Insights into NAFLD burden and epidemiology – what does the data tell us? Global insights

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Disclosures

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Learning objectives

1. Explore the increasing prevalence of NAFLD and NASH worldwide, considering specific countries and any regional differences
2. Understand the burden of NAFLD on clinical, economical and QoL-related factors
3. Describe comorbidities associated with NAFLD and their potential impact on NAFLD outcomes

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

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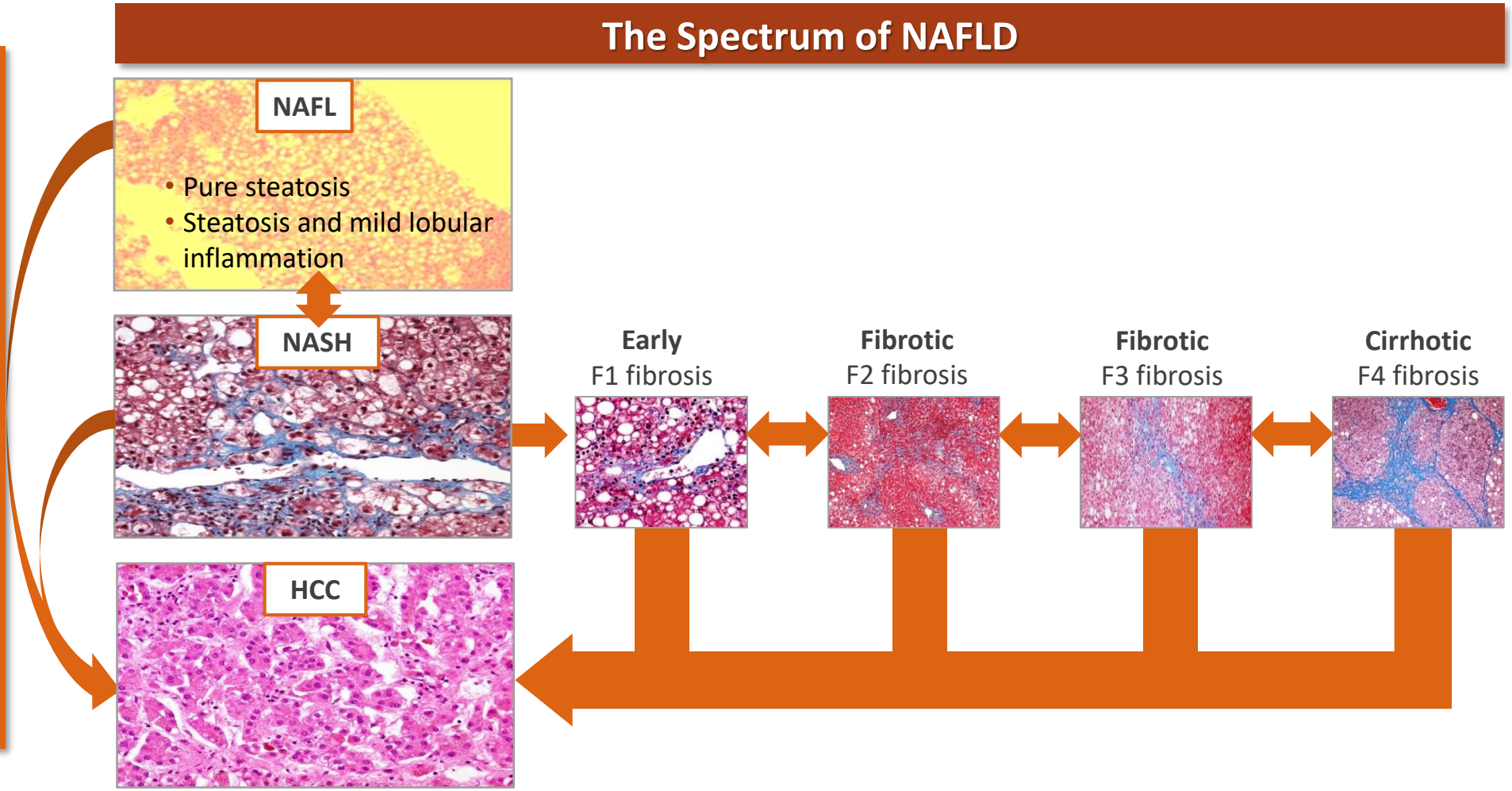
NAFLD and NASH

Diagnosis of NAFLD requires:

- Steatosis in >5% of hepatocytes
- NASH requires specific pathologic criteria
- Exclusion of secondary causes and AFLD
- Associated metabolic risk factors



AFLD, alcoholic fatty liver disease; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

Younossi ZM. Hepatology 2018;68:349–60; Chalasani N, et al. Hepatology 2018;67:328–35; Younossi ZM, et al. Hepatology 2011;53:1874–82; Younossi ZM, et al. Hepatol Commun 2017;1:421–8; EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

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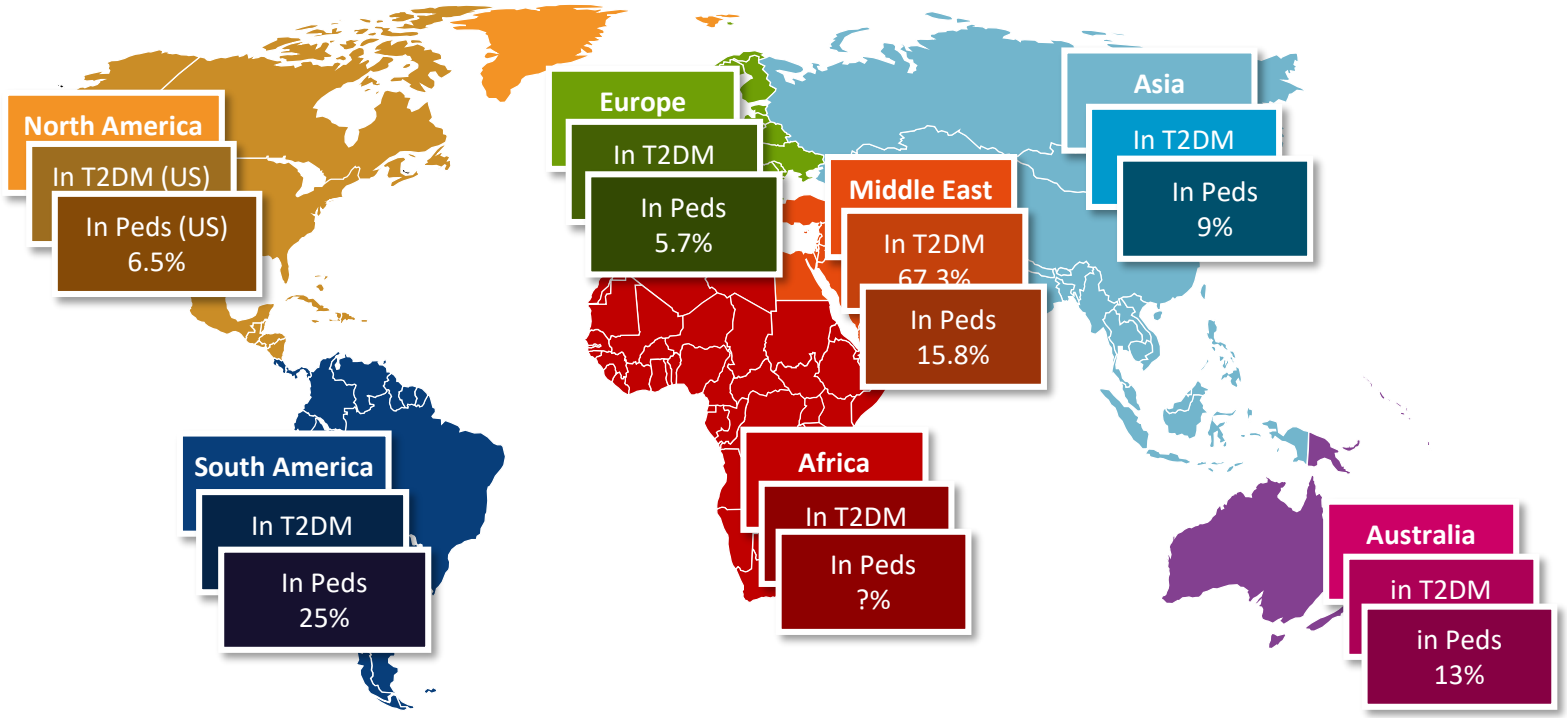
Prevalence of NAFLD and NASH



Worldwide prevalence of NAFLD is 25%

Worldwide prevalence of NAFLD among people with T2DM is 55.5%

Worldwide prevalence of NAFLD among children is 7.6%

Prevalence of NASH in general population is between 1.5–6.5%

Prevalence of NASH among T2DM is 37.3% (24.7-50.0%)

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; Peds, pediatric patients; T2DM, Type 2 diabetes mellitus

Younossi ZM. J Hepatol 2019;70:531–44; Younossi ZM, et al. Clin Liver Dis 2018;11:92–4; Younossi ZM, et al. J Hepatol 2019;71:793–801; Ko JS. Pediatr Gastroenterol Hepatol Nutr 2019;22:501–10

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As a clinician, what proportion of high-risk patients would you screen for NAFLD?

1. >75%
2. 50–75%
3. 25–49%
4. <25%
5. None

NAFLD, non-alcoholic fatty liver disease

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Prevalence of NAFLD across different geographical regions

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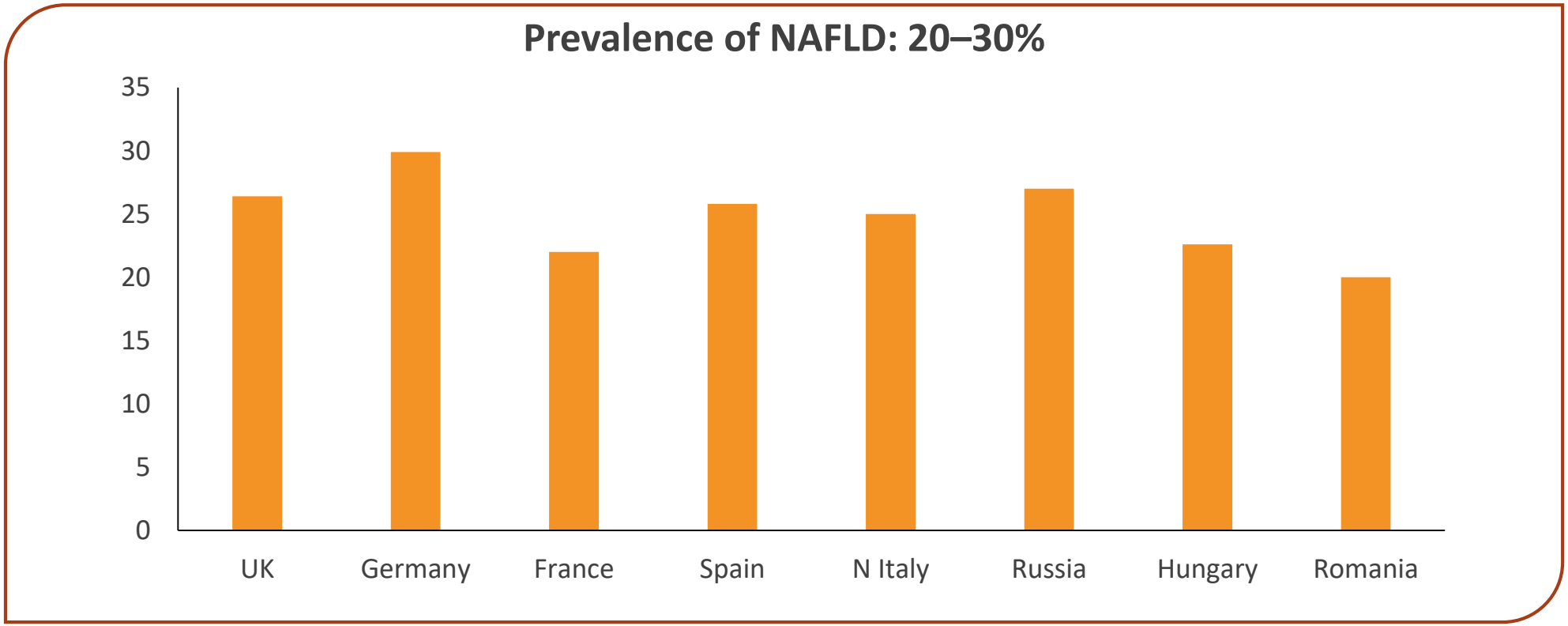
Growing prevalence of NAFLD in Europe



Prevalence of NASH: 3%

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

Younossi Z, et al Hepatology 2019;69:2672–82; Tsukanov V, et al. AGA 2011; Abstract Mo2025; Younossi ZM, et al. Hepatol 2019;70:531–44

