



Epidemiology of NASH and lean NASH in Asia

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Disclosures



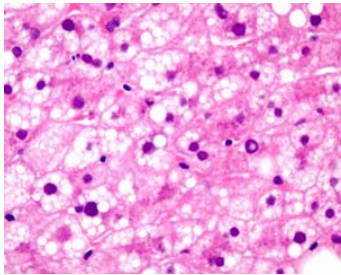
- Consultancy: 3V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Center for Outcomes Research in Liver Diseases, Echosens, Gilead Sciences, Hanmi Pharmaceutical, Intercept, Inventiva, Merck, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, ProSciento, Sagimet Biosciences, TARGET PharmaSolutions, Terns
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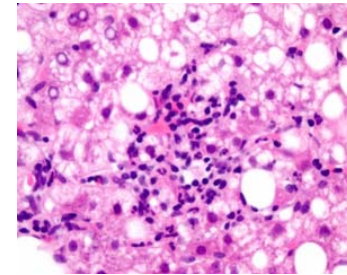
- First things first – Definitions
- Prevalence and incidence in the general population
- Prevalence and incidence in high-risk groups
- NAFLD in lean or non-obese individuals
- MAFLD – The controversy continues!

Nonalcoholic fatty liver disease (NAFLD)



Simple steatosis (nonalcoholic fatty liver)

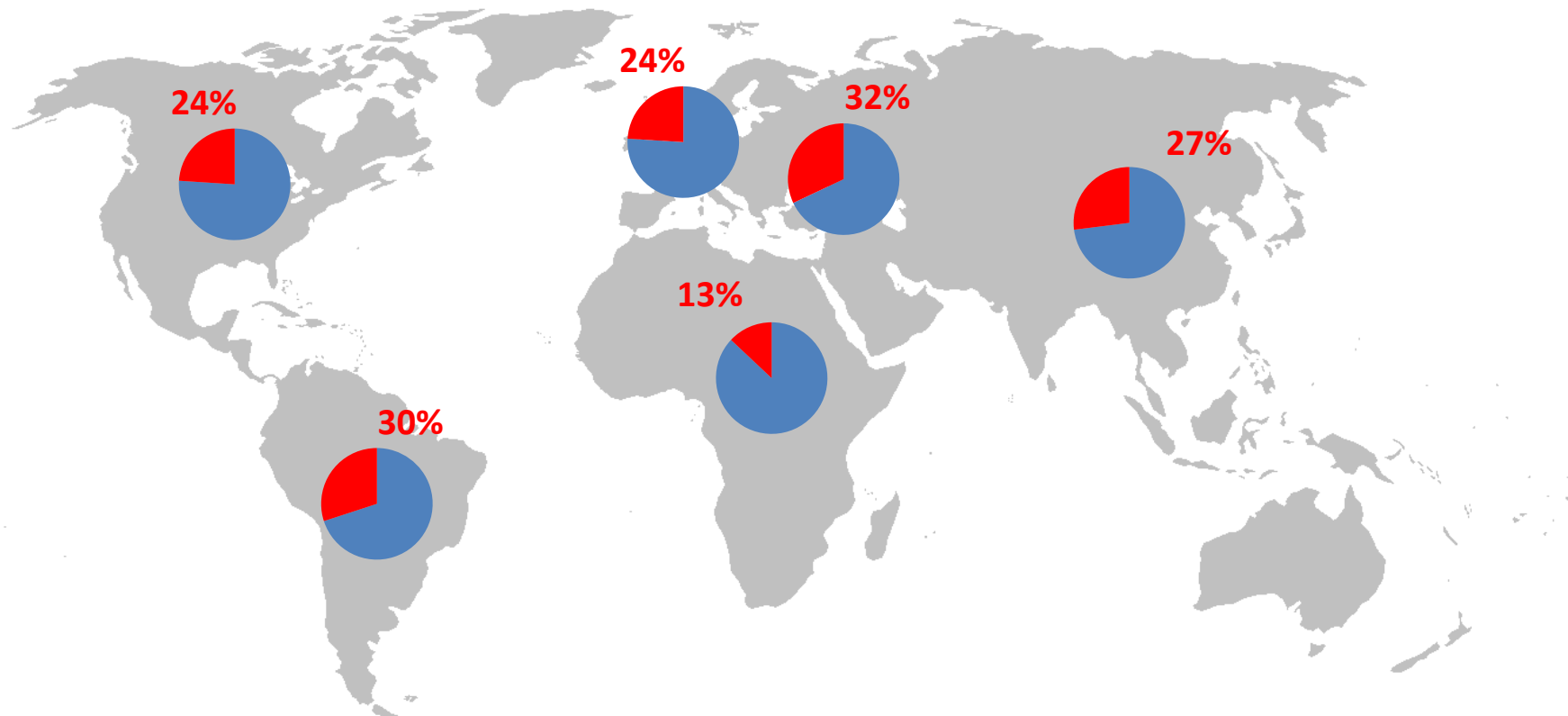
- Hepatic steatosis involving $\geq 5\%$ of hepatocytes
- No or little necroinflammation



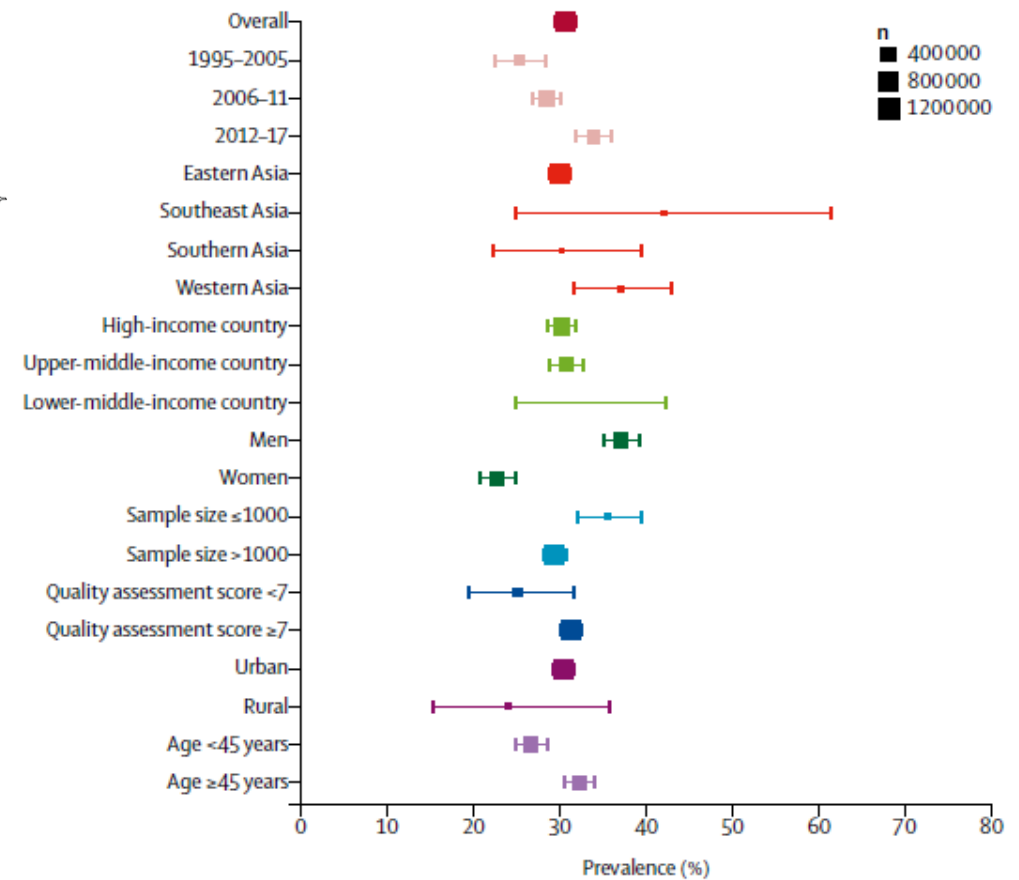
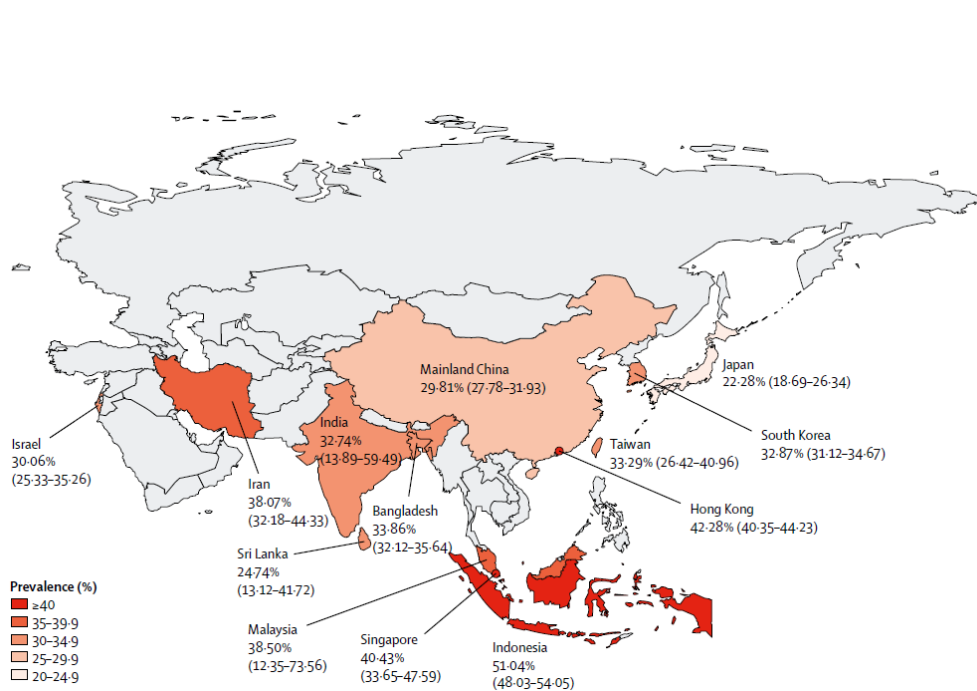
Nonalcoholic steatohepatitis (NASH)

