Clinical Presentation of NASH in Asia: Lean NASH

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Disclosures

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• NIH / NIDDK (NASH CRN) • Bristol Meyers Squibb • Boeringher-Ingelheim • Progenity • Durect • Viking • Poxel	• Genfit Pharmaceuticals • Genentech • Galmed • Enyo • NovoNordisk • Inventiva • Celgene	• Inventiva • Intercept • NGM Biopharma • Madrigal • Allergan • TARGET-NASH
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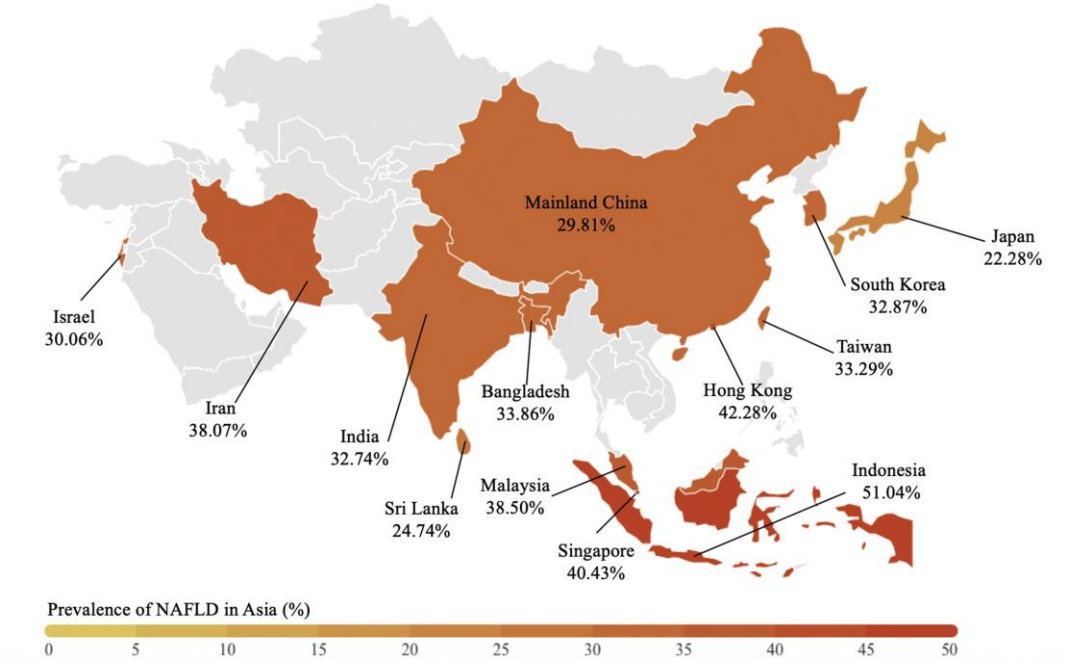
Definition of Lean NAFLD in Asia

- What is “lean”
  - BMI of 25 kg/m2 in Caucasian patients
  - BMI of 23 kg/m2 in Asian patients
- Limitations of definition:
  - Relies on imperfect index (BMI) of body fat topography
  - Fails to incorporate concepts surrounding metabolic health
- False perception of lean NAFLD being “benign”

Prevalence of NAFLD in Asia



Lean NAFLD

- China 7-18%
- Japan 14-19%
- Korea-13%
- West Bengal 5%
- South Korea-12%
- Taiwan 13%
- India 13%
- Hong Kong 15%
- Sri Lanka-10%
- Pakistan 4%

Li J et al. *Lancet Gastro Hepatol*. 2019.

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Other Causes of NAFLD in Lean Subjects

High fructose intake / High fat diet
Metabolically obese normal-weight subjects
Congenital and acquired (highly active antiretroviral therapy for HIV) lipodistrophy
Malnutrition (Kwashiorkor)
Genetic Patatin-like phospholipase domain-containing protein 3 (PNPLA 3) GG variant Congenital defects of metabolism – Familial Hypobetalipoproteinemia (FHBL) – Lysosomal acid lipase deficiency (LAL-D)
Endocrine disorders (polycystic ovary syndrome, hypothyroidism, or growth hormone deficiency)
Drug-related (amiodarone, methotrexate, and tamoxifen)
Jejunoileal bypass, starvation, total parenteral nutrition

Adopted from Younes & Bugianesi. *Semin Liver Dis*. 2019.

