Fatty liver disease as a cardiovascular risk factor

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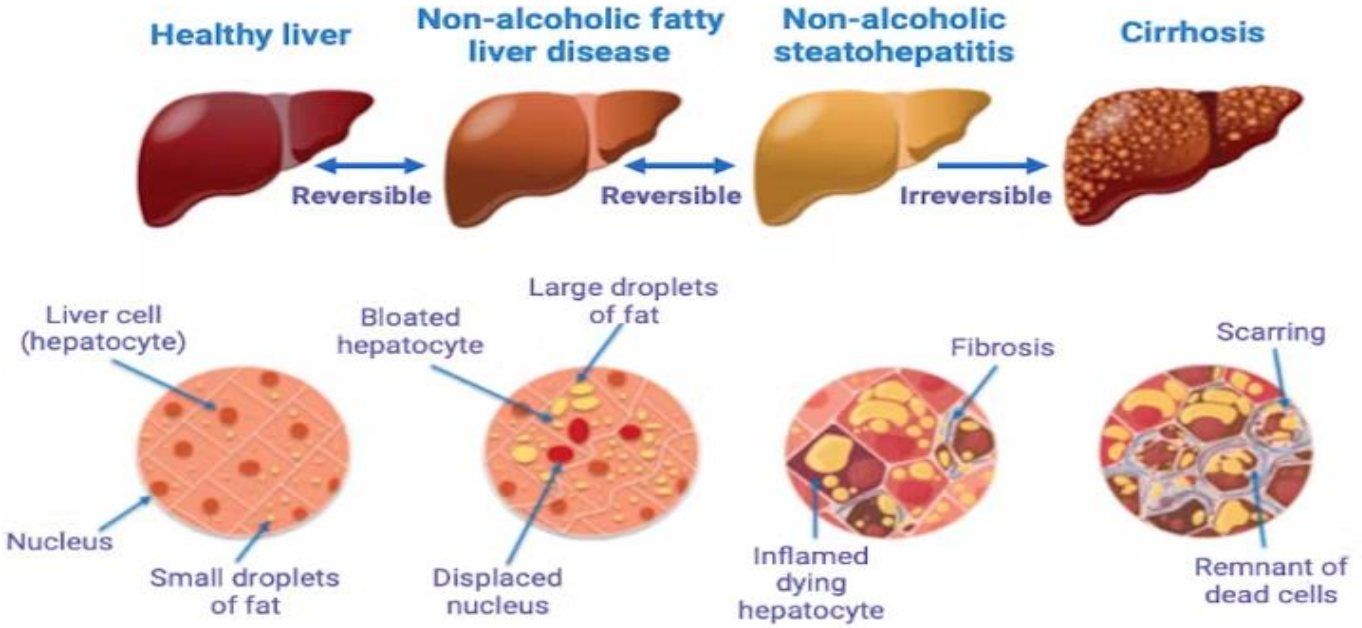
Case

- 64y male , retired
- NASH cirrhosis
- Obese, DM, HTN, Diuretic controlled ascites
- Plt 50K Alb 3.5 INR 1.4 Creatinine 1.2
- Variceal band ligation-preventive
- Chest pain
- Exertional dyspnea

NAFLD

Diseases	Medications
- Alcohol consumption	•Amiodarone
- Hepatitis C (genotype 3)	•Methotrexate
- Wilson's Disease	•Tamoxifen
- Lipodystrophy	•Corticosteroids
- Starvation	•Chemotherapy
- Parenteral nutrition	•Retinoic acid
- Abetalipoproteinemia	



