

The Global Burden of NASH - Regional Disparities Related to Disease Burden

**Zobair M Younossi MD, MPH,
FACP, FAASLD, AGAF, FACG**

President, Inova Medicine Services, Inova Health System
Chairman and Professor of Medicine, Inova Fairfax Hospital,
Falls Church, Virginia, United States

Research funding and/or consultant: NovoNordisk, Gilead Sciences, Intercept, Bristol-Myers Squibb, Terns, Siemens, Quest, Abbvie, Madrigal, Merck, Abbott, 89BIO and Novartis.

Disclosures

- Consultant: Merck, Siemens, Terns, Gilead, Novo Nordisk, Intercept

The Global Burden of NASH - Regional Disparities Related to Disease Burden

- Healthy People 2020 defines health disparity as ***a particular type of health difference that is closely linked with economic, social, or environmental disadvantage.***
- *Health disparities adversely affect groups of people who have systematically experienced greater social or economic **obstacles to health based on** their racial or ethnic group, religion, socioeconomic-status, gender, age, or mental health, cognitive, sensory, or physical disability, sexual orientation or gender identity, geographic location, or other characteristics historically linked to discrimination or exclusion.”*

The Global Burden of NASH - Regional Disparities Related to Disease Burden

- Global health disparities for NAFLD and NASH encompass multi-level complex interactions between:
 - **Immediate or proximal factors** such as **prevalence** of NAFLD and the associated risk factors: **demographic risks** (males, Hispanic, older age, lower socioeconomic status), **clinical risks** (obesity, T2DM), **genetic risks** (PNPLA3), and **health behavior risks** (nutrition, activity)
 - **Intermediate factors** such as social relationships and those related to neighborhoods
 - **Distant factors** such as cultural factors and national health policies
- Health disparities in NAFLD and NASH contribute to:
 - low disease awareness,
 - challenges in understanding disease burden of NAFLD and NASH
 - challenges in risk stratification with NIT
 - applicability of clinical trial data to the real world care of NAFLD patients