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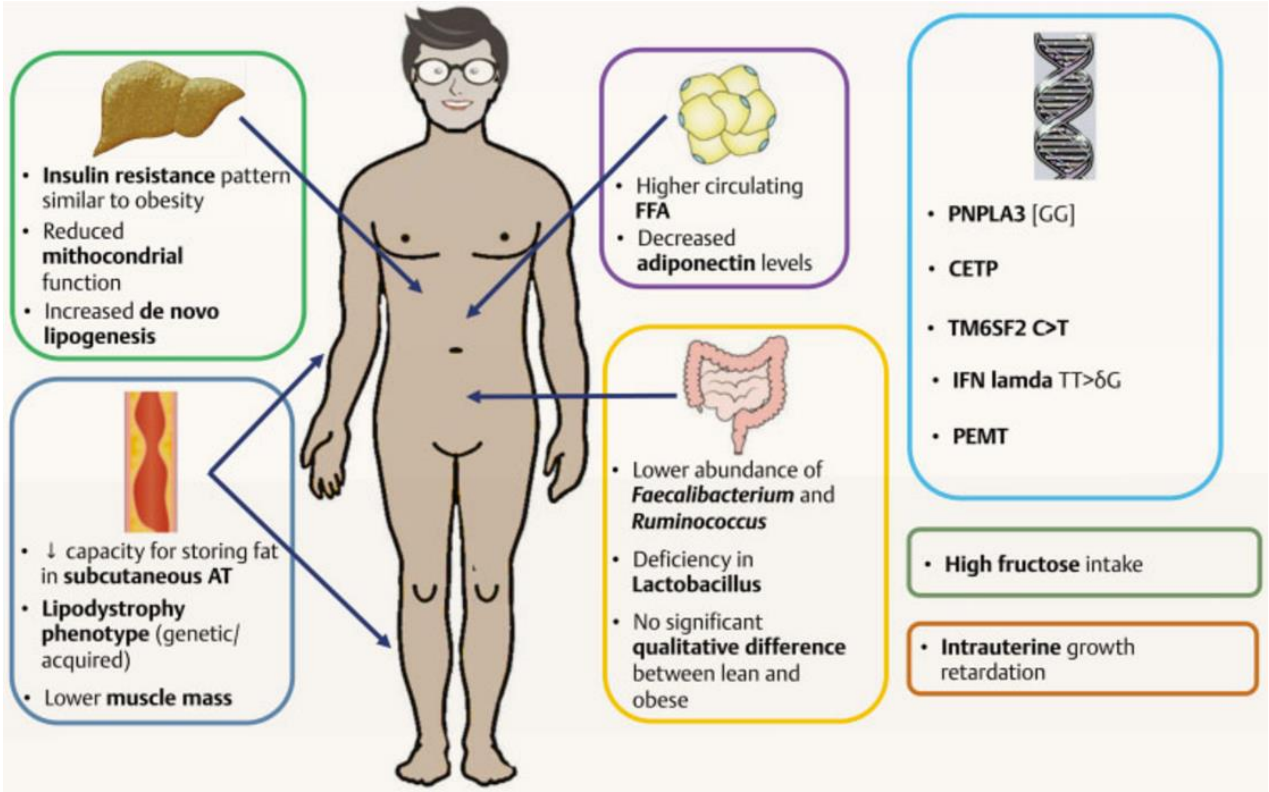
Pathophysiologic Determinants NASH in Lean Subjects



Younes & Bugianesi. *Semin Liver Dis*. 2019; Eslam M et al. *Nat Commun*. 2015; Petta S et al. *Hepatology* 2017.