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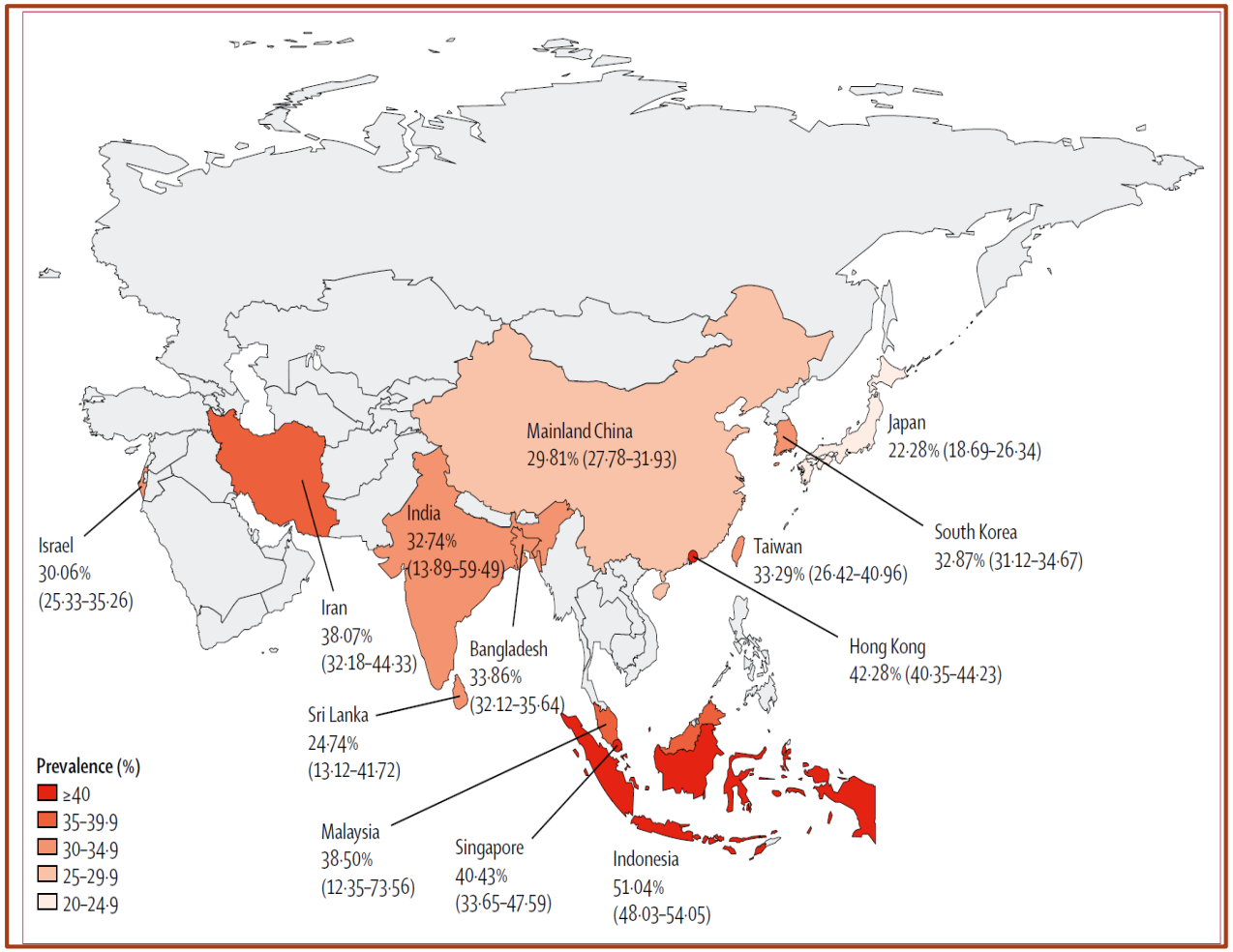
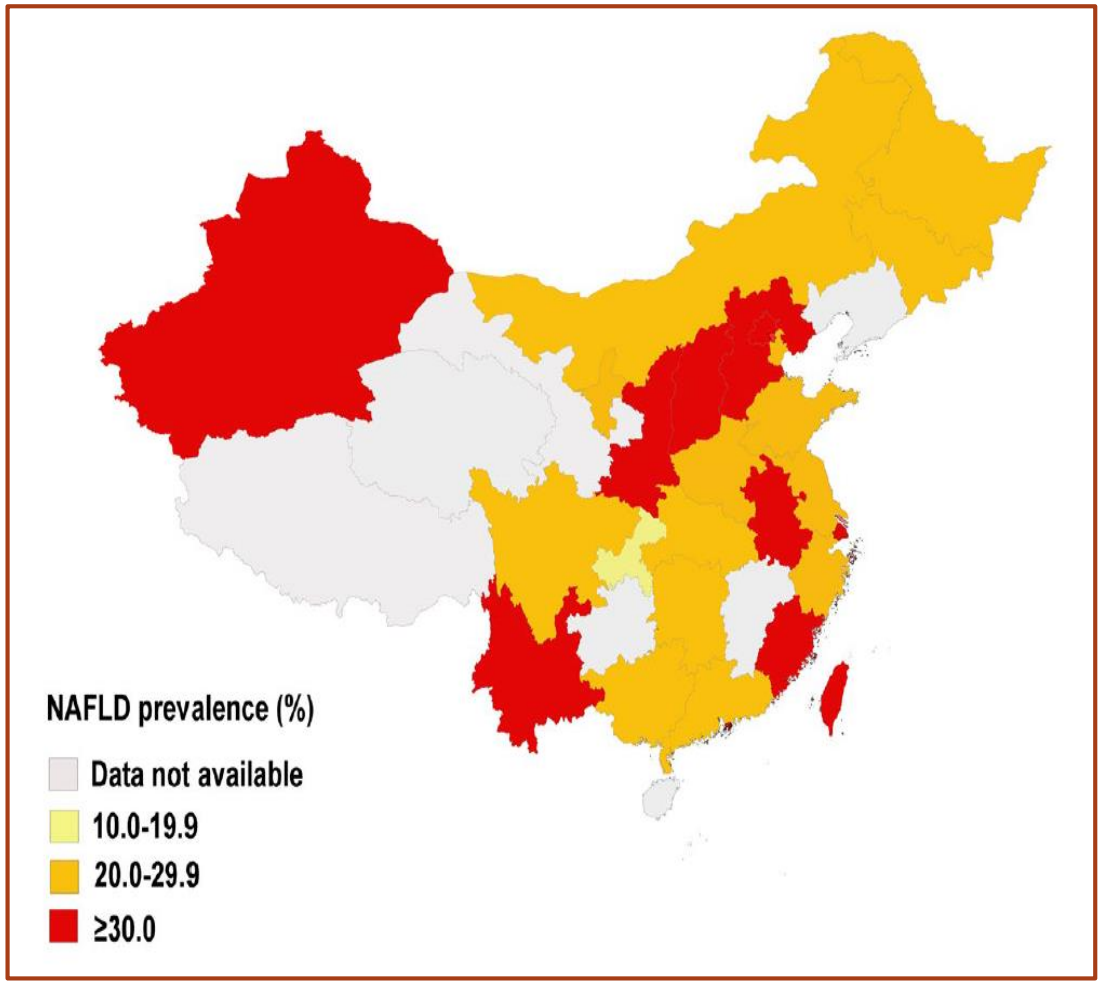
Growing prevalence of NAFLD in Asia





NAFLD, non-alcoholic fatty liver disease. Wong MCS, et al. Nat Rev Gastroenterol Hepatol 2018;1; Zelber-Sagi S, et al. Liver Int 2006;26:856–63; Moghaddasifar I, et al. Int J Organ Transplant Med 2016;7:149; Jie Li, et al. Lancet Gastroenterol Hepatol 2019; Zhou F, et al. Hepatology 2019;70:1119–33

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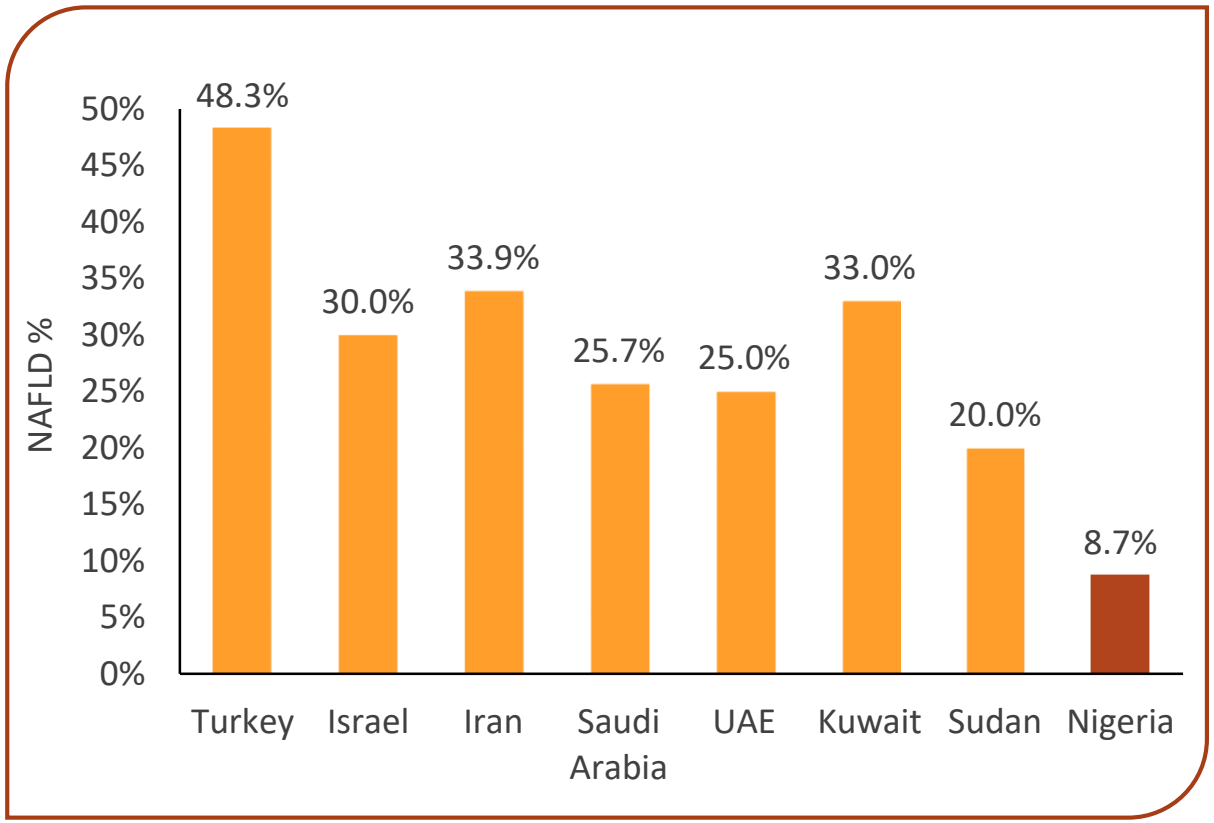
Growing prevalence of NAFLD in the Middle East and Africa

High prevalence of NAFLD tracks the prevalence of metabolic syndrome



No.	Country	Diabetes	Obesity	MS
1	South Africa	7%	29.9%	23.3%
2	Ethiopia	8.9%	20%	12.5%
3	Egypt	14.9%	70%	7.4%
4	Ghana	1.9%	58%	35.9%
5	Saudi	17.6%	23.6%	28%
6	Iran	8.7%	14.2%	30.1%
7	Yemen	9.75%	8.8%	46%
8	Pakistan	16.68%	22.2%	46%
9	Jordan	17.1%	34.8%	37.4%
10	Kuwait	21.1%	78.4%	32.8%
11	Nigeria	1.9%	15%	12.1%
12	Uganda	2.5%	2.3%	58%
13	Kenya	3.3%	8.9%	34.6%
14	Botswana	3.9%	12.7%	11%
15	United Republic of Tanzania	3.5%	19.2%	30%

MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease

Zelber-Sagi S, et al. Liver Int 2006;26:856–63; Moghaddasifar I, et al. Int J Organ Transplant Med 2016;7:149; Alswat K, et al. Saudi J Gastroenterol 2018;24:211; Ahmed M, et al. Gastroenterol Res 2017;10:271–9

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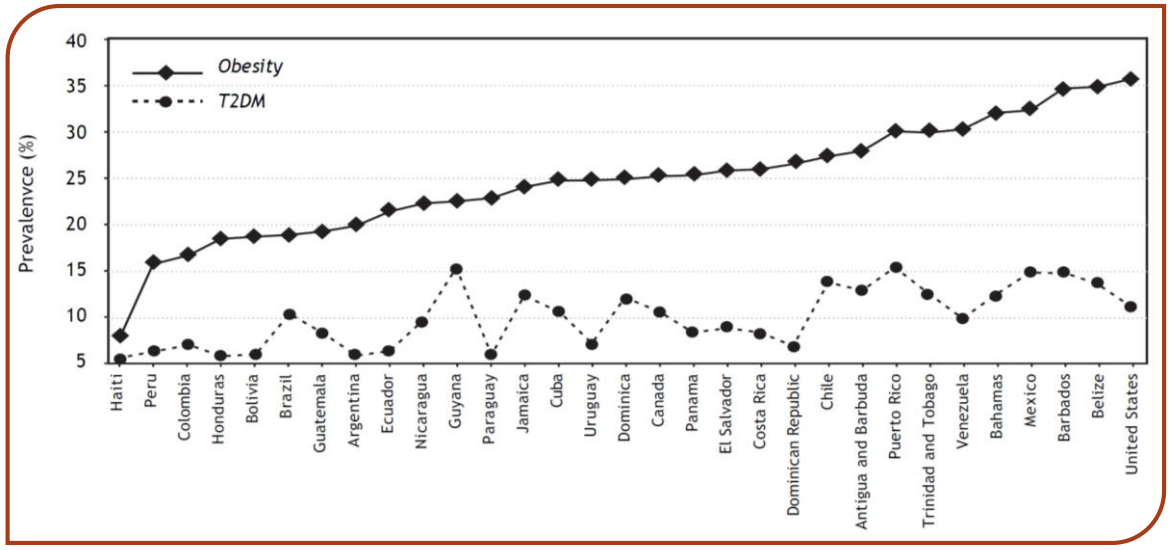
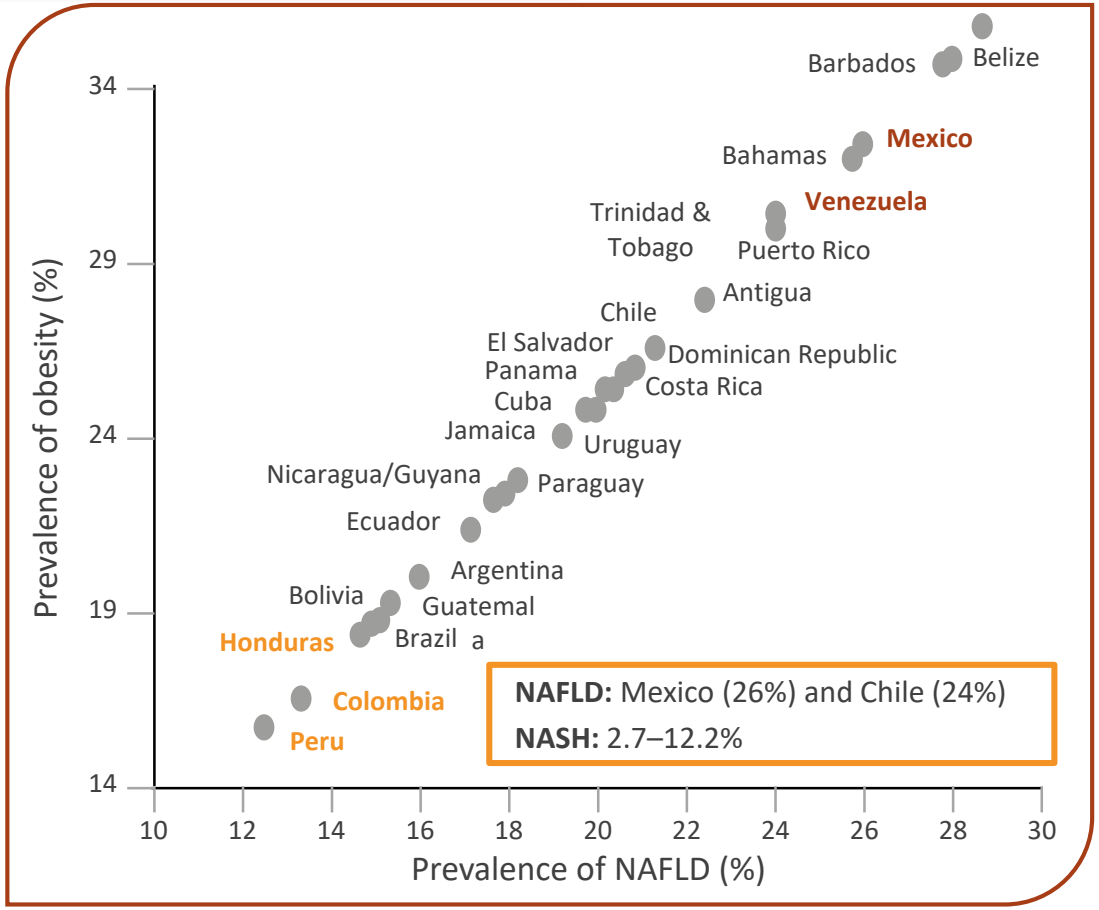
Growing prevalence of NAFLD in Latin America

High prevalence of NAFLD tracks the prevalence of obesity

- Electronic search of main databases (January 2000 to September 2013) with 356 reports





NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis
López-Velázquez JA, Ann Hepatol 2014;13:166–78

