1	2	0	17
F2	4	1	0	1	1	7
F3	0	0	1	0	0	1
F4	0	0	0	0	1	1
Total	28	15	2	4	3	52

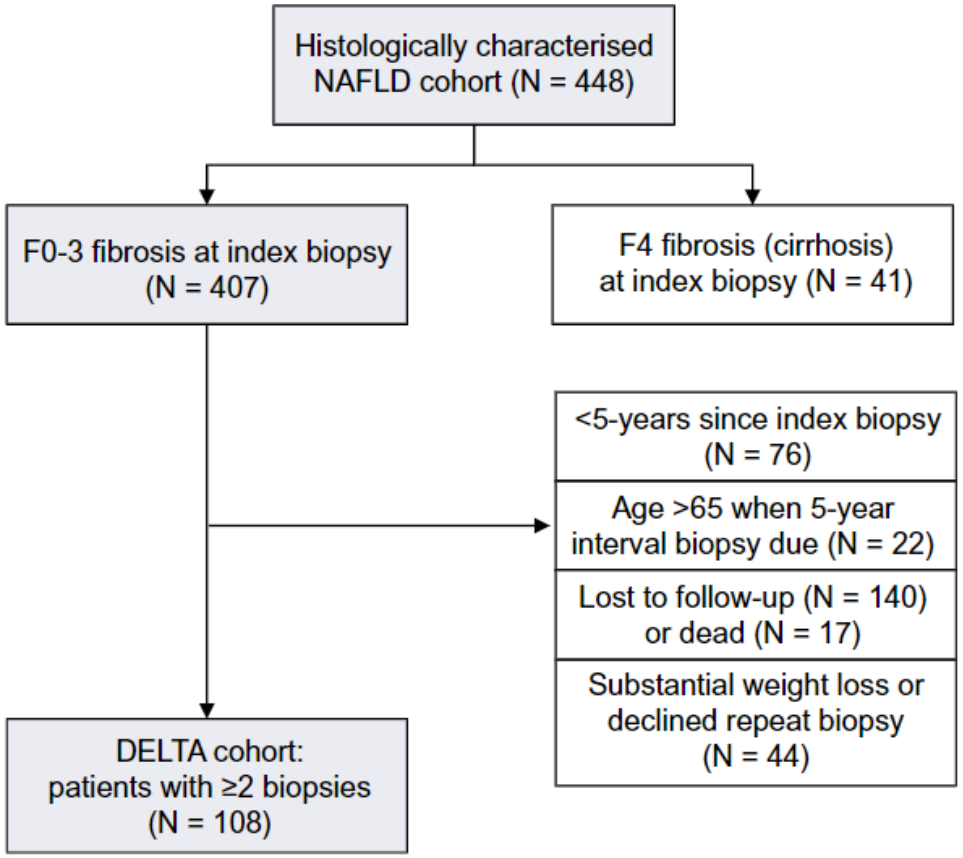
27%

WONG VW, *et al*, Gut 2010;59:969-74

Disease activity and fibrosis progression of NAFLD

Hospital-based cohort study on repeated liver biopsies

(n=108 patients with ≥2 biopsies, median interval 6.6 yrs [range 1.3-22.6] out of 448 patients)



Baseline disease activity	Follow-up disease activity			
	Bland steatosis	Steatosis and mild inflammation	NASH	Total
Bland steatosis	7	**6**	**4**	17
Steatosis and mild inflammation	2	0	**8**	10
NASH	5	1	75	81
Total	14	7	87	108

Numbers in **bold** indicate progression of disease activity.

↑17%

Baseline fibrosis	Follow-up fibrosis stage					
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Total
Stage 0	16	**4**	**1**	**2**	**0**	23
Stage 1	6	7	**3**	**11**	**2**	29
Stage 2	1	7	11	**11**	**3**	33
Stage 3	0	2	4	9	**8**	23
Stage 4	0	0	0	0	0	0
Total	23	20	19	33	13	108

Numbers in **bold** indicate fibrosis progression.

↑42%

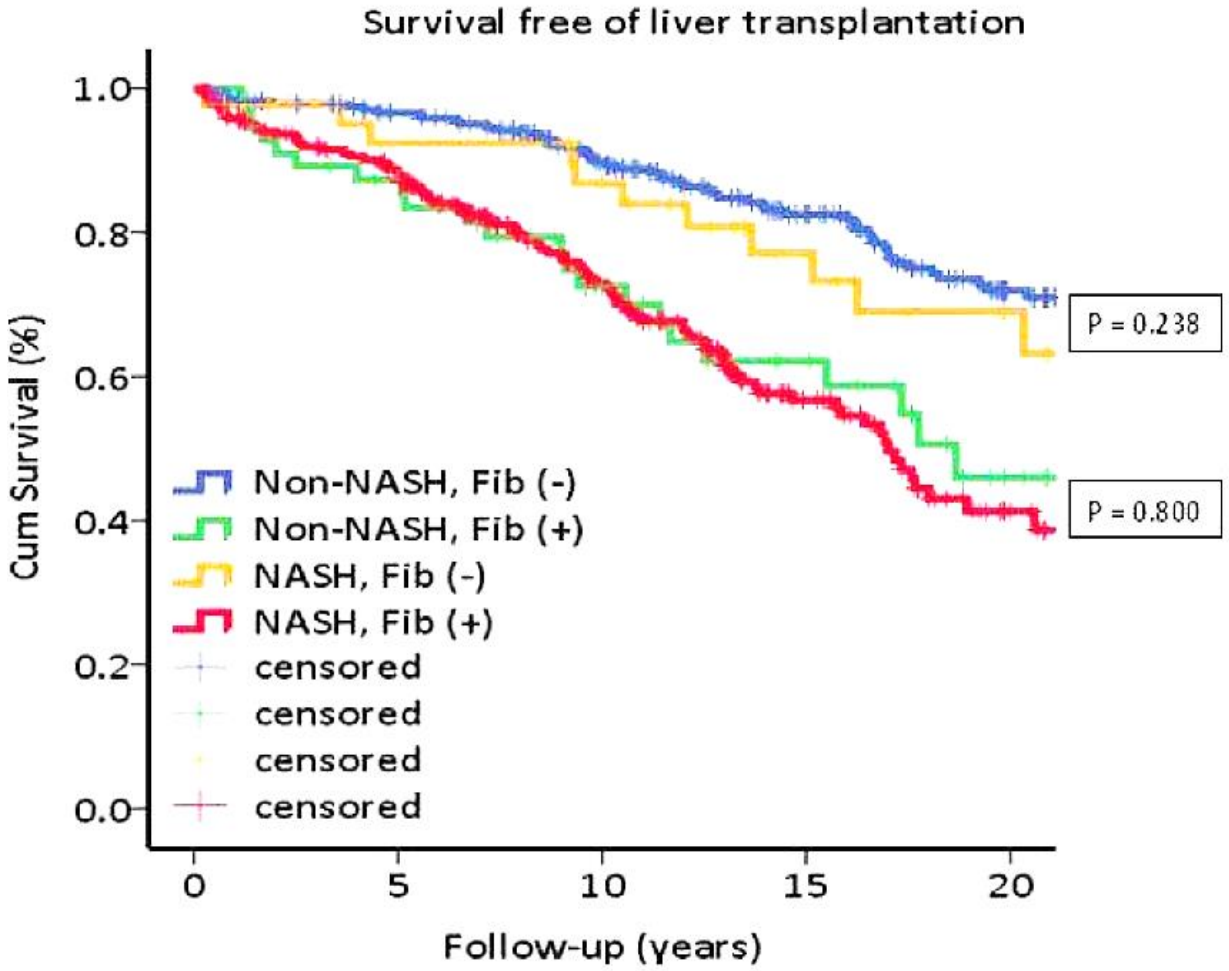
Bland steatosis may progress to NASH (80% had diabetes)

No difference in the proportion with fibrosis progression between those with NAFL or NASH at index biopsy (37% vs. 43%, p=0.65)