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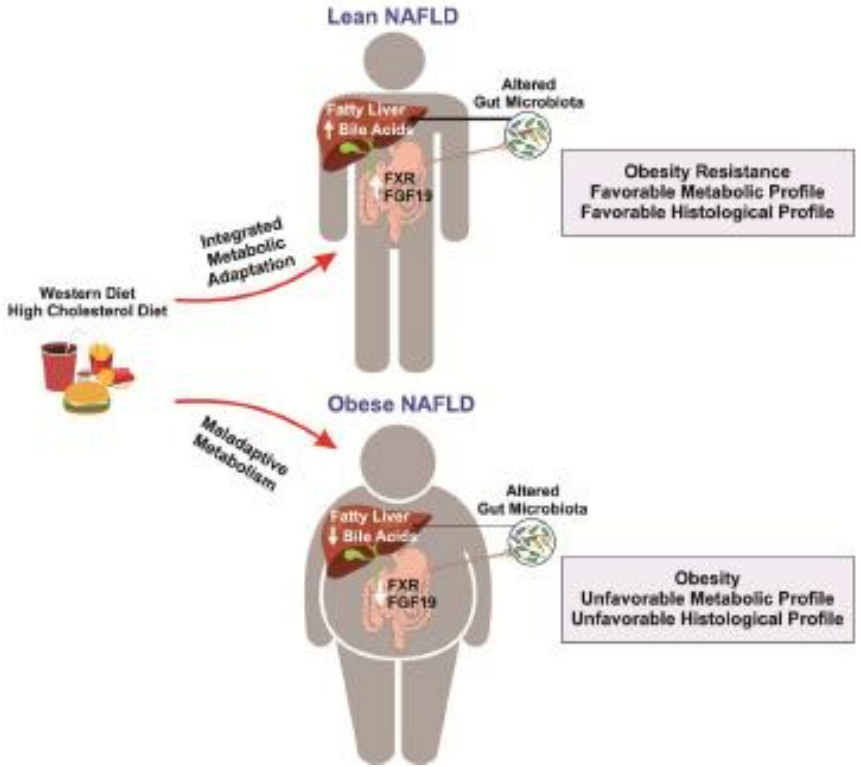
Lean NAFLD: A Distinct Entity Shaped by Differential Metabolic Adaptation



Metabolic Adaptation

Lean NAFLD patients have relative resistance to weight gain

- Higher concentrations of lysine → visceral fat accumulation
- Increased bile acids
- Increased FXR activity (measured by fibroblast growth factor 15/19)
- Distinct microbiota profile

Failure of metabolic adaptation → advancement of liver disease

Chen F et al. *Hepatology*. 2020.

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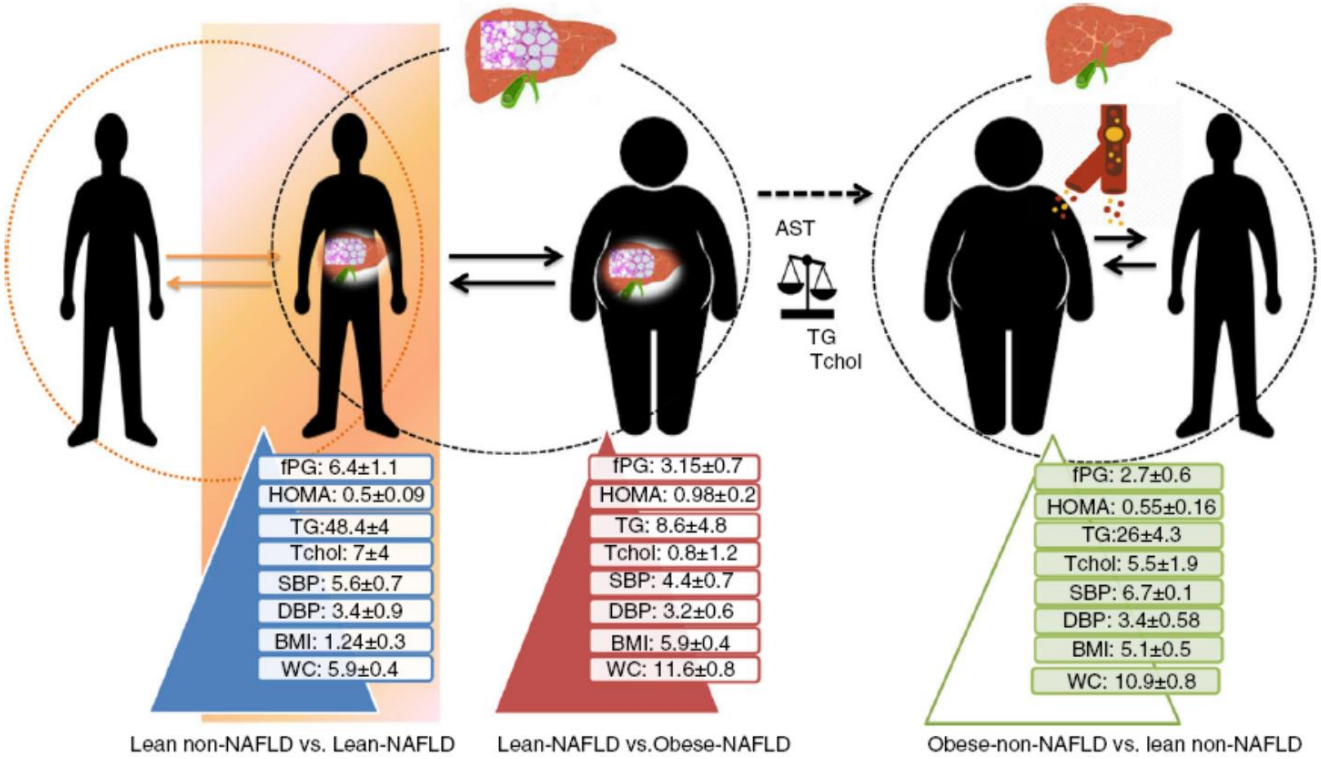
Lean NAFLD Paradox