- Presence of steatosis, lobular inflammation and ballooning
- Associated with faster fibrosis progression

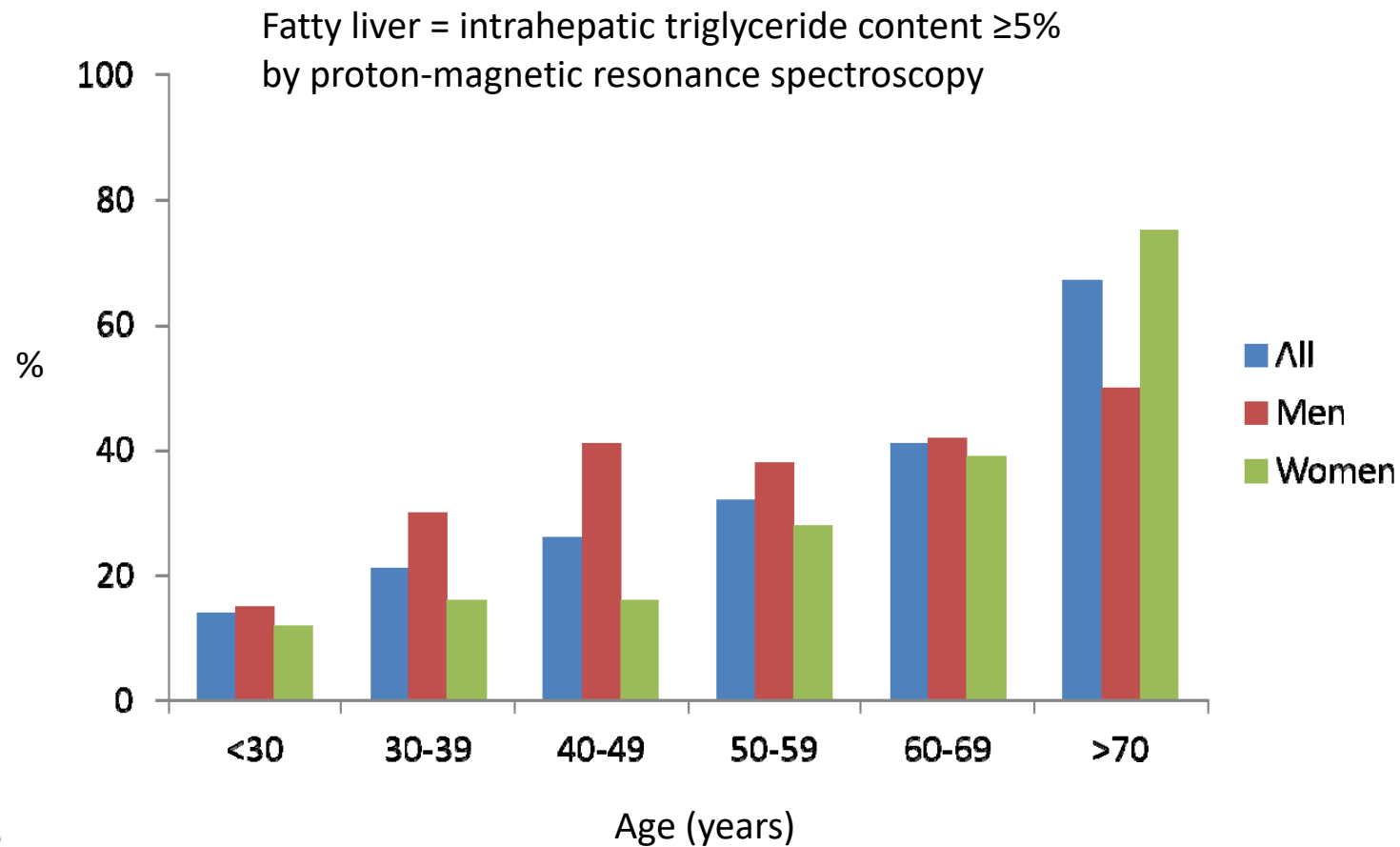
25% of the global population has non-alcoholic fatty liver disease (NAFLD)



NAFLD affects 30% of the Asian adult population



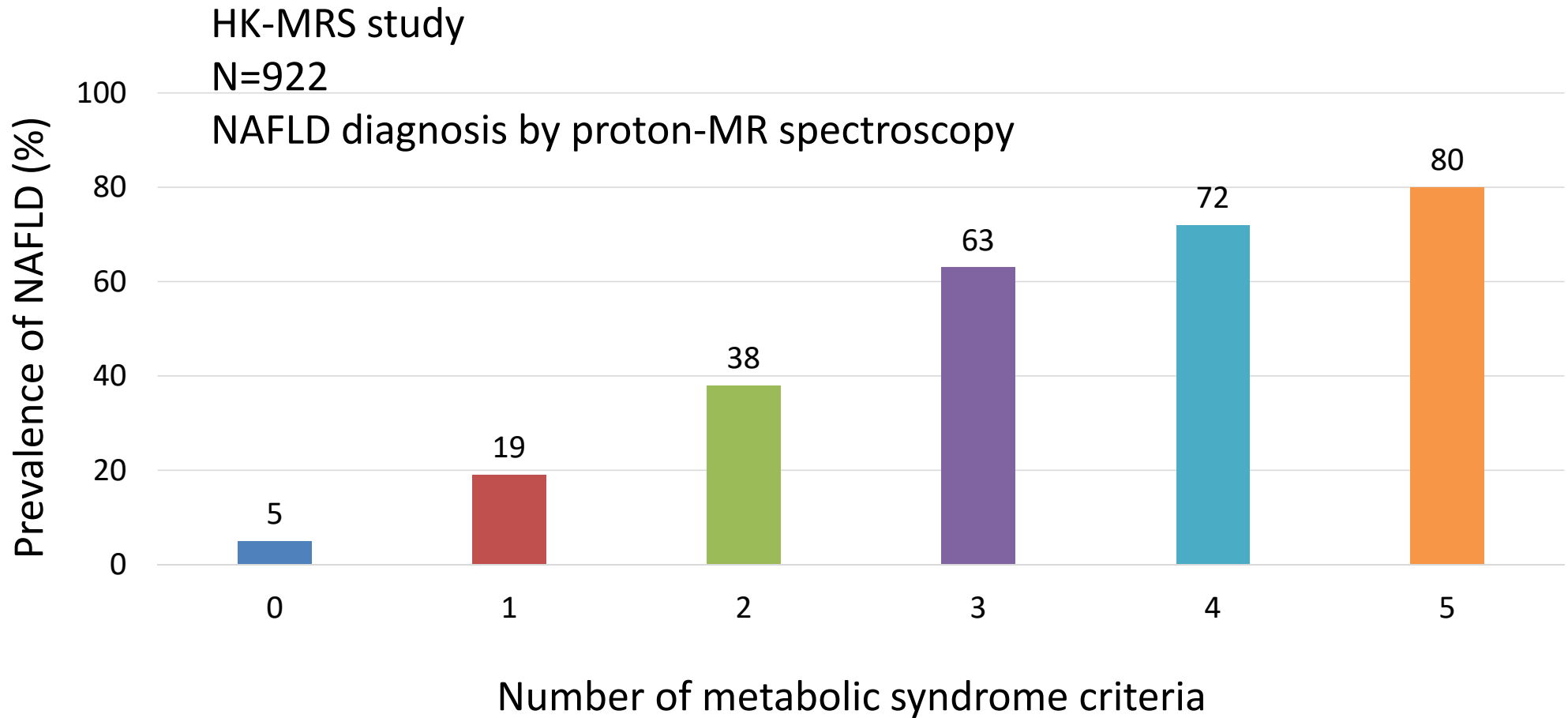
Age and sex distribution of fatty liver in Hong Kong