MCPHERSON S, *et al*. J Hepatol 2015;62:1148-55

Fibrosis, not NASH, predicts survival

Retrospective study, n=619 NAFLD, 1975-2005, US + Europe + Thailand, FU 12.6 yrs

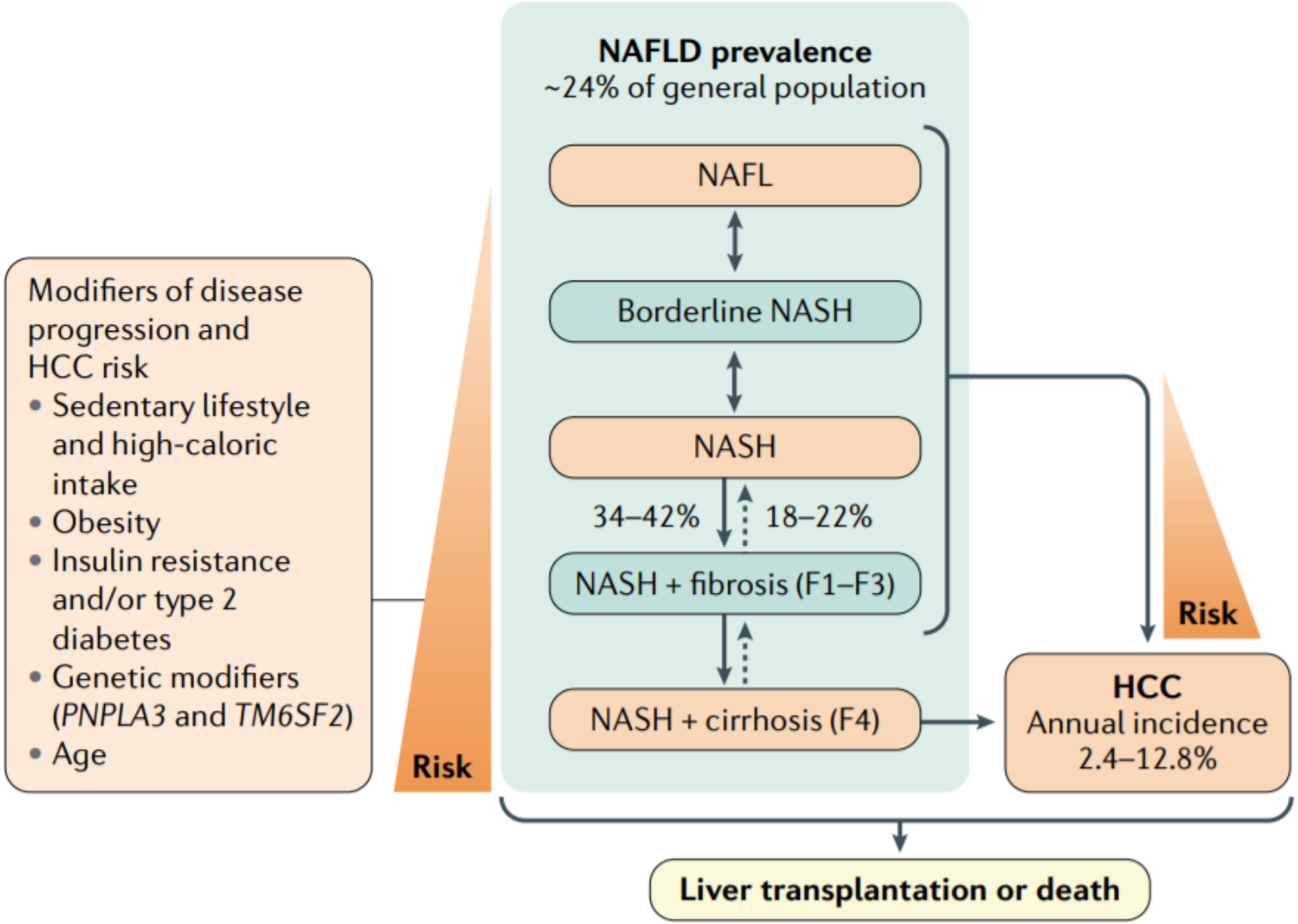


Causes of death: cardiovascular 38%, cancer 19%, cirrhosis 8%, HCC 1%

Independent predictors : fibrosis, diabetes, smoke, no statins

ANGULO *et al,* Gastroenterology 2015

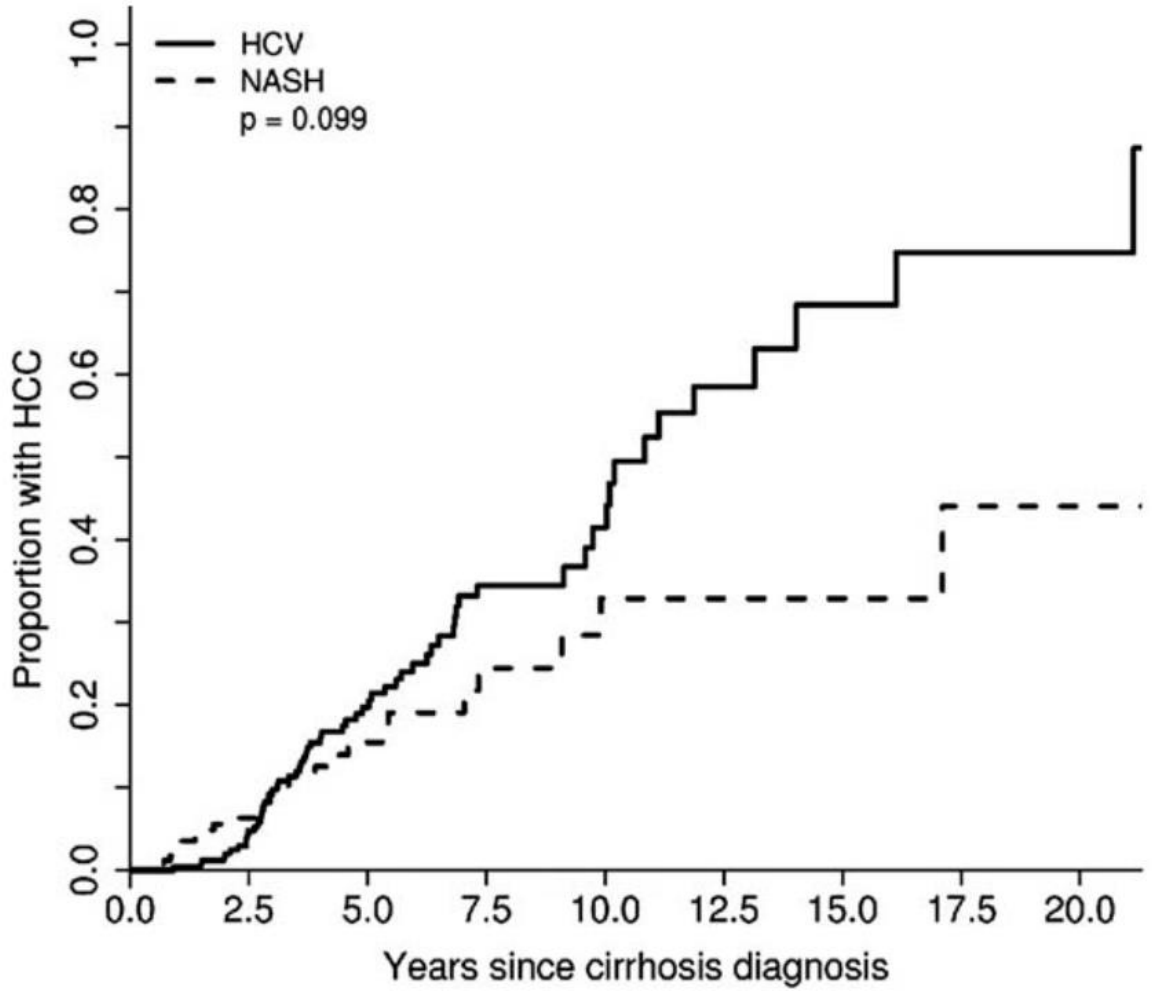
From NAFL to NASH + fibrosis/cirrhosis to HCC



ANSTEE Q, et al. Nat Rev Gastroenterol Hepatol 2019;16:411-428

Incidence of HCC in NAFLD-related cirrhosis is lower than among HCV

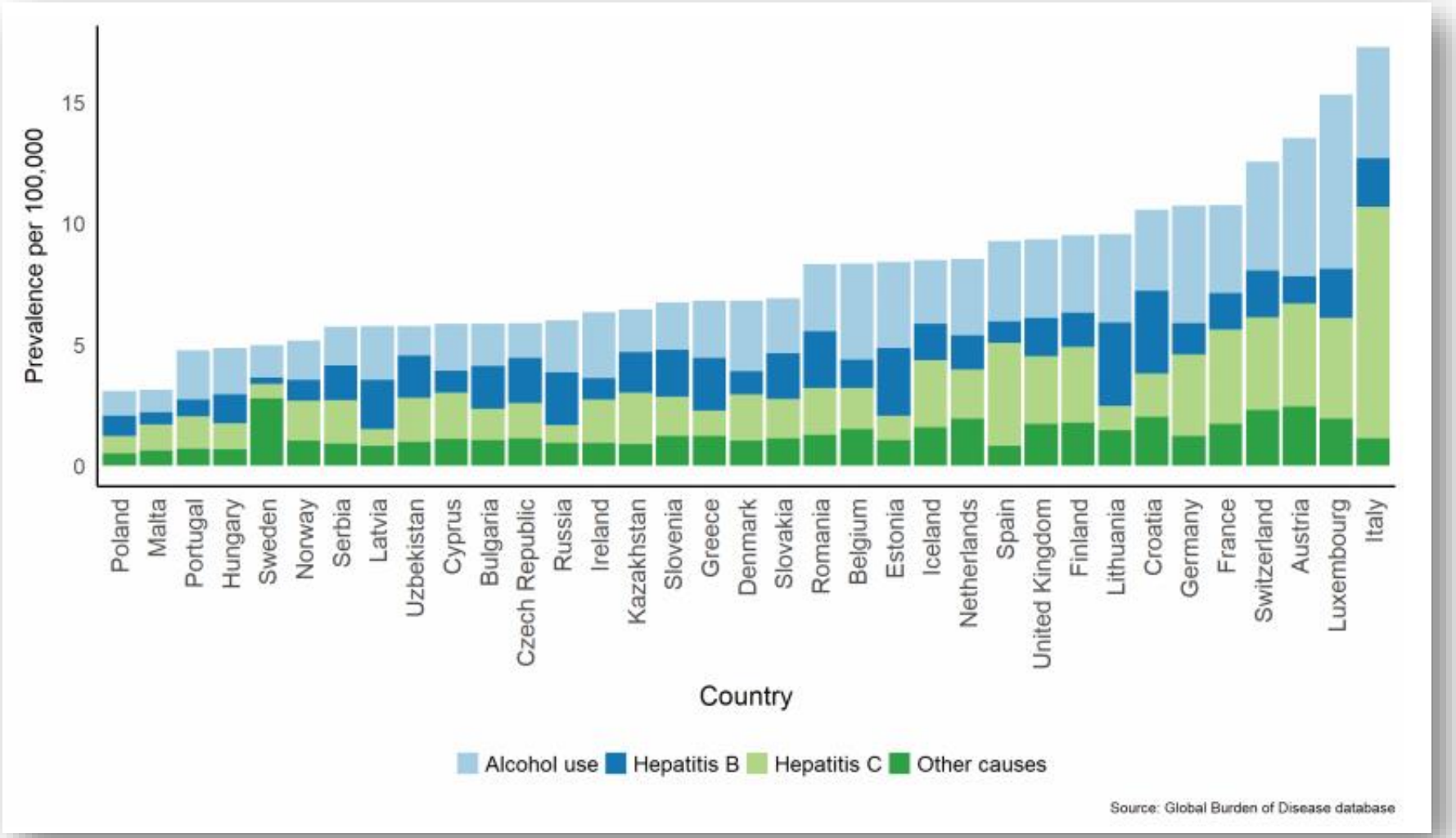
(Cleveland Clinic, n=315 HCV and 195 NASH, referred for LT, median FU 3.2 yrs, IQR 1.7-5.7)



ASCHA MS, *et al.* 2010;51:1972-8

Non-viral-, non-alcohol-related HCC in Europe

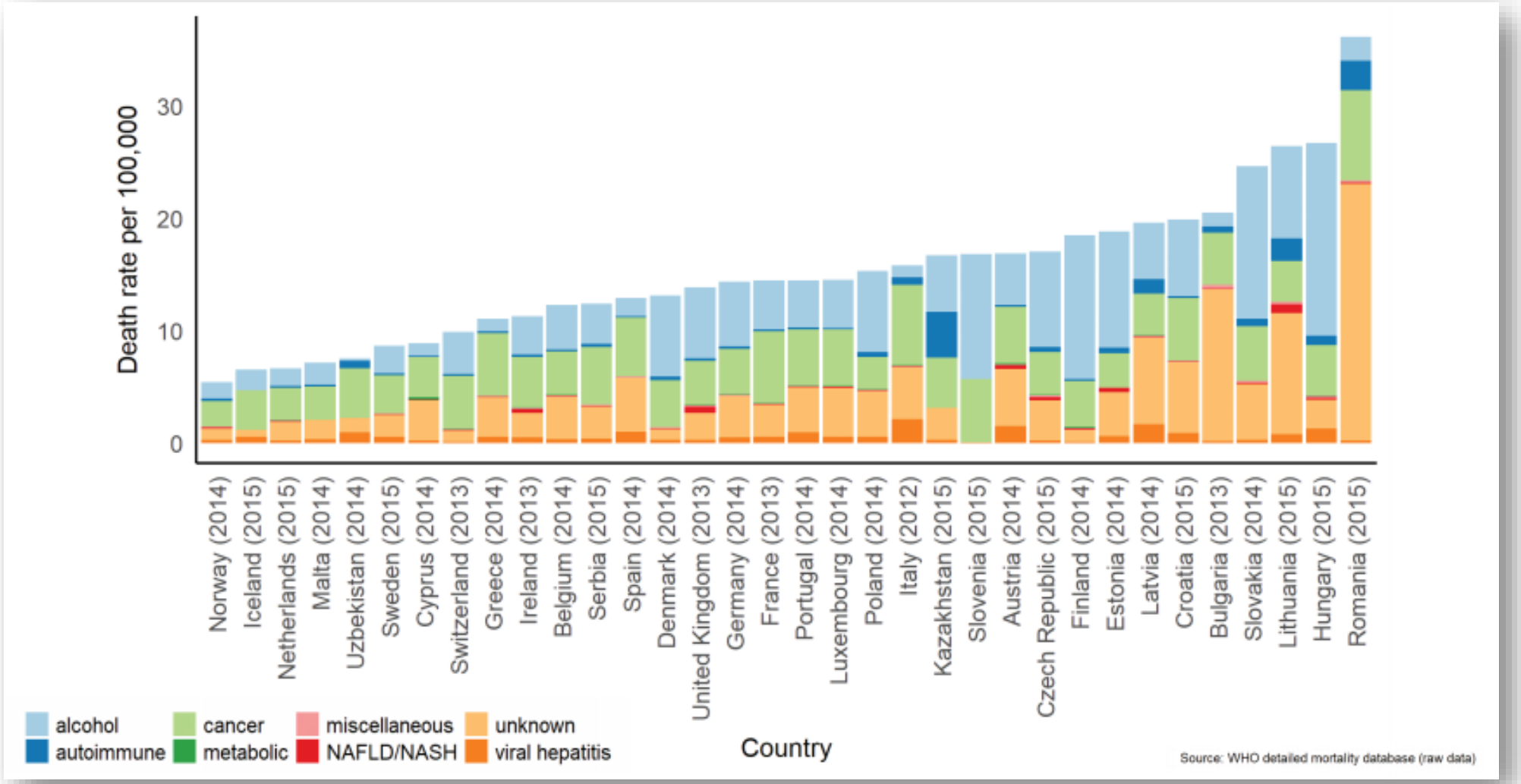
(modelled data, 2016, The HEPAHEALTH I Project)



https://easl.eu/wp-content/uploads/2018/09/EASL-HEPAHEALTH-Report.pdf

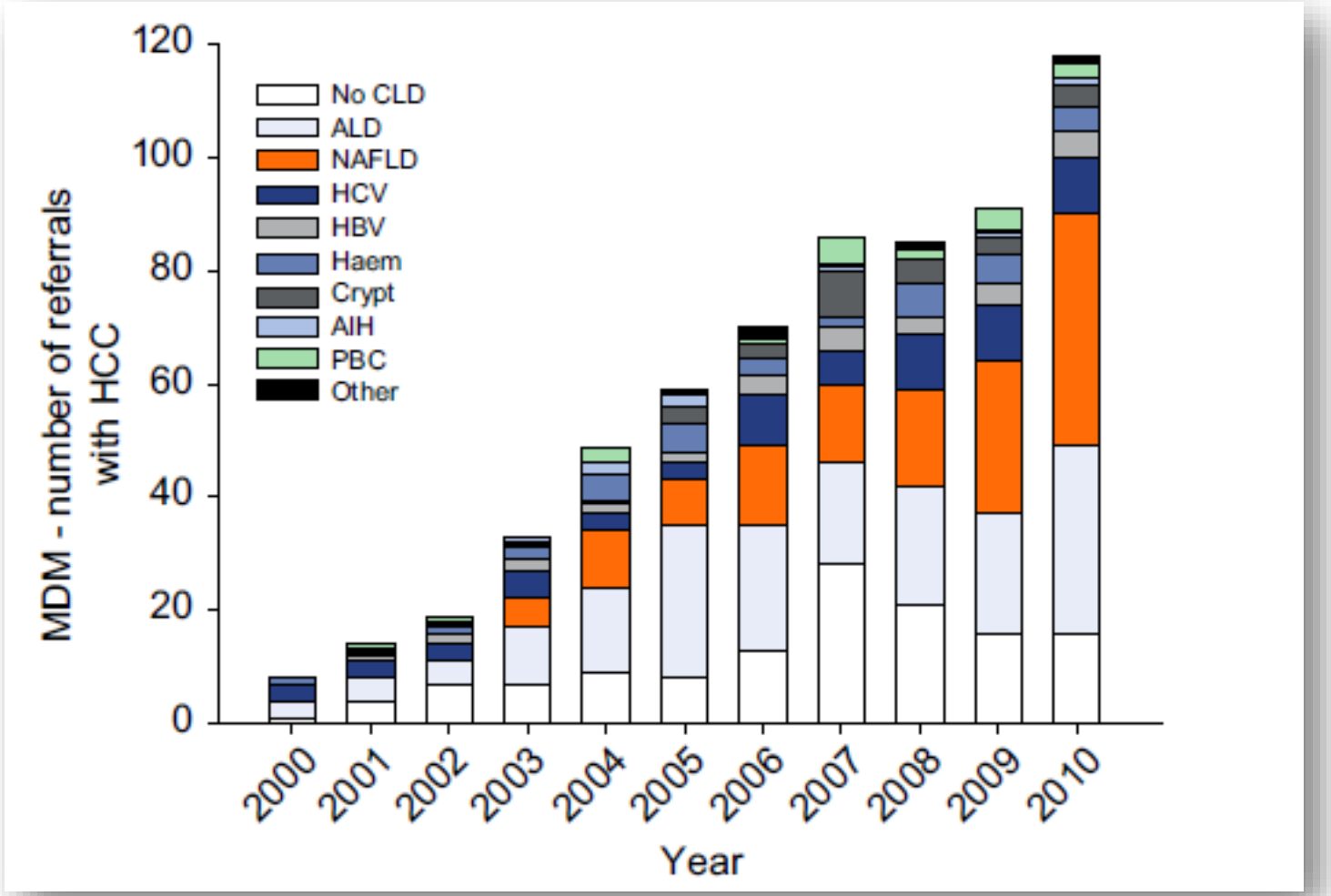
Age standardised liver disease-related mortality in Europe, by aetiology