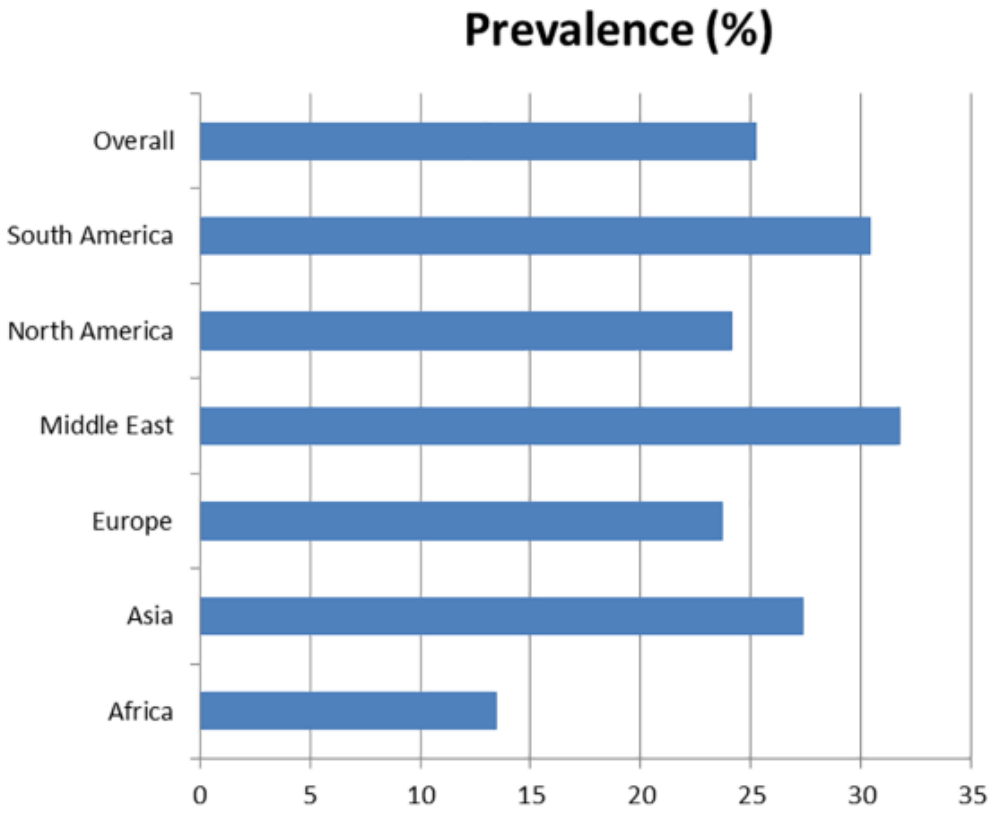
NAFL

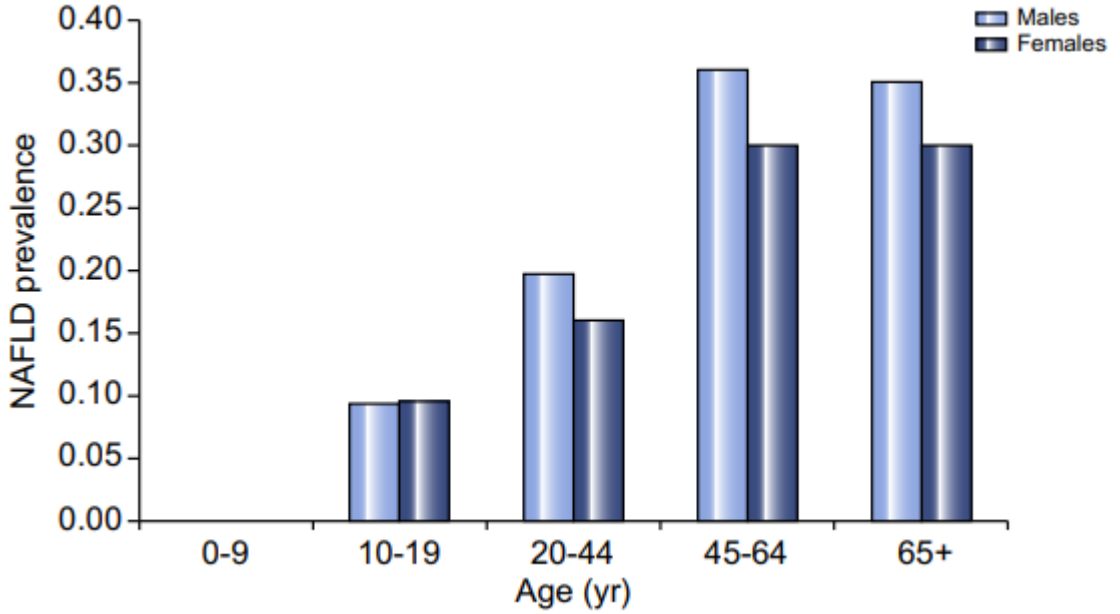
- 5% steatosis without :
  - hepatocellular injury
  - hepatocytes ballooning
  - Fibrosis
- Usually, good liver prognosis

NASH

- 5% steatosis with :
  - Inflammation
  - hepatocellular injury
  - hepatocytes ballooning
  - ± fibrosis

Epidemiology





Common Conditions With Established Association	Other Conditions Associated With NAFLD
Obesity	Hypothyroidism
T2DM	Obstructive sleep apnea
Dyslipidemia	Hypopituitarism
MetS*	Hypogonadism
Polycystic ovary syndrome	Pancreatoduodenal resection
	Psoriasis