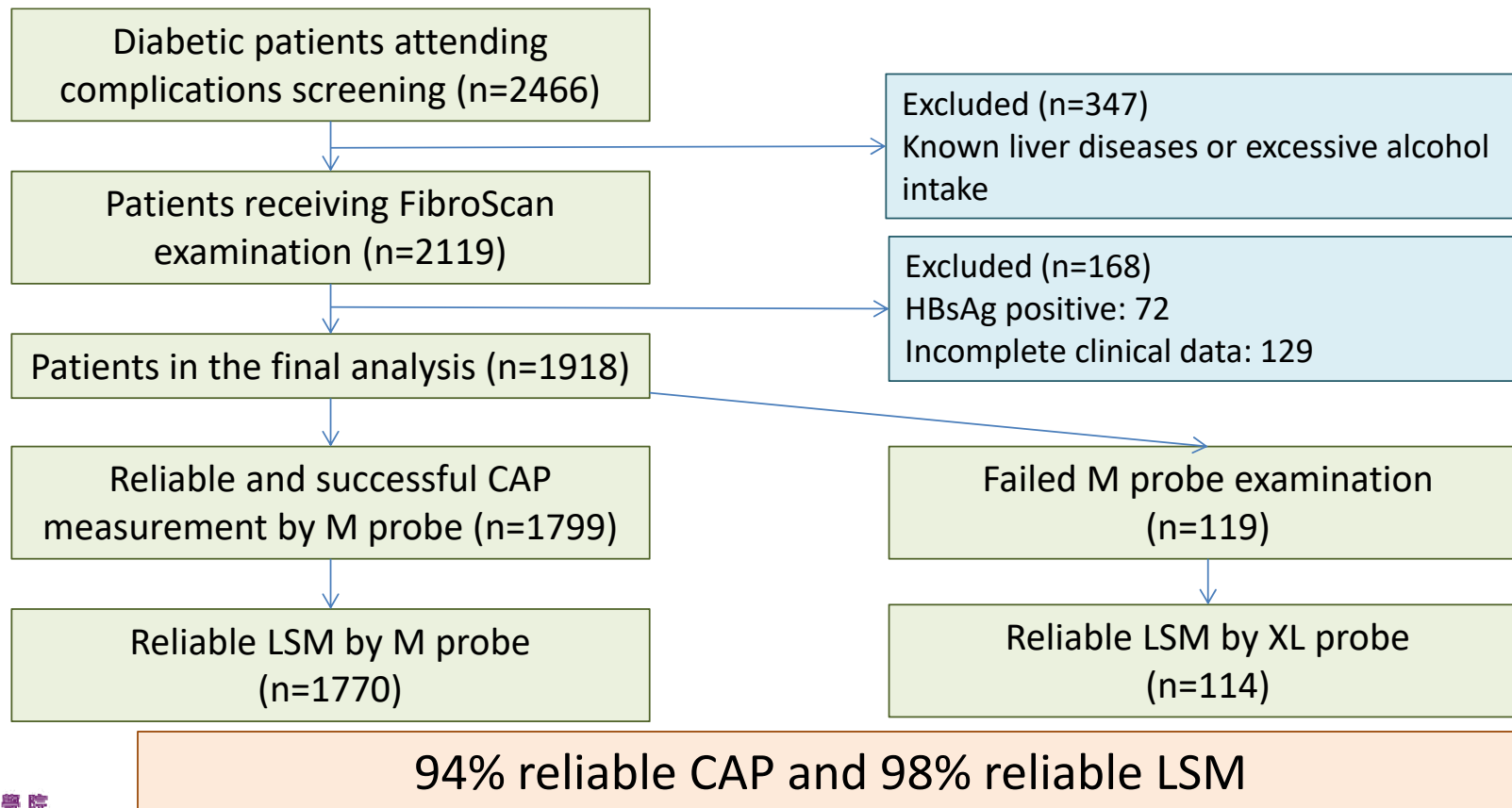
Incidence of NAFLD in Asia

Region	Studies	Participants	Incident cases of NAFLD	Incidence per 1000 person-years
South Korea	8	362 685	71 253	45
Japan	1	3860	443	29
Mainland China	8	49 878	10 053	63
Hong Kong	1	565	78	37

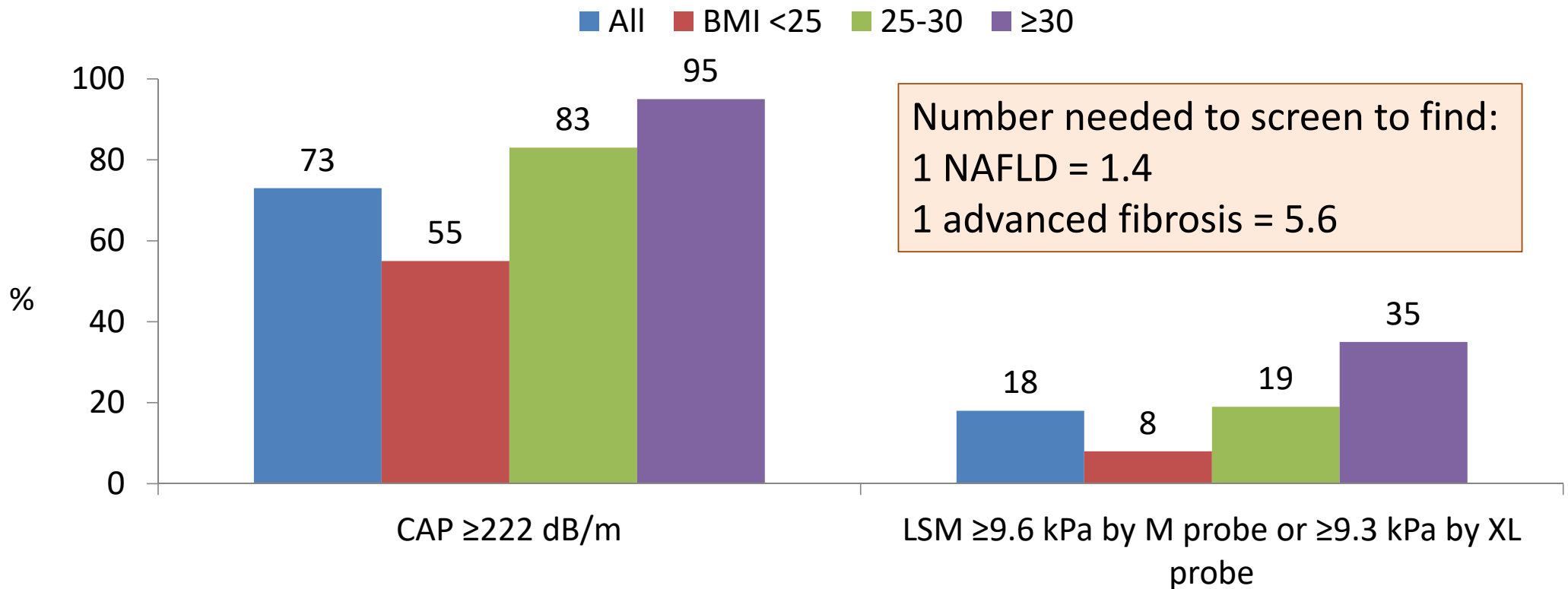
Metabolic syndrome and NAFLD



Screening patients with type 2 diabetes mellitus using transient elastography



Prevalence of fatty liver and fibrosis among patients with type 2 diabetes mellitus

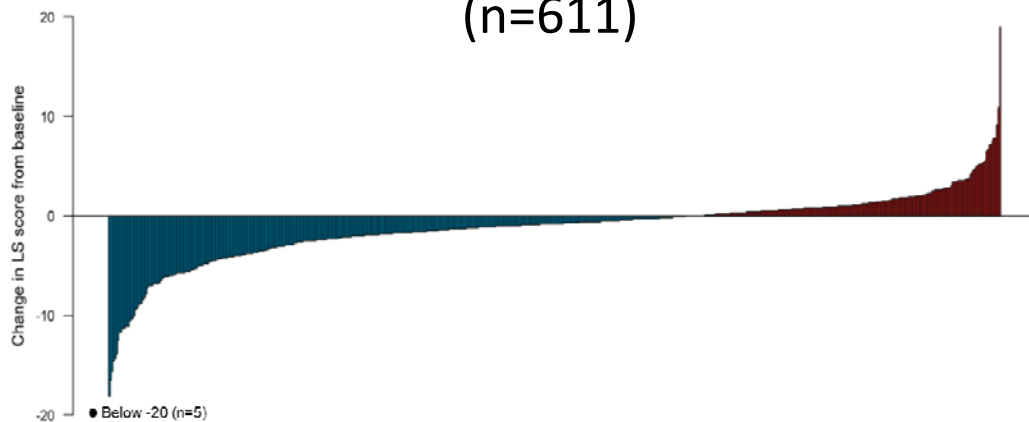


Screening of advanced fibrosis in patients with type 2 diabetes using transient elastography

Study	N	Country/region	Target LSM	Prevalence
Kwok 2016	1918	Hong Kong	≥ 9.6 kPa by M probe or ≥ 9.3 kPa by XL probe	17.7%
Lai 2019	557	Malaysia	≥ 9.6 kPa by M probe or ≥ 9.3 kPa by XL probe	21.0%
Demir 2019	124	Turkey	9.6-11.4 kPa by M probe or 9.3-10.9 kPa by XL probe	16.9%
			≥ 11.5 kPa by M probe or ≥ 11.0 kPa by XL probe	8.0%