Sookoian S et al. *Aliment Pharmacol Ther.* 2017.

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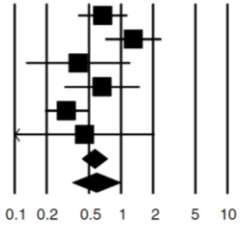
Histological Severity in Lean vs Overweight/Obese NAFLD:

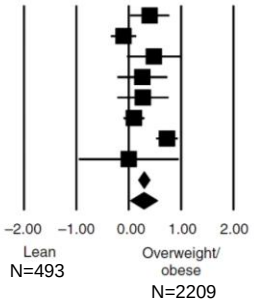
Model	Study name	Popul	outcome	Odds ratio	Lower limit	Upper limit	P-Value
	Leung 2016	HB	NASH	0.673	0.395	1.148	.145890515
	Alam 2014	HB	NASH	1.304	0.710	2.395	.392710402
	Kumar 2013	HB	NASH	0.395	0.128	1.222	.107087507
	Sookoian 2017	HB	NASH	0.663	0.293	1.500	.323738913
	A Fracanzani 2017	HB	NASH	0.306	0.192	0.488	.000000628
	Margariti, 2013	HB	NASH	0.455	0.100	2.067	.307503575
Fixed				0.561	0.428	0.737	.000030970
random				0.583	0.348	0.977	.040337751