The Global Prevalence of NAFLD and NASH

Worldwide prevalence of NAFLD is **25%**

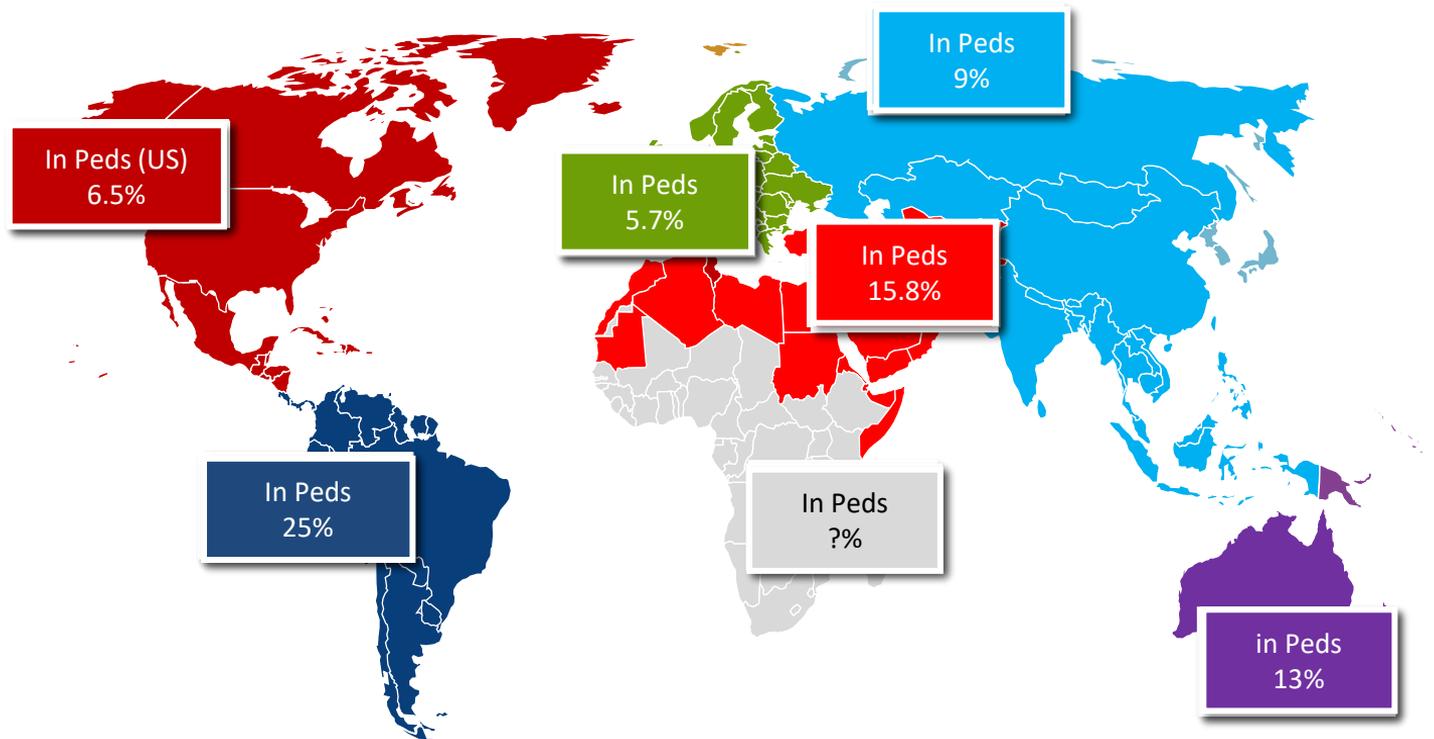


Worldwide prevalence of NAFLD among Children is **7.6%**

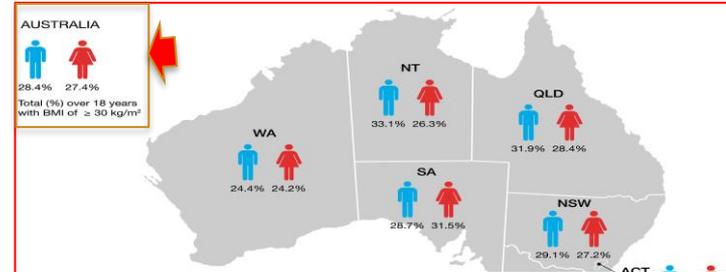
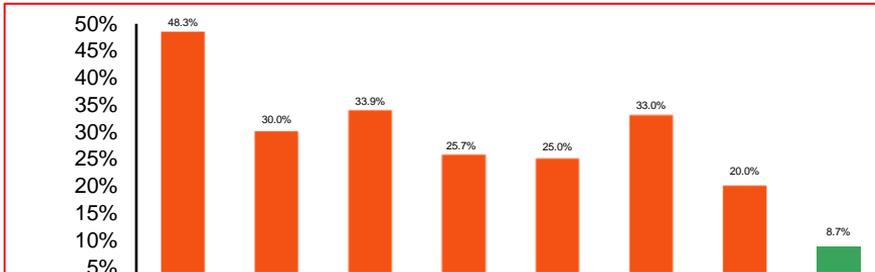
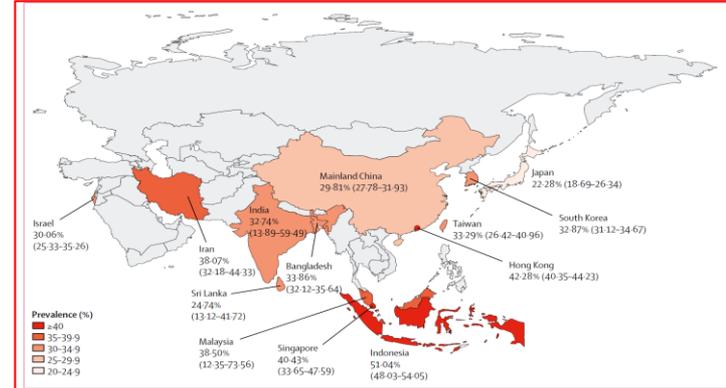
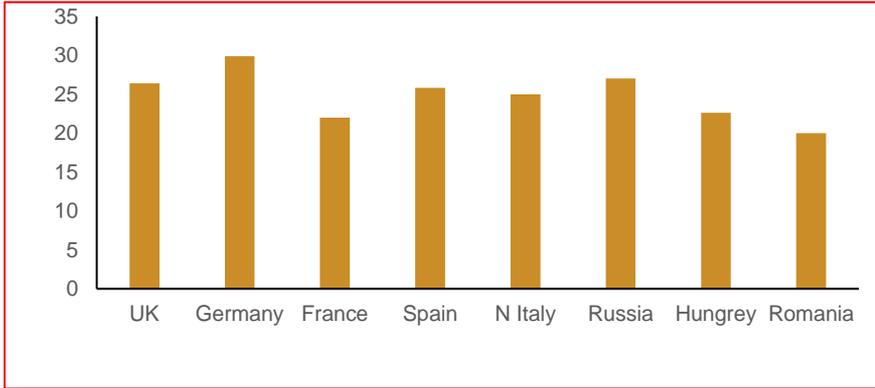
Worldwide prevalence of NAFLD among people with T2DM is **55.5%**

- Prevalence of NASH in general population is between 1.5–6.5%
- Prevalence of NASH among T2DM is 37.3% (24.7-50.0%)

Health Disparities: There are Differences in Regional Prevalence Rates for NAFLD



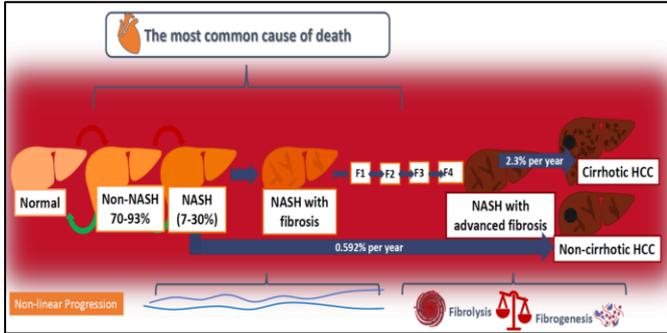
Health Disparities: Differences in the Country-Specific Prevalence Rates for NAFLD in Europe, MENA and Australia