Monitoring patients with type 2 diabetes with transient elastography at 3 years

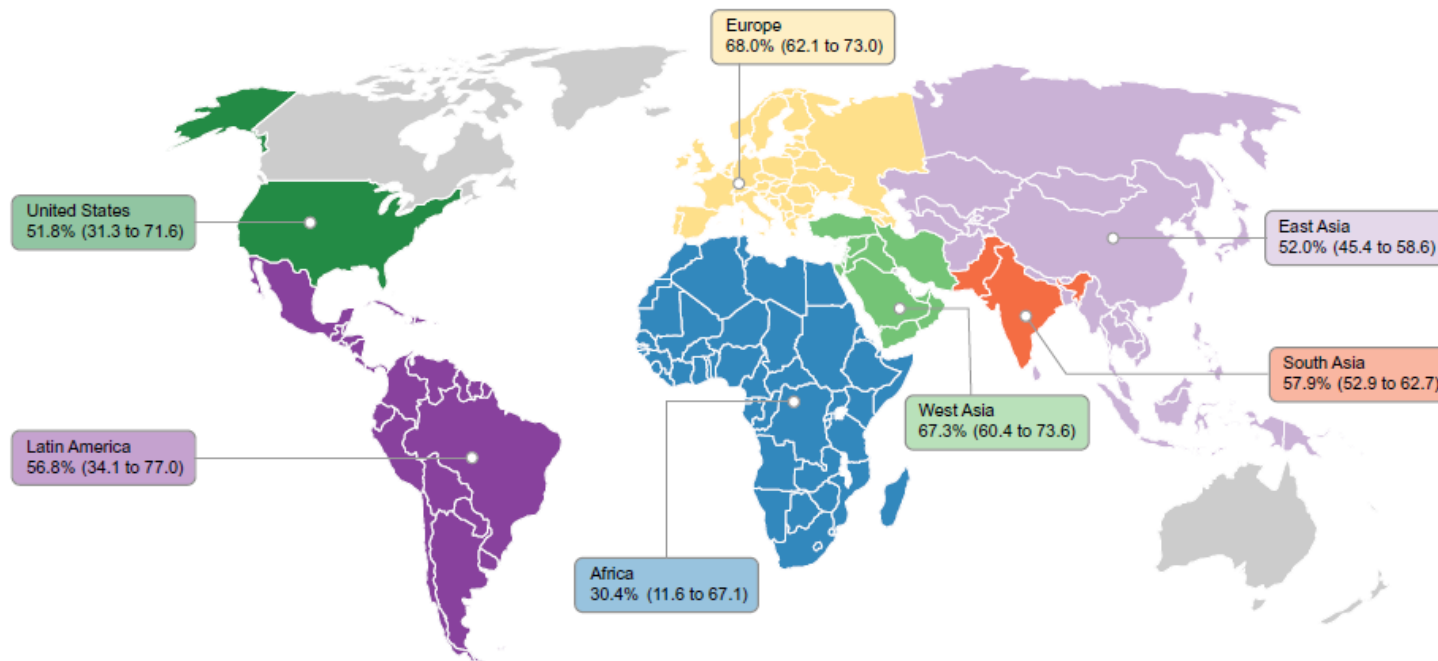
Change in liver stiffness in 3 years
(n=611)



- 73/611 (12%) had $\geq 30\%$ relative increase in LSM
- 21/487 (4%) had LSM increasing from <10 to ≥ 10 kPa

- Factors associated with LSM increase: BMI, ALT, and Δ ALT

Globally, 55.5% (95% CI 47.3-63.7) of patients with type 2 diabetes have NAFLD

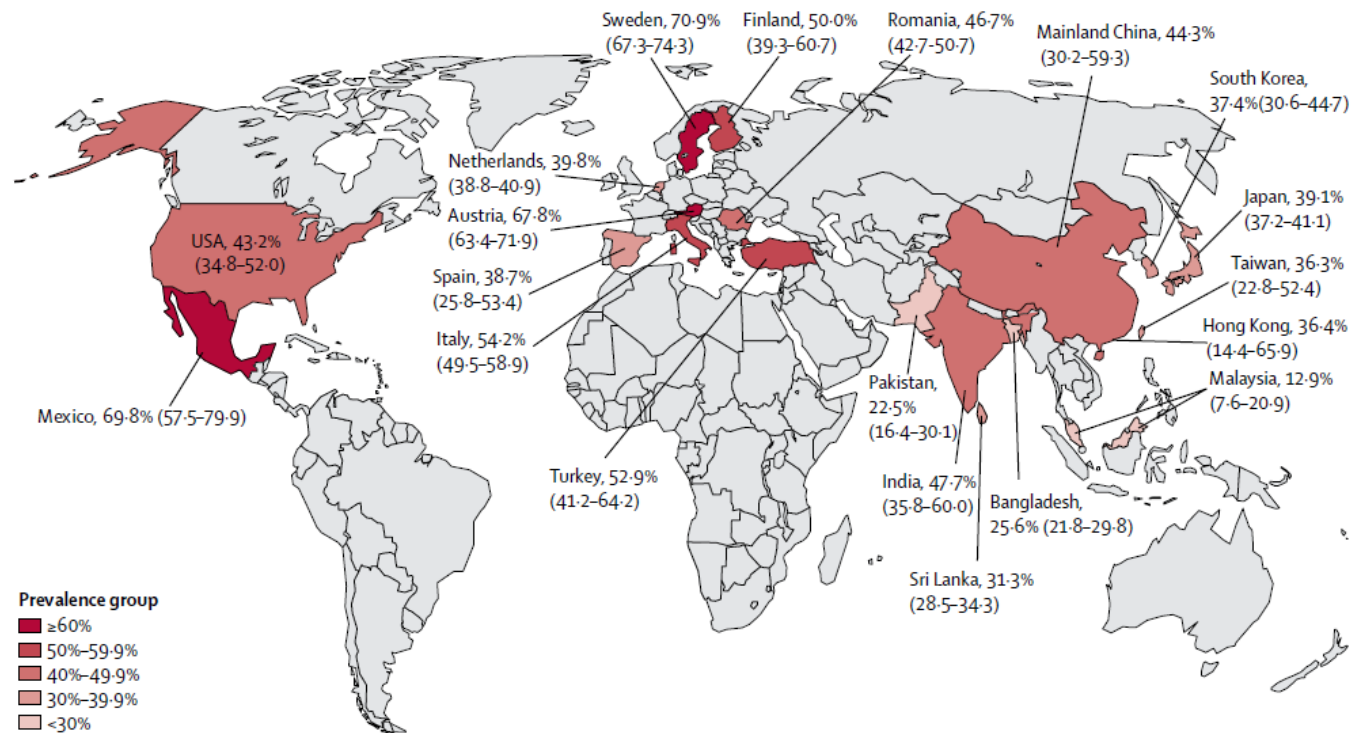


- 37.3% have NASH
- 17.0% have advanced fibrosis

Prevalence of non-obese NAFLD (BMI <25 kg/m²)

Study	Country/region	Prevalence of non-obese NAFLD	Prevalence of NAFLD
Bellentani 2000	Italy	16%	
Kim 2012	USA	21%	34%
Das 2010	India	7%	9%
Omagari 2002	Japan	13%	22%
Chen 2006	Taiwan	4%	12%
Dassanayake 2009	Sri Lanka	17%	33%
Kwon 2012	Korea	13%	20%
Xu 2013	China	7%	
Lankarani 2013	Iran	9%	22%
Wei 2015	Hong Kong	19%	29%

Proportion of non-obese patients among those with NAFLD



$$\text{Body mass index (BMI, in kg/m}^2\text{)} = \frac{\text{Body weight (kg)}}{[\text{Body height (m)}]^2}$$

BMI (kg/m ²)	Interpretation
<18.5	Underweight
18.5-24.9	Healthy
25.0-29.9	Overweight
30.0-34.9	Class I obesity
35.0-39.9	Class II obesity
40.0-49.9	Class III obesity
50.0-59.9	Class IV obesity
≥60.0	Class V obesity



Strength of BMI:

- Easy to use

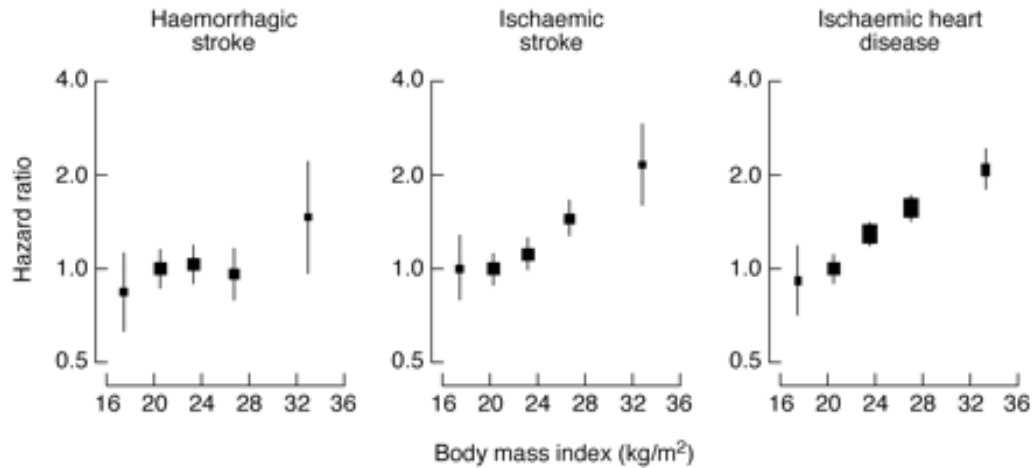
Limitations of BMI:

- Cannot distinguish muscles from fat
- Ethnic differences

Asian BMI

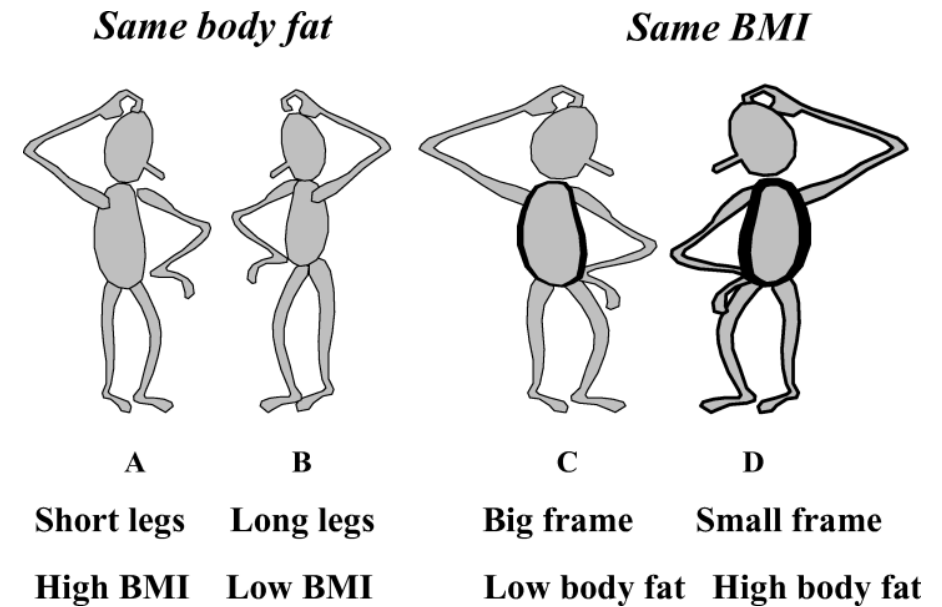
310283 Asians

2148354 person-years of follow-up



Asia Pacific Cohort Studies Collaboration
Int J Epidemiol 2004;33:751

Asians have a higher body fat percentage than Caucasians at the same BMI

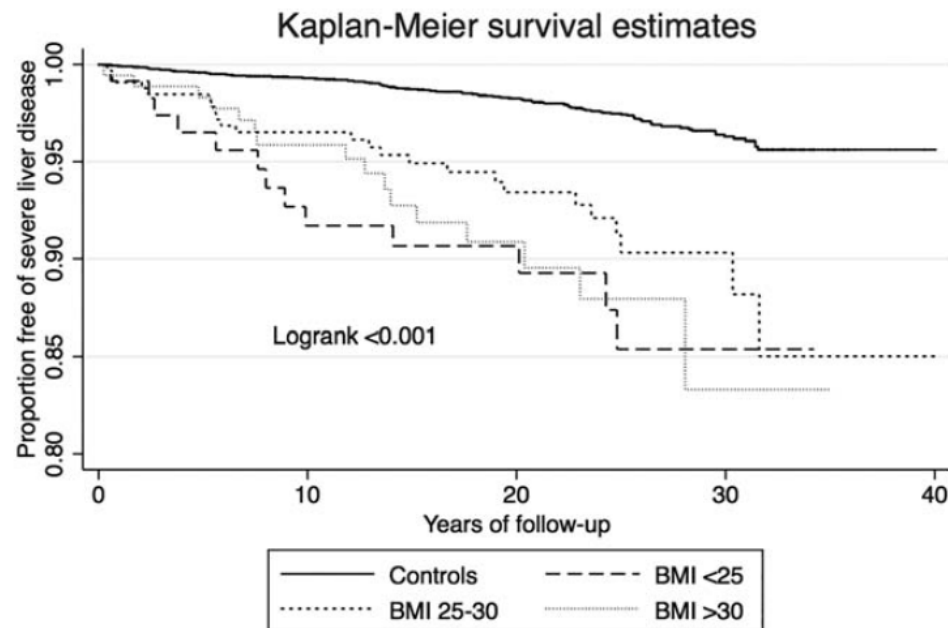


Deurenberg et al. Obes Rev 2002;3:141

Is non-obese NAFLD a different phenotype?

- N=1090; 125 (11.5%) had BMI <25 kg/m²
- Non-obese NAFLD: Non-Caucasian, less diabetes, hypertension, dyslipidemia, central obesity
- Histology: More severe lobular inflammation
- 483 patients had a mean FU of 133 months; 71 (14.7%) died
- Non-obese NAFLD (HR 11.8) and age (HR 1.05) associated with mortality

Clinical outcomes of 646 Swedish patients with biopsy-proven NAFLD



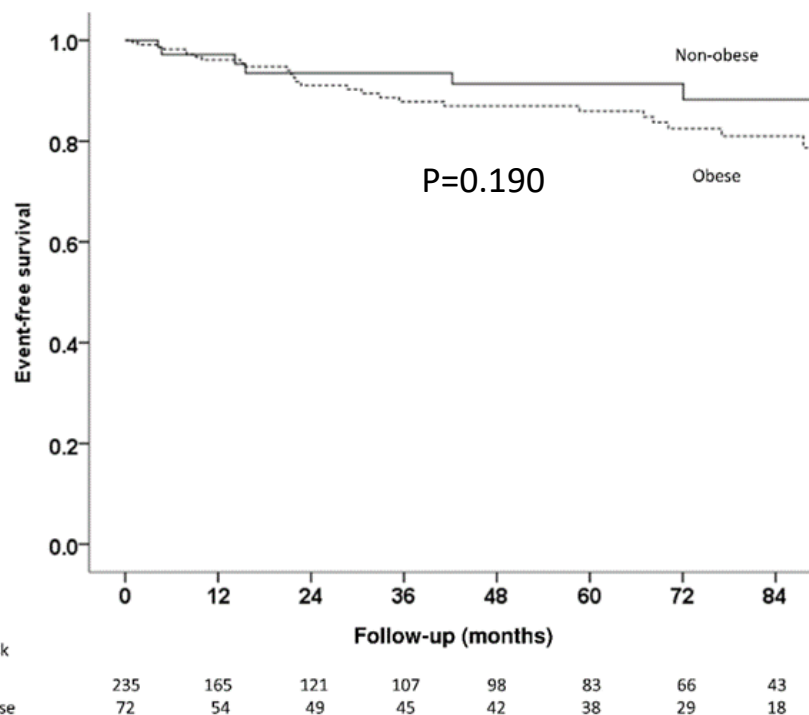
Severe liver disease = liver decompensation, hepatocellular carcinoma or cirrhosis

- Lean patients
 - Lower baseline fibrosis stage
 - Longer time to death
 - More liver-related deaths
 - Lower endocrine-related deaths
 - More severe liver disease (association only significant after adjusting for baseline fibrosis stage)

Histological severity of non-obese NAFLD

	BMI <25	BMI ≥25	P
N	72	235	
NAFLD activity score	3.3	3.8	0.019
Steatosis grade	1.7	2.0	0.014
Lobular inflammation	0.9	1.0	0.305
Ballooning	0.7	0.8	0.068
Fibrosis stage	1.3	1.7	0.004
NASH	44%	52%	0.217
Any fibrosis	55%	80%	<0.001
F3-4	26%	28%	0.791

Clinical outcomes of non-obese NAFLD



Events	BMI <25	BMI ≥25
Death	0	3%
Myocardial infarction	3%	3%
Stroke	1%	3%
HCC	0	1%
Decompensation	0	1%