(most recent year available, The HEPAHEALTH I Project)



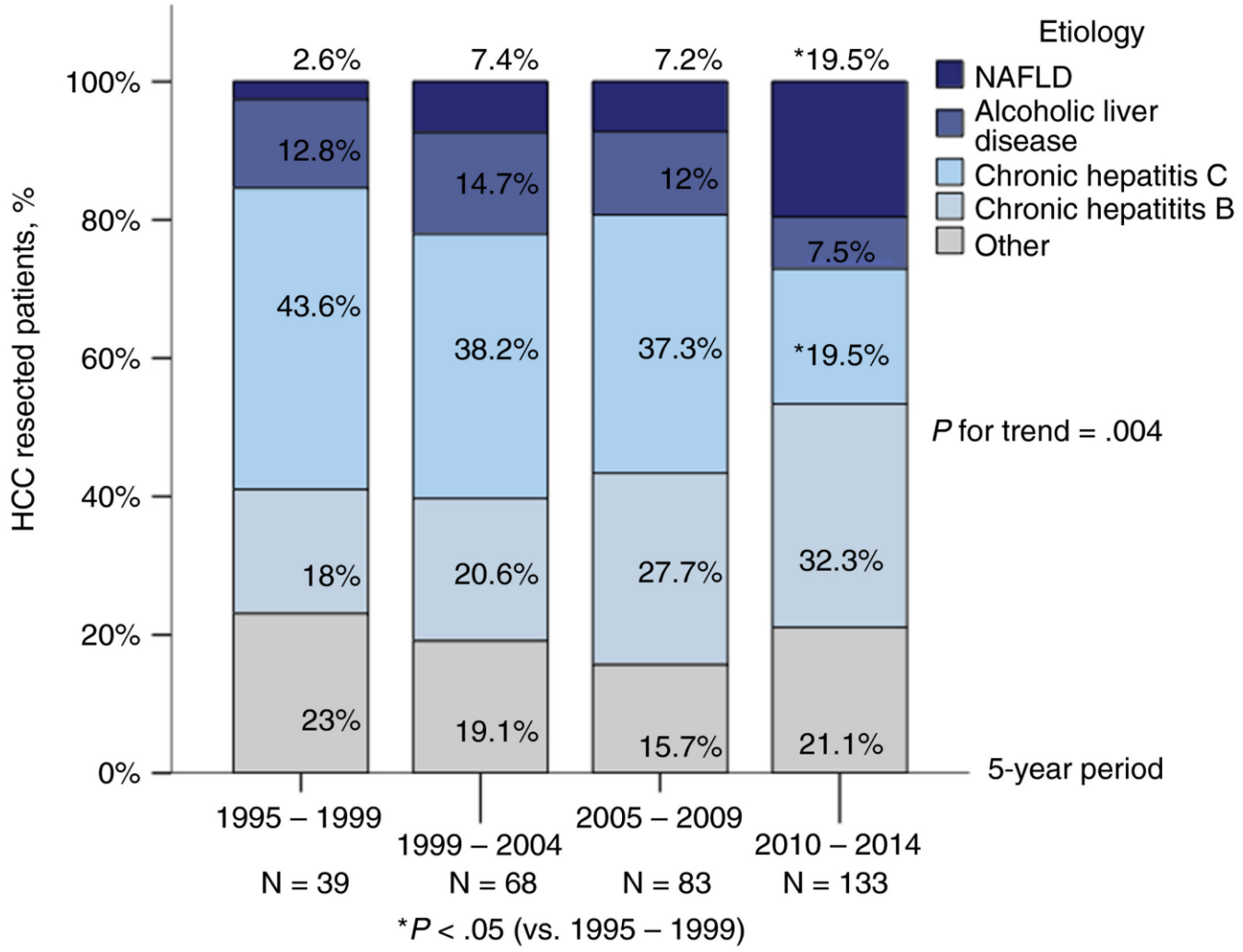
https://easl.eu/wp-content/uploads/2018/09/EASL-HEPAHEALTH-Report.pdf

The proportion of HCC attributable to NAFLD in Newcastle was 34.8% in 2010, i.e. a tenfold increase compared to 2000



DYSON J, *et al.* J Hepatol 2014;60:110-7

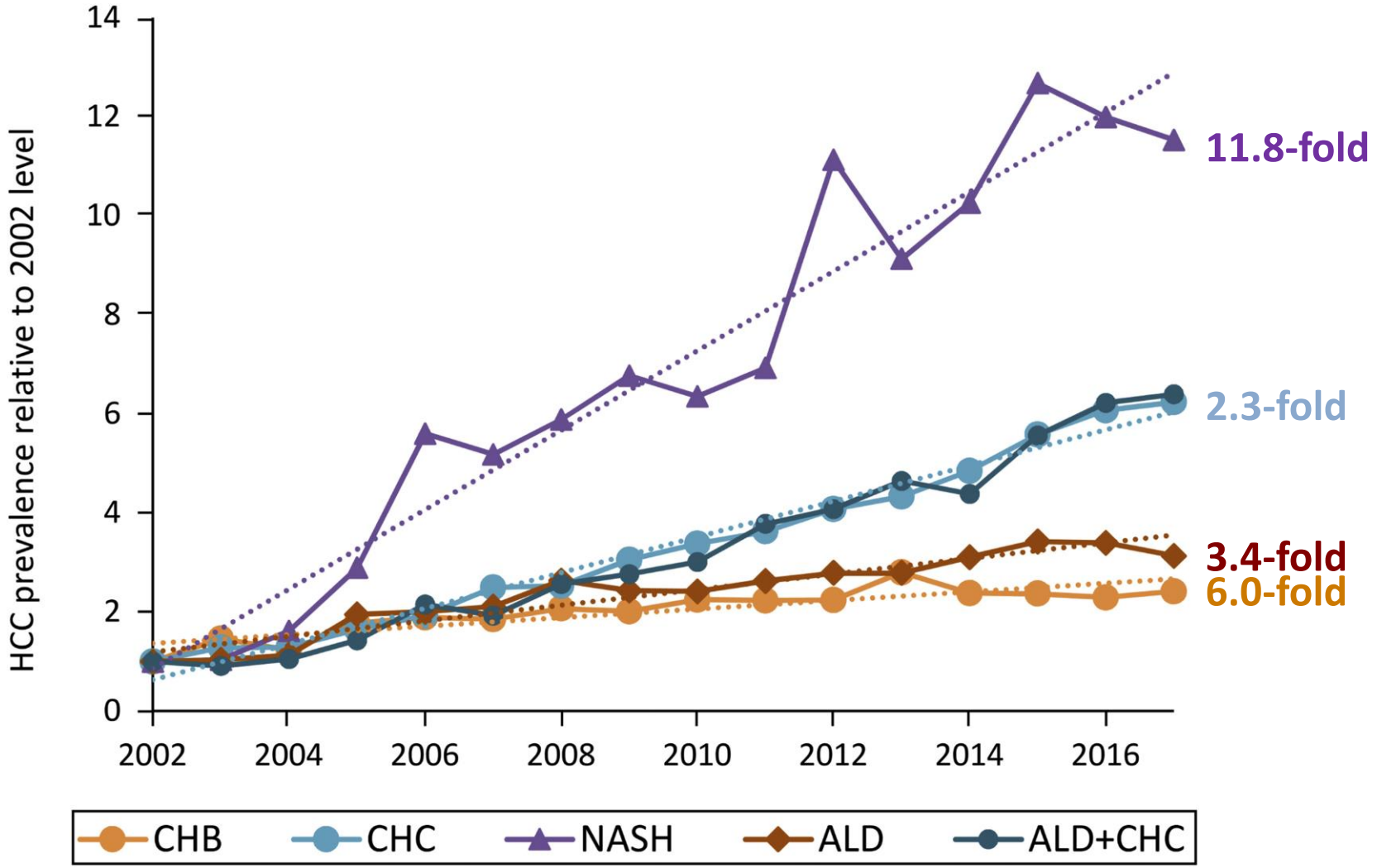
NAFLD-related HCC in patients undergoing liver resection (1995-2014)



PAIS R, *et al.* Aliment Pharmacol Ther 2017;46:856-863

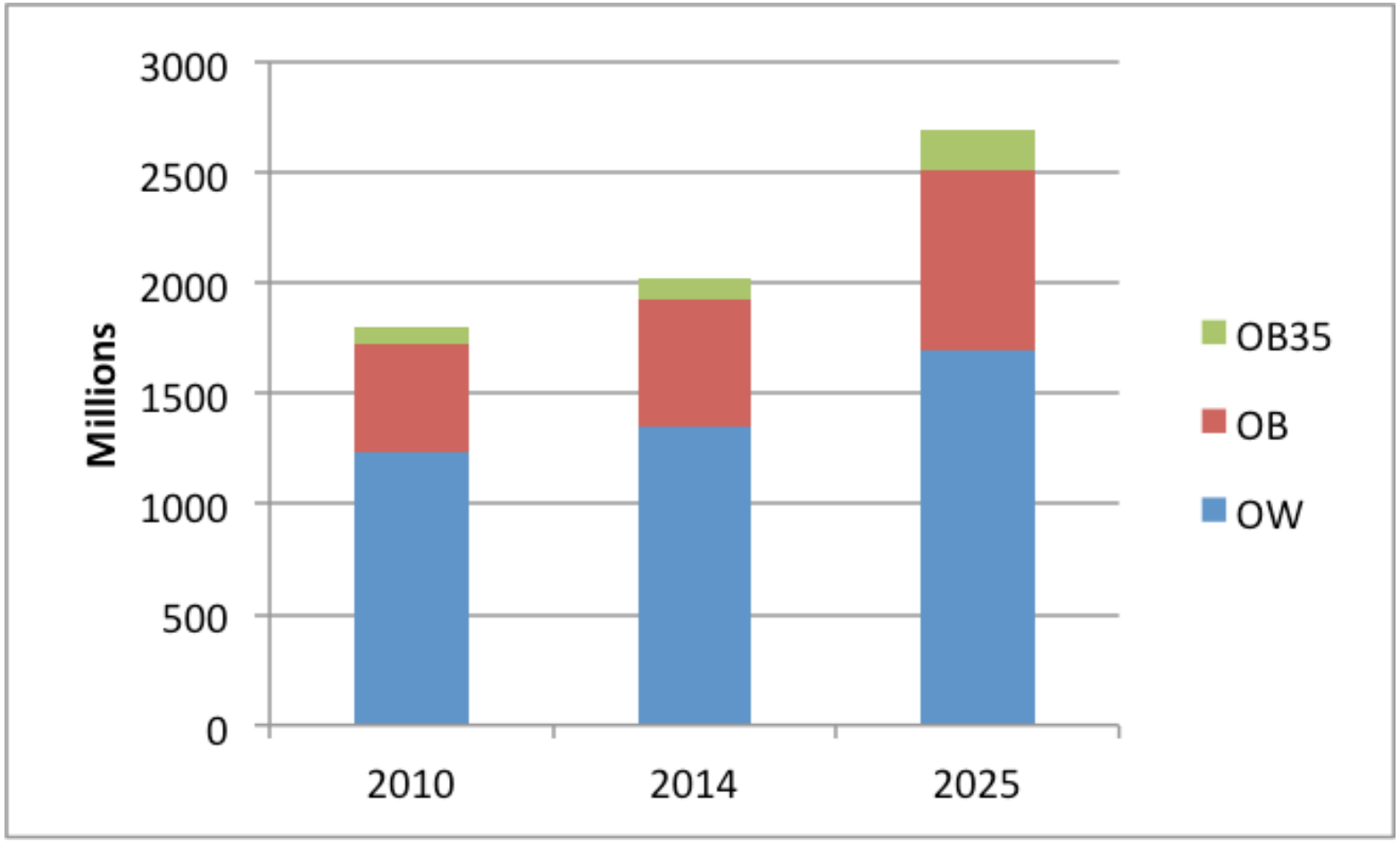
NASH is the fastest growing cause of HCC in liver transplant candidates

(US SRTR, n = 26,121 HCC in 158,347 adult LT candidates, 2002-2016)