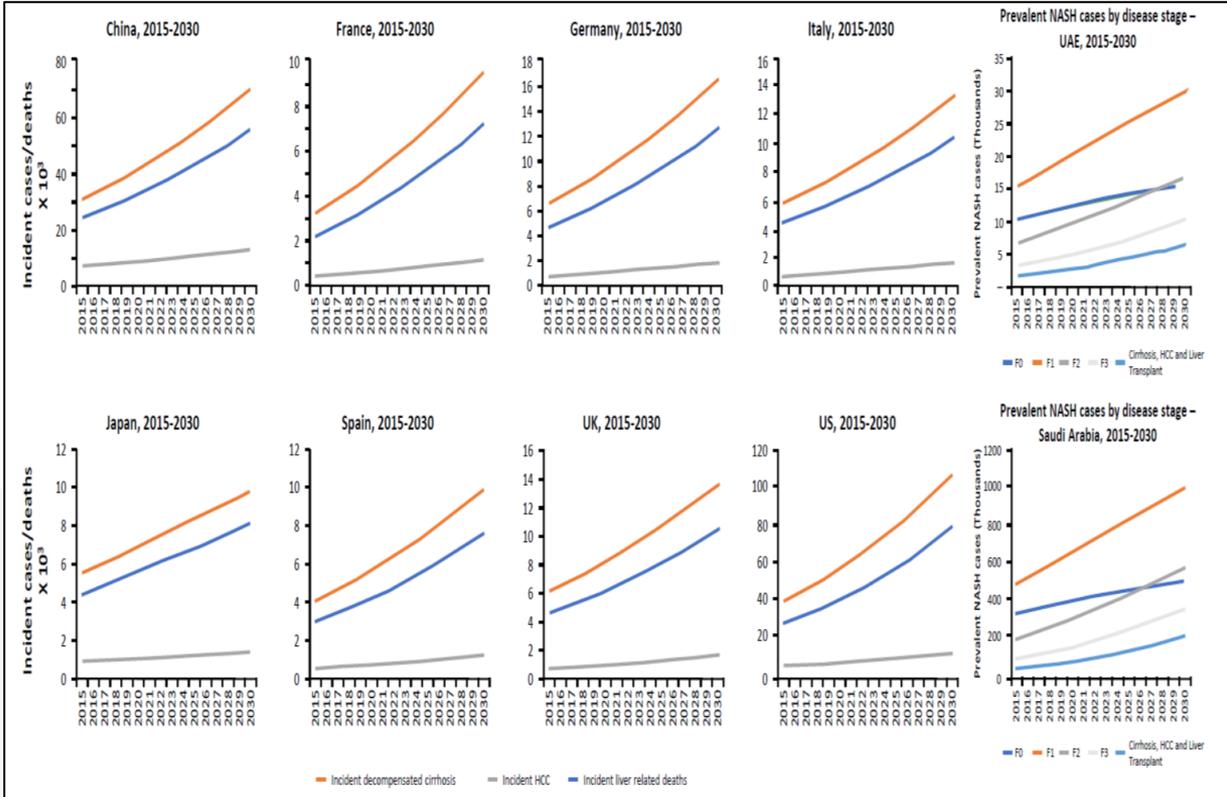
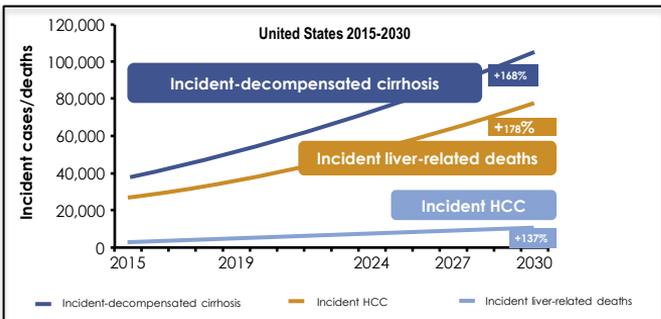
Regional and Country specific prevalence of NAFLD/NASH is impacted by rates of obesity, T2DM, activity, nutrition and possibly genetics (PNPLA3)

Health Disparities: Progression is not Uniform

15-20% of NASH Can Progress to Advanced Liver Disease

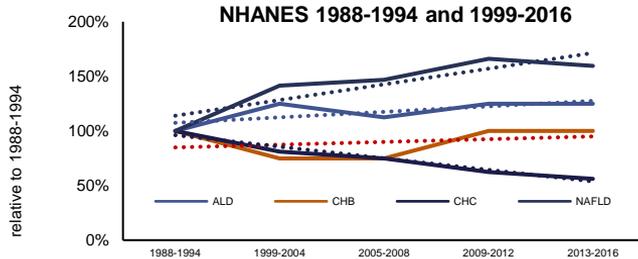


- T2DM and components of MS associated with mortality
- Stage of fibrosis ≥ 2 (or NIT) associated with mortality
- Lean NAFLD may be more aggressive in the West and less aggressive in the East



US Health Disparities: Higher Prevalence of NAFLD is Associated with Age, Male Gender and Hispanic

- 58,731 adults from NHANES (1988-2016)
 - HBV and ALD remained stable, HCV decreased while NAFLD increased
 - Trend analyses showed that only NAFLD consistently increased (trend p=0.01).



Predictor	Odds ratio (95% CI)	p
Study cycle	0.99 (0.96 - 1.02)	0.48
Age, per year	1.015 (1.012 - 1.019)	<.0001
Male (ref.: female)	2.34 (2.11 - 2.61)	<.0001
Black (ref.: white)	0.30 (0.26 - 0.34)	<.0001
Hispanic (ref.: white)	2.71 (2.40 - 3.05)	<.0001
Obesity	10.37 (9.52 - 11.31)	<.0001
Type 2 diabetes	3.68 (3.23 - 4.19)	<.0001
Hypercholesterolemia	2.32 (2.11 - 2.54)	<.0001
Hypertension	1.83 (1.63 - 2.06)	<.0001
Smoking	0.81 (0.71 - 0.91)	0.0006

- NAFLD was determined by US-FLI in the absence of other LD
- Overall prevalence of NAFLD was
 - 18.7% among late adolescents and young adults (18-24 yrs)
 - 24.0% among older young adults (25-30 yrs)
- Among all age groups, **Hispanics had a higher prevalence than Whites and Black.**

TABLE 3. COMPARISONS IN NAFLD PREVALENCE BY AGE GROUP, SEX, AND RACE/ETHNICITY: NHANES 2007-2016

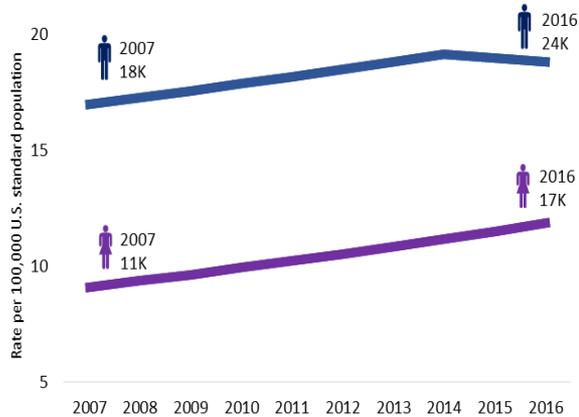
Characteristics	Total Sample Aged 12-29		Early and Middle Adolescents Aged 12-17		Late Adolescents Aged 18-24		Young Adults Aged 25-29	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Aged 12-17	Reference							
Aged 18-24	1.51 (1.18-1.92)	0.0013						
Aged 25-29	2.12 (1.68-2.68)	<0.0001						
Sex and race								
White female	Reference		Reference		Reference		Reference	
White male	1.67 (1.23-2.27)	0.0013	1.65 (0.97-2.83)	0.0663	1.26 (0.79-2.01)	0.3366	2.23 (1.38-3.62)	0.0087
Black female	0.74 (0.49-1.11)	0.1366	0.84 (0.40-1.78)	0.6421	0.40 (0.20-0.80)	0.0106	1.17 (0.72-1.92)	0.5260
Black male	0.67 (0.46-0.97)	0.0363	1.18 (0.63-2.20)	0.6058	0.47 (0.24-0.92)	0.029	0.58 (0.29-1.16)	0.1202
Hispanic female	2.81 (1.99-3.97)	<0.0001	4.18 (2.47-7.08)	<0.0001	2.17 (1.25-3.78)	0.0069	2.81 (1.60-4.91)	0.0004
Hispanic male	3.61 (2.72-4.80)	<0.0001	4.61 (2.81-7.55)	<0.0001	2.80 (1.74-4.50)	<0.0001	3.96 (2.42-6.50)	<0.0001
Other female	0.64 (0.33-1.25)	0.1848	1.21 (0.38-3.84)	0.7442	0.37 (0.11-1.26)	0.1107	0.79 (0.33-1.87)	0.5880
Other male	1.16 (0.72-1.87)	0.5484	1.83 (0.82-4.07)	0.1392	0.82 (0.32-2.10)	0.6797	1.17 (0.55-2.51)	0.6760