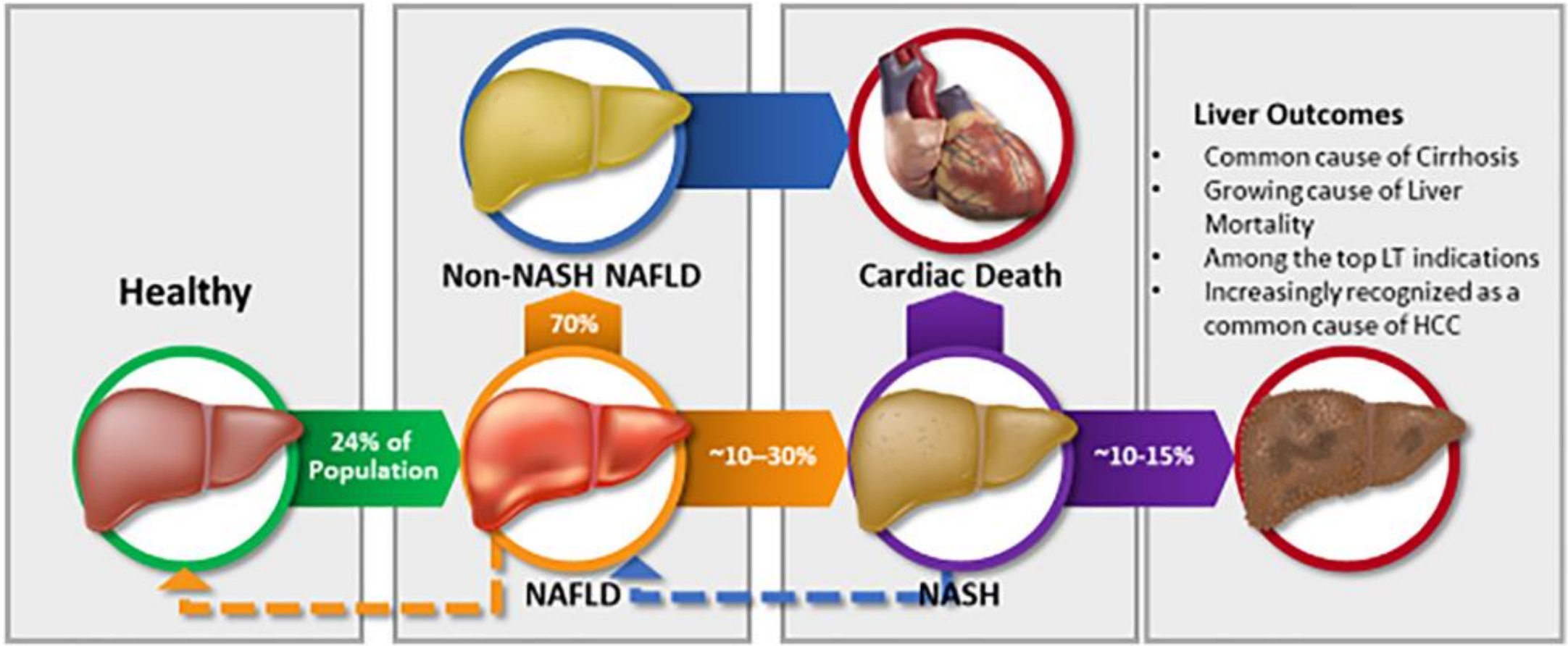
The epidemiology of nonalcoholic steatohepatitis, Volume: 11, Issue: 4, Pages: 92-94, First published: 20 April 2018, DOI: (10.1002/cld.710)

Journal of Hepatology 2019 vol. 70 j 531–544

Fatty liver

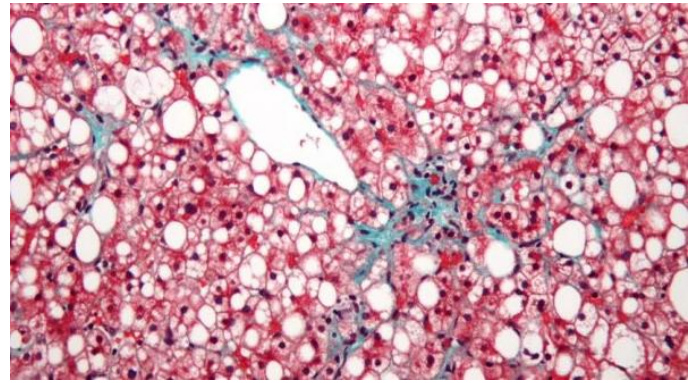
Genetic factors	Drugs
Family history of NAFLD	Alcohol
PNPLA3	Amiodarone
TM6SF2	Mipomersen
HSD17B13	Lomitapide
GCKR	Tamoxifen
MBOAT7	Methotrexate
	Corticosteroids, Valproate, Aspirin (eg, Reye syndrome) NSAID,NRTI,Tetracycline

Natural history



The epidemiology of nonalcoholic steatohepatitis, Volume: 11, Issue: 4, Pages: 92-94, First published: 20 April 2018, DOI: (10.1002/cld.710)