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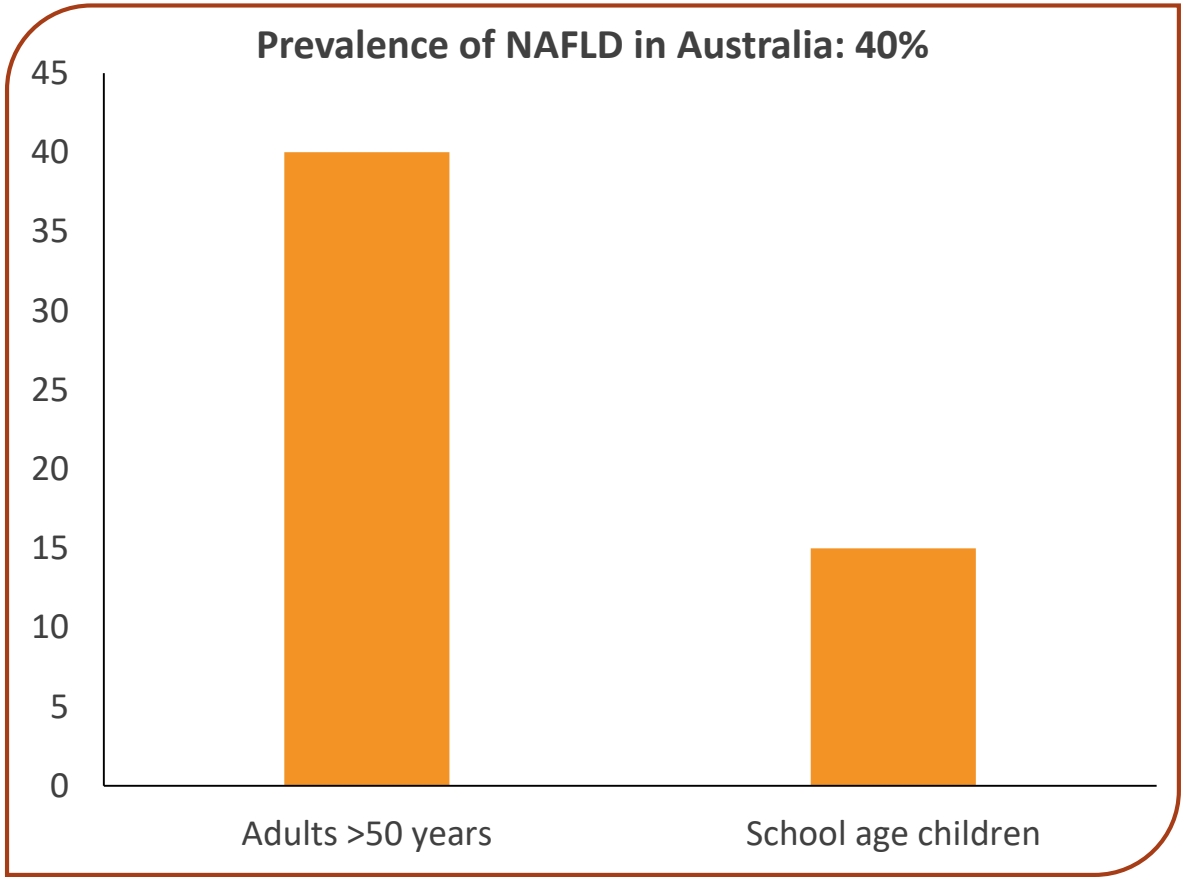
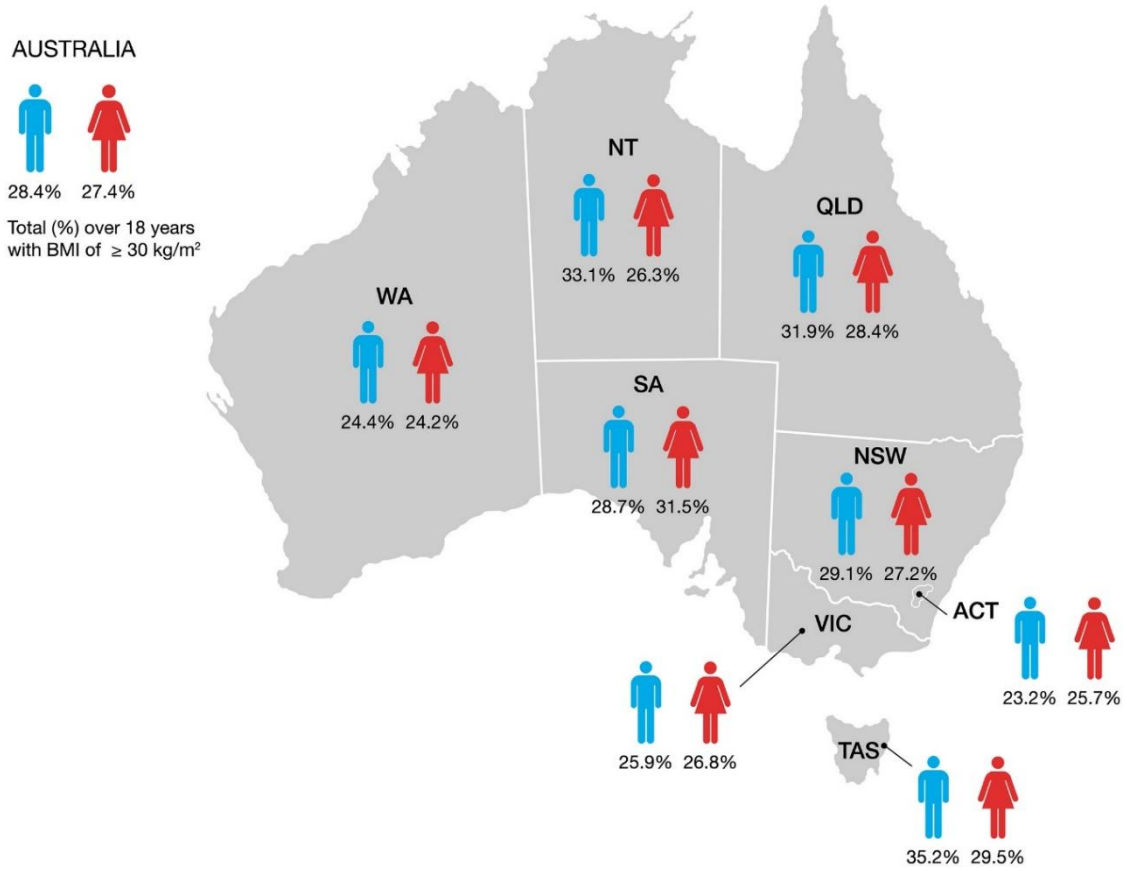
Growing prevalence of NAFLD in Australia





ACT, Australian Capital Territory; NAFLD, non-alcoholic fatty liver disease; NT, Northern Territory; NSW, New South Wales;QLD, Queensland; SA, South Australia; TAS, Tasmania; VIC, Victoria; WA, Western Australia
Deloitte Economic Access. January 2013; Mahady S, et al. Gastroenterol Hepatol 2018;33(Suppl 1): 1–11

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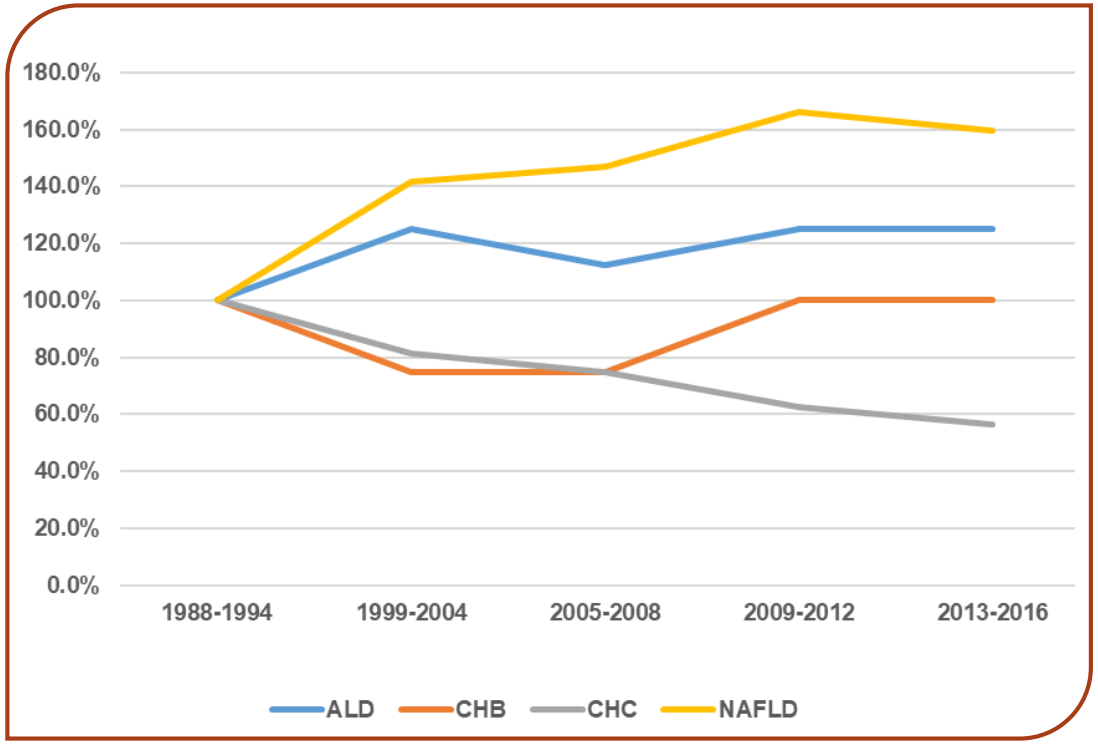
Growing prevalence of NAFLD in the US
NHANES cycles (1988–2016) (N=58,731 adults)

- Prevalence of CHB and ALD remained stable: 0.3%–0.4% and 0.8%–1.0%, respectively (p>0.05)
- Prevalence of CHC decreased from 1.6% (1988–1994) to 0.9% (2013–2016) (p=0.03)
- Prevalence of NAFLD increased from 20.0% (1988–1994) to 28.3% (1999–2004); 33.2% (2009–2012); and 31.9% (2013–2016) (p<0.0001)
- Yearly trend analyses showed that NAFLD is the only liver disease with consistently increasing prevalence (trend p=0.01)



ALD, alcoholic liver disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C; NAFLD, non-alcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey

Younossi Z, et al. Gut 2020;69:564–8

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The burden of NAFLD: Supporting evidence and the health-economic impact

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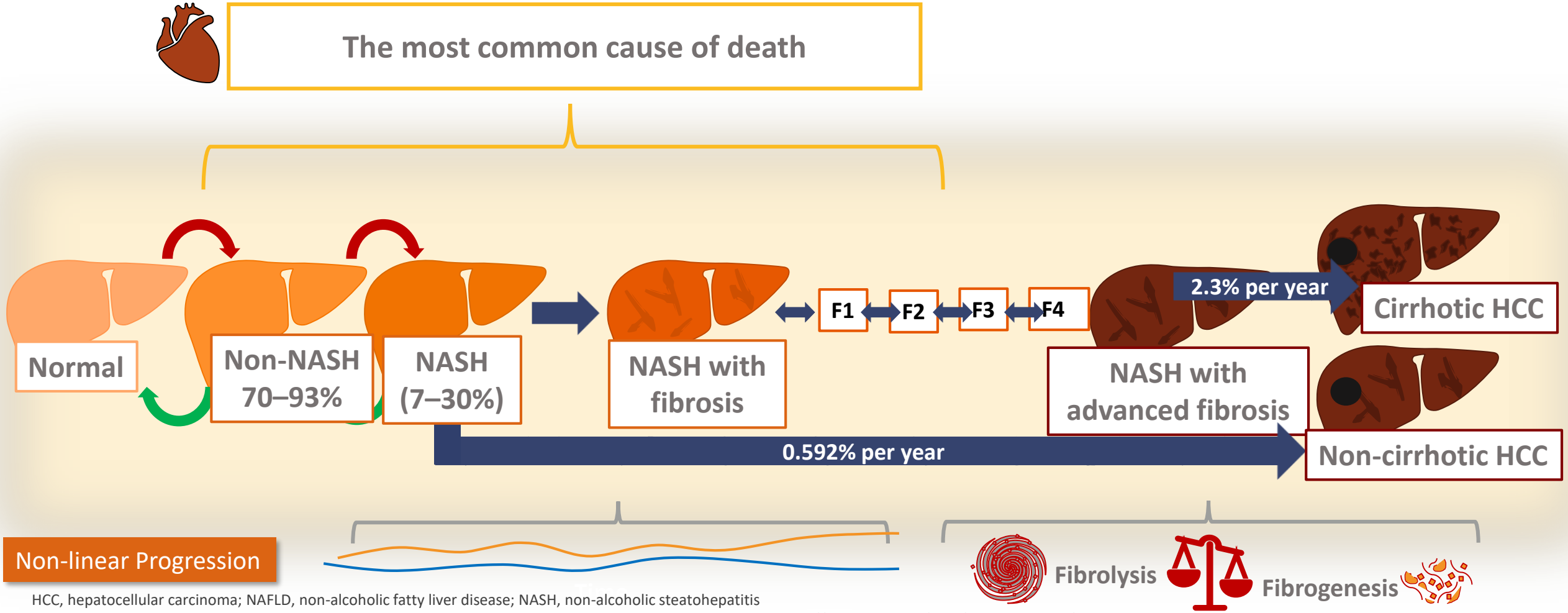
Natural history of NAFLD and NASH



HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

American College of Gastroenterology Virtual Grand Rounds. Presentation by Younossi ZM, 2020. Available at: https://webfiles.gi.org/links/virtgrandround/Week11_ACGVGR_Younossi_Nash2.pdf (Last accessed: September 2020); Younossi ZM et al. *Hepatology*. 2018;68:349–360; Younossi ZM. *J Hepatol*. 2019;70:531–44

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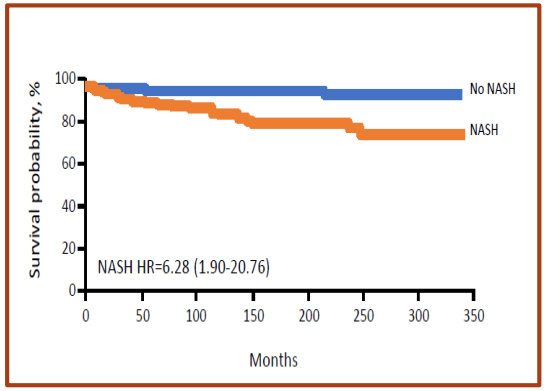
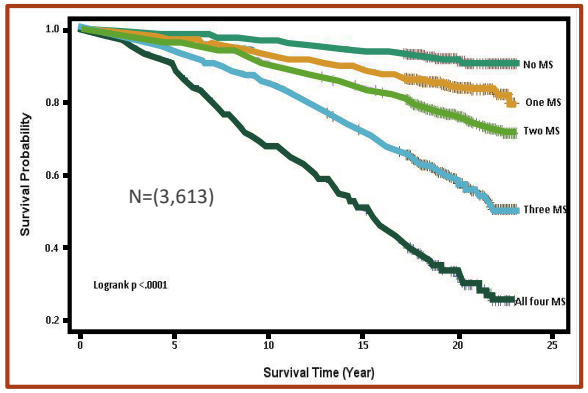
Evidence supporting the burden of NAFLD: The clinical data

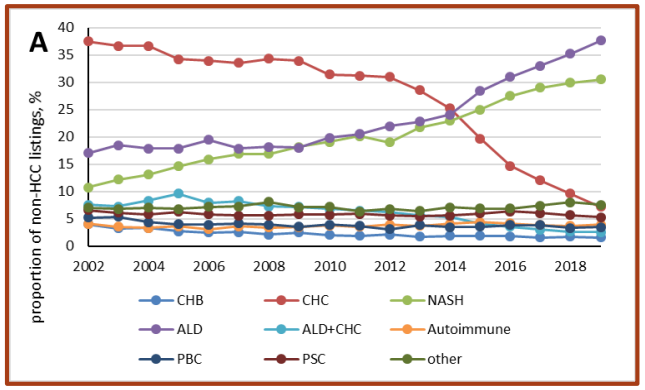
NASH denotes progressive disease



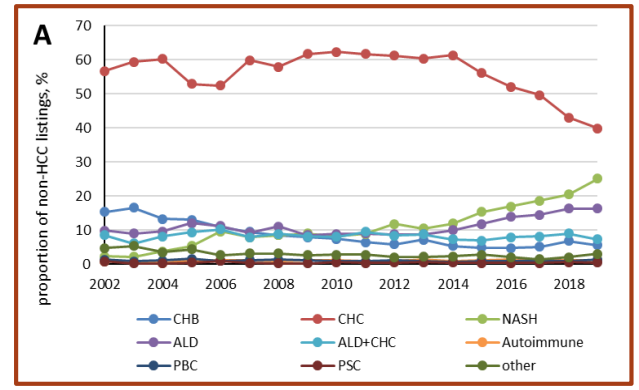
Components of MS predicts mortality-NHANES III