US Health Disparities: Progression is not Uniform

Mortality Related to NAFLD is Increasing in the United State

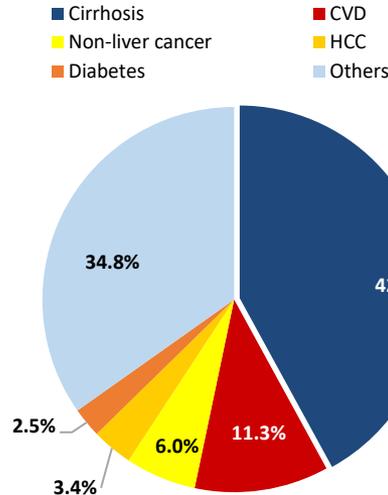
In 2016, more than 40,000 decedents in the U.S. had NAFLD (NVSS)

Age-standardized NAFLD-related Death Rates (2007-2016)



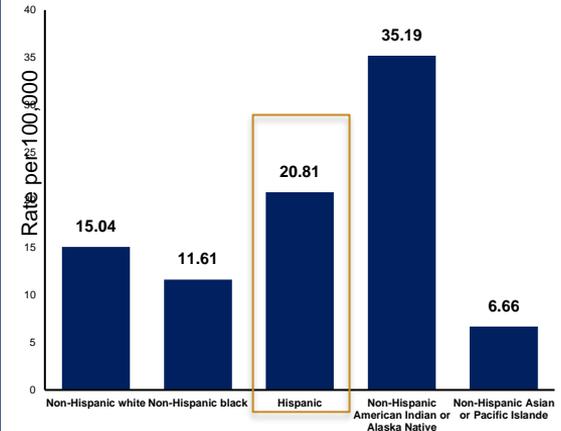
Annual increases in NAFLD-related deaths were observed for women (3.0%) and men (1.2%)

% Distribution of NAFLD-related Deaths, Based on Underlying Causes of Death (2016)



Between 2007-2016, annual increase was highest for HCC (3.8%), followed by diabetes (2.2%), non-liver cancer (2.1%), CVD (2.2%), and cirrhosis(1.0%).

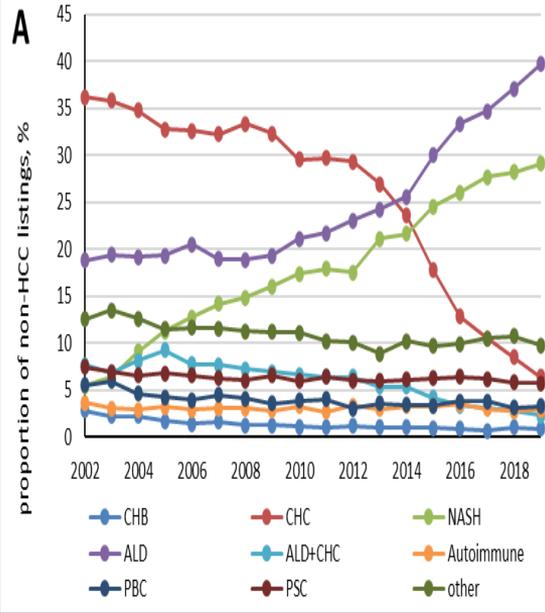
Age-standardized NAFLD-related Death Rate (2016)



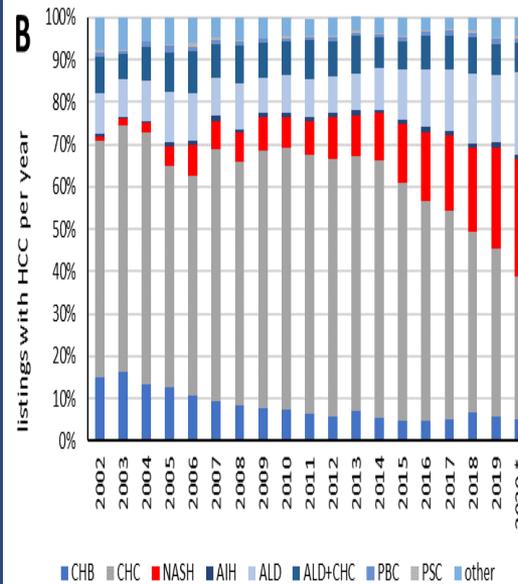
US Health Disparities: Progression is not Uniform

Liver Transplantation Related to NAFLD is Increasing in the United State

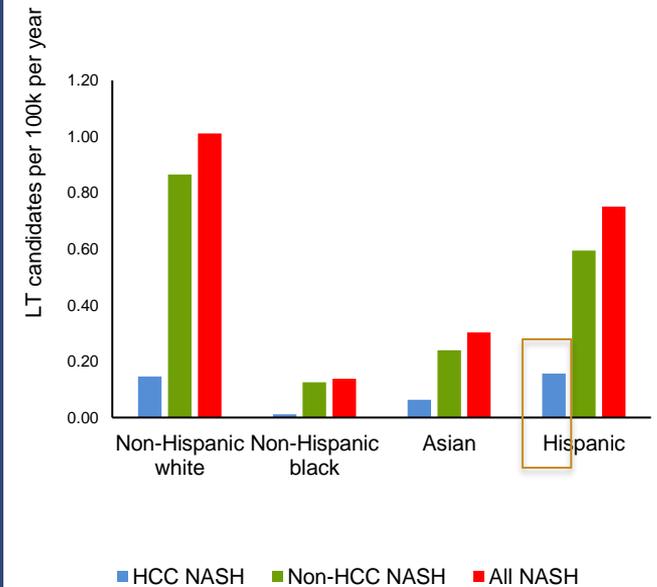
Waitlisted For Liver Transplantation in the U.S (2002-2019)