Fibrosis-best prognostic factor

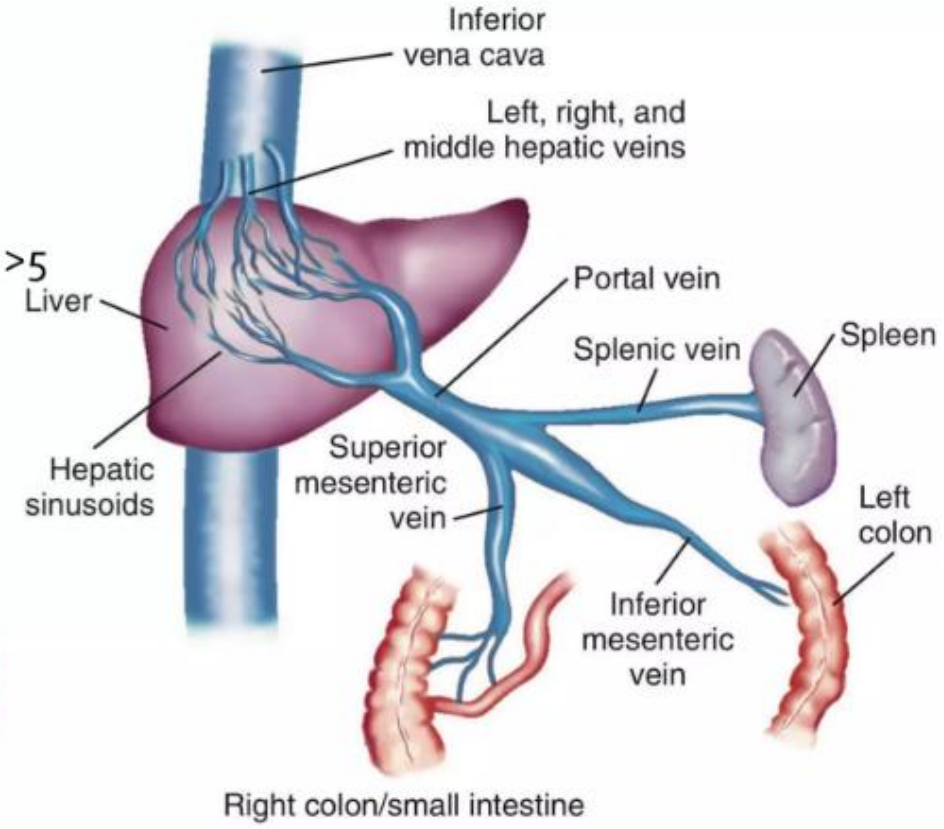


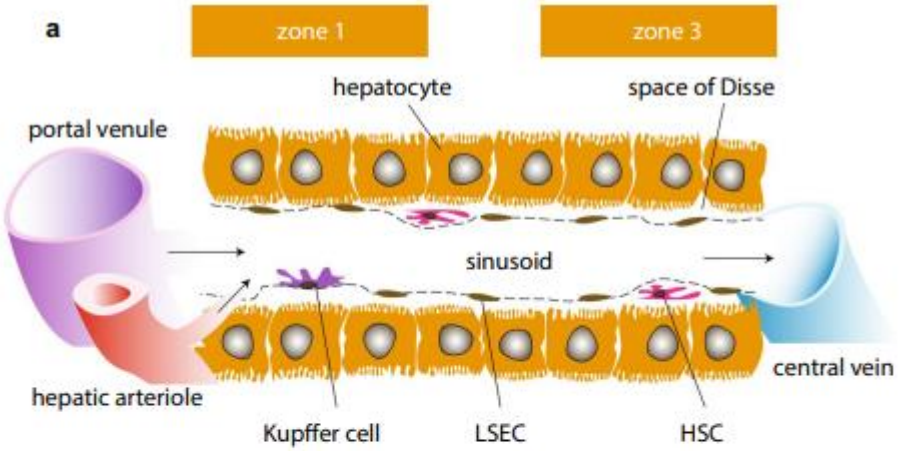
Portal hypertension

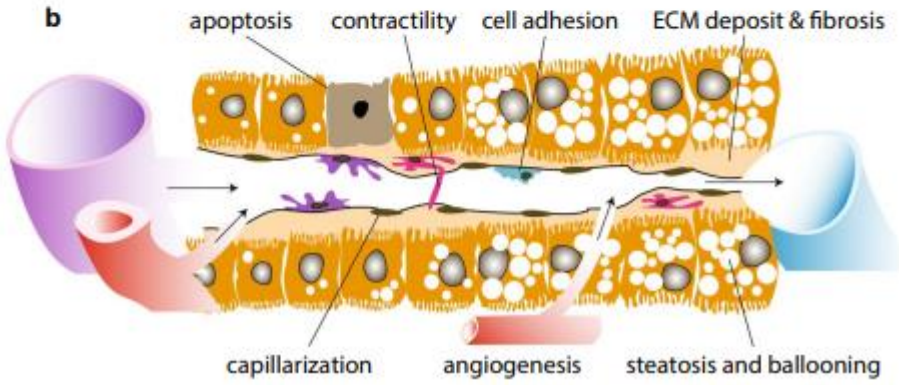
Normal portal pressure gradient 1-5 mmHg

Portal hypertension = portal pressure gradient >5 mmHg

Clinically significant portal hypertension >= 10 mmHg.