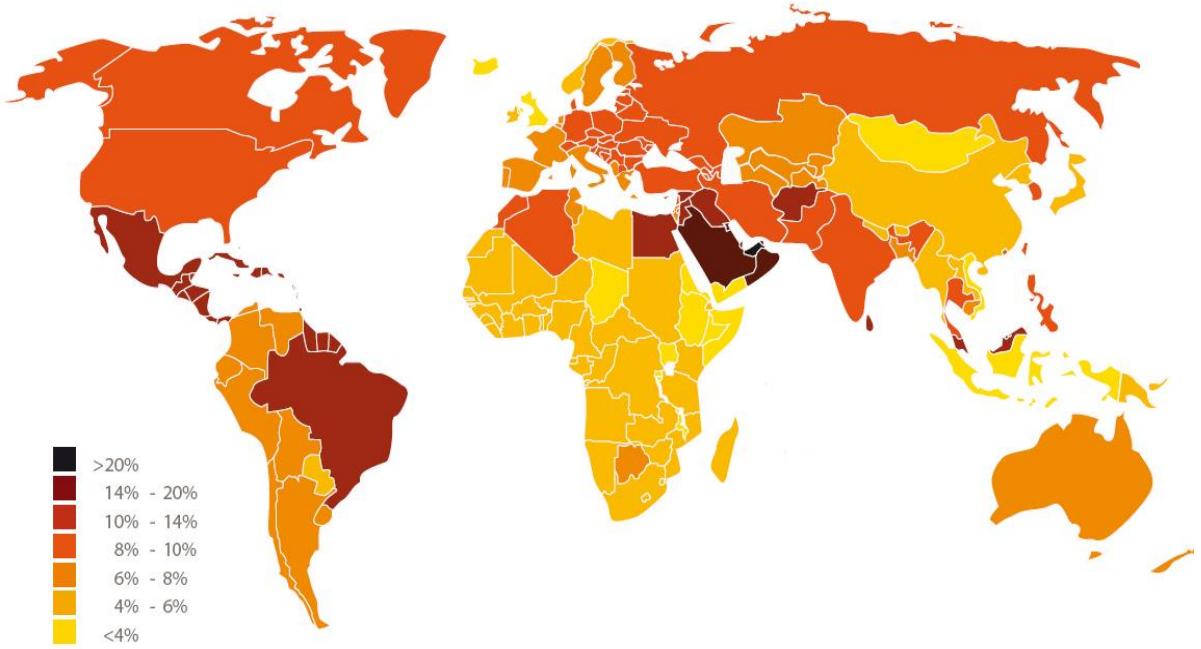
YOUNOSSI Z, *et al.* Clin Gastroenterol Hepatol 2019;17:748-755

Trends for global overweight, obesity and severe obesity



http://blog.wcrf.org/wp-content/uploads/2015/09/WOGraph.png

Diabetes in 2010

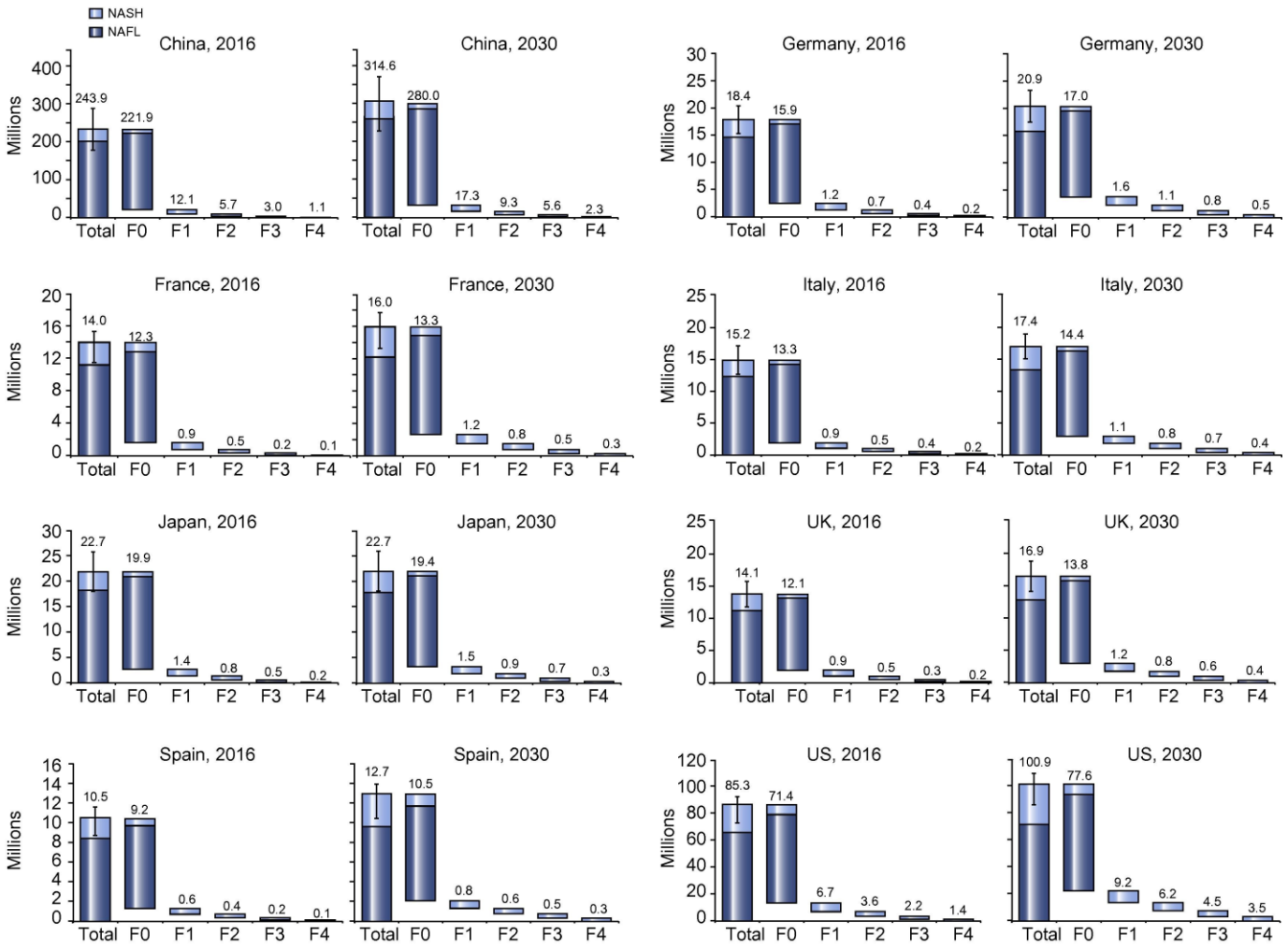


Diabetes in 2025

Source: www.who.org

Modeling NAFLD disease burden for the period 2016–2030

A Markov model for China, France, Germany, Italy, Japan, Spain, UK and the US

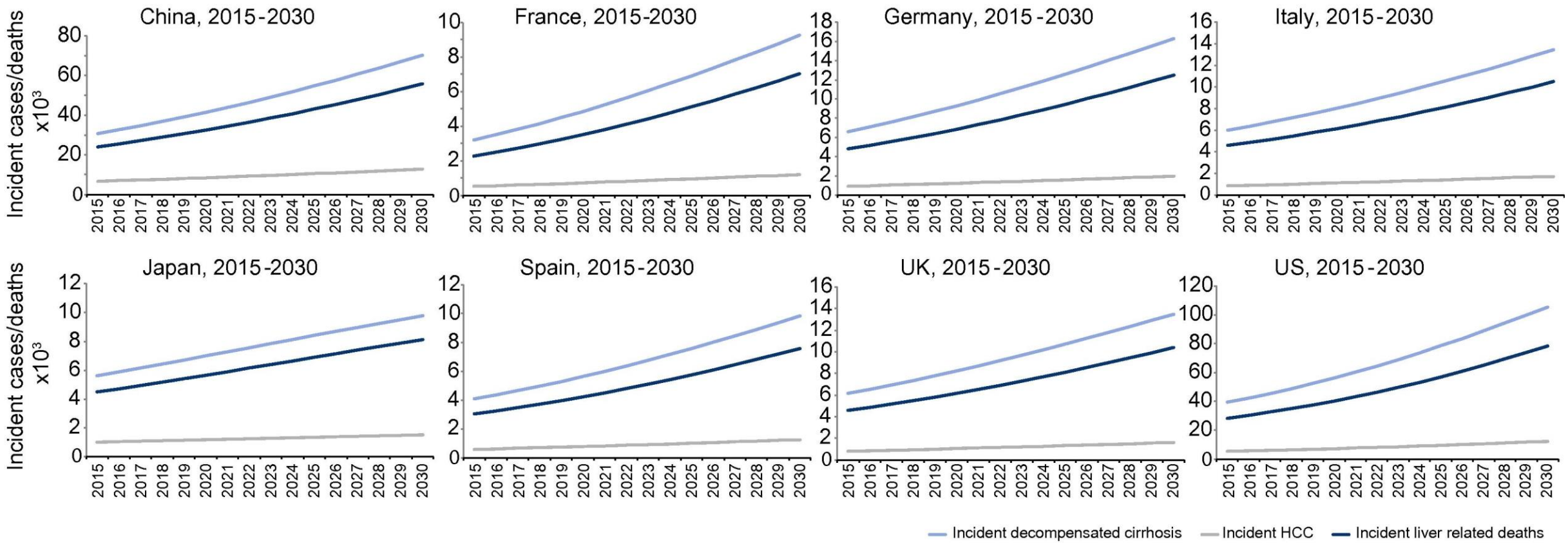


In countries with 30%
of the global population
severe fibrosis cases related to NAFLD
would increase
from 10.7 million (2016)
to 22.9 million (2030)

ESTES C, *et al.* J Hepatol 2018;69:896-904

Modeling NAFLD disease burden for the period 2016–2030

A Markov model for China, France, Germany, Italy, Japan, Spain, UK and the US

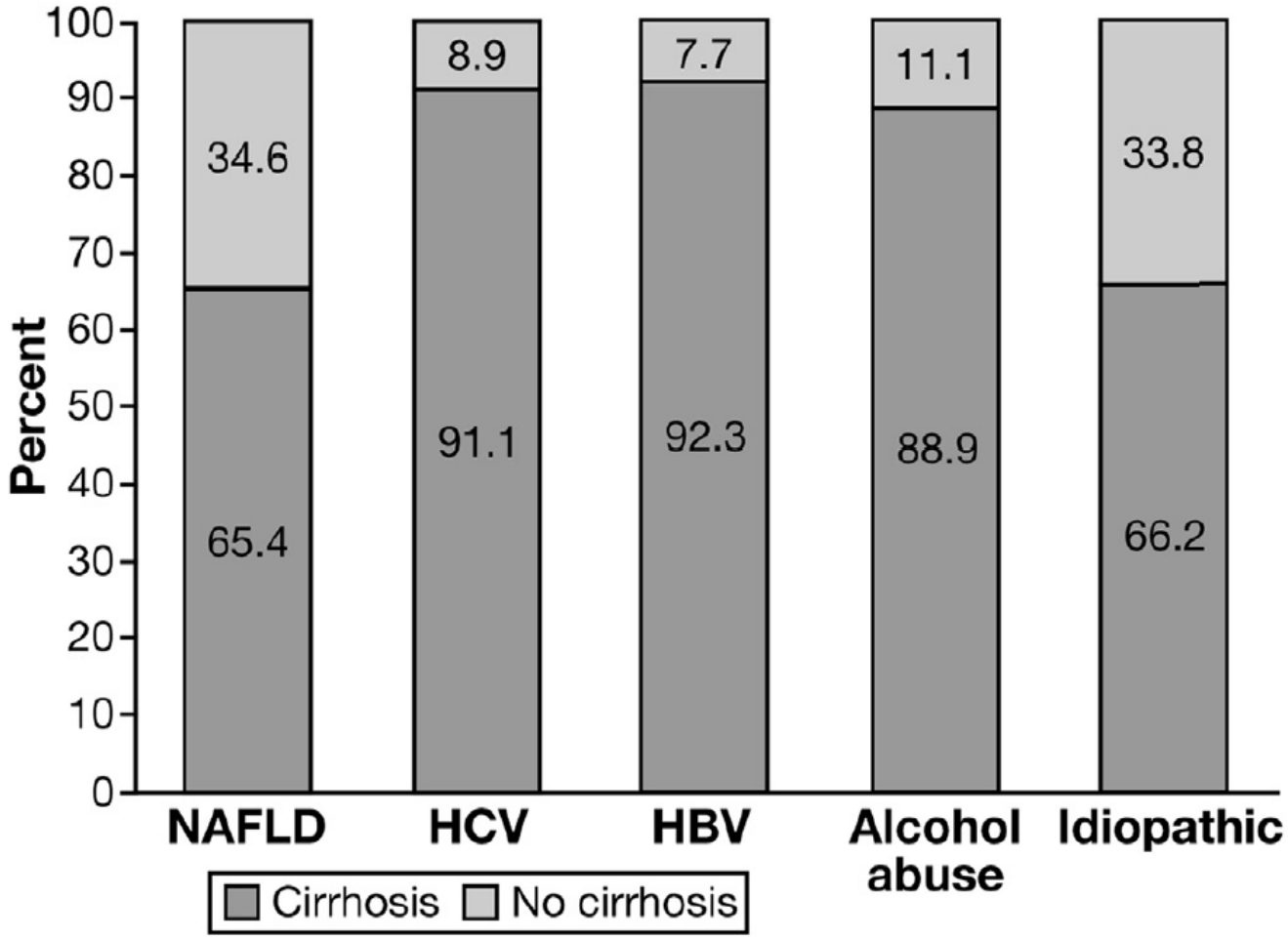


NAFLD liver-related deaths will increase from 2016 to 2030 between 73% (Japan) and 182% (France)