Proportions of LT Candidates Listed for HCC (2002-2020)

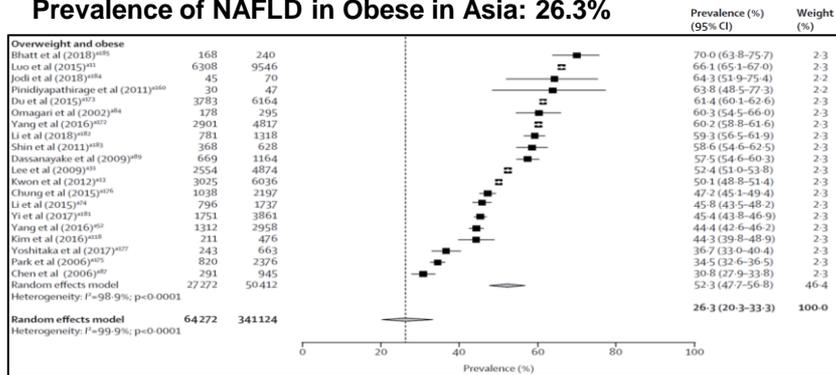


% LT Candidates Listed for NASH per 100,000 (2014-2020)

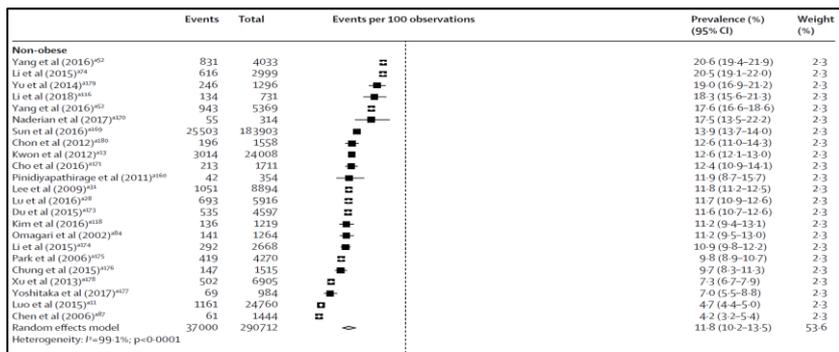


Health Disparities: Risk Factors Related to Obesity, Metabolic Syndrome and Nutrition

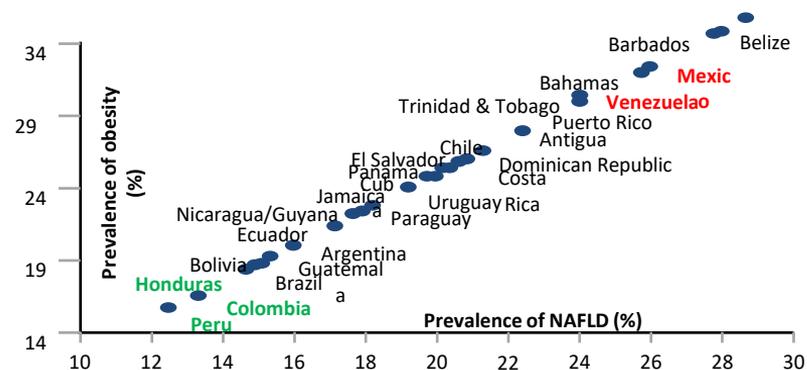
Prevalence of NAFLD in Obese in Asia: 26.3%



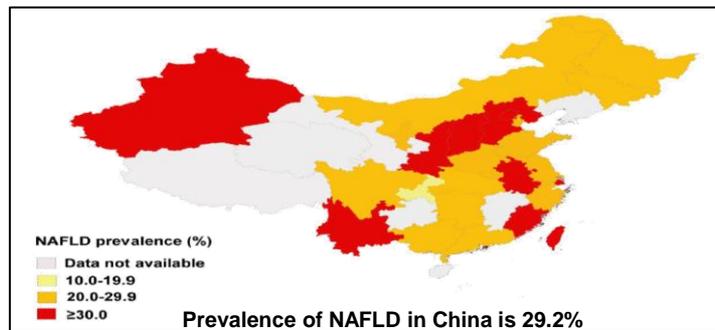
Prevalence of NAFLD in Non-Obese in Asia: 11.8%



Latin America: Prevalence of NAFLD Tracks Prevalence of Obesity



China: Prevalence of NAFLD Related to Urbanization and Diet



Global Health Disparities: Regional Differences in Incidence, Mortality and DALYs (GBD Data)