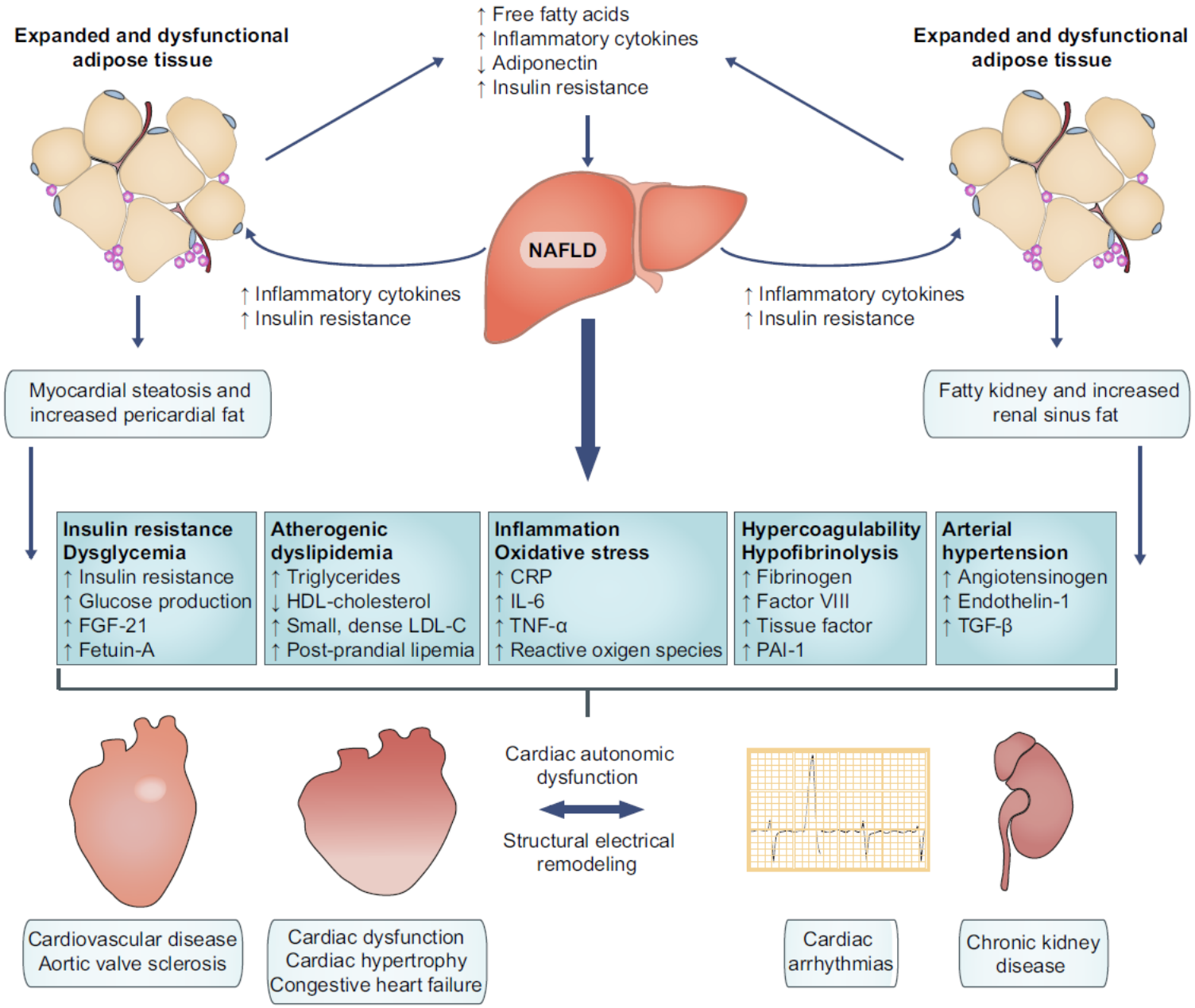
Digestive Diseases and Sciences (2018) 63:563–576

Assessment of NAFLD

- **NAFLD fibrosis score**
  - -1.675 + 0.037 x Age (years) + 0.094 x BMI (kg/m2) + 1.13 x IFG/diabetes (yes = 1, no = 0) + 0.99 x AST/ALT ratio - 0.013 x platelet (x109/l) - 0.66 x Albumin (g/dl)
  - A score of less than -1.455 excludes fibrosis, a score of greater than 0.676 predicts fibrosis

Ultrasound	Fibroscan	CT unenhanced	MRI
Fat	Fat	Fat	Fat
Hyperechoic liver	Quantitation- CAP	Hounsfield units	PDFF
Sensitivity	Fibrosis	Structural change	Fibrosis
Liver morphology	Elasticity KPA	Liver spleen size	Elastography
Spleen size	Cheap, available, validated	Sensitive	Highly accurate
Operator	Limitations	Expensive, radiation	Very expensive

The contribution of NAFLD to the increased risk of cardiovascular disease



Journal of Hepatology 2015 vol. 62 j S47–S64

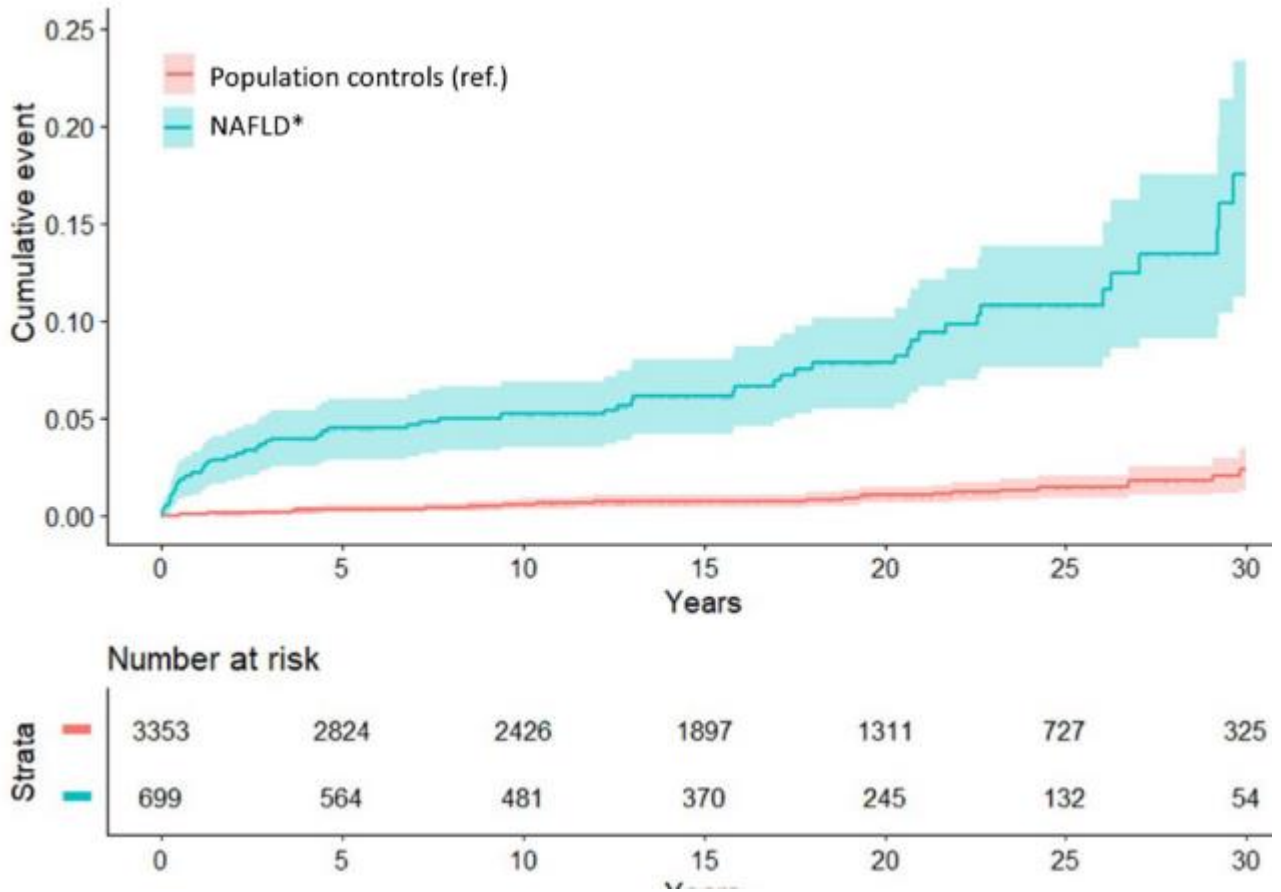
TABLE 3. Incidence and IRR for Progression of NAFLD and NASH