ESTES C, *et al.* J Hepatol 2018;69:896-904

Proportion of HCC patients with (n=1203) or without (n=194) cirrhosis

Retrospective VA cohort diagnosed with HCC from 2005 to 2010



Patients with HCC and NAFLD or metabolic syndrome **had >5-fold risk of having HCC in the absence of cirrhosis** compared with patients with HCV-related HCC

MITTAL *et al,* Clin Gastroenterol Hepatol 2016;14:124–131

The trouble with non-cirrhotic, NAFLD-associated HCC

(Italian multicenter prospective observational study, n=656)

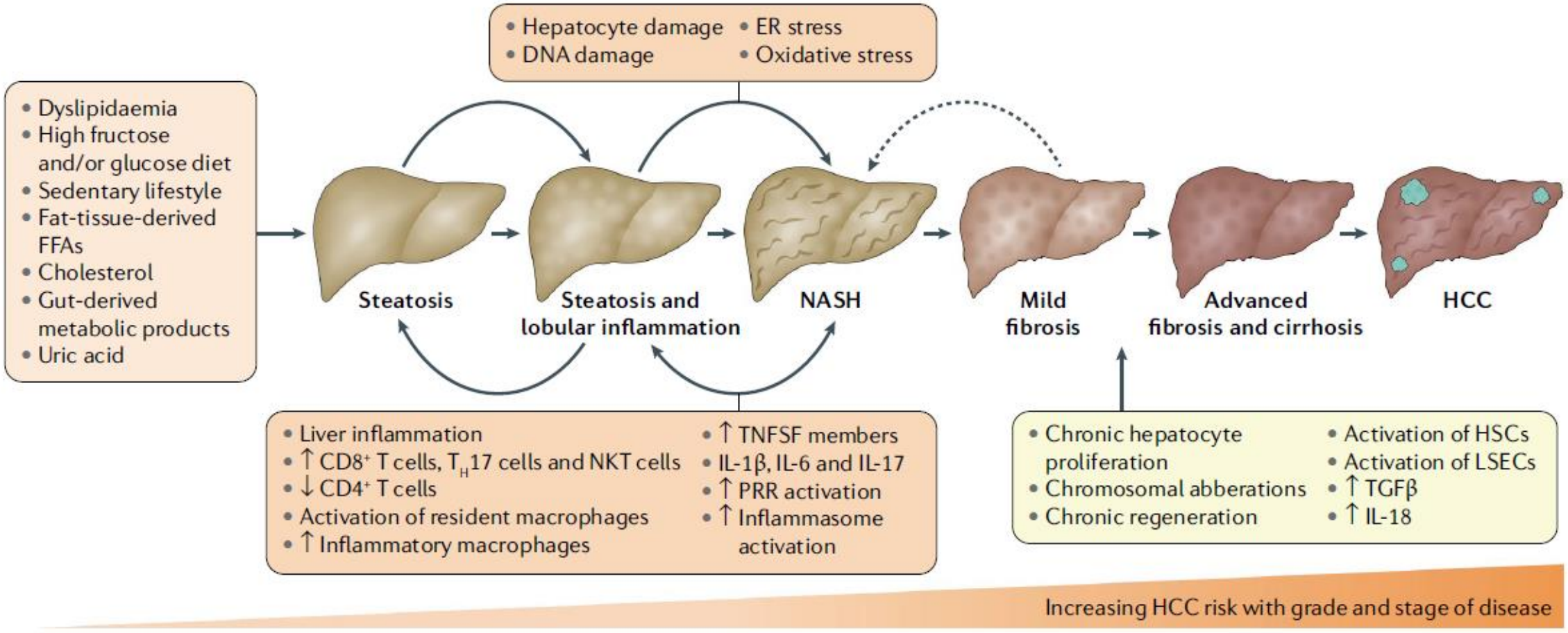
- As many as 53.8% of HCC occurred in the absence of cirrhosis
- Compared to HCV-HCC (n=611), NAFLD-HCC (n=145) were:
  - Younger (67.8 ± 9.0 versus 71.1 ± 9.5 years, p<.0001)
  - Less frequently diagnosed during surveillance programs (47.7% vs. 63.3%)
  - Larger (4.1 ± 2.6 cm vs. 3.3 ± 2.9 cm, p=.003)
  - Less frequently within Milan criteria (55.2% vs. 68.4%, p=.005)
  - Less frequently BCLC stage 0 (0% vs. 11.1%, p<.0001)
  - More frequently showing infiltrative pattern (15.4% vs. 4.0%, p<.0001)

However:

The overall rate of patients submitted to curative treatments (resection, LTx, percutaneous ablation)
was similar in the two groups (45.5% versus 49.1% in HCV-HCC, p=NS)

PISCAGLIA F, *et al.* Hepatology 2016;63:827-38

The risk of HCC progresses together with the progression of NAFLD grade and stage



ANSTEE Q, et al. Nat Rev Gastroenterol Hepatol 2019;16:411-428

Features of NAFLD- *vs.* HCV-associated HCC

(US VA cohort, n= 1133 and Italian multicenter prospective observational study, n=656)

	US VA			Italy		
	NAFLD (n=120)	HCV (n=1013)	P	NAFLD (n=145)	HCV (n=611)	p
Age	74.7	60.2	<.01	67.8	71.1	<.0001
Male	99%	100%	NS	79.3%	61.2%	<.0001
Diabetes	89.2%	32.9%	<.01	73.1%	24.9%	<.0001
BMI	na	na	na	29.1	27.6	NS
Hypertension	95.8%	69.9%	<.01	73.1%	37.1%	<.0001

MITTAL S, *et al.* Clin Gastroenterol Hepatol 2015;13:594-601
PISCAGLIA F, *et al.* Hepatology 2016;63:827-38

Obesity is a risk factor for HCC in cryptogenic and alcoholic cirrhosis

(but not in HCV, HBV or autoimmune)

(n=19,271, of whom 5,358 obese; UNOS database 1991-2000)

Table 4. Multivariate Analysis of HCC Incidence

	OR	95% CI	*P* Value
Age	1.04	1.02-1.06	.0001
Sex (indicator female)			
Male	2.57	1.86-3.55	.0001
Race (indicator white)			
Black	0.59	0.25-1.32	NS
Hispanic	0.95	0.58-1.55	NS
Asian	3.55	2.14-5.19	.0001
Obesity*			
BMI >30 kg/m^2	1.65	1.22-2.22	.002
Diabetes status	1.48	1.07-2.03	.007
Waiting time	1.02	1.01-1.03	.0001

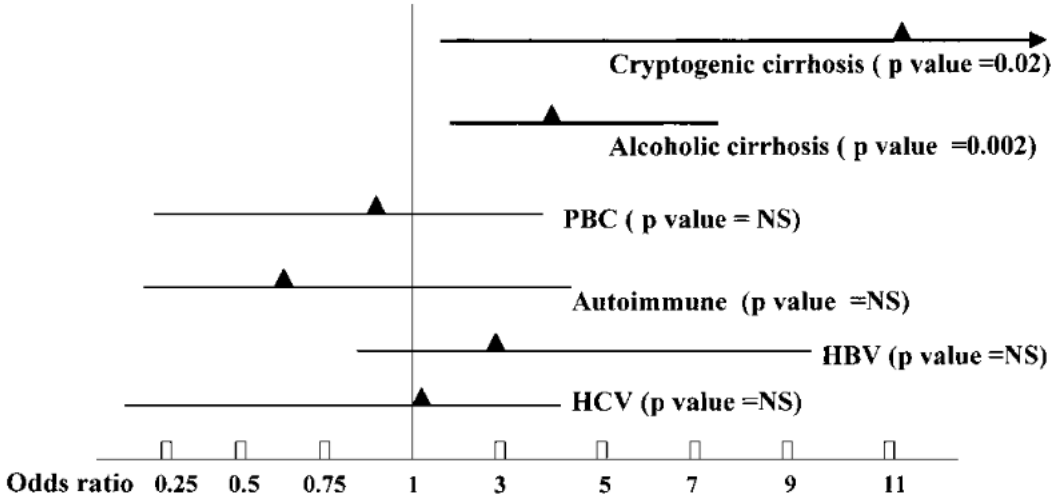


Fig. 1. Multiple regression analysis showing the ORs for obese (BMI, >30 kg/m^2) versus lean (BMI, <25 kg/m^2) patients with different liver diseases after controlling for age, sex, diabetes status, and waiting time. Obesity is an independent predictor only in alcoholic and cryptogenic cirrhosis. PBC, primary biliary cirrhosis; NS, not significant; HBV, hepatitis B virus; HCV, hepatitis C virus.

NAIR S, *et al.* Hepatology 2002;36:150-5

Obesity is a risk factor for HCC in cryptogenic and alcoholic cirrhosis

(but not in HCV, HBV or autoimmune)

(n=19,271, of whom 5,358 obese; UNOS database 1991-2000)

Table 4. Multivariate Analysis of HCC Incidence

	OR	95% CI	*P* Value
Age	1.04	1.02-1.06	.0001
Sex (indicator female)			
Male	2.57	1.86-3.55	.0001
Race (indicator white)			
Black	0.59	0.25-1.32	NS
Hispanic	0.95	0.58-1.55	NS
Asian	3.55	2.14-5.19	.0001
Obesity*			
BMI >30 kg/m^2	1.65	1.22-2.22	.002
Diabetes status	1.48	1.07-2.03	.007
Waiting time	1.02	1.01-1.03	.0001

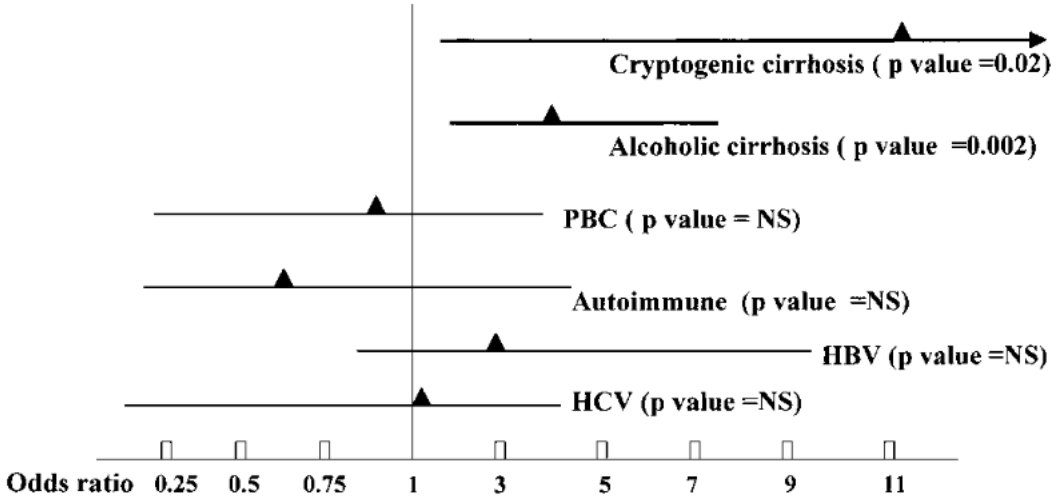


Fig. 1. Multiple regression analysis showing the ORs for obese (BMI, >30 kg/m^2) versus lean (BMI, <25 kg/m^2) patients with different liver diseases after controlling for age, sex, diabetes status, and waiting time. Obesity is an independent predictor only in alcoholic and cryptogenic cirrhosis. PBC, primary biliary cirrhosis; NS, not significant; HBV, hepatitis B virus; HCV, hepatitis C virus.