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 MASH	Liver cancer due to Other causes	Cirrhosis	Cirrhosis due to HBV	Cirrhosis due to HCV	Cirrhosis due to Alcohol Use	Cirrhosis due to MASH	Cirrhosis due to Other causes
Global	1.17	1.38	0.75	0.8	1.95	1.61	0.10	-0.90	0.29	0.21	1.27	0.76
Australasia	1.78	1.13	1.49	1.04	1.31	1.09	1.02	1.29	1.13	0.94	1.31	0.61
High-income Asia Pacific	-2.06	-0.75	-2.89	-2.11	-1.57	-1.98	-0.44	-0.53	-0.65	-0.49	-0.13	-0.24
High-income North America	0.60	0.33	0.60	0.5	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	1.34	1.40	0.55	0.48	-0.85	0.55	0.74	1.14	0.71
Western Europe	0.23	0.00	0.10	0.33	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	3.26	-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	2.00	2.23	2.36	0.28	-0.76	1.58	1.59	2.71	1.15
Southeast Asia	-0.11	-0.30	-0.20	0.00	0.56	-0.59	0.00	-0.51	0.33	0.67	0.50	0.00
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	1.14	1.41	0.83	1.19	0.80	1.26	1.14	1.56	1.14
Andean Latin America	-1.43	-2.00	-1.04	-1.32	-0.54	-1.55	0.00	-0.89	-2.5	-0.6	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	2.53	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	-0.64	1.07	-0.58	0.27	-0.32	0.19	0.44	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	-0.43	-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	-2.95	-2.92	-1.61	-2.56	-1.72	-1.17	-1.12	-1.21
Western Sub-Saharan Africa	-1.58	-2.24	-1.24	-1.27	-0.66	-1.15	-0.28	-0.88	-0.48	-0.24	0.86	0.21
High SDI	-0.26	0.60	-1.00	-0.27	0.36	-0.32	-0.23	-0.77	-0.49	-0.21	0.71	0.13
High-middle SDI	2.71	2.61	2.91	2.54	3.06	3.10	0.00	-0.77	0.60	-0.34	1.66	0.27
Middle SDI	1.15	0.89	1.40	1.31	2.06	1.44	0.25	-0.11	0.57	1.04	1.47	0.91
Low-middle SDI	-0.12	-0.88	0.00	0.44	0.93	-0.03	-0.15	-1.27	-0.04	0.33	0.83	0.51
Low SDI	-0.92	-1.50	-0.72	-0.6	-0.31	-0.82	0.44	-0.40	0.64	0.66	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 MASH	Liver cancer due to Other causes	Cirrhosis	Cirrhosis due to HBV	Cirrhosis due to HCV	Cirrhosis due to Alcohol Use	Cirrhosis due to MASH	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	0.71	0.43	-1.33	-1.68	-1.36	-1.00	-0.46	-1.18	0.00
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	0.8	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	0.96	0.45	-0.44	-0.99	-0.57	-0.39	0.00	-0.31	0.00
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	-1.80	-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	-2.91	-1.76	-1.92
High SDI	-0.81	0.00	-1.28	-0.68	0.00	0.28	-0.83	-1.14	-0.95	-0.91	-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	0.00	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	-0.4	0.00	-0.71

Burden of Disability Related to NAFLD (2007-2017)

	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
Australasia	17.46	18.93	7.74	2.89	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
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	-5.00	-0.73	4.81
S Latin America	-2.22	-0.70	-13.30	-1.66	6.55
C Latin America	-6.34	-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	-14.08
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

Health Disparities: Outcomes of NAFLD in Asia and MENA id Driven by Metabolic risks, Activity and Nutrition (GBD 2009-2019)

- Globally in 2019, 168,969 deaths were related to liver complications (LC) of which, NAFLD accounted for 8.6% of LC deaths from all CLDs.
- **Of the global incident and death cases related to LC-NAFLD, about half occurred in Asia and MENA,**
- Between 2009 and 2019, the pattern of change for incidence rate of LC-NAFLD shows a worsening trend (APC >0%) in most Asian (31 out of 34) and MENA countries (18 out of 21)
- From 2009 to 2019, regions in Asia and MENA experienced a steep rise in DALY rate of LC-NAFLD
- **In Asia and MENA, age-standardized DALY rate of LC-NAFLD was associated dietary and metabolic risks**
- **In MENA, low physical activity was also a risk**

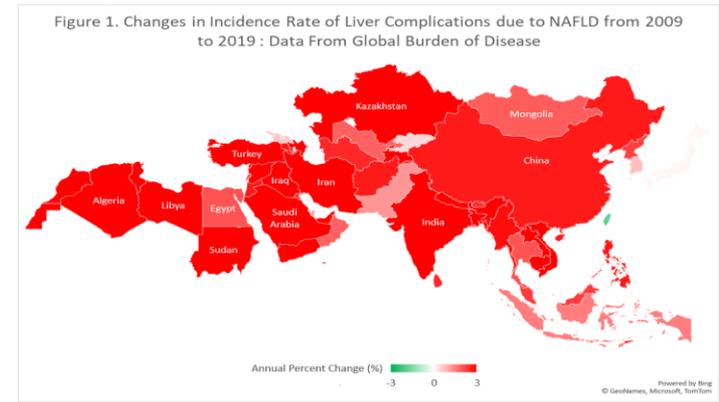
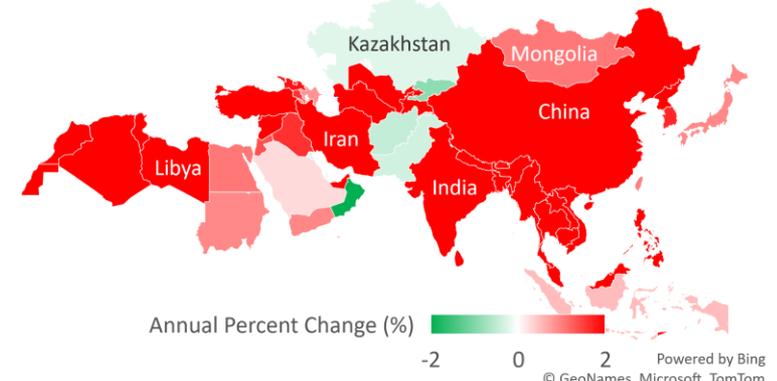
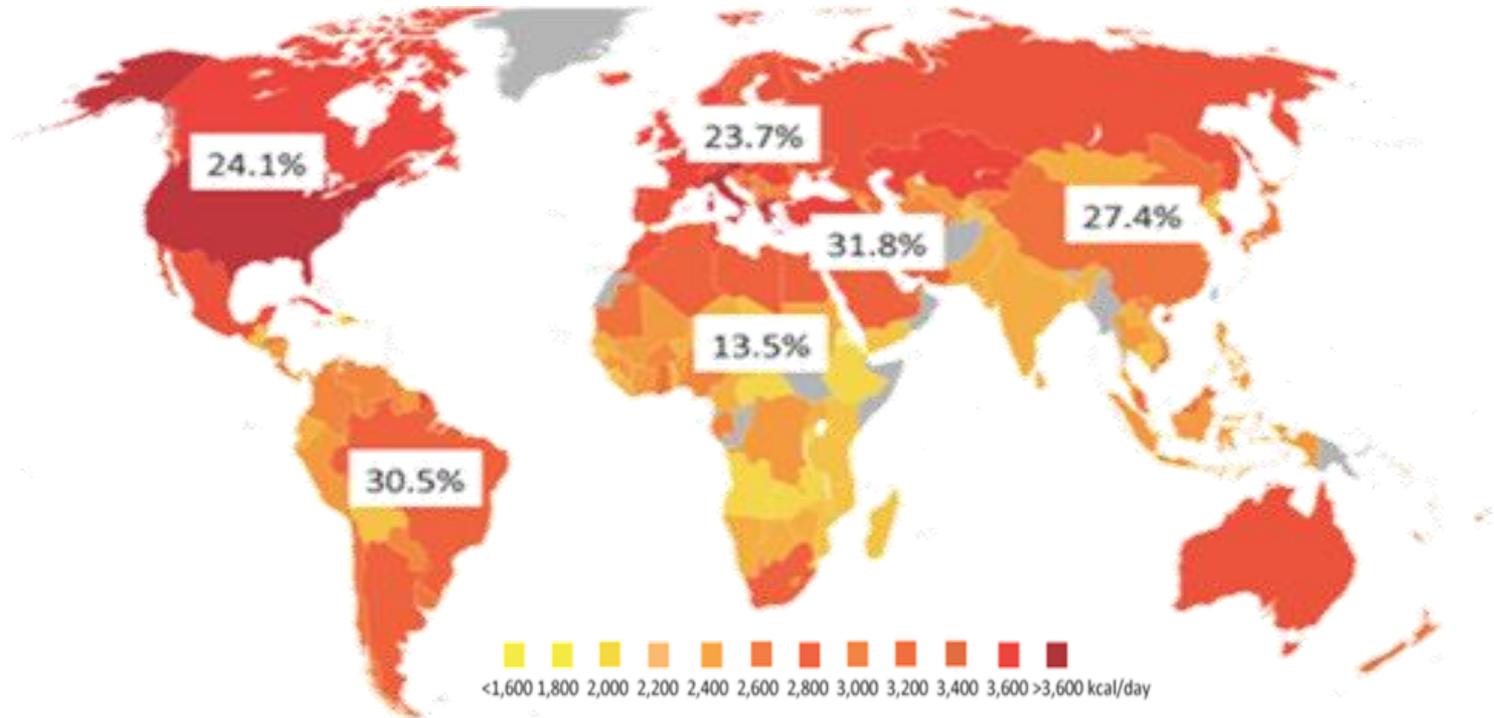