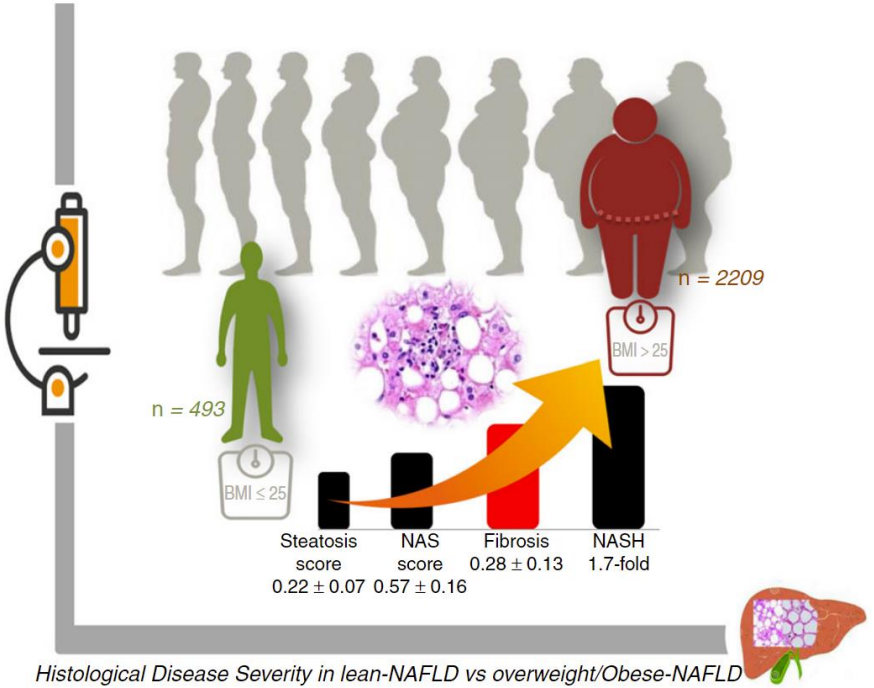
Odds ratio and 95%CI



Model	Study name	Popul	outcome	Difference in means	Standard error	Lower limit	Upper limit	P-Value
	Leung 2016	HB	Fibrosis	0.400	0.192	0.024	0.776	.037024165
	Alam 2014	HB	Fibrosis	−0.100	0.124	−0.343	0.143	.419301290
	Kumar 2013	HB	Fibrosis	0.480	0.263	−0.036	0.996	.068156269
	Akyuz 2015	HB	Fibrosis	0.260	0.244	−0.218	0.738	.286678784
	Sookoian 2017	HB	Fibrosis	0.270	0.250	−0.220	0.760	.280379721
	Y Honda 2016	HB	Fibrosis	0.100	0.102	−0.100	0.300	.327751926
	A Fracanzani 2017	HB	Fibrosis	0.730	0.106	0.522	0.938	.000000000
	Margariti, 2013	HB	Fibrosis	0.000	0.487	−0.955	0.955	1.000000000
Fixed				0.287	0.055	0.179	0.395	.000000200
random				0.283	0.132	0.024	0.542	.032338661

Difference in means and 95%CI





Histological Disease Severity in lean-NAFLD vs overweight/Obese-NAFLD

Sookoian S et al. *Aliment Pharmacol Ther.* 2017.

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Genetics

Japan
Biopsy-proven NAFLD (n=762)

Prevalence of metabolic comorbidities and PNPLA3 risk alleles did not differ between nonobese and obese NAFLD

Men		BMI < 25	BMI 25–30	BMI ≥ 30	*P*-value
n		116	173	115	—
Age		49.9 (±16.6)	46.8 (±15.9)	40.5 (±13.5)	< 0.01
BMI (kg/m^2)		22.8 (±1.7)	27.2 (±1.4)	34.7 (±5.3)	—
Diabetes (%)		41.7	37.7	54.9	n.s.
Dyslipidemia (%)		61.4	71.3	69.0	n.s.
Hypertension (%)		38.0	44.5	63.2	< 0.01
FLIP					
NASH (%)		63.8	71.7	79.1	n.s.
SAF					
S3 (%)		35.3	58.4	69.6	< 0.01
A3 (%)		55.2	69.4	82.6	< 0.01
F3–4 (%)		31.0	41.6	60.9	< 0.01
PNPLA3 (*n* = 66)	*n*	16	27	23	—
GG (%)		31.3	7.4	8.7	n.s.
BIA (*n* = 60)	*n*	20	21	19	—
Limb skeletal muscle amount (kg)		21.0 ± 1.92	23.2 ± 3.23	26.0 ± 3.30	< 0.01
SMI (kg/m^2)		7.37 ± 0.50	8.01 ± 0.71	9.09 ± 0.60	< 0.01
Body fat amount (kg)		16.9 ± 4.9	23.6 ± 4.3	37.0 ± 7.5	< 0.01
CT (*n* = 153)	*n*	45	59	49	—
Visceral fat area (cm^2)		133.6 ± 39.3	167.7 ± 61.3	208.5 ± 63.1	< 0.01
Subcutaneous fat area (cm^2)		134.3 ± 34.6	215.2 ± 74.3	379.7 ± 127.6	< 0.01