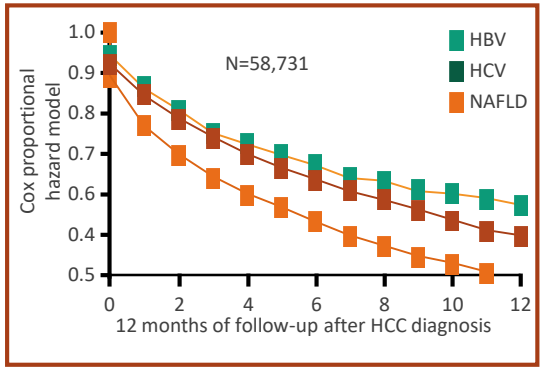
LT candidates in the US (non-HCC)



LT candidates in the US (HCC)



HCC and NAFLD- SEER 2004–2009

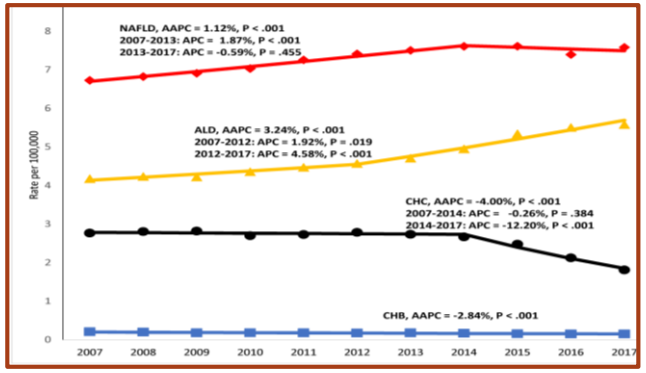


Changes in CLD NHANES 1988–1994 and 1999–2016

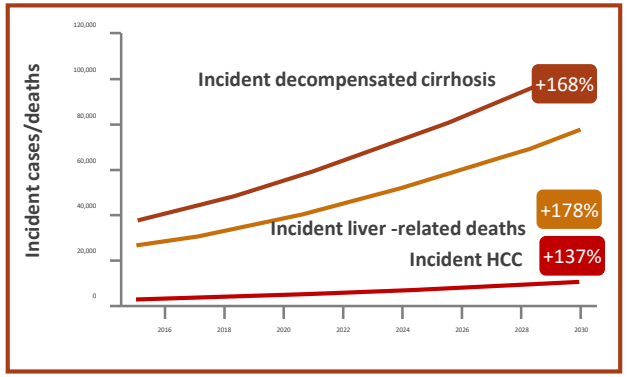
Changes in CLD mortality

National Center for Health Statistics Mortality data

28,132,187 reported deaths with 700,402 LD-related deaths



Future clinical burden of NAFLD 2015–2030



CLD, chronic liver disease; HCC, hepatocellular carcinoma; LT, liver transplant; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NHANES, National Healthy and Nurtition Examination Survey. Stepanova M, et al. Dig Dis Sci 2013;58:3017–23; Golabi P, et al. Medicine (Baltimore) 2018;97:e0214; Younossi ZM, et al. Clin Gastroenterol Hepatol 2020;20:30775-8; Younossi ZM, et al. Clin Gastro Hepatol 2019;17:748–55; Younossi ZM, et al. Hepatology 2015;62:1723–30; Younossi ZM, et al. Gut 2020. Paik J, et al. Hepatology Communication 2020;4:890–903; Estes C, et al. Hepatology 2018;67:123–33

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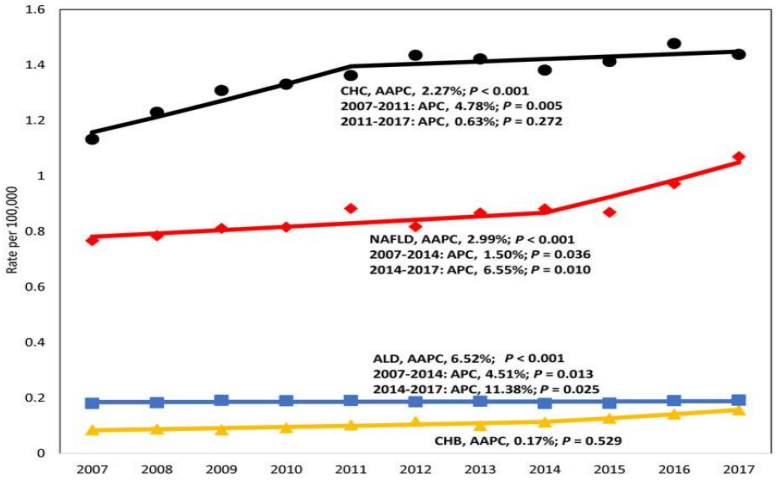
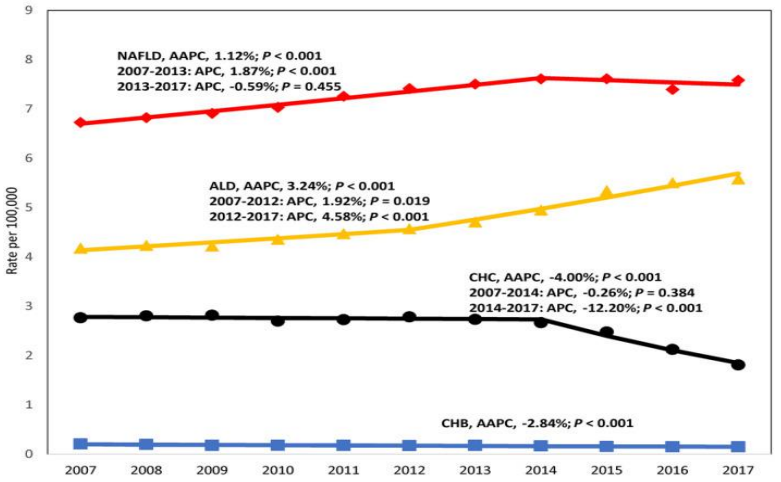
Age-standardized cause-specific death rates among NAFLD: U.S. 2007–2016

- Multiple-cause mortality data (2007–2017) from the National Center for Health Statistics
- Annual percent change (APC) in age-standardized-death-rate-per-100,000 (ASDR) and age-standardized-years-of-life-lost-per-100,000 (ASYLLR)
- In 2017, in the US, there were 2,797,265 deaths with 73,424 liver deaths, contributing to 1,467,742 of years-of-life-lost
- **Liver deaths:** HCC:16.6% and cirrhosis: 82.0%
  - **HCC deaths: CHC, 50.4%; NAFLD, 35.4%;** HBV, 6.0%; ALD, 5.4%; and others, 2.8%
  - **Cirrhosis deaths: NAFLD 48.9%; ALD, 34.7%;** CHC, 12.3%; CHB, 0.9%; and others, 3.2%
- Between 2007 and 2017, the increase in **ASDR for HCC due to ALD and NAFLD accelerated** after 2014 while CHC stabilized





ALD, alcoholic liver disease; CHC, chronic hepatitis C; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease. Paik J, et al. Hepatology Communication 2020;4:890–903

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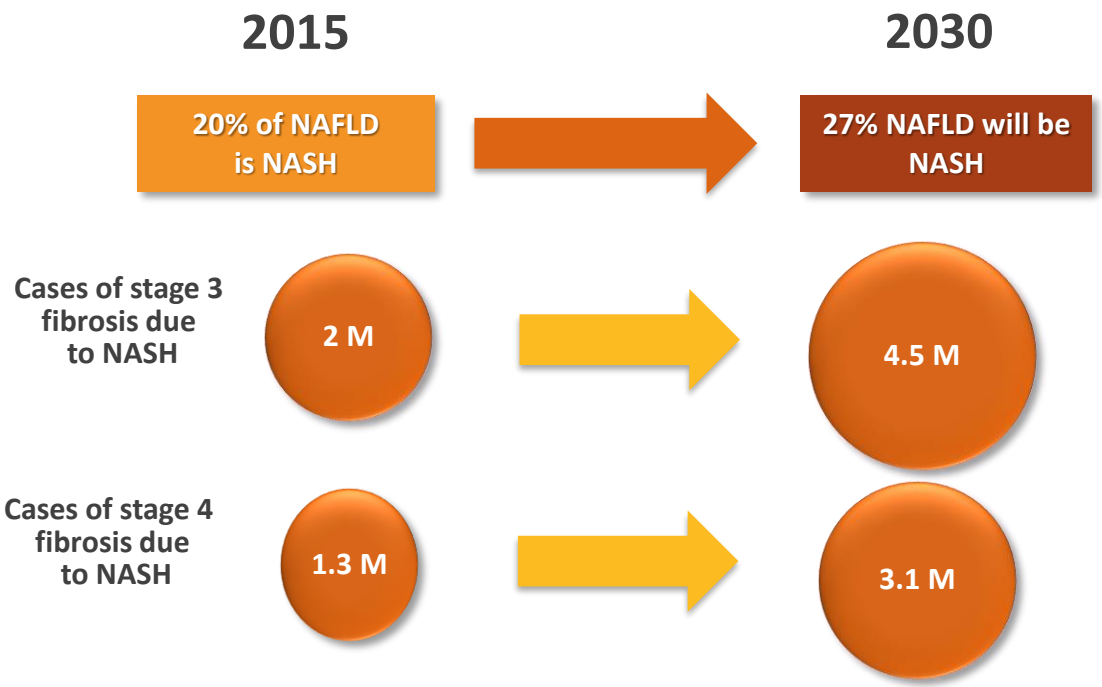
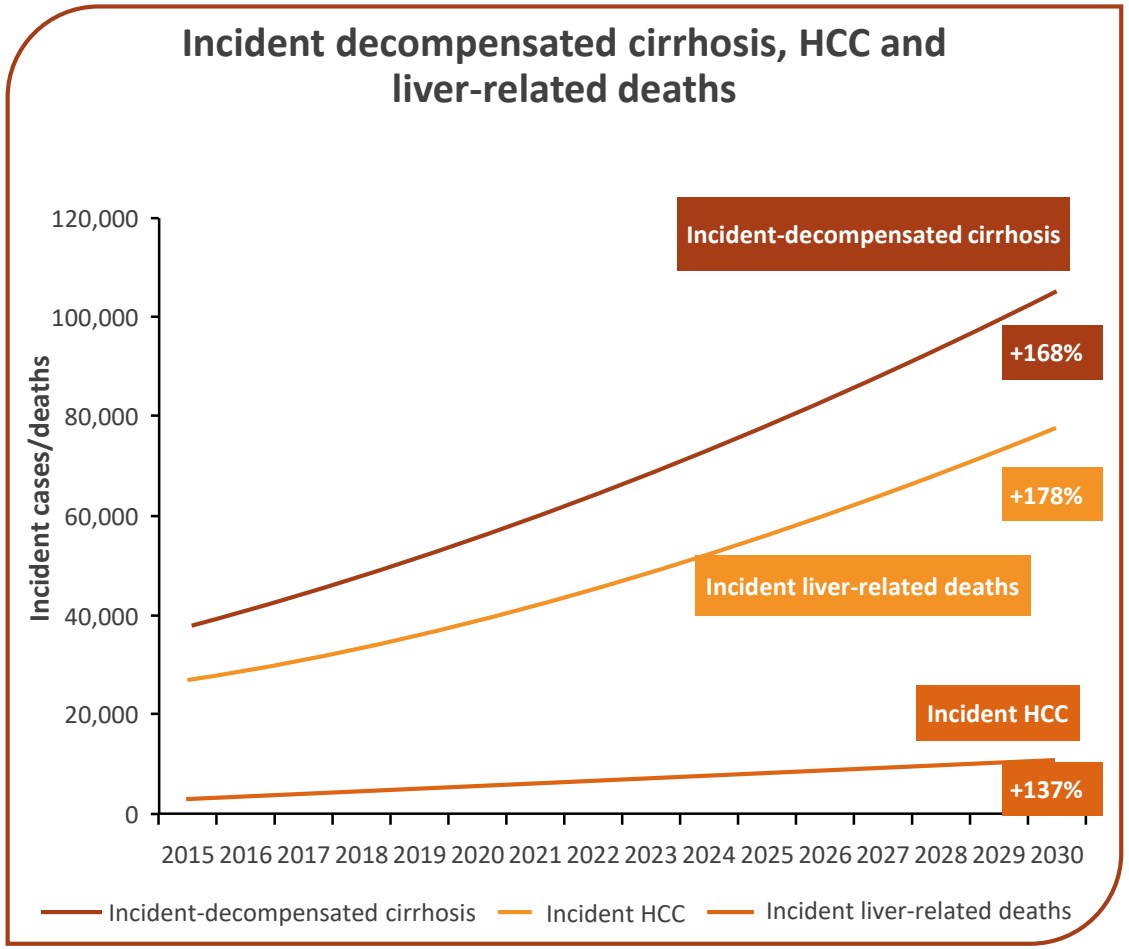
Evidence supporting the burden of NAFLD: The modelling data





HCC, hepatocellular carcinoma; M, million; NAFLD, non-alcoholic fatty liver disease;
NASH, non-alcoholic steatohepatitis T2DM, type 2 diabetes mellitus. Estes C et al. *Hepatology*. 2018;67:123–33

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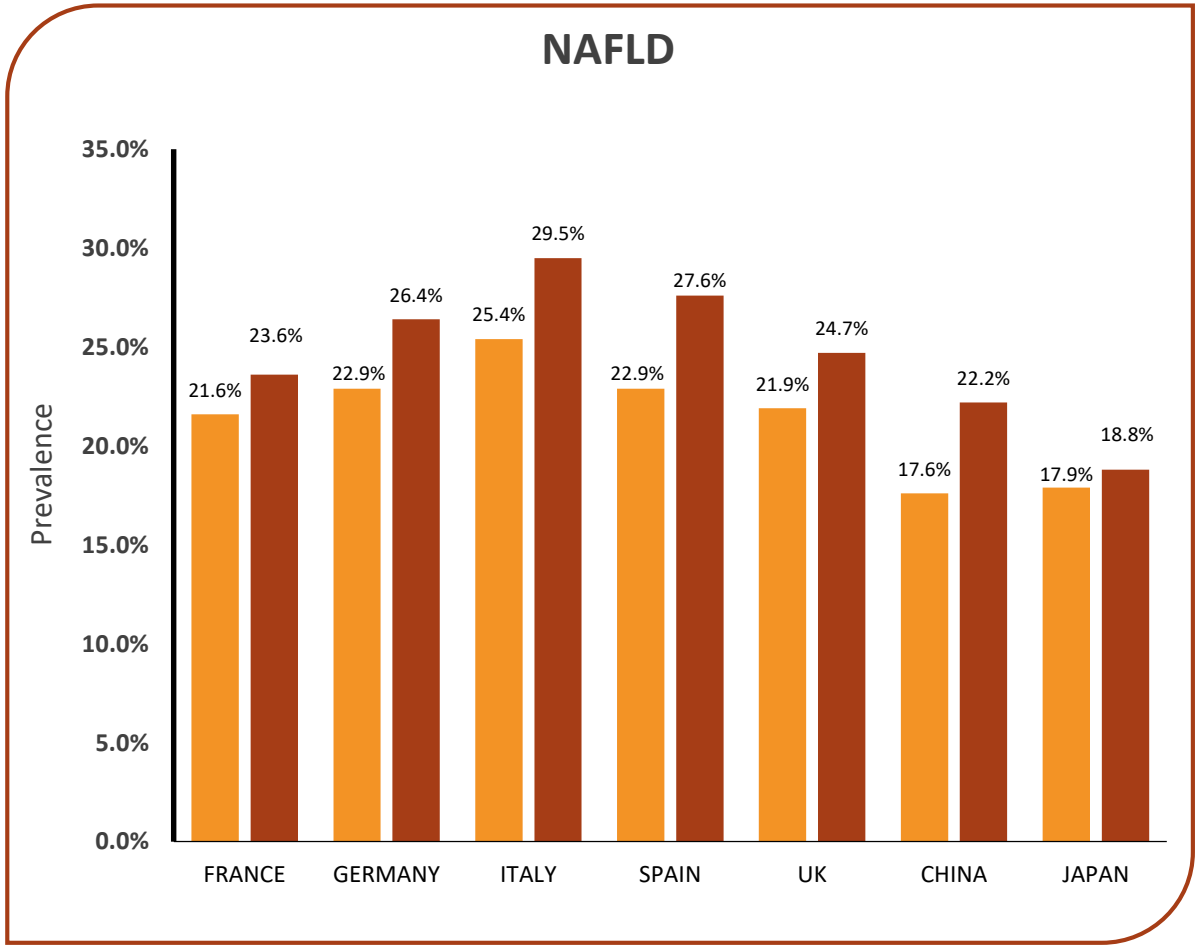