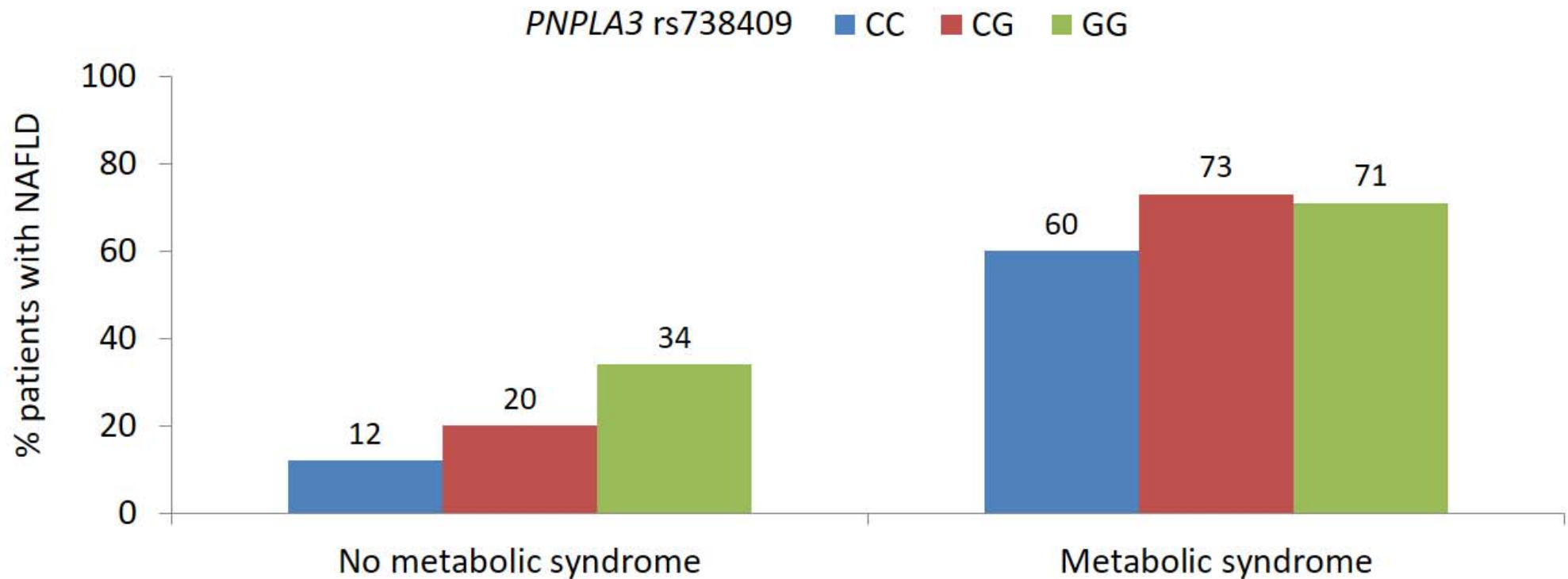
Severity of non-obese NAFLD in the general population of Hong Kong

Characteristics	BMI <25	BMI ≥25	P
N	135	127	
Intrahepatic triglyceride content (%)	9.8	9.9	0.10
Cytokeratin-18 fragments (CK-18; U/L)	149	182	0.018
CK-18 >338 U/L	8%	18%	0.019
Liver stiffness (kPa)	4.6	5.6	<0.001
LSM ≥9.6 kPa	3%	5%	0.47
NAFLD fibrosis score >-1.455	10%	23%	0.006

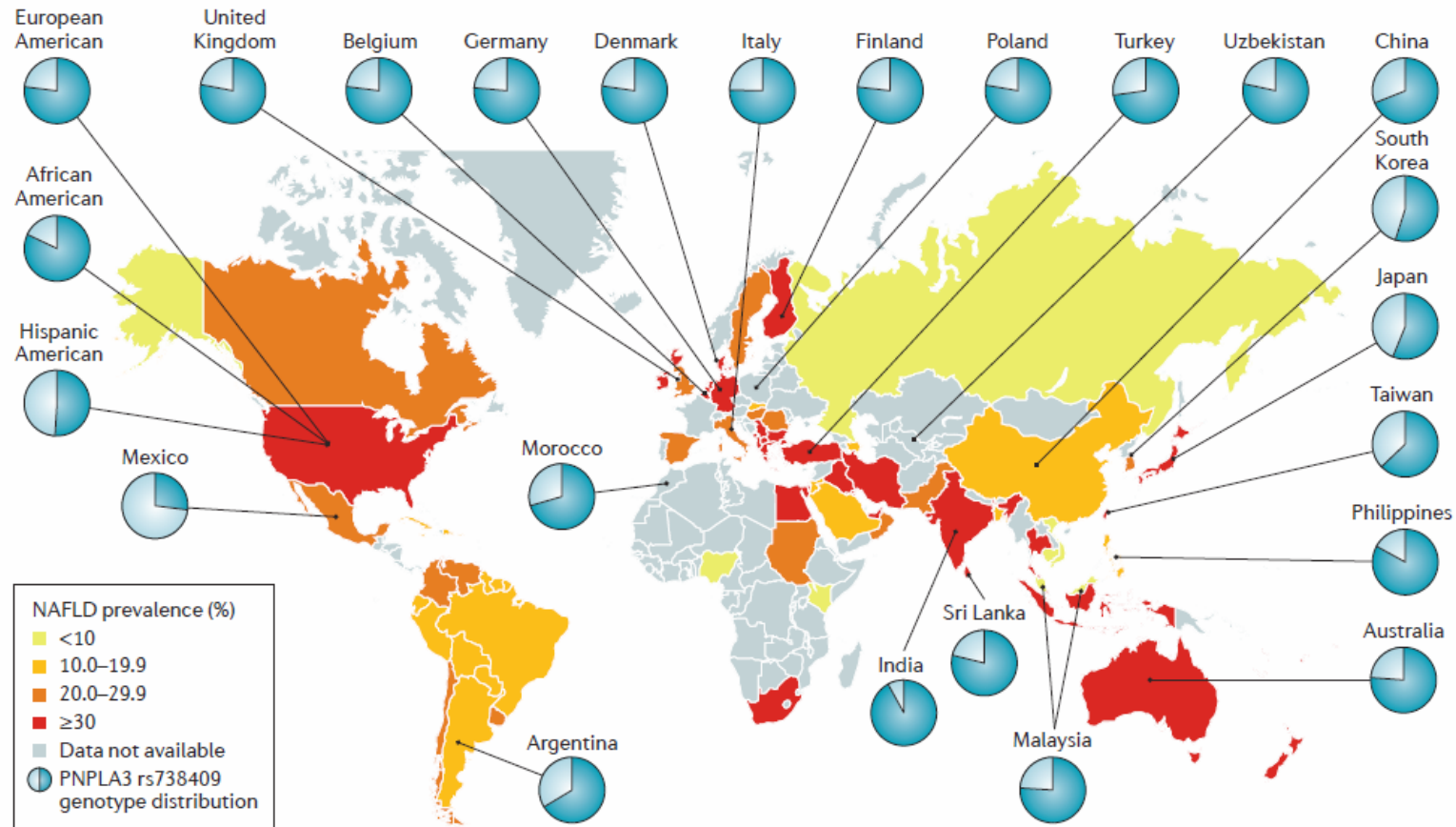
Factors associated with NAFLD in non-obese subjects

Factors	Adjusted odds ratio	P
Body mass index (kg/m ²)	1.327 (1.106-1.592)	0.002
Waist circumference (cm)	1.105 (1.052-1.160)	<0.001
HbA _{1c} (%)	1.827 (1.027-3.251)	0.040
HOMA-IR (%)	1.240 (1.089-1.411)	0.001
Ferritin (ng/ml)	1.001 (1.000-1.001)	0.008
<i>PNPLA3</i> CC vs CG/GG	4.372 (2.448-7.806)	<0.001