NAIR S, *et al.* Hepatology 2002;36:150-5

Diabetes is a risk factor for HCC in NAFLD-related cirrhosis

N=354 cirrhoses who developed 30 HCC across a 47 months FU

	HR (95% CI)*	p
Age, per decade	1.8 (1.2 – 2.6)	<.01
Diabetes	4.2 (1.2 – 14.2)	.02
Serum albumin	0.48 (0.35 – 0.68)	<.001

*BMI, hyperlipidemia and hypertension were not associated with HCC risk

N=6,630 UNOS registrants with NAFLD cirrhosis, who developed 291 HCC across a median FU of 21 months

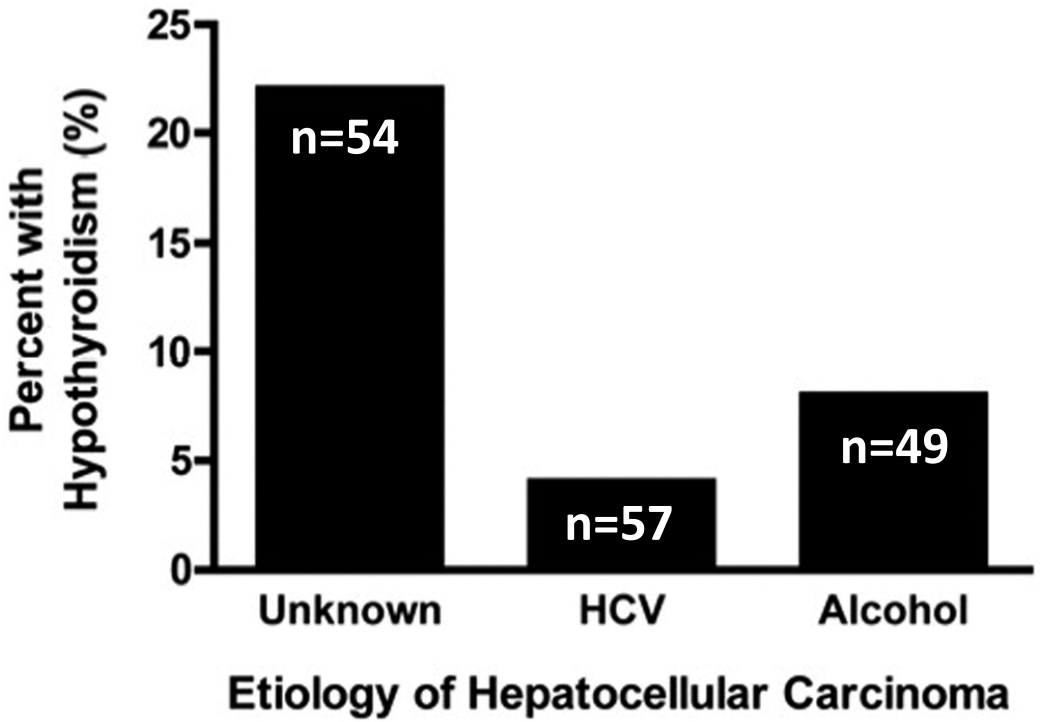
	HR (95% CI)*	p
Age, per decade	1.71 (1.45 – 2.05)	<.001
Male sex	1.71 (1.35 – 2.16)	<.001
Diabetes	1.30 (1.02 – 1.66)	.03
Low serum albumin	0.67 (0.54 – 0.82)	<.001

*BMI was not associated with HCC risk

YANG JD, *et al.* Hepatology 2002;36:150-5

Hypothyroidism as a risk factor of HCC in NAFLD independent of age and diabetes

Case-control study, Mayo Clinic



HCC of unknown etiology had a history of hypothyroidism:
aOR 12.7 (95% CI 1.4-117.1) compared to HCV
aOR 6.8 (95% CI 1.1-42.1) compared with all controls

REDDY A, *et al.* Clin Gastroenterol Hepatol 2007:118-23

Case-control study, MD Anderson Cancer Center

	Women		
Thyroid Variable	Case N = 121	Control N = 468	AOR (95% CI)‡
Thyroid condition			
None	80	380	1 (reference)
Hypothyroidism	33	60	2.8 (1.6-5.1)
Hyperthyroidism	3	6	2.4 (0.5-12.1)
Other thyroid conditions	5	22	1.0 (0.3-3.2)
Hypothyroidism duration			
≤ 2	2	8	2.6 (0.5-14.5)
3-10 years	10	20	2.6 (1.0-7.2)
> 10 years	19	32	2.9 (1.3-6.3)

OR adjusted for age, race, educational level, diabetes, smoking, alcohol consumption, HCV, HBV, and family history of cancer

HASSAN MM, *et al.* Hepatology 2009:49:1563-70

Factors suggesting genetic susceptibility in NAFLD

- Variability in response to obesity and insulin resistance
- Disorder clusters in family
- Liver enzyme levels are heritable
- Dallas Heart Study: prevalence varies among ethnic groups (Hispanics > Europeans > Africans)
- Lean NAFLD risk factors: ethnicity matters (Hispanics)

The effect of *PNPLA3* genotype on NAFLD-related HCC risk is independent of its role in fibrosis progression

(n=100 NAFLD-HCC and 275 non-HCC controls; UK + Switzerland)

Variables	OR (95% CI)	*p* value
PNPLA3 rs738409 genotype	2.26 (1.23-4.14)	0.0082
Age	1.24 (1.17-1.32)	<0.0001
Sex (Male)	11.11 (4.17-33.33)	<0.0001
BMI	0.94 (0.87-1.02)	0.148
Diabetes	2.33 (0.93-5.81)	0.070
Cirrhosis	9.37 (3.82-23.00)	<0.0001

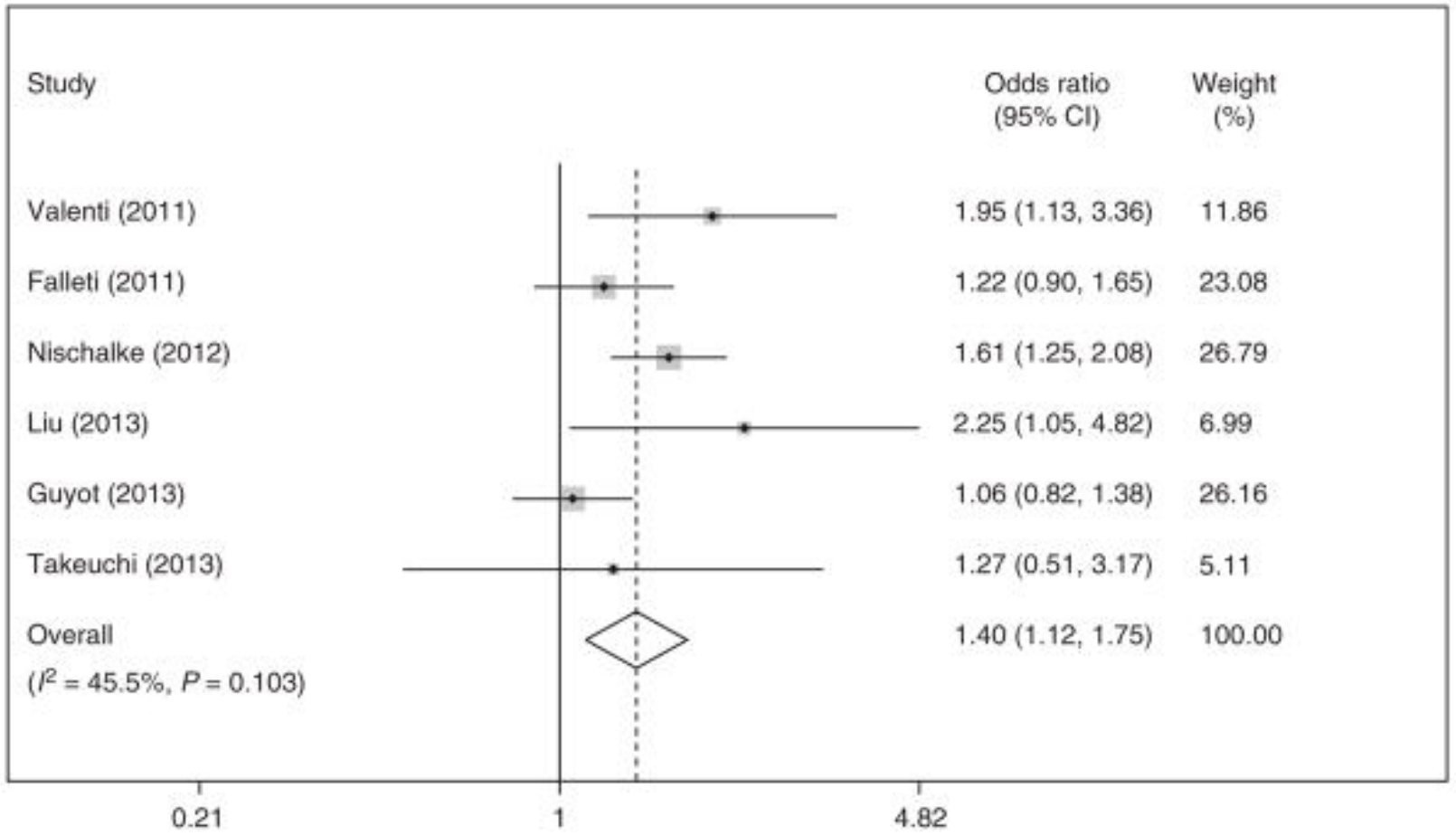
Additive model including age, gender, BMI, diabetes, and cirrhosis as covariates.

Carriage of each G allele is associated with a doubling of HCC risk

LIU *et al*, J Hepatol 2014;61:75-81

PNPLA3 rs738409 genotype and HCC (dominant model)

A meta-analysis (9 studies, 2,937 patients)



***PNPLA3* associated with HCC risk only among ALD and NAFLD, not HCV**

SINGAL AG *et al*, Am J Gastroenterol 2014;109:325-34

NAFLD and genetics: the EASL position (2016)

- Carriers of *PNPLA3* I148M and *TM6SF2* E167K have an increased risk of fatty liver (not necessarily associated with insulin resistance) and NASH (*PNPLA3*)
- Genotyping may be considered in selected patients or in clinical studies, but it is not recommended routinely (**B2**)
- Although NAFLD is a risk factor for HCC (also at pre-cirrhotic stages), and the risk is further increased by the *PNPLA3* rs738409 C>G polymorphism, no recommendation can be made at this stage on the timing of surveillance and its cost-effectiveness (**B1**)

https://easl.eu/publication/the-management-of-non-alcoholic-fatty-liver-disease-nafld/

TM6SF2 ? ***MBOAT1*** ? ***TERT*** promoter ?

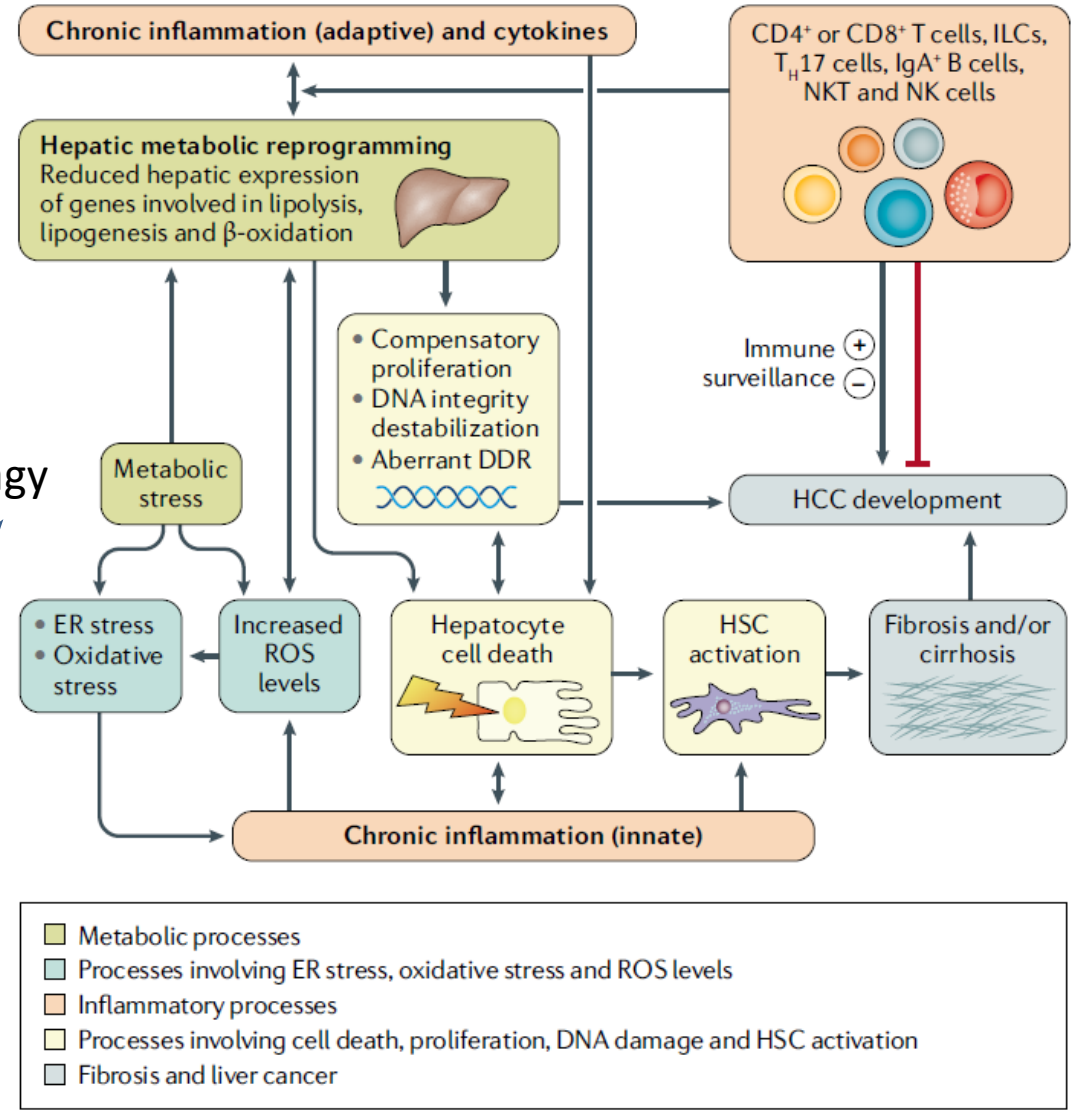
DONGIOVANNI P, *et al.* Hepatology 2015;61:506-14; DONATI B, *et al.* Sci Rep 2017;7:4492
ZUCMAN-ROSSI J, *et al.* Gastroenterology 2015;149:1226-39