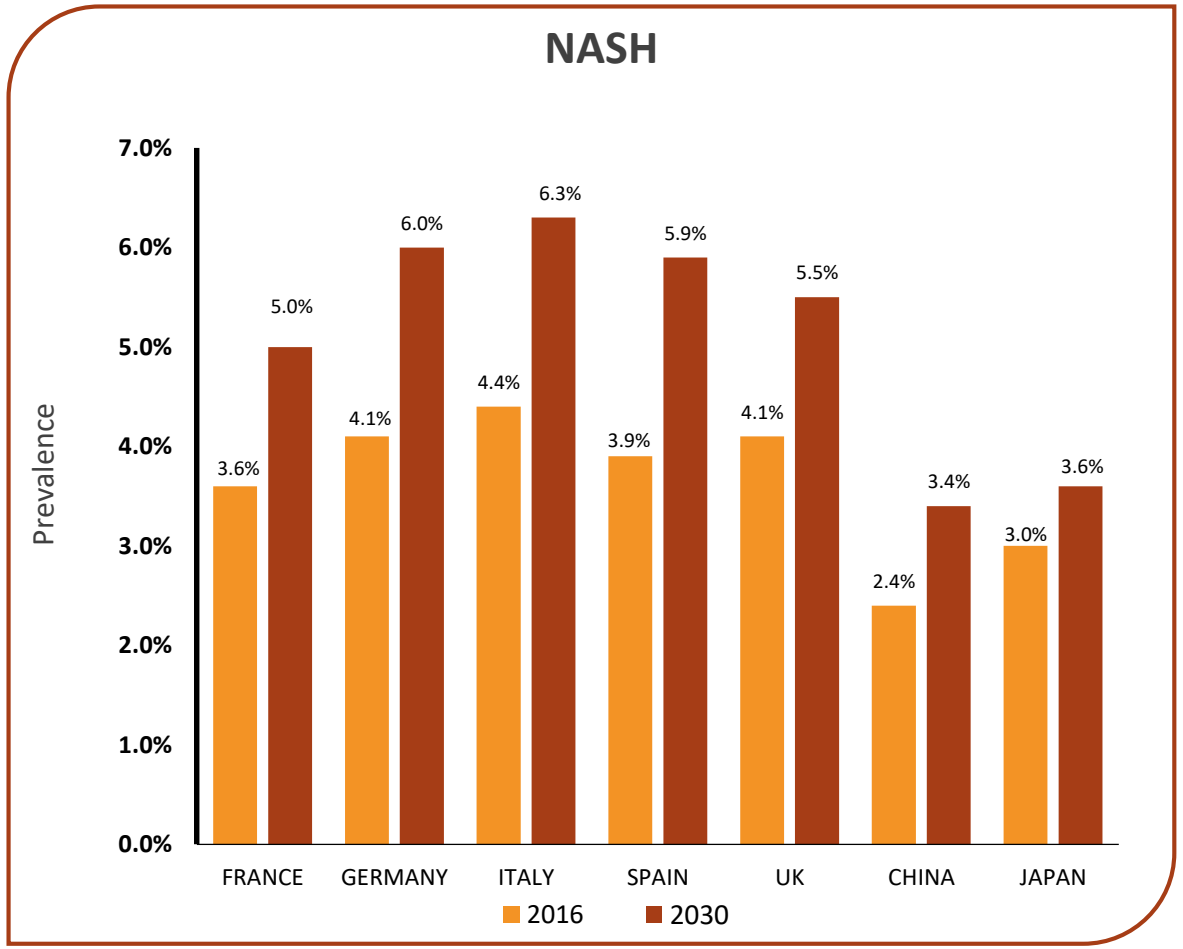

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis. Estes C, et al. J Hepatology 2018;69:896–904

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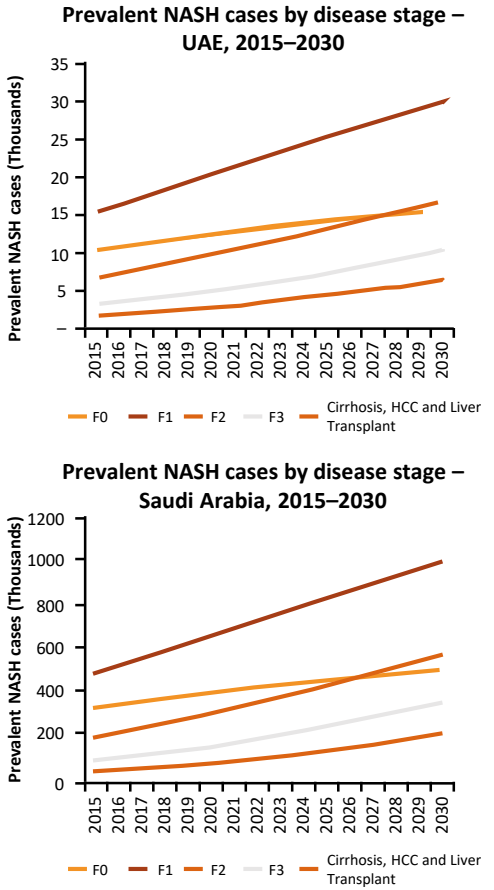
Evidence supporting the burden of NAFLD: The modelling data

Incident decompensated cirrhosis, HCC, liver-related deaths among prevalent NAFLD population[1]

Prevalent NASH cases by disease stage in the UAE and Saudi Arabia[2]



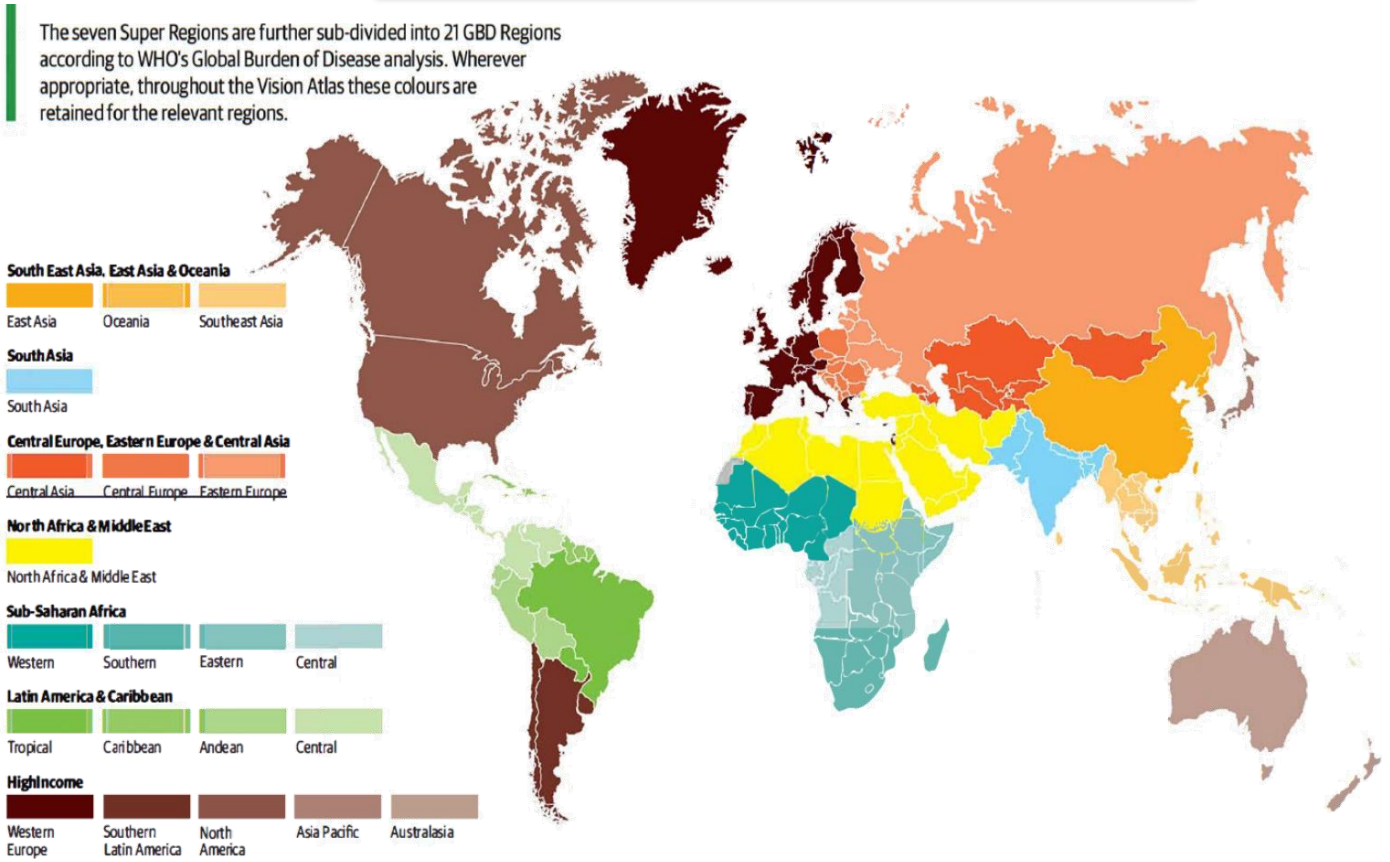
NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis. Estes C, et al. *J Hepatol* 2018;69:896–904; 2. Alswat K, et al. Saudi J Gastroenterol 2018;24:211–219

Evidence for progressiveness of NASH from global data

Global burden of disease related to cirrhosis and liver cancer (2012–2017)

- GBD: Initiated by the Institute for Health Metrics and Evaluation (IHME) in 1990, as an international collaborative effort to quantify health loss from hundreds of diseases, injuries, and risk factors
- We used GBD database to estimate burden attributable to liver cancer and cirrhosis
- 5 etiologies were used (alcohol use, CHB, CHC, NASH, and other causes)
- We calculated (rates per 100,000):
  - Age-standardized incidence (ASIR)
  - Age-standardized death (ASDR)
  - Age-standardized DALYs (ASDALY)
- Temporal trends and annual percentage change (APC) were also calculated

The global burden of disease 21 regions



GBD; Global Burden of Disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C; HBV, hepatitis B virus; NASH, non-alcoholic steatohepatitis. Paike J and Younossi Z 2019; Vision Atlas. Available at: http://atlas.iapb.org/gvd-maps/gbd-regions/ (Last accessed: September 2020)

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The growing burden of disease related to cirrhosis and liver cancer: Data from global burden of disease 2012–2017

Trends in incidence rates (GBD 2012–2017)

	Liver cancer						Cirrhosis					
	Liver cancer	Liver cancer due to HBV	Liver cancer due to HCV	Liver cancer due to Alcohol use	Liver cancer due to NASH	Liver cancer due to Other causes	Cirrhosis	Cirrhosis due to HBV	Cirrhosis due to HCV	Cirrhosis due to Alcohol use	Cirrhosis due to NASH	Cirrhosis due to Other causes
Global	1.17	1.38	0.75	0.87	1.95	1.61	0.10	-0.90	0.29	0.23	1.27	0.76
Australasia	1.28	1.13	1.49	1.09	1.31	1.09	1.02	1.29	1.13	0.99	1.31	0.61
High-income Asia Pacific	-2.06	-0.75	-2.89	-2.19	-1.57	-1.96	-0.44	-0.53	-0.65	-0.49	-0.13	-0.24
High-income North America	0.60	0.33	0.60	0.56	0.74	0.49	1.30	0.94	1.14	1.31	1.86	1.41
Southern Latin America	0.66	-0.31	0.42	1.36	1.40	0.55	0.48	-0.85	0.55	0.74	1.14	0.71
Western Europe	0.23	0.00	0.10	0.32	0.72	0.46	0.05	-0.39	-0.51	0.00	0.52	0.48
Central Asia	0.26	-0.23	0.23	0.49	0.87	0.11	-1.14	-2.49	-0.96	-0.78	0.00	-1.10
Central Europe	-0.44	-1.01	-0.47	-0.27	-0.19	-0.62	-0.99	-1.80	-1.02	-1.33	-0.59	-0.15
Eastern Europe	0.62	-0.34	0.80	1.02	1.33	0.83	-1.02	-3.20	-0.88	-0.69	0.00	-0.47
South Asia	1.10	0.65	1.13	1.40	1.61	1.00	0.59	0.00	0.81	1.04	1.59	0.56
East Asia	2.09	1.73	2.52	3.08	3.22	2.36	0.28	-0.76	1.58	1.50	2.71	1.15
Southeast Asia	-0.11	-0.30	-0.20	0.00	0.56	-0.59	0.00	0.00	-0.51	0.33	0.67	0.50
Oceania	-0.15	-0.31	-0.08	0.00	0.28	-0.27	0.61	0.35	0.77	0.54	1.00	0.93
Caribbean	1.00	0.85	0.87	1.16	1.41	0.83	1.19	0.80	1.26	1.18	1.56	1.14
Andean Latin America	-1.43	-2.00	-1.04	-1.32	-0.54	-1.55	0.00	-0.89	-0.25	-0.61	0.74	0.65
Central Latin America	0.21	0.00	0.00	0.59	0.74	0.14	0.69	0.26	0.51	0.86	1.01	0.68
Tropical Latin America	1.66	1.61	1.48	1.74	2.55	1.46	-0.21	-0.89	-0.53	-0.43	0.70	0.25
North Africa and Middle East	-0.47	-0.46	-0.84	-0.66	1.07	-0.58	0.27	-0.32	0.19	0.45	1.47	0.46
Central Sub-Saharan Africa	-2.46	-3.15	-2.77	-1.14	-1.85	-2.64	-0.15	-1.39	0.40	0.62	1.03	0.30
Eastern Sub-Saharan Africa	-0.74	-1.34	-0.57	-0.45	-0.29	-0.86	-0.11	-1.55	0.30	-0.07	0.52	0.41
Southern Sub-Saharan Africa	-2.46	-2.73	-2.41	-2.20	-1.95	-2.92	-1.61	-2.56	-1.72	-1.77	-1.12	-1.21
Western Sub-Saharan Africa	-1.58	-2.24	-1.24	-1.27	-0.66	-1.15	-0.28	-0.88	-0.08	-0.20	0.86	0.21
High SDI	-0.26	0.60	-1.00	-0.27	0.36	0.32	-0.23	-0.77	-0.49	-0.20	0.71	0.13
High-middle SDI	2.71	2.61	2.91	2.54	3.69	3.01	0.00	-0.77	0.60	-0.36	1.66	0.27
Middle SDI	1.15	0.89	1.40	1.37	2.06	1.44	0.25	-1.01	0.57	1.04	1.47	0.91
Low-middle SDI	-0.12	-0.88	0.00	0.48	0.93	-0.03	-0.15	-1.27	-0.04	0.39	0.83	0.51
Low SDI	-0.92	-1.50	-0.72	-0.63	-0.31	-0.82	0.44	-0.40	0.64	0.60	1.18	0.90