Women		BMI < 25	BMI 25–30	BMI ≥ 30	*P*-value
n		140	132	86	—
Age		60.2 (±12.2)	59.6 (±12.8)	48.5 (±15.1)	< 0.01
BMI (kg/m^2)		22.7 (±1.8)	27.3 (±1.4)	33.9 (±3.7)	—
Diabetes (%)		51.5	53.5	66.3	n.s.
Dyslipidemia (%)		60.4	65.2	68.2	n.s.
Hypertension (%)		61.9	56.5	57.0	n.s.
FLIP					
NASH (%)		70.7	74.2	84.9	n.s.
SAF					
S3 (%)		34.3	50.0	67.4	< 0.01
A3 (%)		68.6	71.2	79.1	n.s.
F3–4 (%)		51.4	62.9	33.7	< 0.01
PNPLA3 (*n* = 51)	*n*	13	22	16	—
GG (%)		15.4	18.2	37.5	n.s.
BIA (*n* = 63)	*n*	19	23	21	—
Limb skeletal muscle amount (kg)		13.4 ± 2.6	16.2 ± 2.2	18.7 ± 2.8	< 0.01
SMI (kg/m^2)		5.77 ± 0.69	6.58 ± 0.54	7.41 ± 0.70	< 0.01
Body fat amount (kg)		17.5 ± 4.6	26.0 ± 3.5	37.1 ± 7.1	< 0.01
CT (*n* = 155)	*n*	46	55	55	—
Visceral fat area (cm^2)		128.7 ± 34.2	167.9 ± 46.0	190.5 ± 62.8	< 0.01
Subcutaneous fat area (cm^2)		193.3 ± 59.5	255.8 ± 62.6	358.8 ± 110.4	< 0.01

Tobari M et al. *J Gastro Hepatol*. 2019.

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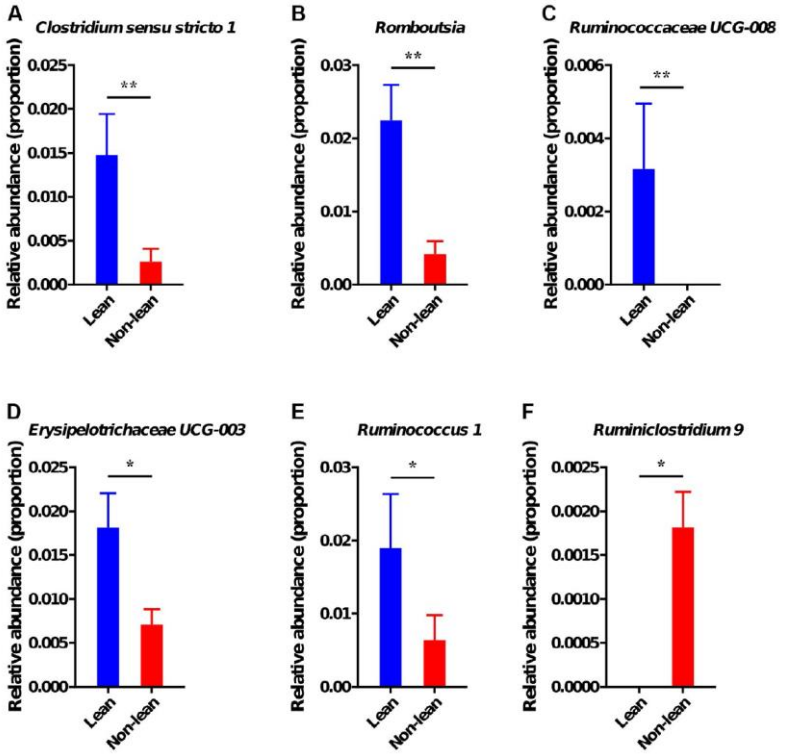
Alterations of Gut Microbiota in Lean NAFLD

Abundance of bacterial genera and species that differ between lean and obese NAFLD

Abundance of Clostridium or Ruminococcaceae family → bile acid formation



Chen F et al. *Hepatology*. 2020.