Population	Outcome	Incidence Rate Per 1,000 Person-Years*	Number of Studies	95% CI	I^2 (%)	Follow-up (Years)
NAFLD	CVD-specific mortality	4.79	6	(3.43-6.7)	91.17	12.96
NAFLD	HCC	0.44	3	(0.29-0.66)	0.00	5.82
NAFLD	Liver-specific mortality	0.77	7	(0.33-1.77)	91.84	13.17
NAFLD	Overall mortality	15.44	7	(11.73-20.34)	97.17	13.17
NASH	Advanced fibrosis	67.95	3	(46.84-98.56)	9.80	4.05
NASH	HCC	5.29	1	(0.75-37.56)	NA	4.50
NASH	Liver-specific mortality	11.77	3	(7.1-19.53)	0.00	8.08
NASH	Overall mortality	25.56	2	(6.29-103.8)	73.85	6.17
		IRR*				
NAFLD	Liver-specific mortality	1.94	5	(1.28-2.92)	26.78	13.38
NAFLD	Overall mortality	1.05	5	(0.7-1.56)	97.99	13.38
NASH	Liver-specific mortality	64.6	3	(35.43-117.8)	0.00	8.08
NASH	Overall mortality	2.56	2	(0.63-10.39)	73.76	6.17
		AHR Ratio*				
NAFLD	Liver-specific mortality	2.6	5	(0.91-7.42)	76.66	13.23
NAFLD	Overall mortality	1.04	5	(1.03-1.04)	0.08	13.23
		Fibrosis Progression				
NASH	Percent fibrosis progression†	40.76	4	(34.69-47.13)	5.70	4.91
NASH	Mean fibrosis annual progression rate†	0.09	2	(0.06-0.12)	0.00	4.01

*Study sources in Supporting Table F.
†Study sources in Supporting Table E.
Abbreviation: NA, not applicable.

HEPATOLOGY, VOL. 64, NO. 1, 2016

Cardiovascular disease risk in paediatric and young adult non-alcoholic fatty liver disease