Trends in mortality rates (GBD 2012–2017)

	Liver cancer						Cirrhosis					
	Liver cancer	Liver cancer due to HBV	Liver cancer due to HCV	Liver cancer due to Alcohol use	Liver cancer due to NASH	Liver cancer due to Other causes	Cirrhosis	Cirrhosis due to HBV	Cirrhosis due to HCV	Cirrhosis due to Alcohol use	Cirrhosis due to NASH	Cirrhosis due to Other causes
Global	0.51	0.00	0.00	0.53	1.41	0.86	-0.70	-1.43	-0.50	-0.44	0.29	-0.52
Australasia	1.55	0.00	1.28	0.00	0.00	0.00	1.63	1.07	1.43	1.27	1.61	0.92
High-income Asia Pacific	2.88	-1.48	-3.25	-2.54	-2.02	2.44	-1.51	0.00	-1.87	0.00	0.00	-1.21
High-income North America	0.64	0.46	0.52	0.00	0.51	0.52	0.00	0.00	0.00	0.00	0.00	1.11
Southern Latin America	0.00	-0.82	0.00	0.95	1.01	0.00	-0.18	-1.51	0.00	0.00	0.64	0.00
Western Europe	0.00	-0.66	-0.58	0.00	0.00	0.00	-1.08	-1.39	-1.24	-0.96	0.00	0.00
Central Asia	0.71	0.00	0.75	0.97	1.35	0.56	-0.91	-1.79	-0.65	-0.78	0.21	-0.58
Central Europe	0.00	-0.45	0.00	0.00	0.00	0.00	-1.87	-2.15	-1.86	-1.60	-1.12	-1.59
Eastern Europe	2.18	0.00	2.17	2.48	2.46	2.00	0.00	0.00	0.00	0.00	0.00	0.00
South Asia	1.40	0.94	1.44	1.59	1.94	1.46	0.00	-0.95	0.00	0.48	1.29	0.00
East Asia	0.68	0.00	1.21	1.68	1.84	0.94	-1.09	-2.37	0.00	0.00	1.12	0.00
Southeast Asia	0.00	0.00	0.00	0.00	0.71	-0.43	-1.33	-1.68	-1.36	-1.08	-0.46	-1.18
Oceania	-0.15	-0.31	-0.09	0.00	0.26	-0.23	-0.60	-0.77	-0.46	-0.58	-0.10	-0.60
Caribbean	1.48	1.24	1.38	1.60	1.88	1.33	0.74	0.00	0.63	0.81	1.23	0.46
Andean Latin America	0.00	-1.39	0.00	0.00	0.00	0.00	-1.74	-2.50	-1.91	-1.80	-0.87	-1.76
Central Latin America	0.47	0.00	0.00	0.90	0.96	0.45	-0.44	-0.99	-0.57	-0.39	0.00	-0.31
Tropical Latin America	1.44	1.38	1.29	1.54	2.31	1.34	0.00	0.00	0.00	0.00	0.00	0.00
North Africa and Middle East	-0.43	-0.69	-0.62	-0.67	0.95	-0.57	-1.27	-1.62	-1.31	-1.27	0.00	-1.48
Central Sub-Saharan Africa	-2.07	-2.96	-2.21	-1.01	-1.38	-2.10	-0.82	-1.95	-0.49	0.00	0.49	-0.45
Eastern Sub-Saharan Africa	-0.61	-1.30	-0.42	-0.35	-0.15	-0.69	-2.08	-3.10	-1.67	-1.86	-1.30	-1.62
Southern Sub-Saharan Africa	-1.24	-1.38	-1.33	-0.99	0.00	-1.63	-1.87	-2.43	-1.70	-1.63	0.00	-2.35
Western Sub-Saharan Africa	-1.27	-1.96	-0.98	-0.89	-0.38	-0.86	-2.83	-3.24	-2.32	-2.98	-1.76	-1.92
High SDI	-0.81	0.00	-1.28	-0.68	0.00	-0.28	-0.83	-1.14	-0.95	-0.92	-0.44	0.00
High-middle SDI	1.26	0.00	1.67	1.46	2.31	1.35	-1.15	-2.21	-0.75	-0.94	0.00	-1.05
Middle SDI	0.00	0.00	0.86	0.99	1.51	0.78	-0.71	-1.49	-0.70	0.00	0.00	-0.59
Low-middle SDI	0.29	-0.42	0.40	0.72	1.26	0.50	-0.84	-1.87	0.00	0.00	0.55	-0.60
Low SDI	-0.59	-1.20	-0.37	-0.30	0.00	-0.49	-0.90	-1.66	-0.66	-0.41	0.00	-0.71

GBD, Global Burden of Disease. Paike J, et al. Hepatology 2020; American College of Gastroenterology Virtual Grand Rounds. Presentation by Younossi ZM, 2020. Available at: https://webfiles.gi.org/links/virtgrandround/Week11_ACGVGR_Younossi_Nash2.pdf (Last accessed: September 2020)

SANOFI

The growing burden of disability related to NAFLD: Data from global burden of disease 2007–2017

- GBD-2017 was used to assess years lost due to disability (YLD), years-of-life-lost (YLL) and disability-adjusted life-years (DALYs)
- In 2017, there were 62.16 million DALYs (33.4% LC; 66.5% cirrhosis)
- The majority of DALYs from CLD were attributed to YLL (96.8%) and only 3.2% from years-of-life-lived with disability
- **Between 2007–2017, CLD DALYs increased from 54.8 to 62.6 million. NAFLD showed the largest increase in DALYs from 2007 to 2017**

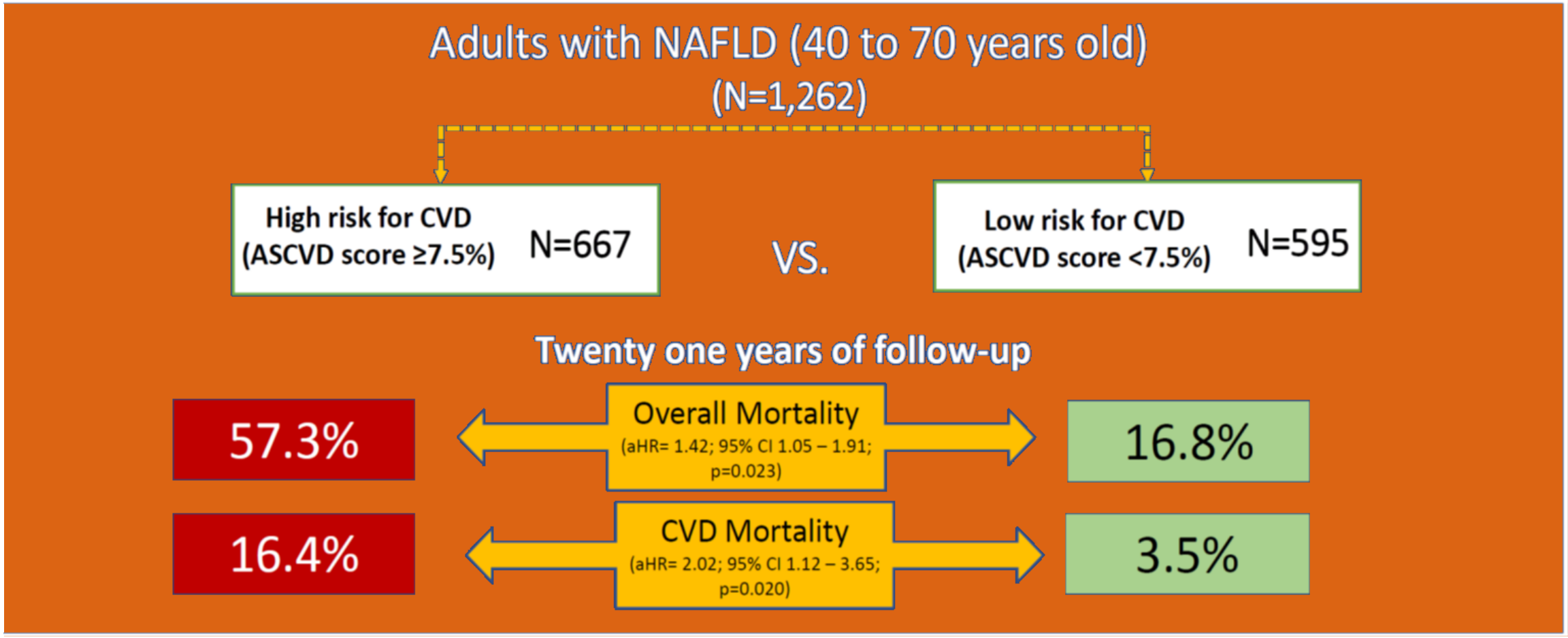
	LC	LC Due to ALD	LC Due to HBV	LC Due to HCV	LC Due to NAFLD
Global	-4.52	-0.48	-8.22	-2.89	6.40
Australasia	17.86	16.93	7.74	23.45	20.98
Trop Latin America	10.13	10.66	5.60	10.12	20.18
S Asia	11.73	15.44	8.06	11.66	18.65
MENA	2.72	3.02	1.79	0.48	16.98
HI N America	13.70	13.04	9.05	16.19	16.78
E Europe	2.28	5.95	-5.93	3.64	10.13
C Asia	1.30	3.97	-3.68	1.91	9.70
Caribbean	3.36	5.58	0.96	2.54	8.45
S Latin America	0.70	4.34	-8.00	-0.38	7.97
C Latin America	-1.91	0.20	-8.13	-2.34	5.25
SE Asia	-2.91	0.21	-5.48	-3.95	4.20
E Asia	-6.31	0.32	-9.63	-1.30	3.88
W Europe	-2.43	-2.33	-6.13	-2.09	2.34
Oceania	-1.78	-0.18	-3.16	-0.72	1.75
A Latin America	-8.69	-6.02	-13.87	-4.54	1.17
C Europe	-3.51	-0.99	-9.00	-3.12	0.98
E Sub-Sah Africa	-7.50	-4.32	-10.49	-7.95	-3.62
W Sub-Sah Africa	-13.88	-11.66	-17.60	-11.50	-6.81
C Sub-Sah Africa	-19.55	-13.28	-24.67	-19.50	-14.94
S Sub-Sah Africa	-28.07	-25.88	-31.53	-25.10	-23.12
HI Asia Pac	-28.73	-29.67	-22.81	-33.24	-25.19

	Cirrhosis	Cirrhosis Due to ALD	Cirrhosis Due to HBV	Cirrhosis Due to HCV	Cirrhosis Due to NAFLD
Global	-10.58	-9.33	-14.69	-8.91	-2.04
Australasia	7.60	8.79	-1.37	8.82	15.97
Trop Latin America	-9.93	-10.76	-19.72	-10.43	1.93
S Asia	-5.76	0.34	-9.16	-3.57	5.09
MENA	-10.46	-9.52	-13.44	-9.50	2.06
HI N America	4.83	2.68	3.62	2.97	7.57
E Europe	-13.64	-10.63	-24.87	-10.91	-4.44
C Asia	-7.30	-3.91	-16.61	-4.30	4.90
Caribbean	-1.10	-0.43	-5.10	-0.73	4.81
S Latin America	-2.22	-0.70	-13.30	-1.66	6.55
C Latin America	-6.44	-6.53	-14.80	-7.58	-0.59
SE Asia	-15.23	-12.07	-18.16	-14.98	-8.88
E Asia	-14.87	-7.68	-21.06	-9.86	0.46
W Europe	-15.16	-15.95	-18.74	-16.44	-11.17
Oceania	-5.61	-3.58	-8.17	-3.44	-1.19
A Latin America	-15.02	-15.35	-25.97	-14.84	-4.73
C Europe	-20.67	-19.41	-25.31	-20.80	-14.03
E Sub-Sah Africa	-20.48	-19.20	-25.29	-19.67	-14.37
W Sub-Sah Africa	-23.85	-26.69	-25.73	-20.90	-18.66
C Sub-Sah Africa	-2.96	3.55	-9.82	-0.64	7.10
S Sub-Sah Africa	-38.23	-38.15	-42.42	-36.76	-32.30
HI Asia Pac	-14.88	-14.80	-15.24	-16.23	-11.84

Data gathered between 2007–2012 from 21 regions and 195 countries
CLD, chronic liver disease; LC, HBV, hepatitis B virus; HCV, hepatitis C virus; liver cirrhosis; NAFLD, non-alcoholic fatty liver disease
Paike J, et al. J Hepatol 2020;73:S19–S57. Abstract AS063

SANOFI

CV and overall mortality risks detected by atherosclerotic cardiovascular disease score in patients with NAFLD

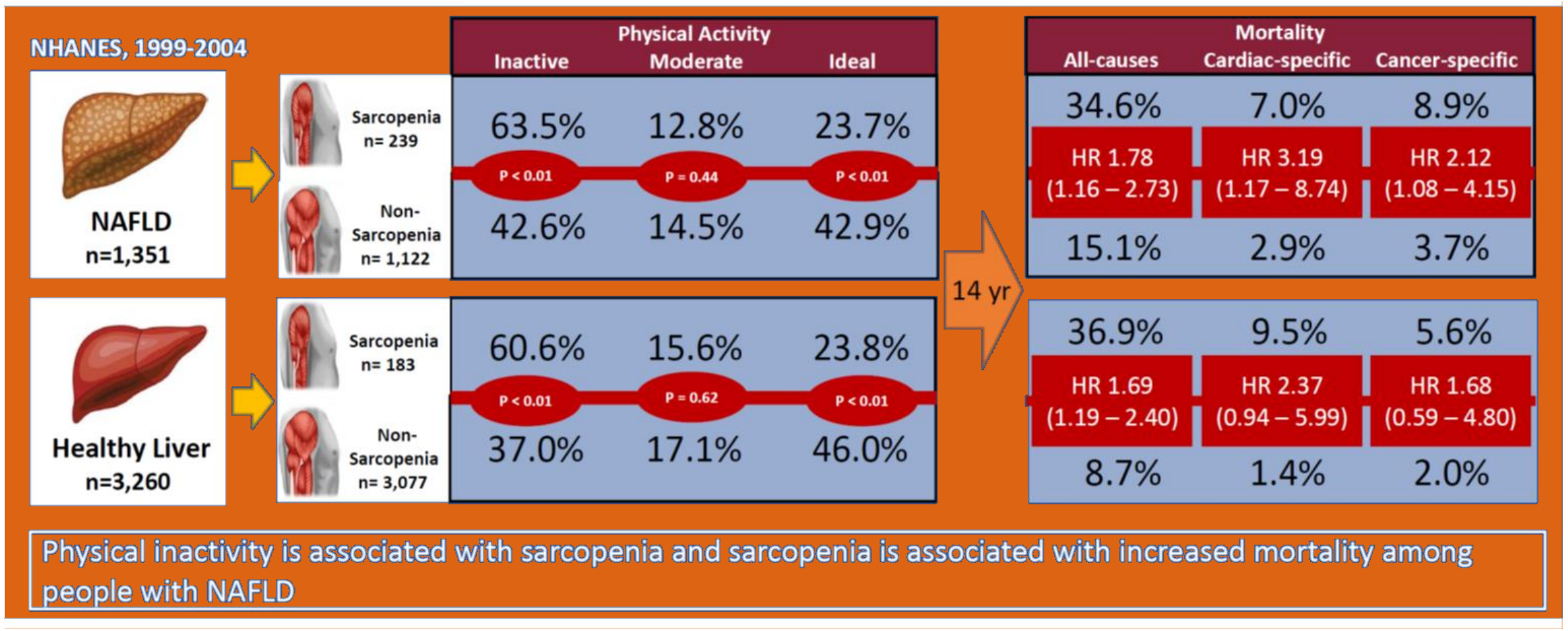


aHR, adjusted hazard ratio; ACSVD, artherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease

Golabi P, et al. Hepatology Communications 2019;31050–60

SANOFI

Sarcopenia and physical inactivity can impact mortality among patients with NAFLD



HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease

Golabi P, et al. JHEP Reports 2020;2:100171

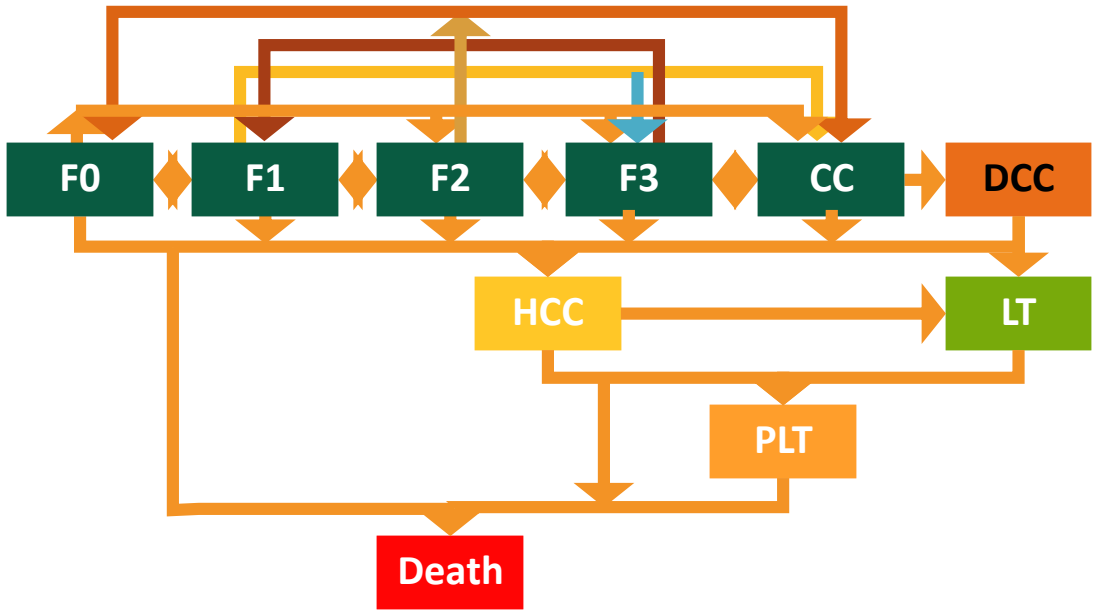
SANOFI

Economic burden of NASH

Markov models (prevalence and incidence)

- 6.65 million adults with NASH in the US and 232,000 incident cases in 2017
- 688,000 cases of advanced NASH in the US
- Lifetime direct costs of all NASH will be $222.6 billion
- **Lifetime direct costs of the advanced NASH population will be $95.4 billion**

Markov model structure



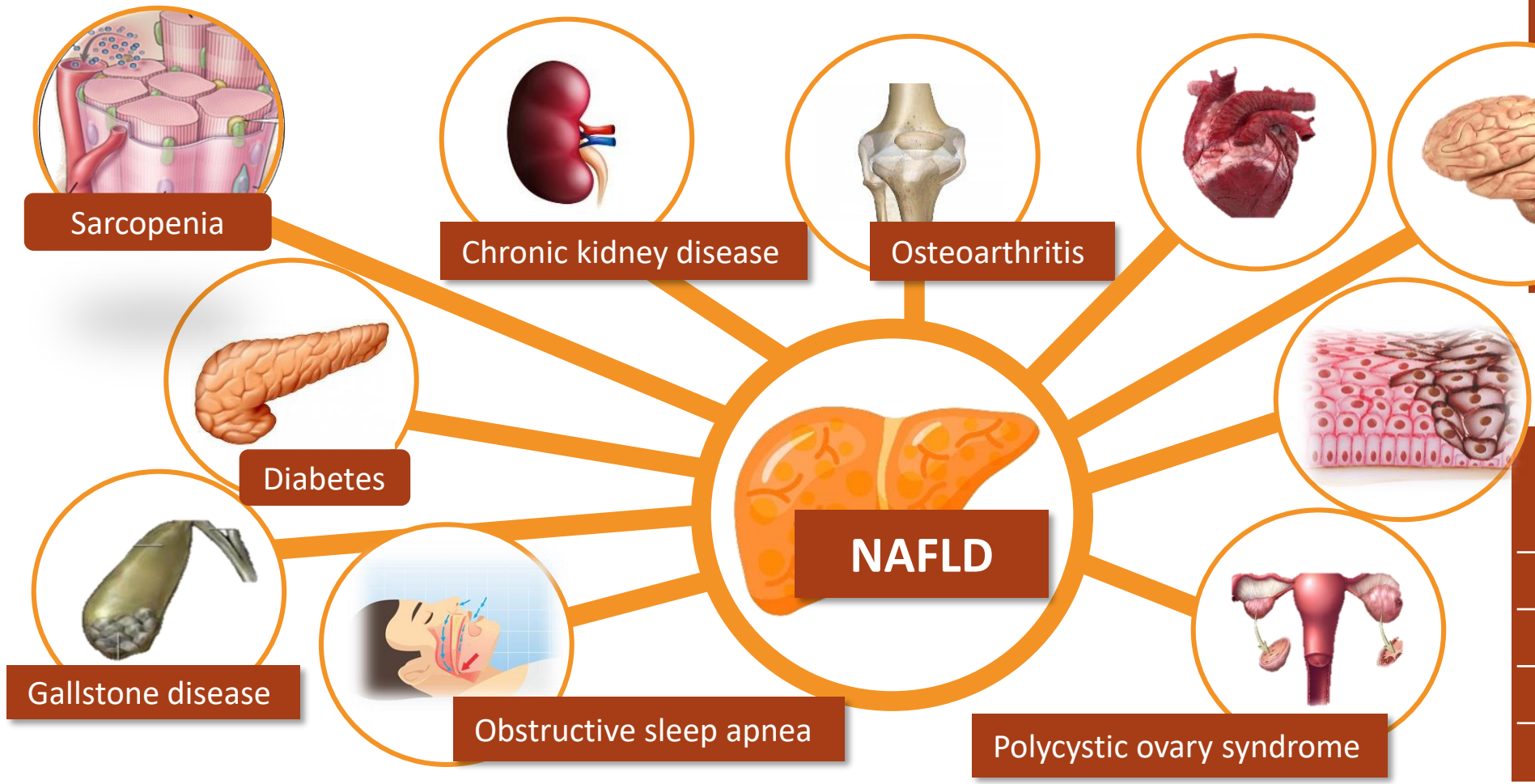
DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PLT, post-liver transplant
Younossi ZM, et al. Hepatology 2016;64:1577–86; Younossi ZM, et al. Hepatology 2019;69:564–72

SANOFI

The burden of NAFLD: The impact of associated comorbidities

Non-liver related outcomes of NAFLD

NAFLD is part of a multisystem disorder



CV Deaths	
	38.3%
	30%
	16%
	38%
	12.7%

Malignancy	
Site	**Fold increase***
Liver	4.0
Stomach	3.5
Pancreas	2.7
Lung	2.0

*Fold increase in incidence of malignant cancer diagnosis in patients with NAFLD compared to healthy controls. CV, cardiovascular; NAFLD, non-alcoholic fatty liver disease

Angulo P, et al. Gastroenterology 2015;149:389–97; Söderberg C, et al. Hepatology 2010;51:595–602; Ekstedt M, et al. Hepatology 2006;44:865–73; Dam-Larsen S, et al. Scand J Gastroenterol 2009;44:1236–43; Rafiq N, et al. Clin Gastroenterol Hepatol 2009;7:234–8; Hicks SB, et al. Oral abstract presented at AASLD 2018; Younossi ZM, et al. Hepatology 2019;69:2672–82

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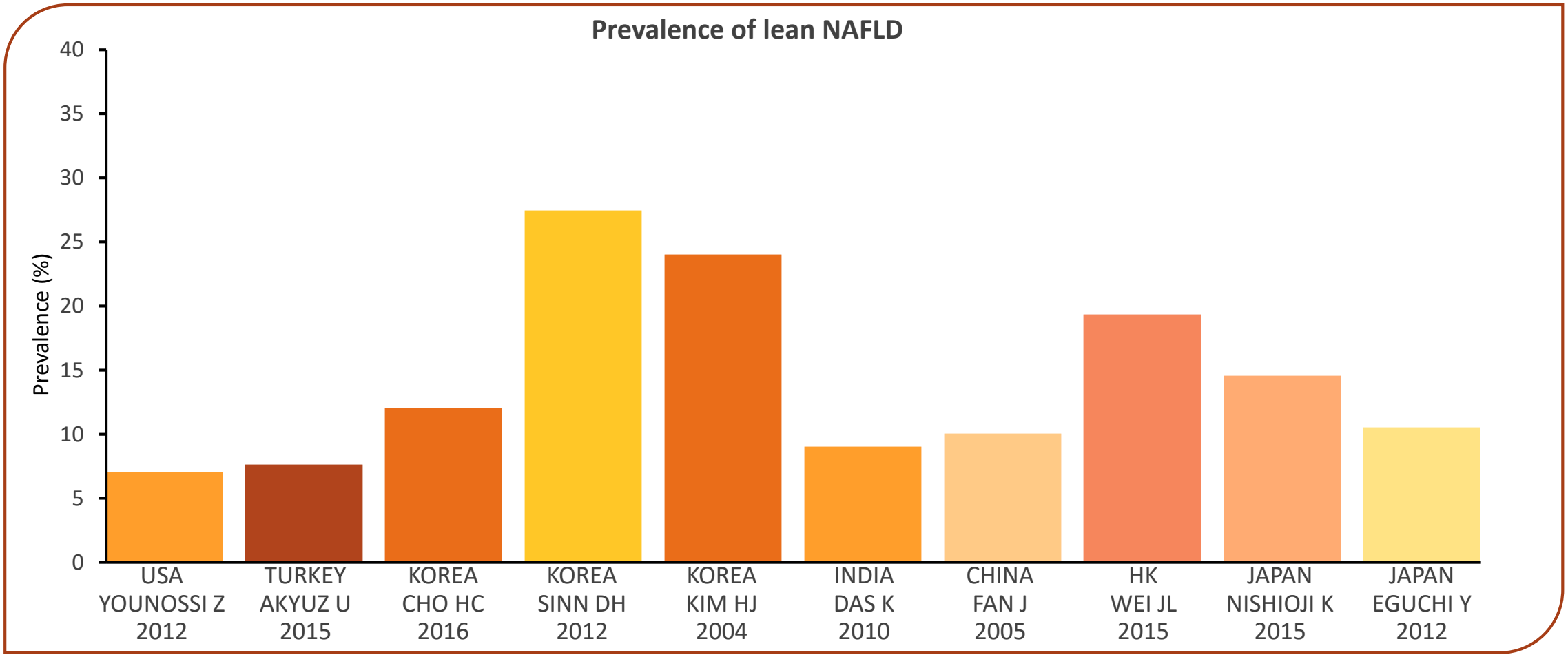
Although most NAFLD patients are obese, there are some patients with lean NAFLD



NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; UAE, United Arab Emirates. Younossi ZM, et al. Hepatology 2019;69:2672–82

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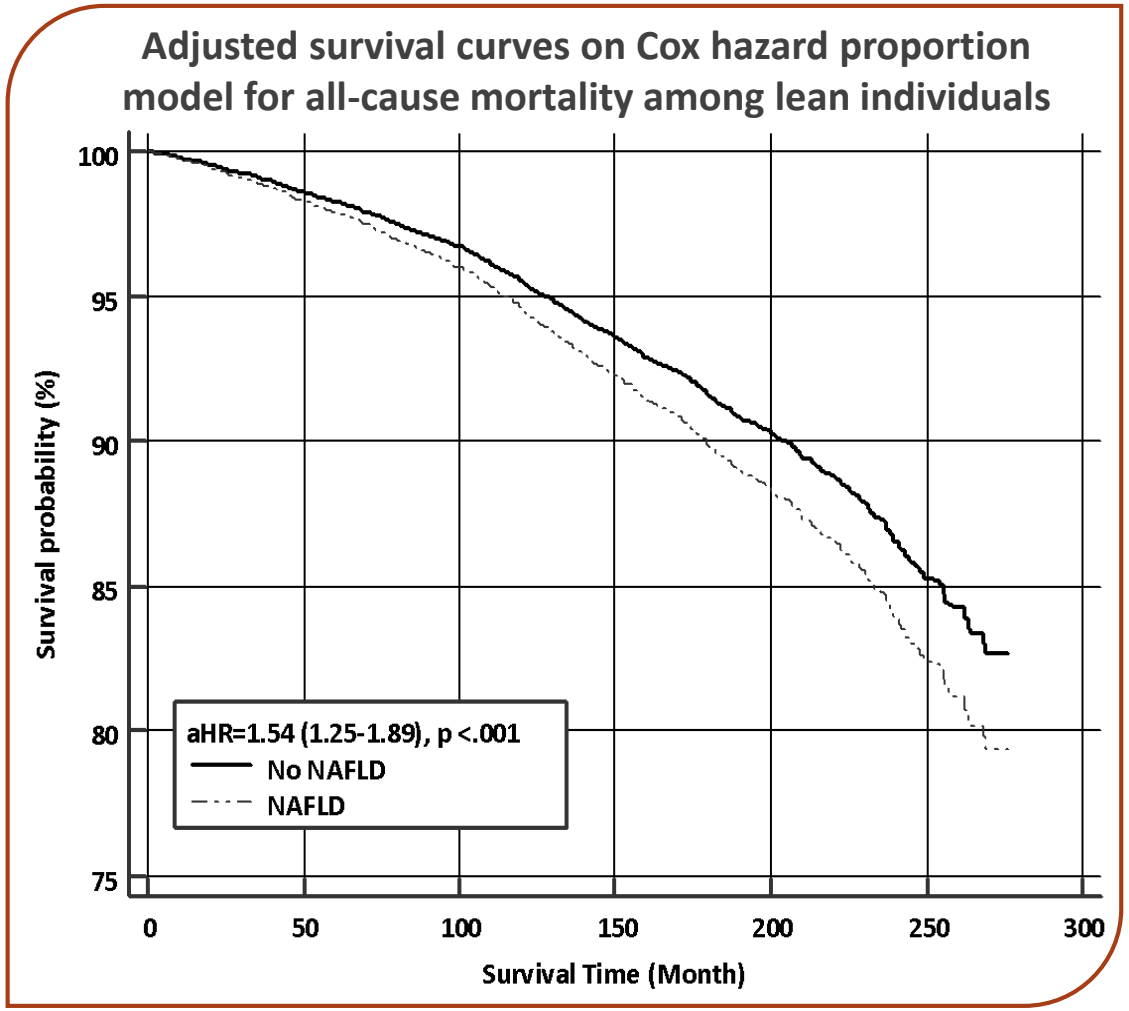
Long-term outcomes of lean NAFLD

- Lean (BMI ≤ 25) adult participants of NHANES-III (1988-1994) with mortality follow-up data
- The lean study cohort consisted of 5,375 individuals
- 10.8% of lean cohort (N=581) had NAFLD
- Compared to lean individuals without NAFLD, people with lean NAFLD were significantly more likely to be:
  - Older: 50.92 ± 1.26 vs. 41.8 ± 0.60, p<0.001
  - Male: 58.67 ± 3.13 vs. 39.19 ± 0.86, p<0.001
  - Diabetes 20.28 ± 2.27 vs. 0.29 ± 0.11, p<0.001
  - High cholesterol 35.03 ± 2.52 vs. 13.19 ± 0.74, p<0.001
  - Hypertension 31.29 ± 2.59 vs. 13.29 ± 0.80, p<0.001
- In the fully adjusted model, NAFLD was independently associated with an increased risk of all-cause (aHR=1.54, 95% CI: 1.25-1.89) and cardiovascular (aHR=2.38, 95% CI: 1.50-3.77) mortality



aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey

Golabi P, et al. Clinical Diabetes 2018;cd180026

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Which of these patient-reported outcomes do you feel is the most important to address in NAFLD?