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More Favorable Metabolic Profile and Liver Histology in Lean NAFLD, Compared to Obese NAFLD: A Meta-Analysis

	Obese Versus Lean NAFLD
Demographics	Higher BMI; no difference in age and sex
Comorbidities	Higher odds for metabolic syndrome with all its components
PNPLA3 and *TM6SF2* polymorphisms	No difference
Metabolic markers	Increased measurements on insulin resistance and all components of metabolic syndrome
Biochemical and hematologic	Higher ALT, serum creatinine, and hemoglobin levels
Inflammatory markers	Higher serum CRP and uric acid levels
Liver histology	Higher odds for NASH with its components and fibrosis
	Higher mean score for steatosis grade, ballooning, and NAS
	Higher mean fibrosis stage
Liver stiffness measurement	Higher mean liver stiffness measurement

Young S et al. *Hepatol Comm*. 2020.

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Incidence of NAFLD in a Hong Kong Cohort

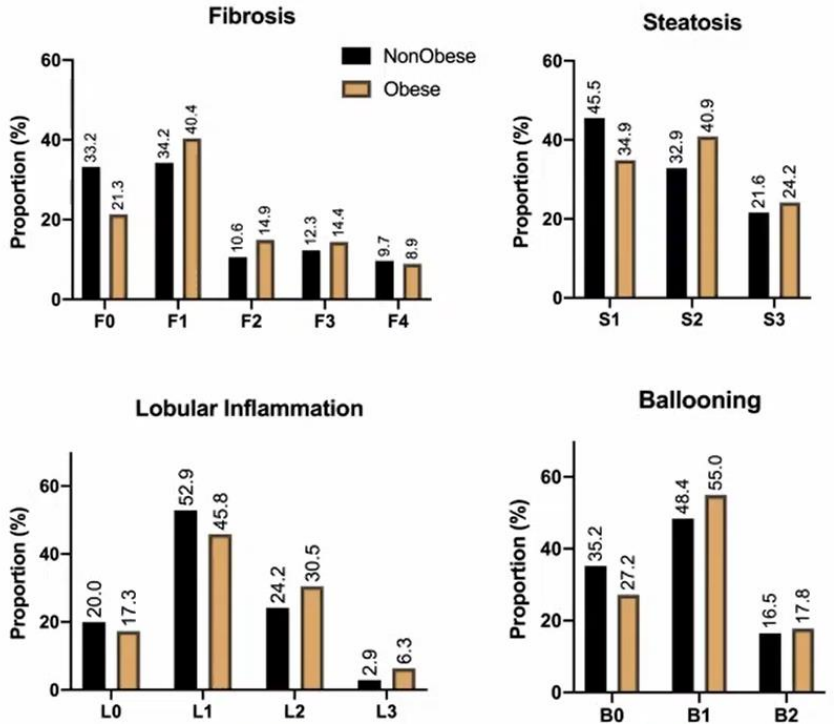
- Population incidence of NAFLD at 3–5 years was 13.5% (95% CI 10.6–16.3%; **3.4%** per year).
- Cohort included 406 lean subjects (BMI< 23)

Table 2. Factors associated with incident fatty liver.

Factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (years)	1.03 (1.00-1.05)	0.040	1.03 (1.01-1.06)	0.021
Female gender	0.58 (0.36-0.94)	0.026		
Change in BMI (kg/m^2)	1.24 (1.04-1.49)	0.018		
Change in waist circumference (cm)	1.11 (1.06-1.16)	<0.001	1.11 (1.06-1.16)	<0.001
Change in fasting glucose (mmol/L)	1.60 (0.97-2.64)	0.065		
Change in total cholesterol (mmol/L)	1.20 (0.87-1.66)	0.28		
Change in HDL-cholesterol (mmol/L)	0.18 (0.07-0.44)	<0.001	0.36 (0.13-1.00)	0.050
Change in LDL-cholesterol (mmol/L)	1.13 (0.79-1.62)	0.51		
Change in triglycerides (mmol/L)	3.29 (1.92-5.64)	<0.001	2.58 (1.48-4.50)	0.001

Wong VWS et al. *J Hepatol*. 2015.