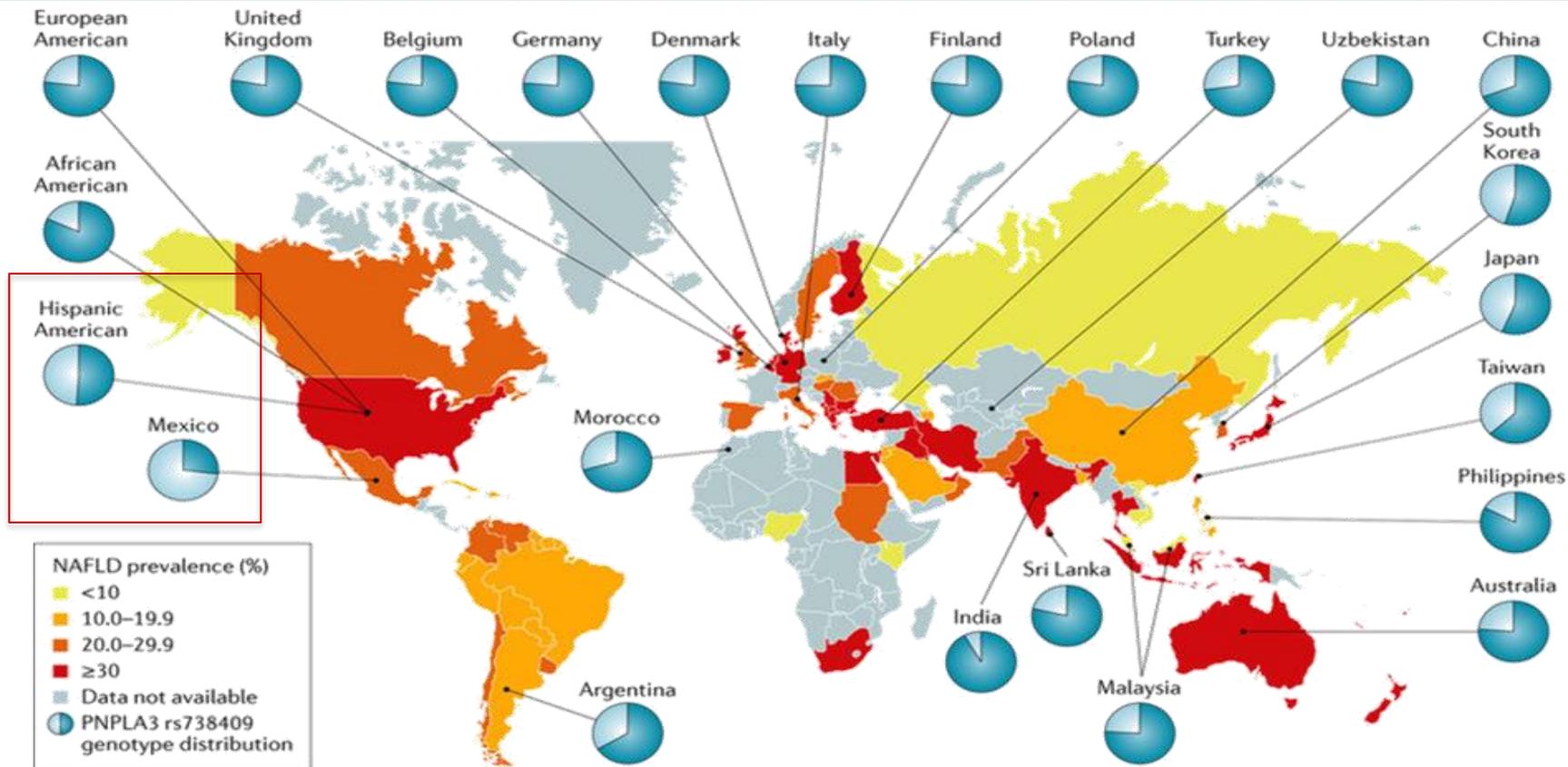
Figure 2. Changes in Death Rate of Liver Complications due to NAFLD from 2009 to 2019 : Data From Global Burden of Disease