PNPLA3 polymorphism and NAFLD in people with and without metabolic syndrome



Worldwide distribution of *PNPLA3* genotype

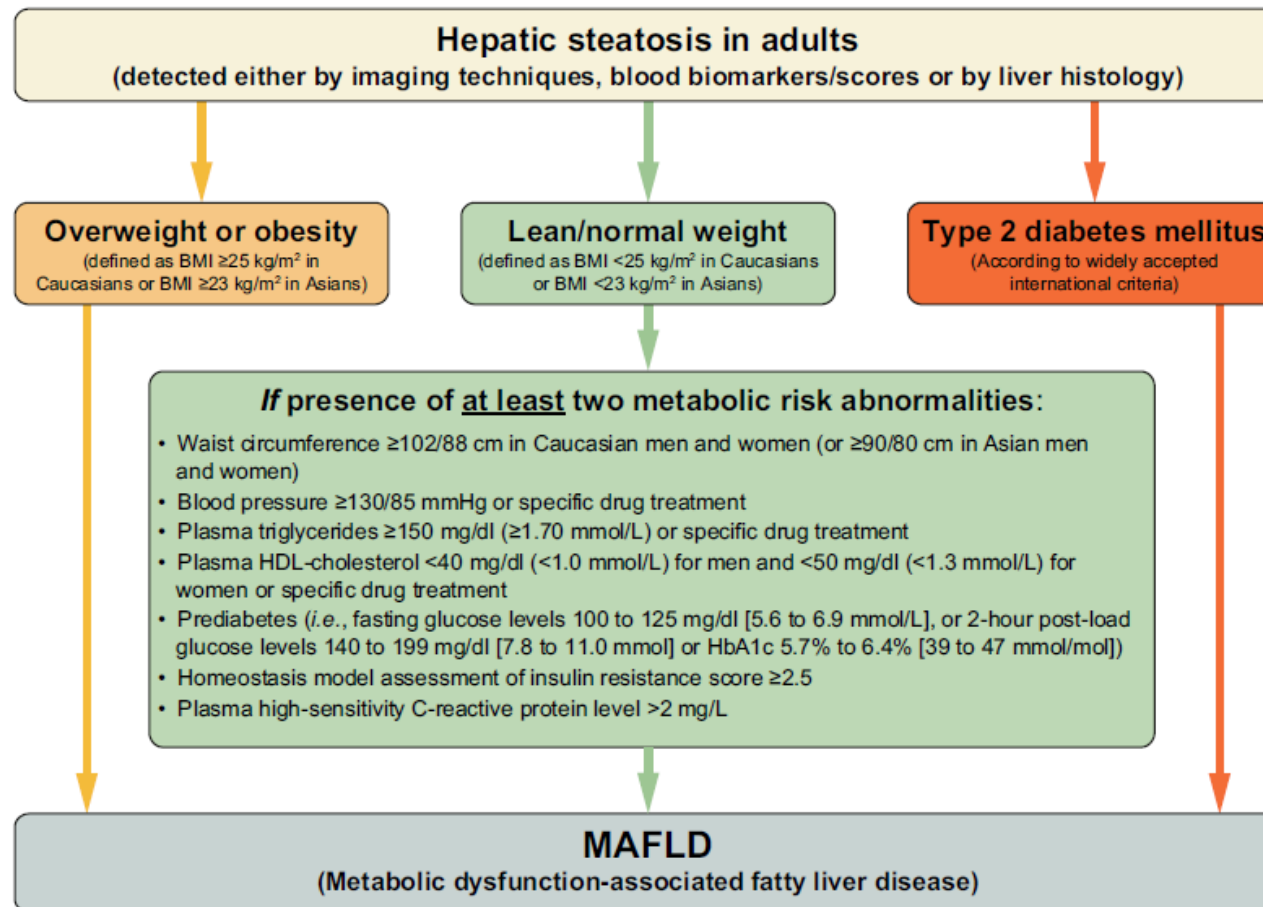


MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease

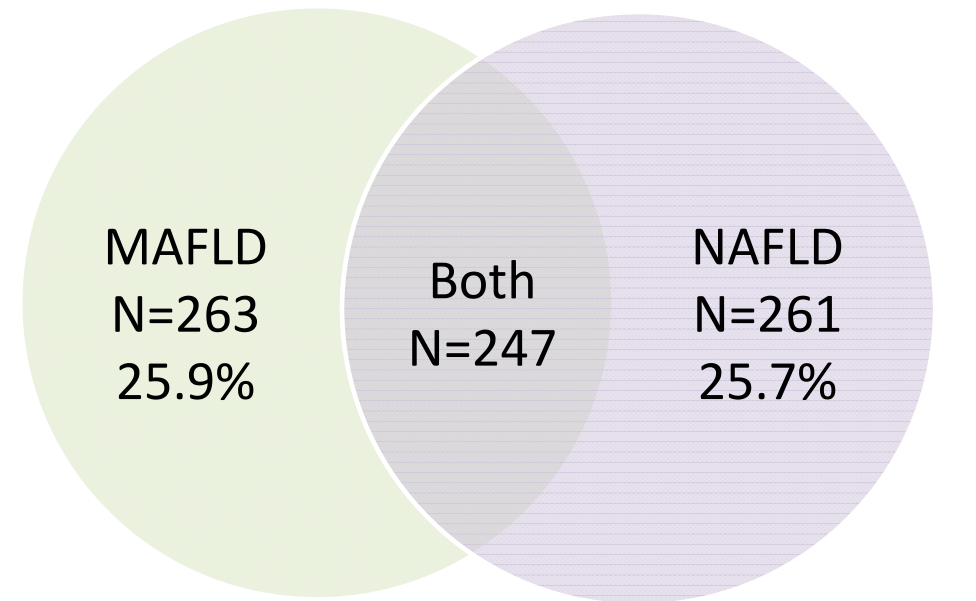
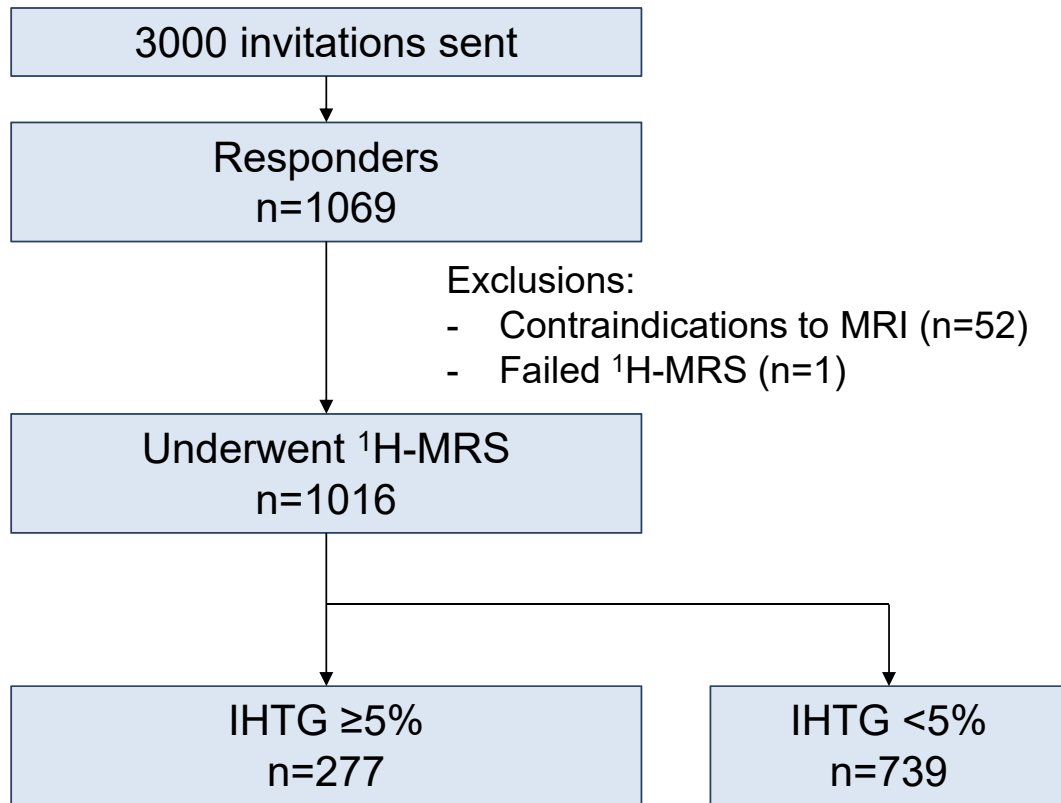


- Heterogeneity and complex pathophysiology
- Better to have a positive diagnosis now that we understand its close relationship with metabolic disorders
- Inappropriate to adopt a diagnosis of exclusion for the most common chronic liver disease
- Recognize the role of MAFLD in patients with concomitant diseases

Proposed “positive” diagnostic criteria for MAFLD



HK-MRS study

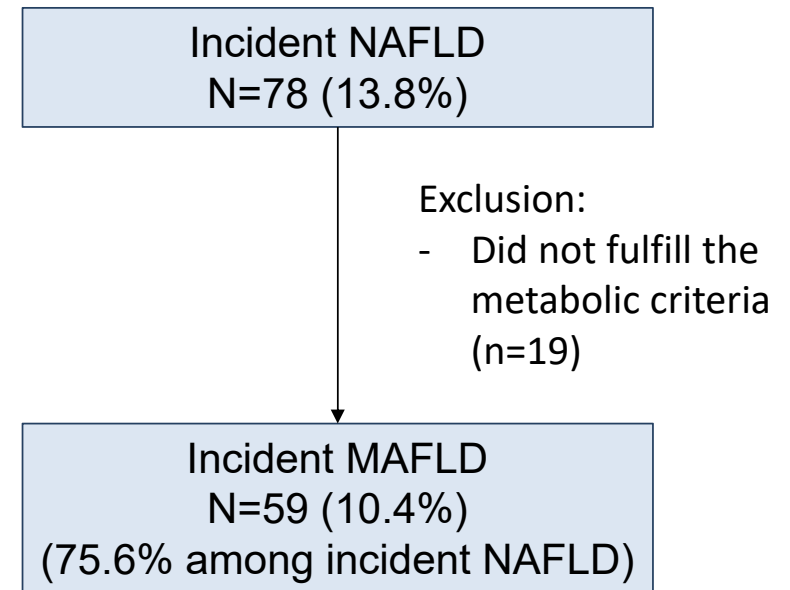
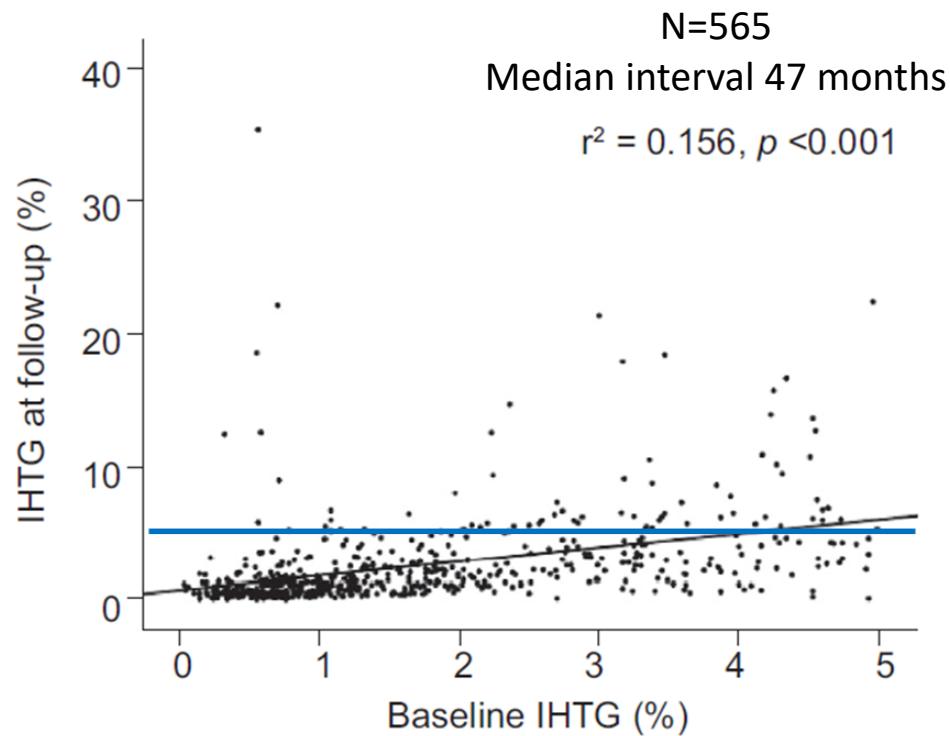