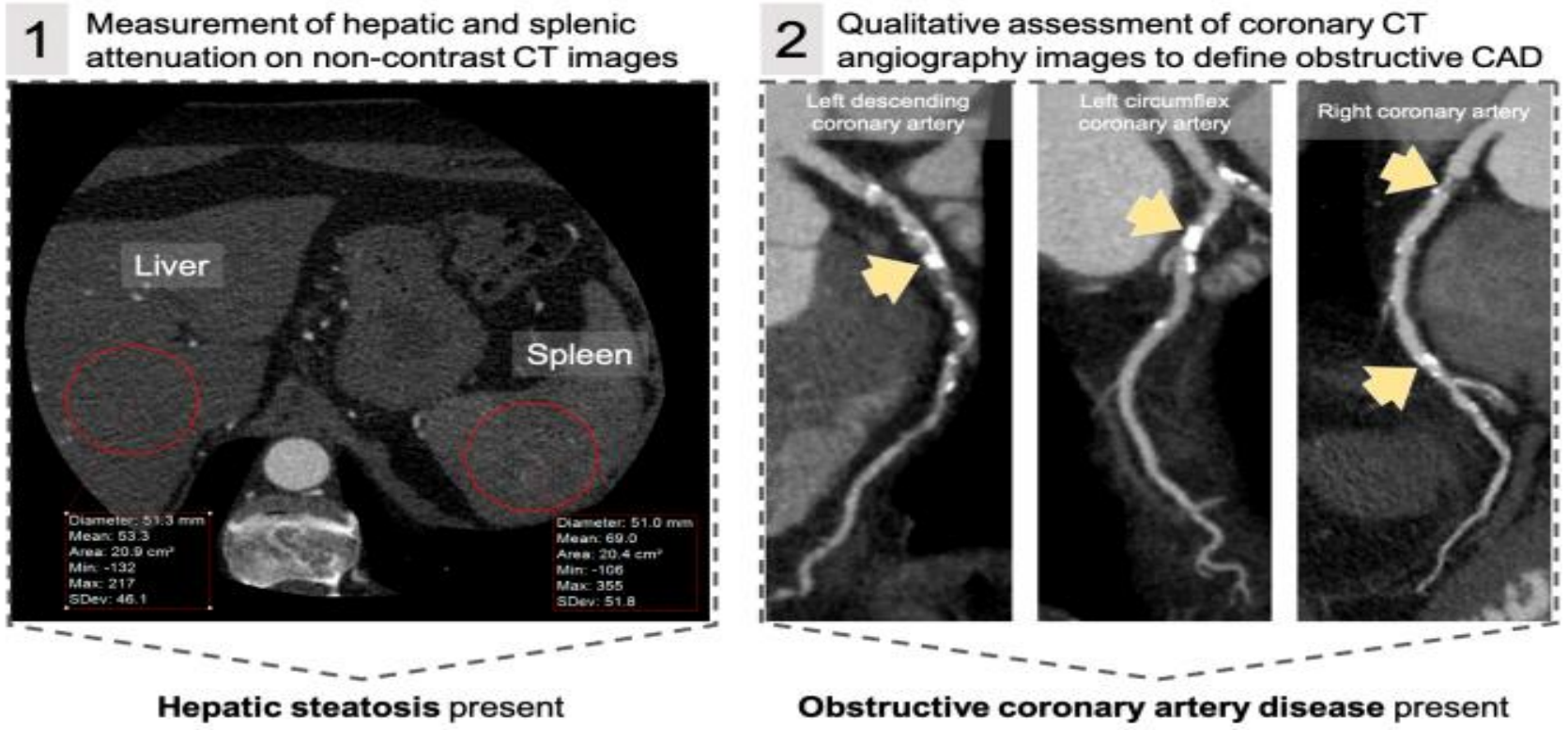


Simon TG, et al. Gut 2022;0:1–8. doi:10.1136/gutjnl-2022-328105

NAFLD and vascular disease

Carotid intima-media thickness (CIMT)
Coronary artery calcification (CAC)

- NAFLD is independently associated with increased CIMT and CAC
- NAFLD :impaired flow-mediated vasodilation, increased CIMT, and increased carotid atherosclerotic plaques independent of metabolic syndrome



NAFLD and thicker EAT (>3.18 mm) are at increased risk for coronary calcification (CAC score >0)