Lean NAFLD Severity



12 Centers

9 Countries

1656 – Biopsy proven

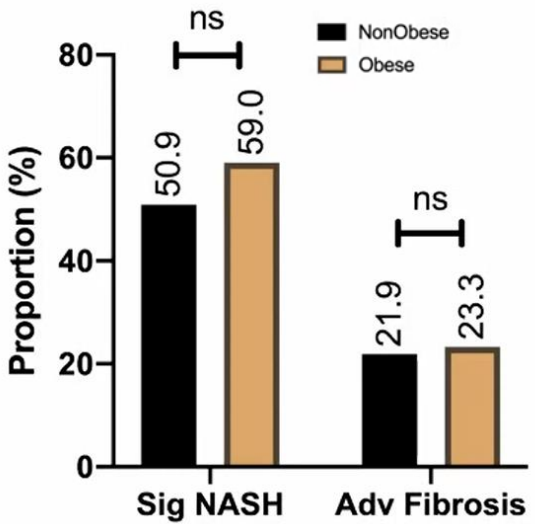
NAFLD

- Overall, non-obese NAFLD patients had less severe grades of steatosis, and steatohepatitis
- Non-obese NAFLD patients were also less likely to have liver fibrosis
  - F0: 33.2% vs 21.3%

Lee WJJ et al. AASLD 2019 (Oral).

Lean NAFLD-Severity

GOASIA Study



12 Centers

9 Countries

1656 – Biopsy proven NAFLD

- No significant difference in the proportion of
  - Significant NASH, or
  - Advanced Fibrosis
    between non-obese and obese NAFLD
- One-fifth of non-obese NAFLD patients have F3-4 fibrosis

Lee WJJ et al. AASLD 2019 (Oral).

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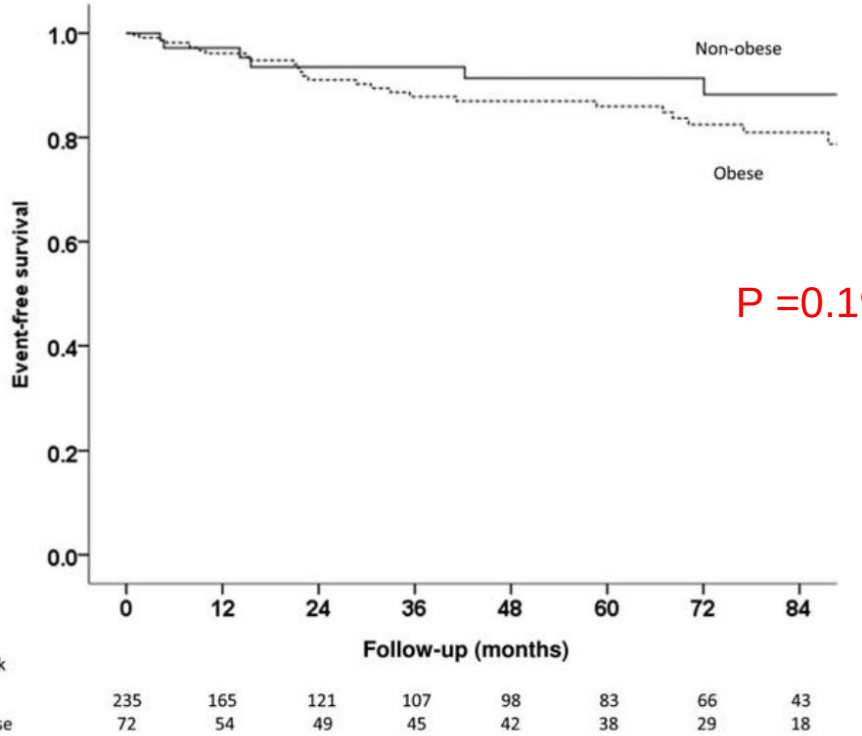
Event-Free Survival in Lean and Obese NAFLD Patients



P =0.190 by log-rank test

Leung J et al. *Hepatology.* 2017.

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Summary

- BMI does not define metabolic health
- Lean NAFLD patients are not healthy but are best considered ‘lean metabolically diseased’
- Lean NAFLD: lower incidences of hepatic and nonhepatic outcomes, but all were NOT statistically significant (vs non-lean)
- Lean NAFLD is not “benign”.

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