Exclusions:
- Not fulfilling metabolic definitions (n=14)

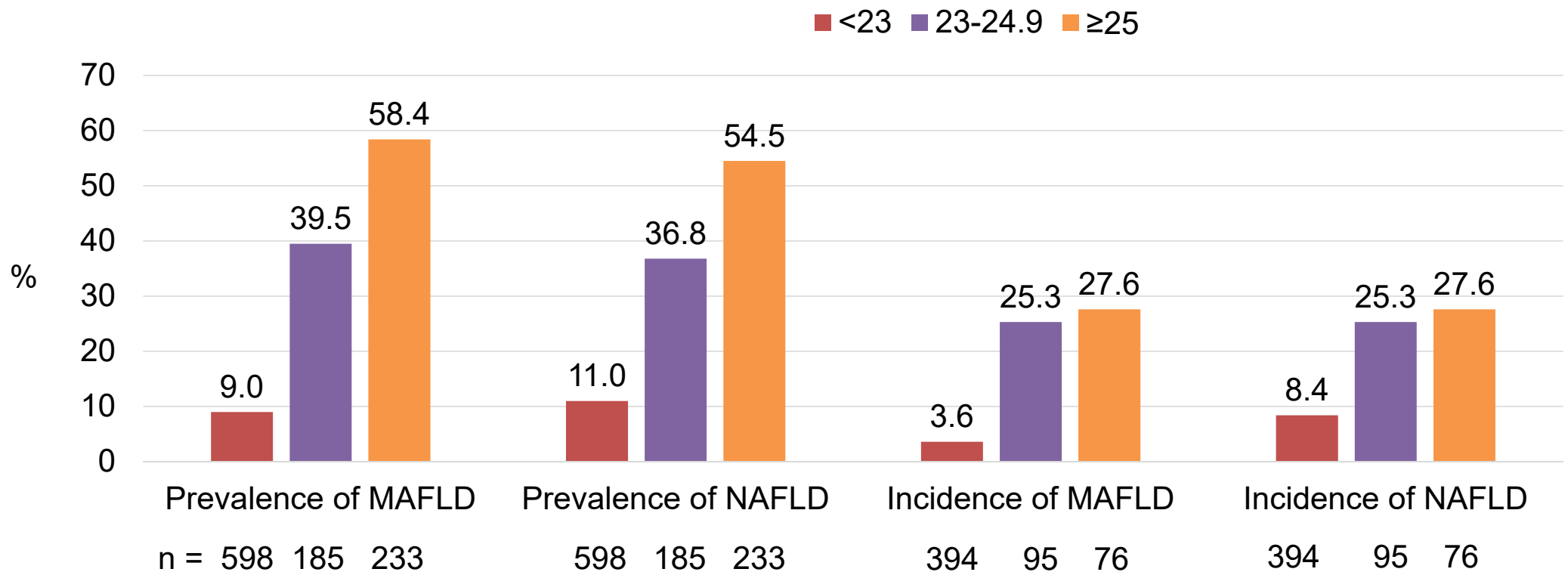
Exclusions:
- Excessive alcohol consumption (n=3)
- Positive HBsAg (n=13)

¹H-MRS, proton-magnetic resonance spectroscopy
IHTG, intrahepatic triglyceride content

HK-MRS incidence study



The new MAFLD definition mainly affects the incidence rate in lean individuals



Clinical characteristics of 14 subjects who fulfilled the definition of NAFLD but not MAFLD in the prevalence study

Subject	Age	Sex	BMI (kg/m ²)	WC (cm)	Clinical profile	ALT (IU/l)	IHTG (%)	LSM (kPa)
1	25	M	22.3	77	High triglycerides	68	13.5	Failed
2	32	M	20.3	75	Good past health	30	5.1	11.3*
3	34	M	22.5	92	Central obesity	110	7.2	3.9
4	37	M	22.9	88	Dyslipidaemia	38	9.9	4.1
5	40	F	20.0	81	Central obesity	35	10.9	5.1
6	45	M	20.4	83	Good past health	50	15.6	4.0
7	47	M	22.2	70	High triglycerides	52	11.2	4.0
8	78	M	22.2	72	Good past health	25	6.2	3.8
9	49	M	19.7	77	Good past health	25	17.3	4.2
10	52	F	22.3	64	Good past health	17	8.2	3.8
11	53	M	22.0	82	Good past health	20	8.5	4.1
12	54	M	21.0	78	Dyslipidaemia	32	17.0	3.8
13	61	M	22.6	79	Good past health	42	8.7	4.2
14	62	M	22.0	82	High triglycerides	55	15.2	5.4

*Good past health, APRI 0.21, FIB-4 0.49, NAFLD fibrosis score -4.549, repeated LSM 7.9 kPa

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Clinical characteristics of 19 subjects who had incident NAFLD but not MAFLD

Subject	Sex	Age	Baseline					Follow-up				
			BMI (kg/m ²)	WC (cm)	ALT (IU/l)	IHTG (%)	LSM (kPa)	BMI (kg/m ²)	WC (cm)	ALT (IU/l)	IHTG (%)	LSM (kPa)
1	F	29	17.4	65	32	4.5	5.0	18.9	70	25	13.8	4.0
2	M	34	20.0	80	18	2.3	3.8	20.0	75	24	5.1	5.9
3	M	37	22.0	78	22	2.9	4.6	22.5	76	26	5.9	3.7
4	F	37	21.7	76	18	1.1	4.0	21.4	90	21	6.1	3.6
5	F	41	21.1	75	16	2.0	2.8	21.8	77	43	8.1	2.3
6	F	42	21.1	76	15	1.9	2.6	22.6	77	17	5.2	3.3
7	F	44	21.3	76	13	0.6	3.3	21.5	73	13	12.6	4.0
8	M	47	19.6	66	14	0.6	4.5	20.8	72	21	5.9	3.4
9	F	47	19.8	74	18	1.3	3.4	20.6	75	39	5.4	3.3
10	F	47	20.0	68	16	4.3	7.1	22.1	70	43	16.7	3.6
11	F	48	21.7	70	19	3.6	3.4	21.7	77	26	5.8	2.8
12	F	52	22.7	76	18	2.4	3.7	22.5	76	21	5.2	3.6
13	M	53	23.0	88	44	4.2	4.3	22.9	86	47	14.0	3.1
14	F	54	20.5	80	18	2.5	3.6	20.2	75	23	5.7	3.2
15	M	55	20.6	86	27	1.0	4.9	21.1	79	29	5.6	4.9
16	F	55	20.8	72	20	3.5	3.2	19.7	78	40	6.3	3.9
17	M	56	19.6	82	23	3.3	4.8	19.8	83	21	5.4	7.6
18	M	59	19.4	71	50	4.2	12.1*	18.4	72	54	11.0	37.4*
19	M	59	20.1	73	20	4.2	4.6	20.0	77	21	6.3	4.4

Take home messages



- NAFLD is **highly prevalent** in Asia and is on the rise
- 15-20% of patients with **type 2 diabetes** have significant liver fibrosis, making a strong case for screening in this high-risk group
- NAFLD in **lean and non-obese** individuals is not unique in Asia, but one should recognize that Asians start to develop metabolic complications at a lower BMI
- The new **MAFLD** definition selects patients with metabolic risk factors; future studies should clarify its impact on patient care

Thank you very much!

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