1. Fatigue/tiredness
2. Obesity
3. Abdominal discomfort/stomach pain
4. Sleeping problems
5. Nausea
6. Muscle cramps
7. Mental health issues

NAFLD, non-alcoholic fatty liver disease

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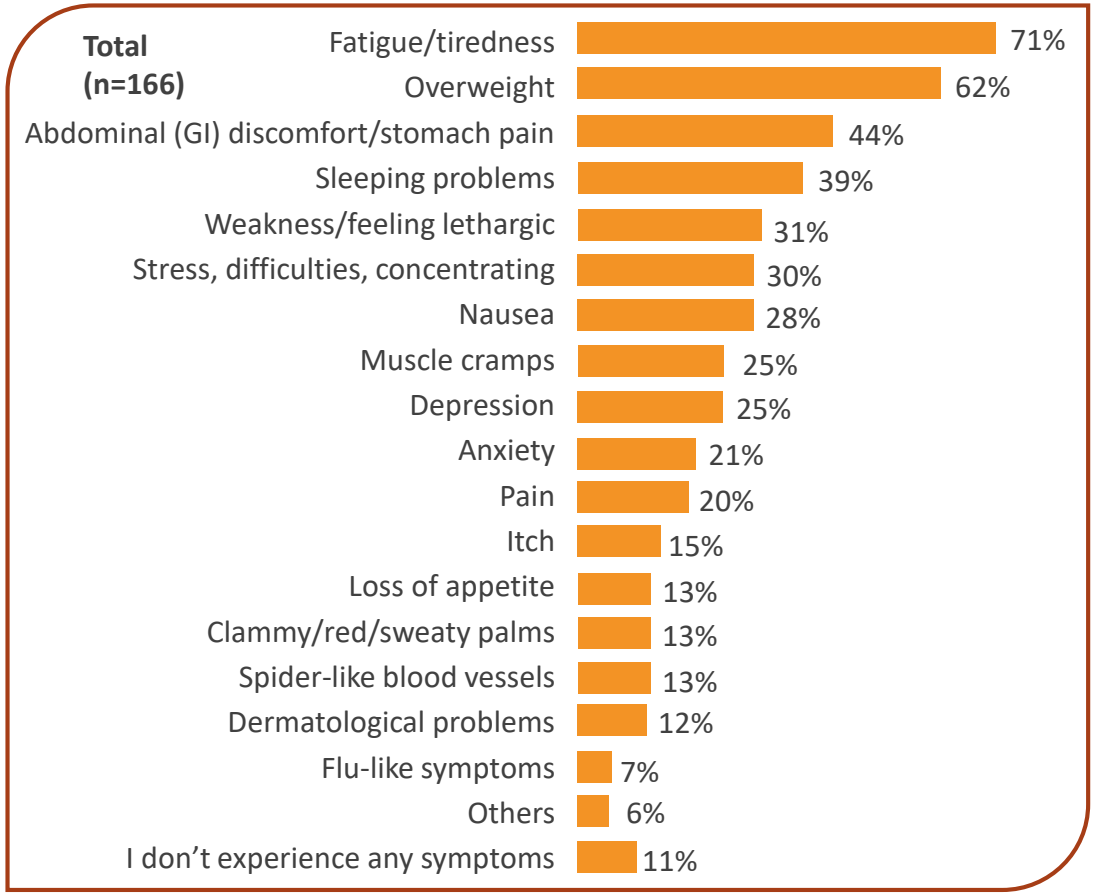
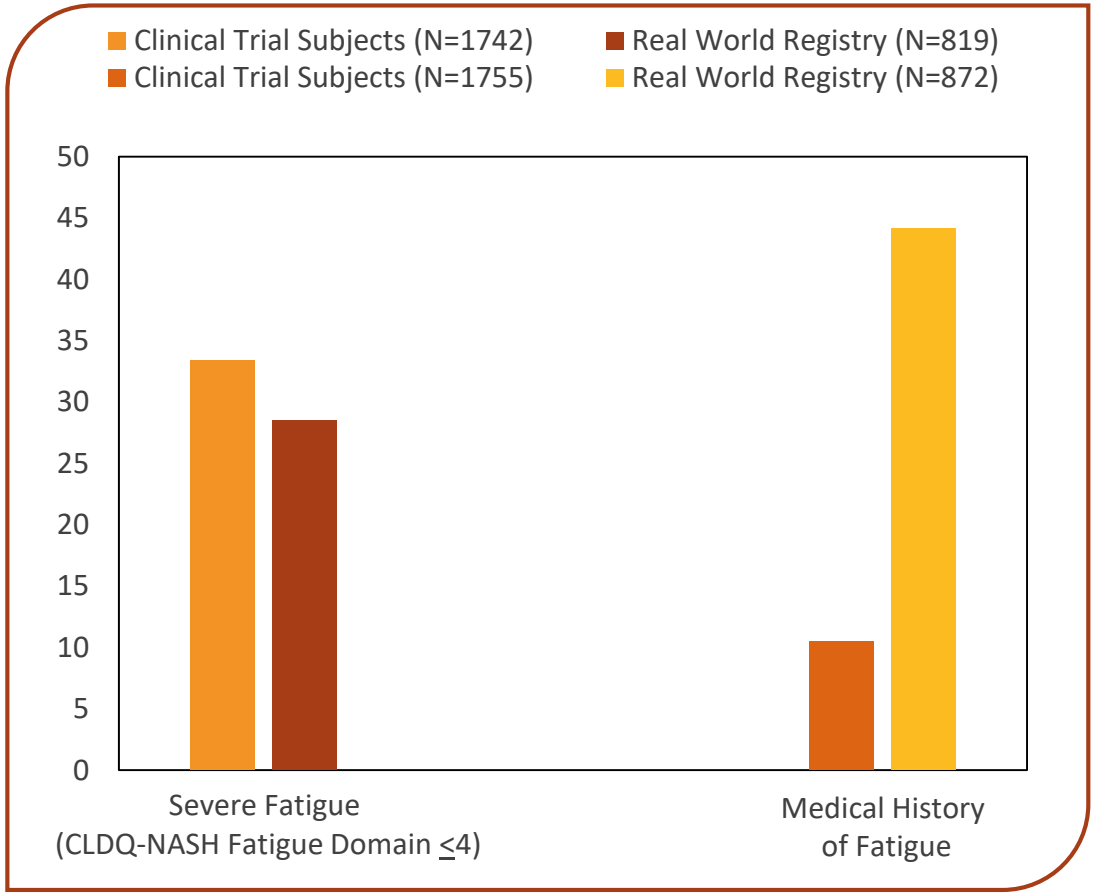
The burden of NAFLD: Patient-reported outcomes

SANOFI

Patient reported outcomes in NASH





CLDQ, Chronic Liver Disease Questionnaire; NASH, non-alcoholic steatohepatitis

Cook N, et al. Frontier in Medicine 2019; American College of Gastroenterology Virtual Grand Rounds. Presentation by Younossi ZM, 2020. Available at: https://webfiles.gi.org/links/virtgrandround/Week11_ACGVGR_Younossi_Nash2.pdf (Last accessed: September 2020)

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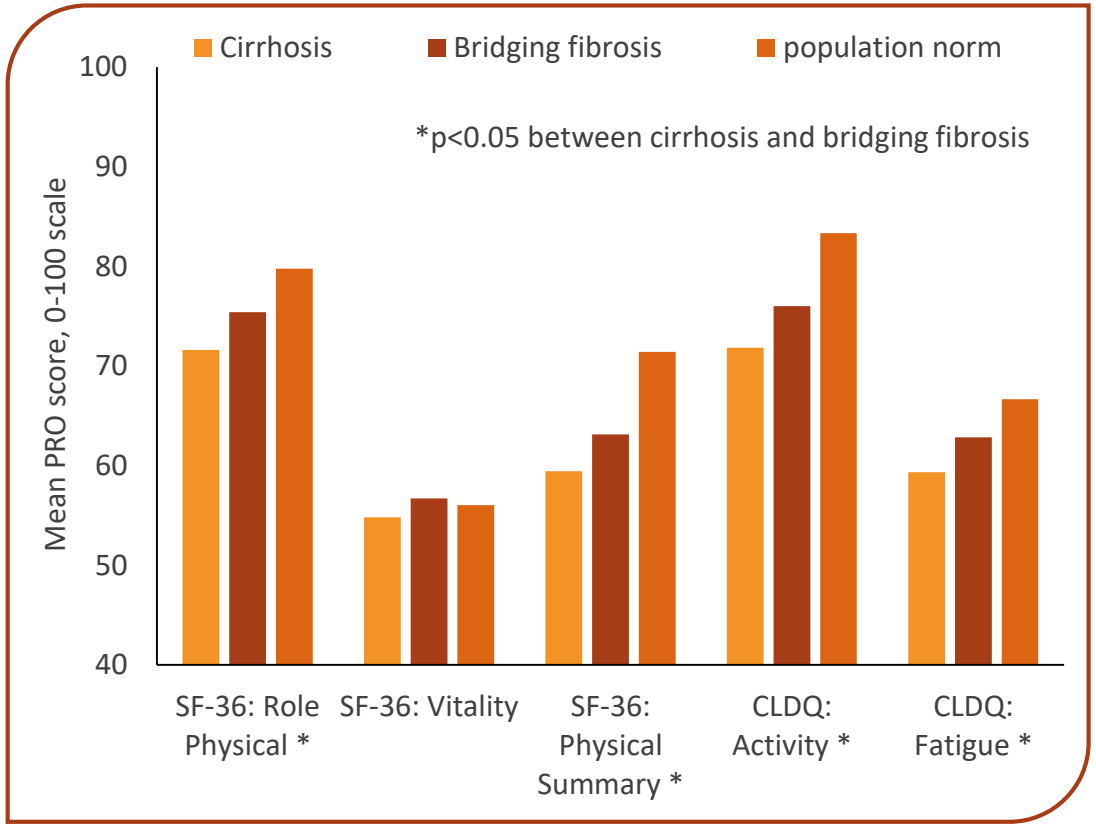
Fatigue in NASH with advanced fibrosis

- Biopsy proven NASH from STELLAR 3 and 4 (N=1667) completed 4 PRO questionnaires [SF-36, CLDQ-NASH, EQ-5D, WPAI:SHP] prior to treatment initiation
  - **CLDQ-NASH is the disease-specific instrument for clinical trials of NASH**
  - **Fatigue and physical health-related PRO scores were lower than population norms** (all p<0.01)
  - **Compared to NASH patients with F3, those with cirrhosis (p<0.02) had lower fatigue scores (CLDQ-NASH Fatigue Domain [4.56 vs. 4.77, p=0.002])**
  - MVA: Independent **predictors of lower Fatigue-related PRO scores** included female gender, lower albumin and **presence of diabetes** and other comorbidities (p<0.01)



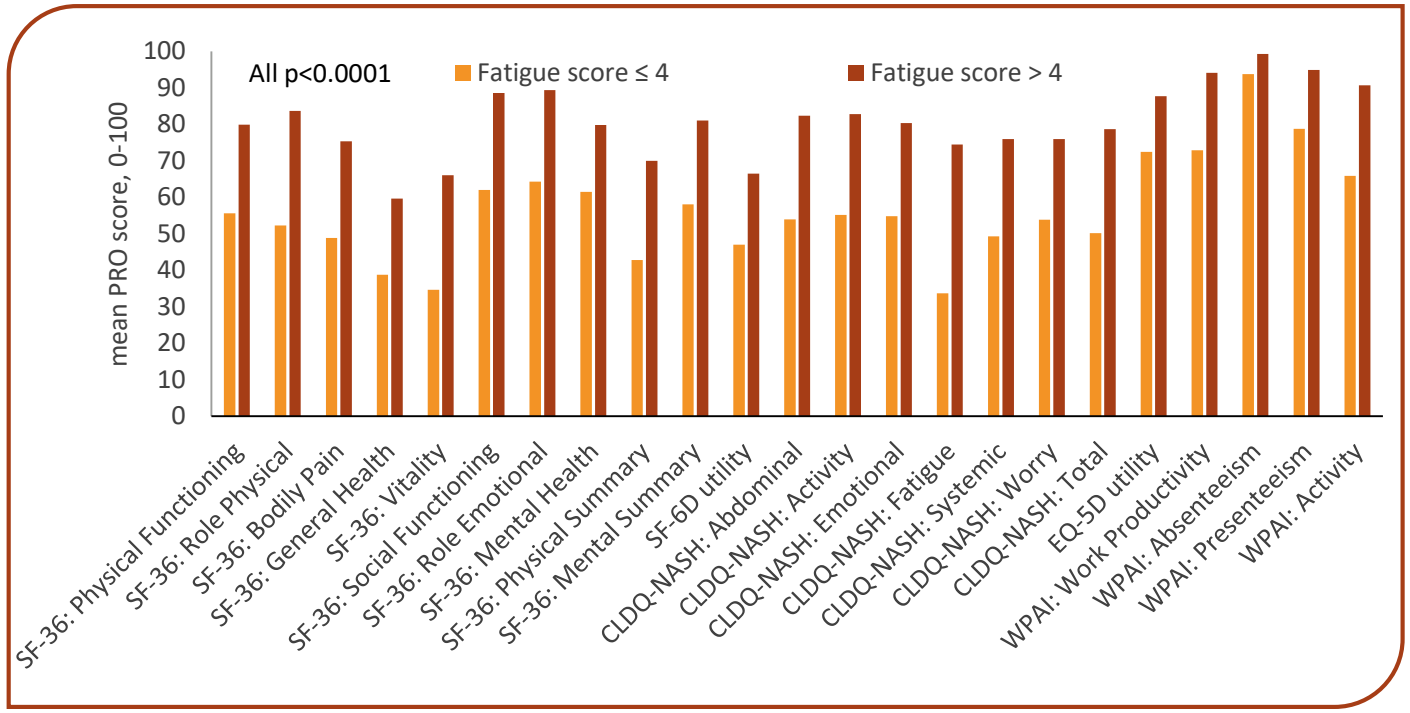
CLDQ, Chronic Liver Disease Questionnaire; NASH, non-alcoholic steatohepatitis; PRO, patient-reported outcomes

Younossi ZM, et al. Clin Gastro Hepatol 2019;17:2552–60

SANOFI

Impact of fatigue on health related quality of life in NASH

- In a multivariate analysis, predictors of clinically significant fatigue were:
  - Female gender [OR=1.47 (1.15-1.89)
  - History of depression [2.18 (1.67-2.83)],
  - Nervous system disorders [1.39 (1.10-1.77)]
  - Lower serum albumin (0.40 (0.28-0.59) per g/dL)
  - Younger age, non-Asian race, diabetes, and other psychiatric comorbidities and some laboratory tests



ALP, alkaline phosphatase; CLDQ, Chronic Liver Disease Questionnaire; CRP, C-reactive protein; ELF, enhanced liver fibrosis; GGT, gamma-glutamyl transferase; NASH, non-alcoholic steatohepatitis; NFS, NAFLD fibrosis score; OR, odds ratio; PRO, patient-reported outcomes.

Younossi Z, et al. Hepatology Communication 2020; American College of Gastroenterology Virtual Grand Rounds. Presentation by Younossi ZM, 2020. Available at: https://webfiles.gi.org/links/virtgrandround/Week11_ACGVGR_Younossi_Nash2.pdf (Last accessed: September 2020)

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Summary

1. NASH is the potentially **progressive** type of NAFLD
2. NAFLD/NASH are part of a **multisystemic disease** related to metabolic abnormalities
3. NAFLD/NASH are rapidly becoming the **most common cause of liver disease** in the world
4. NAFLD and NASH have a significant and growing **clinical, economic and quality of life burden**

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

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