Pathogenesis of NAFLD-associated HCC

FFA

mTOR

↓Autophagy



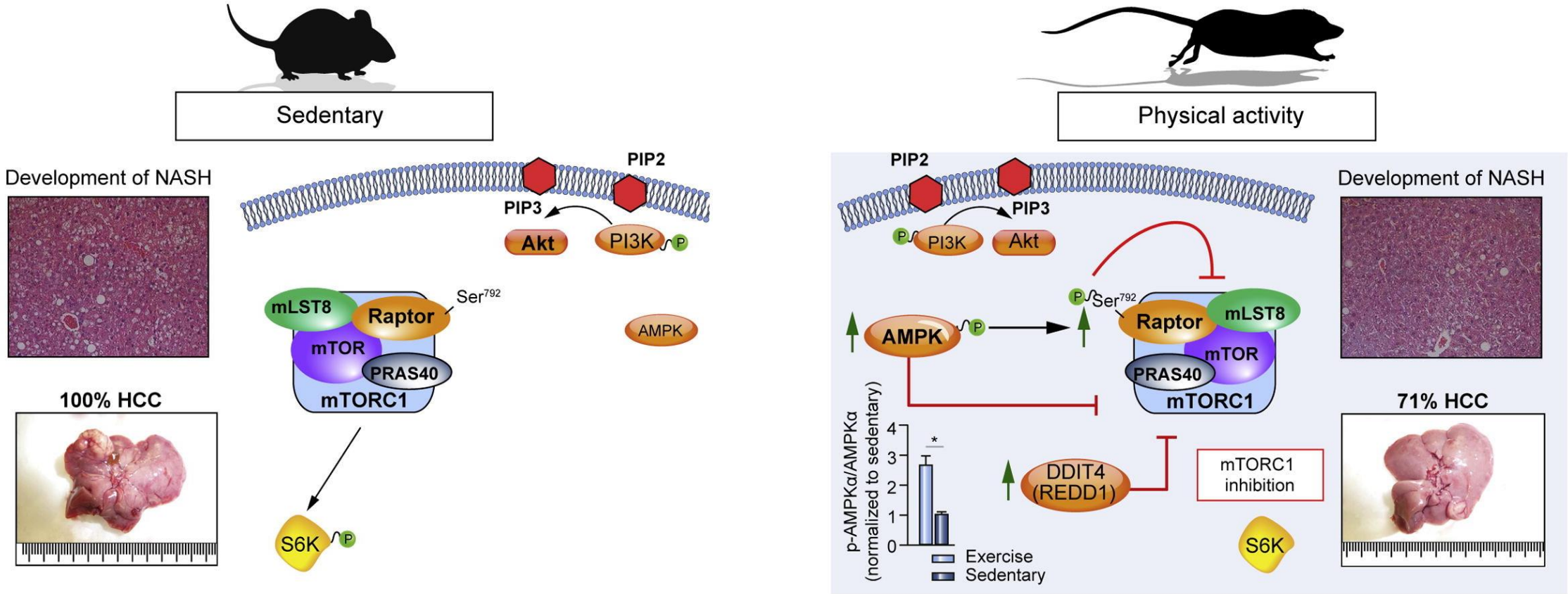
ANSTEE Q, et al. Nat Rev Gastroenterol Hepatol 2019;16:411-428

Regular exercise decreases liver tumors development in hepatocyte-specific PTEN-deficient mice independently of steatosis

- Hepatocyte-specific PTEN-deficient mice (AlbCrePten[flox/flox]), which spontaneously develop steatohepatitis and HCC
- Fed standard 10% fat diet
- Randomly divided into exercise or sedentary groups
- The exercise group ran on a motorized treadmill for 60 min/day, 5 days/week for 32 weeks

PIGUET AC, *et al.* J Hepatol 2015;62:1296-303

Regular exercise decreases liver tumors development in hepatocyte-specific PTEN-deficient mice independently of steatosis



Exercise reduced tumor (≥15mm^3) number, size, total mass per liver and cell proliferation (by Ki-67)

Exercise did not affect steatosis or the NAS

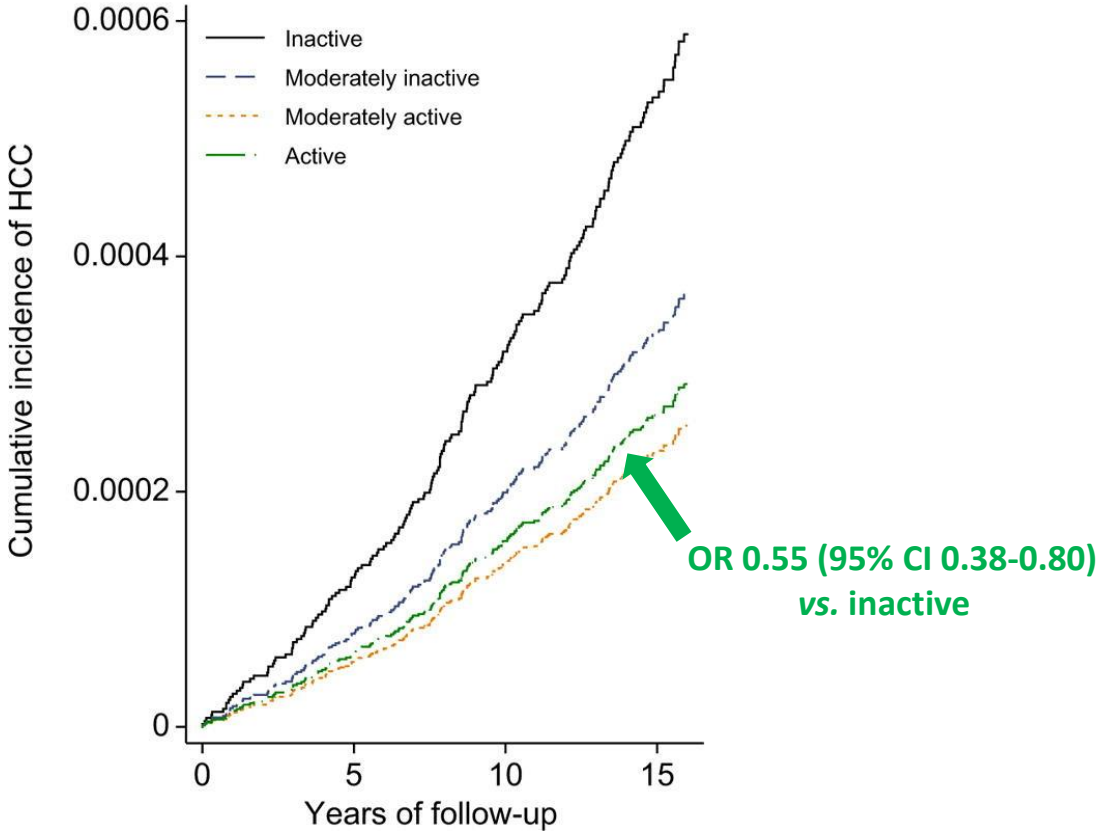
Exercise stimulated the phosphorylation of AMPK and its substrate raptor, which decreased the kinase activity of mTOR

PIGUET AC, *et al.* J Hepatol 2015;62:1296-303

Association between physical activity and risk of hepatobiliary cancers
A multinational cohort study (EPIC)

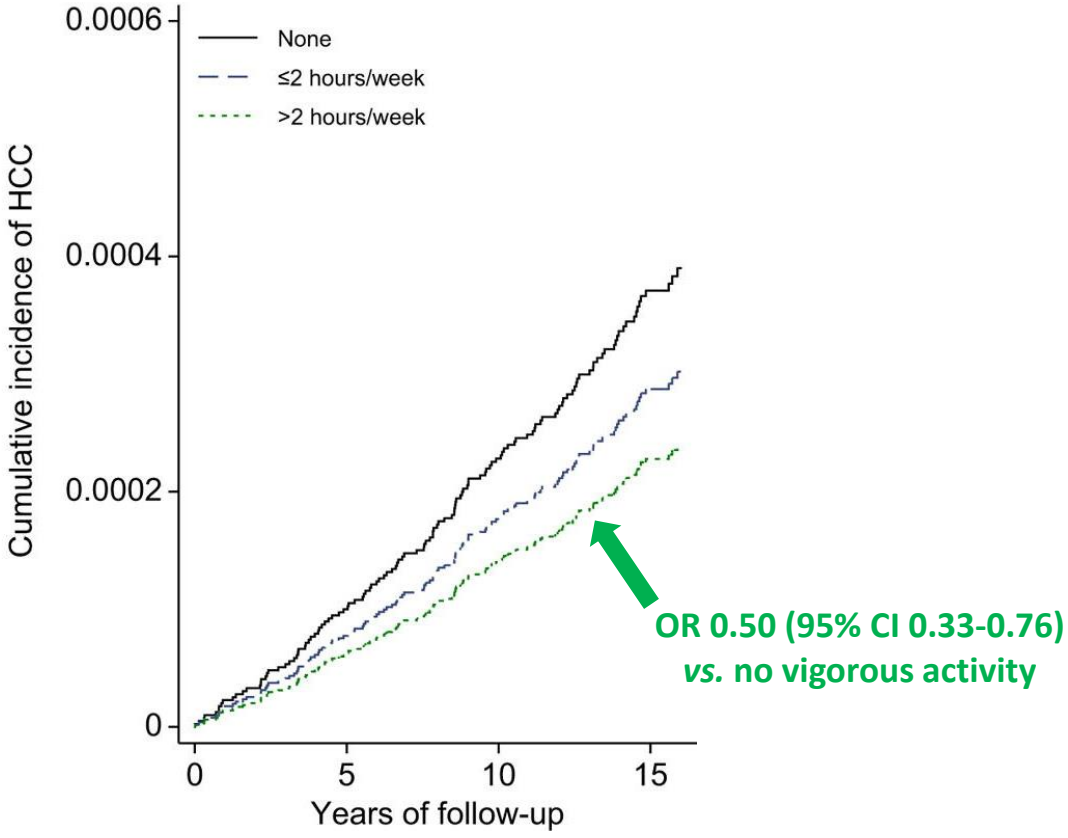
(n=467,336 persons, median FU 14.9 years; 275 HCC, 93 intrahepatic BDC, 164 non-gallbladder extrahepatic BDC)

Total physical activity



OR 0.55 (95% CI 0.38-0.80)
***vs.* inactive**

Vigorous physical activity



OR 0.50 (95% CI 0.33-0.76)
***vs.* no vigorous activity**

BAUMEISTER SE, *et al.* J Hepatol 2019;70:885-92

Association between physical activity and risk of hepatobiliary cancers
A multinational cohort study (EPIC)

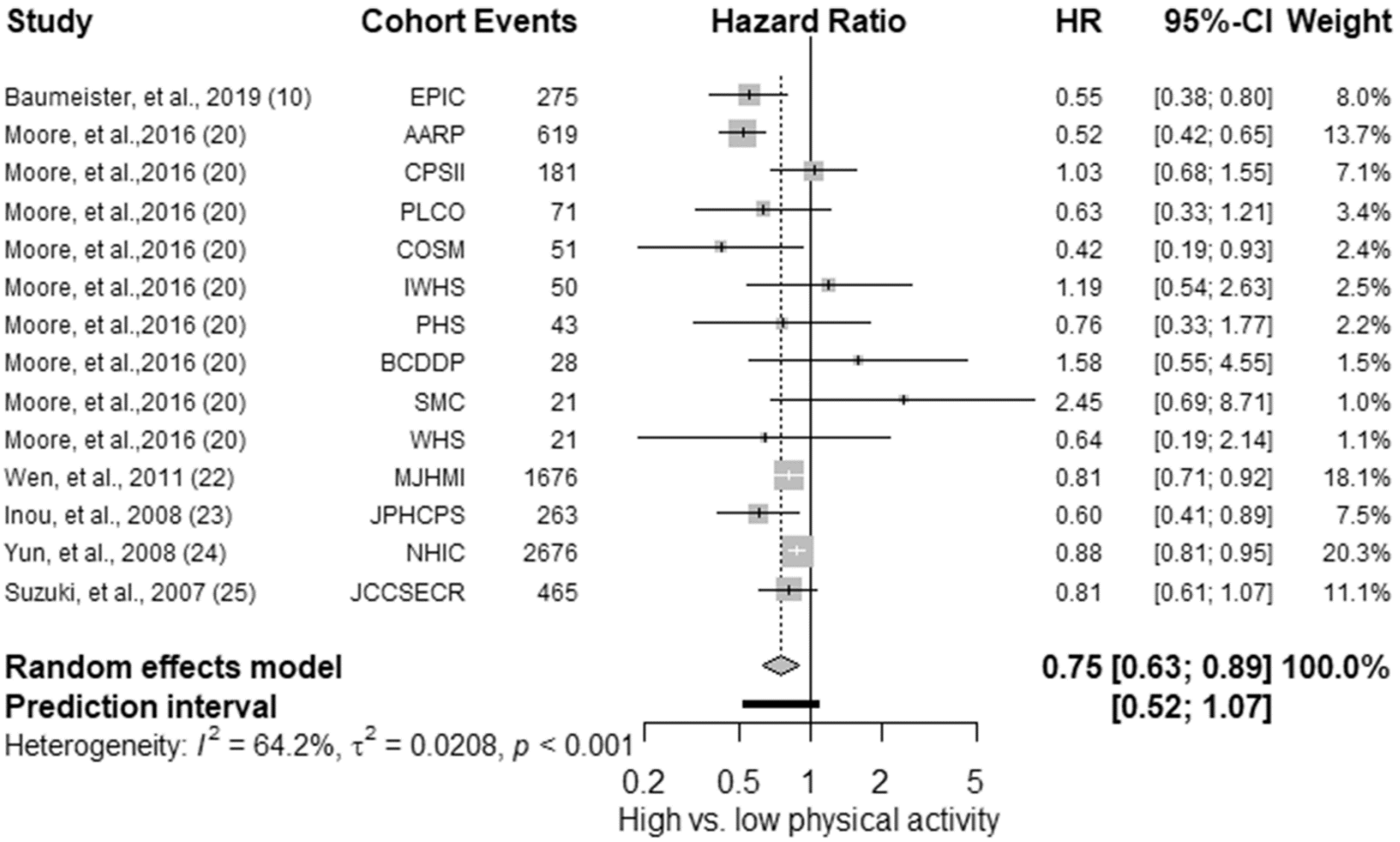
(n=467,336 persons, median FU 14.9 years; 275 HCC, 93 intrahepatic BDC, 164 non-gallbladder extrahepatic BDC)