Health Disparities: Regional Prevalence Rates According Caloric Intake (Diet)

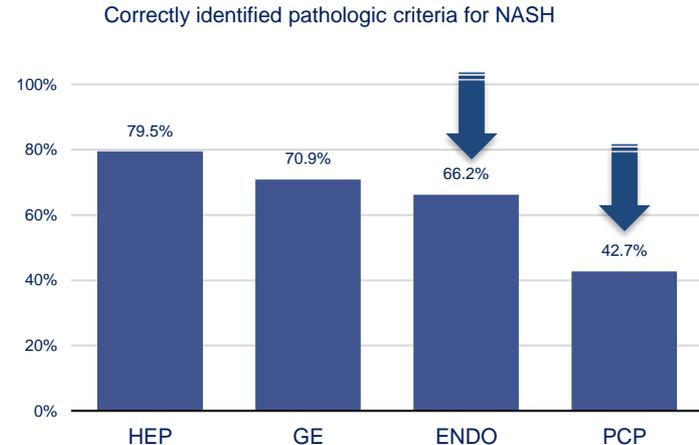
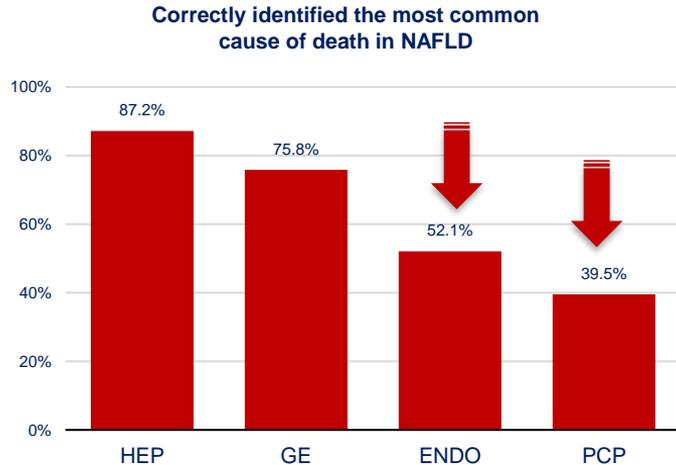


Health Disparities: Impact of Genetic Predisposition for Prevalence and Progression of NAFLD (PNPLA3)



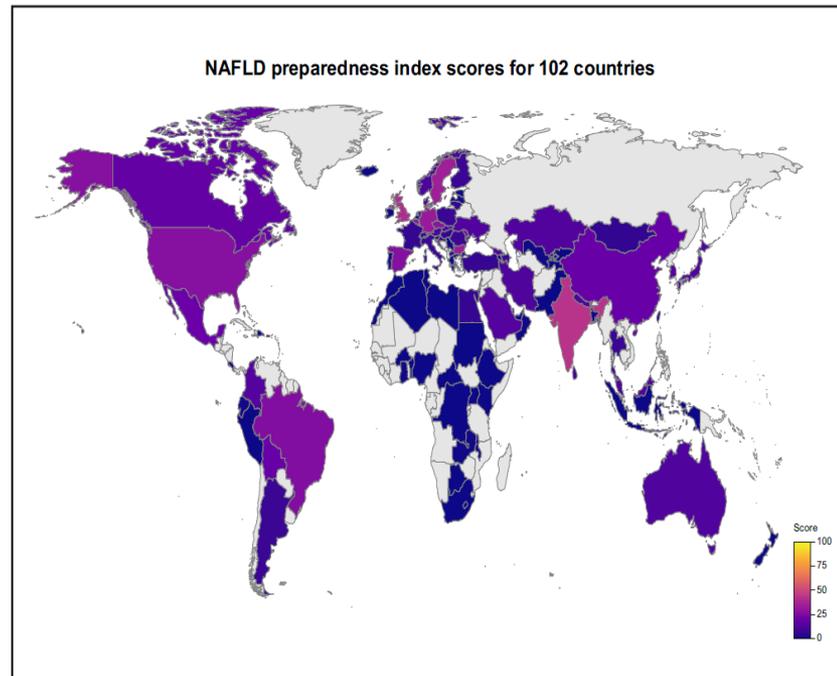
Health Disparities: Awareness and Knowledge Gaps

- Provider level:** Survey (54 and 59 Questions) of 2202 clinicians (HEP, GI, ENDO and PCP) from 40 countries



Health Disparities: Where Are We with the Global NAFLD Policy and Preparedness Index (PI)?

- Data from 102 countries (86% of the world population), on NAFLD policies, guidelines, civil society engagement, clinical management, and epidemiology.
- PI was developed by coding questions into 6 domains with responses as high, medium, and low
 - 1) policies, 2) guidelines, 3) civil awareness, 4) epidemiology, 5) NAFLD detection, and 6) NAFLD care management
- 1/3 of countries (n=32/102) scored 0 on PI
- No country had a NAFLD national or sub-national strategy
- NAFLD was rarely mentioned in the strategies of related conditions such as diabetes.
- Only 32 countries had national NAFLD clinical guidelines.
- **A comprehensive NAFLD public health response is lacking in all countries**



The Global and Regional Disparities Related to Disease Burden

Summary

- The challenge of the global health disparities for NAFLD/NASH is plagued by complex and inter-related factors (proximal, intermediate and distal)
- This is further compounded by the complex pathogenic mechanism of NASH (multiple hits or pathways), low disease awareness and limited therapeutic options
- Potential Solutions: Multi-prong comprehensive approach inclusive of all important stakeholders to better understand the disease burden, increase disease awareness, create accurate risk stratification algorithms with NITs, develop targeted therapy and produce National and Regional Health Policies to deal with NASH as an important non-communicable chronic disease