- Total and vigorous physical activity were unrelated to both intrahepatic and non-gallbladder extrahepatic BDC
- Waist circumference explained about 40% and body mass index 30% of the overall association of total physical activity and HCC
- The risk was independent of other liver cancer risk factors
- The risk did not vary by age, gender, smoking status, body weight, and alcohol consumption

BAUMEISTER SE, *et al.* J Hepatol 2019;70:885-92

Physical activity and risk of liver cancer
A systematic review and meta-analysis of prospective studies and a bias analysis

14 prospective studies (n=6,440 liver cancers)



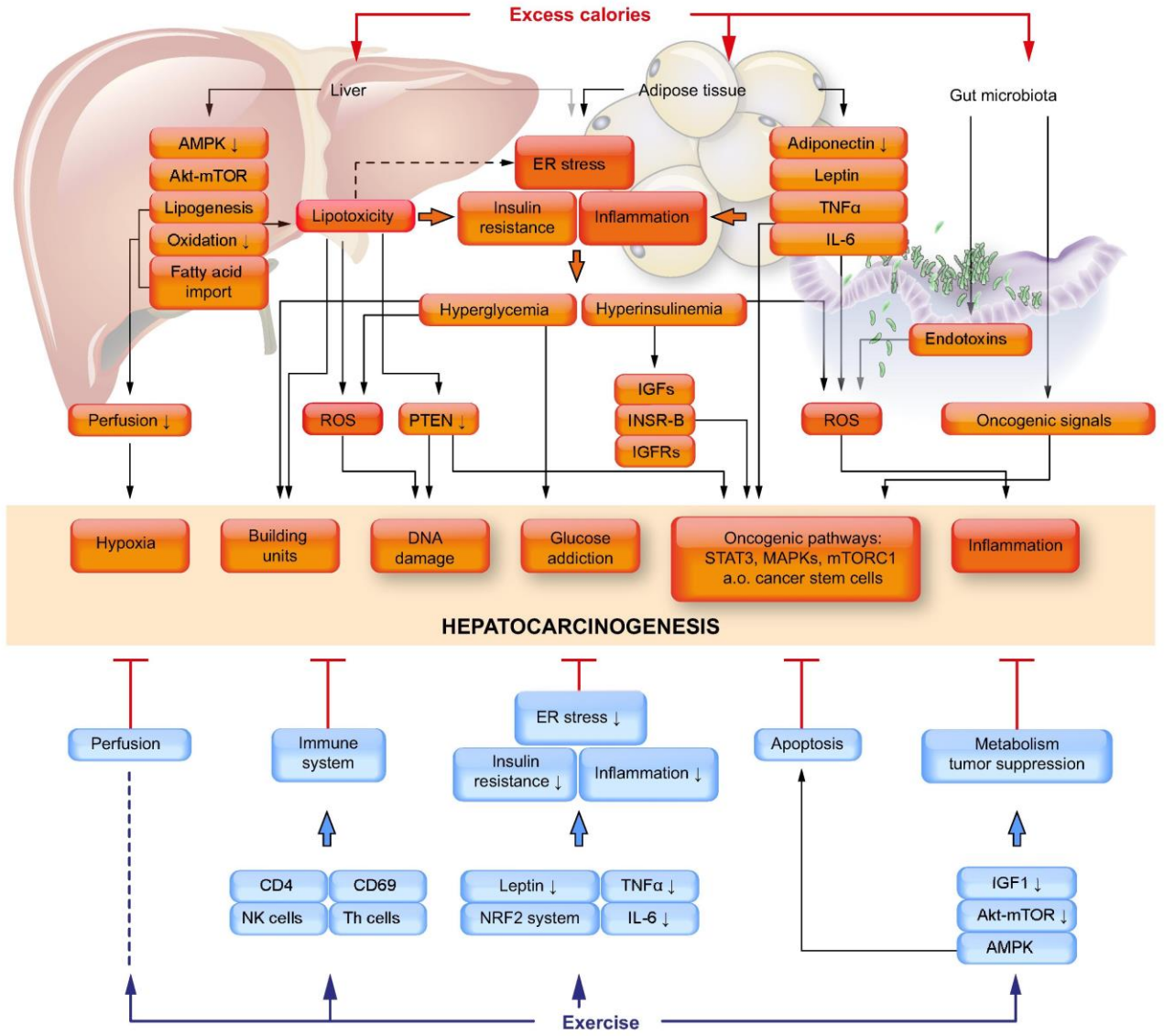
BAUMEISTER SE, *et al.* J Natl Cancer Inst 2019;111:1142-51

Physical activity and HCC: some notes of caution

- Potential for uncontrolled (residual) confounding
- A modestly strong unobserved confounder, with a 1.99-fold increase of the risk of the outcome, would suffice to explain the mean HR of 0.75
- Individual studies rely on self-reported measures of physical activity
- Self-reported measures of activity may be affected by mood states, social desirability, or cognitive biases
- Type, duration, and intensity of physical activity vary across studies
- Objectively measured physical activity, possibly assessed at multiple time points, and adjustment for viral hepatitis status are needed

BAUMEISTER SE, *et al.* J Natl Cancer Inst 2019;111:1142-51

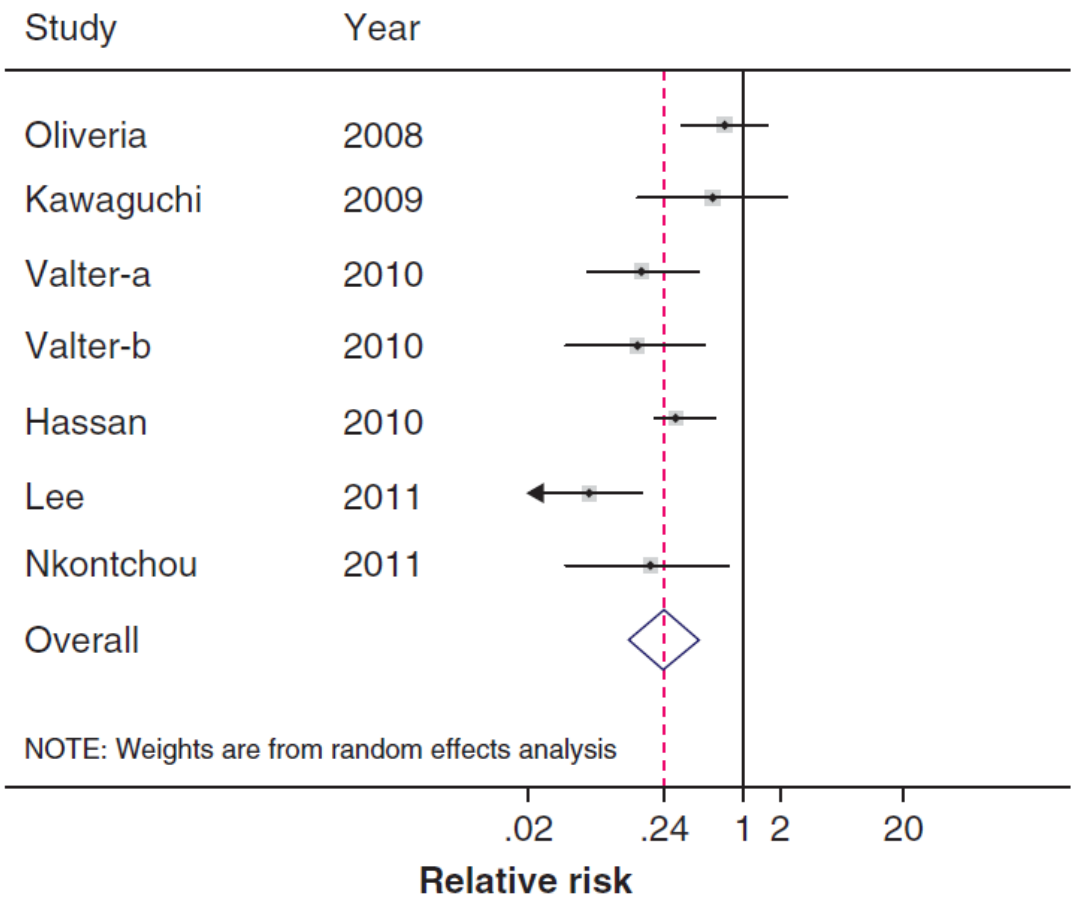
Excess calories *vs.* physical activity in HCC pathogenesis



SARAN U, *et al.* J Hepatol 2016;64:203-14

Pooled relative risk for HCC in diabetic patients treated with metformin

(A meta-analysis of 7 studies, n=191,223, HCC 3.40%)



Significantly reduced risk of HCC in metformin users *vs.* nonusers in diabetic patients (RR 0.24, 95% CI 0.13 - 0.46)

ZHANG H, *et al.* Scand J Gastroenterol 2013;48:78-87

Chemopreventive effect of metformin on HCC in diabetic patients by incremental years

Taiwan nationwide case-control study, n=97,430 HCC and 19,860 age-, gender- and physician visit date-matched controls

Diabetic patients (N = 47 820)	ORs (95% CI)	p Value
Metformin use (each incremental year)	0.93 (0.91 to 0.94)	<0.0001
Age (each incremental year)	1.00 (1.00 to 1.00)	0.8437
Gender (male vs female)	1.03 (0.99 to 1.08)	0.1629
Hepatitis B	13.81 (12.61 to 15.13)	<0.0001
Hepatitis C	17.07 (15.57 to 18.71)	<0.0001
Liver cirrhosis	4.29 (3.61 to 5.10)	<0.0001
End stage renal failure	0.83 (0.77 to 0.89)	<0.0001
DM duration (each incremental year)	0.96 (0.95 to 0.96)	<0.0001
DM control (each incremental visit per year)	1.02 (1.02 to 1.03)	<0.0001
Other OHA agents use (each incremental year)	1.02 (1.01 to 1.04)	0.0052
Thiazolidinediones use (each incremental year)	0.91 (0.87 to 0.95)	<0.0001
Insulin use (each incremental year)	1.13 (1.10 to 1.16)	<0.0001

DM, diabetes mellitus; OHA, oral hypoglycaemic agent.

Each year of metformin use reduces the risk of HCC by 7%

CHEN HP, *et al.* Gut 2013;62-606-15

The chemopreventive effect of statins on HCC is independent of diabetes and cirrhosis

Korea nationwide nested case-control study, n=1,642 HCC and 8,210 age-, sex and time of the FU

Characteristics	With diabetes mellitus				Without diabetes mellitus			
	Cases (n = 317)	Controls (n = 1,560)	Crude	Adjusted	Cases (n = 1,324)	Controls (n = 6,620)	Crude	Adjusted
	n (%)	n (%)	OR (95% CI)	OR (95% CI)*	n (%)	n (%)	OR (95% CI)	OR (95% CI)**
Statin use								
Never use	278 (87.7)	1,054 (67.6)	1.00	1.00	1,252 (94.6)	5,937 (89.7)	1.00	1.00
Ever use	39 (12.3)	506 (32.4)	0.27 (0.19–0.39)	0.28 (0.17–0.46)	72 (5.4)	683 (10.3)	0.48 (0.38–0.63)	0.53 (0.39–0.73)

Characteristics	With liver cirrhosis				Without liver cirrhosis			
	Cases (n = 513)	Controls (n = 1,574)	Crude	Adjusted	Cases (n = 513)	Controls (n = 1,574)	Crude	Adjusted
	n (%)	n (%)	OR (95% CI)	OR (95% CI)*	n (%)	n (%)	OR (95% CI)	OR (95% CI)*
Statin use								
Never use	480 (93.6)	1,318 (83.7)	1.00	1.00	1,004 (93.1)	4,704 (87.2)	1.00	1.00
Ever use	33 (6.4)	256 (16.3)	0.34 (0.22–0.50)	0.39 (0.26–0.60)	75 (7.0)	691 (12.8)	0.49 (0.38–0.63)	0.42 (0.32–0.57)

The beneficial effect of statins was dose-dependent

KIM G, *et al.* J Hepatol 2018;68:476-84

Take-home messages

- NAFLD is the most prevalent chronic liver disorder worldwide
- Due to the increasing prevalence of metabolic syndrome and aging of the population, NAFLD prevalence and complications (including HCC) are projected to increase
- As many as 40 to 50% of HCC associated with NAFLD occur in non-cirrhotic livers
- The most important risk factors for HCC in NAFLD are metabolic
- Lifestyle modifications are currently the most effective measures to reduce the risk of HCC in NAFLD