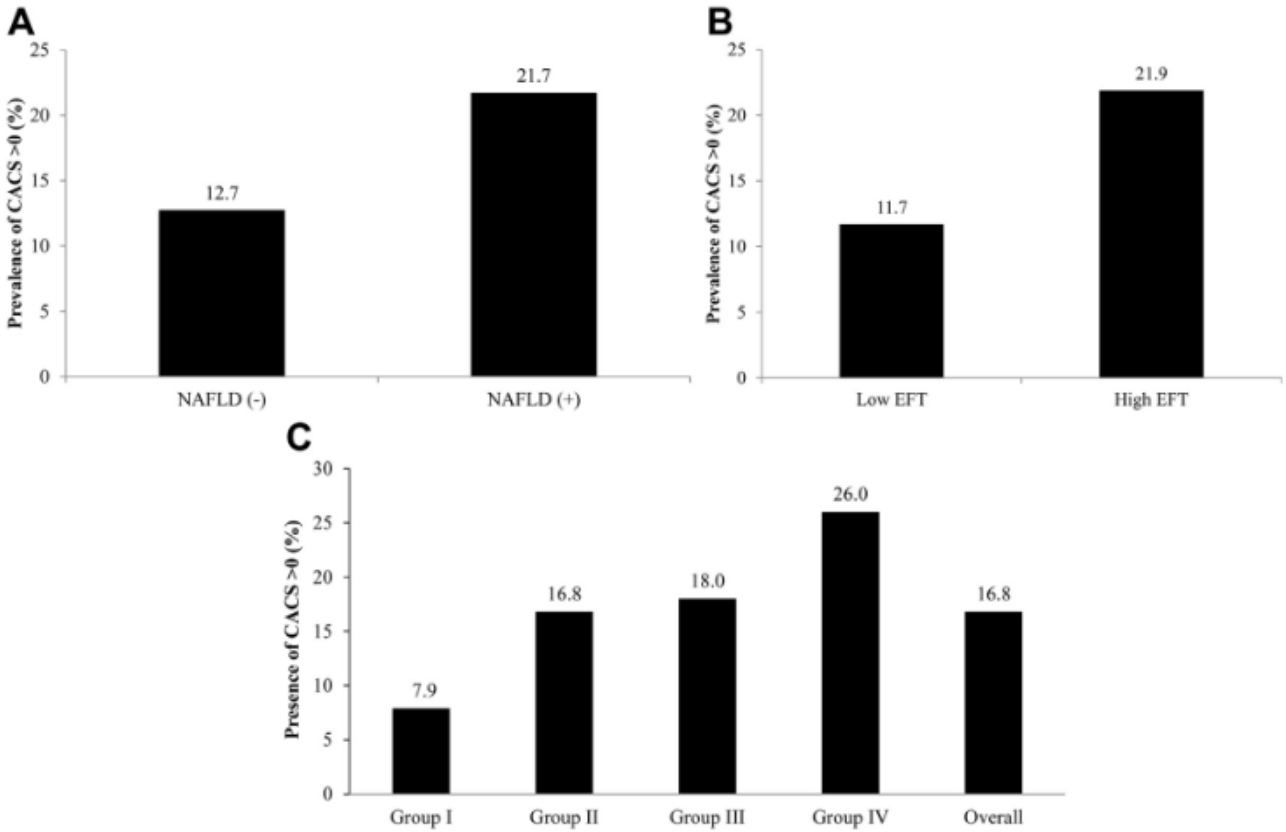
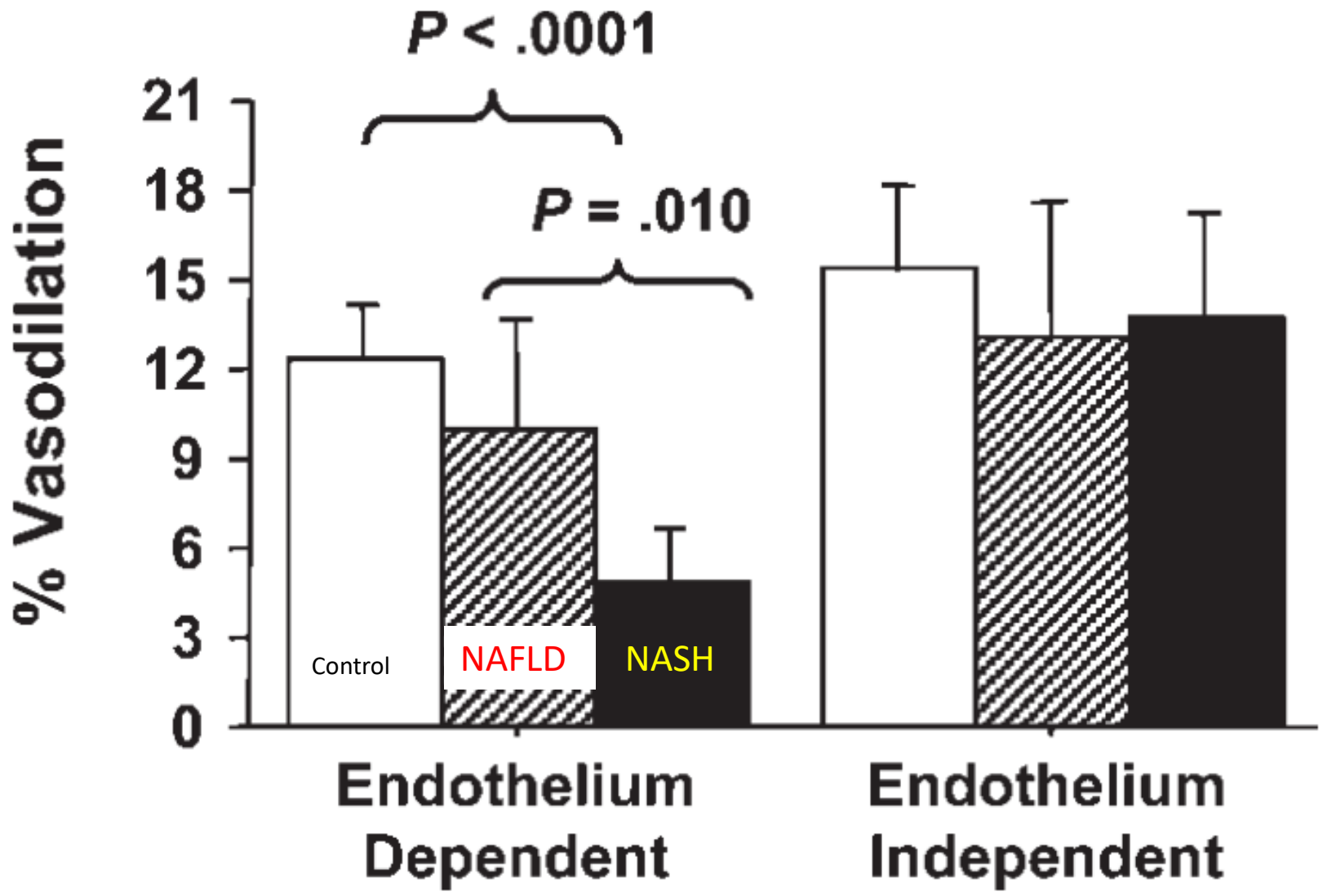


Figure 1 Prevalence of CACS > 0 according to of epicardial fat thickness and nonalcoholic fatty liver disease. (A) Prevalence of CACS > 0 in two groups according to the presence of NAFLD; (B) Prevalence of CACS > 0 in two groups according to the degree of epicardial fat thickness; (C) Prevalence of CACS > 0 in four groups according to the presence of NAFLD and degree of epicardial fat thickness. Group I (low EFT and absence of NAFLD); Group II (low EFT and presence of NAFLD); Group III (high EFT and absence of NAFLD); Group IV (high EFT and presence of NAFLD). CACS, coronary artery calcium score.

Journal of Clinical Lipidology, Vol 10, No 3, June 2016


P < .0001
P = .010
% Vasodilation
21
18
15
12
9
6
3
0
Control
NAFLD
NASH
Endothelium Dependent
Endothelium Independent

Echo in NAFLD

- lower early diastolic relaxation velocity
- higher LV filling pressure (E/e’ ratio)
- worse absolute global longitudinal strain

NAFLD and the heart

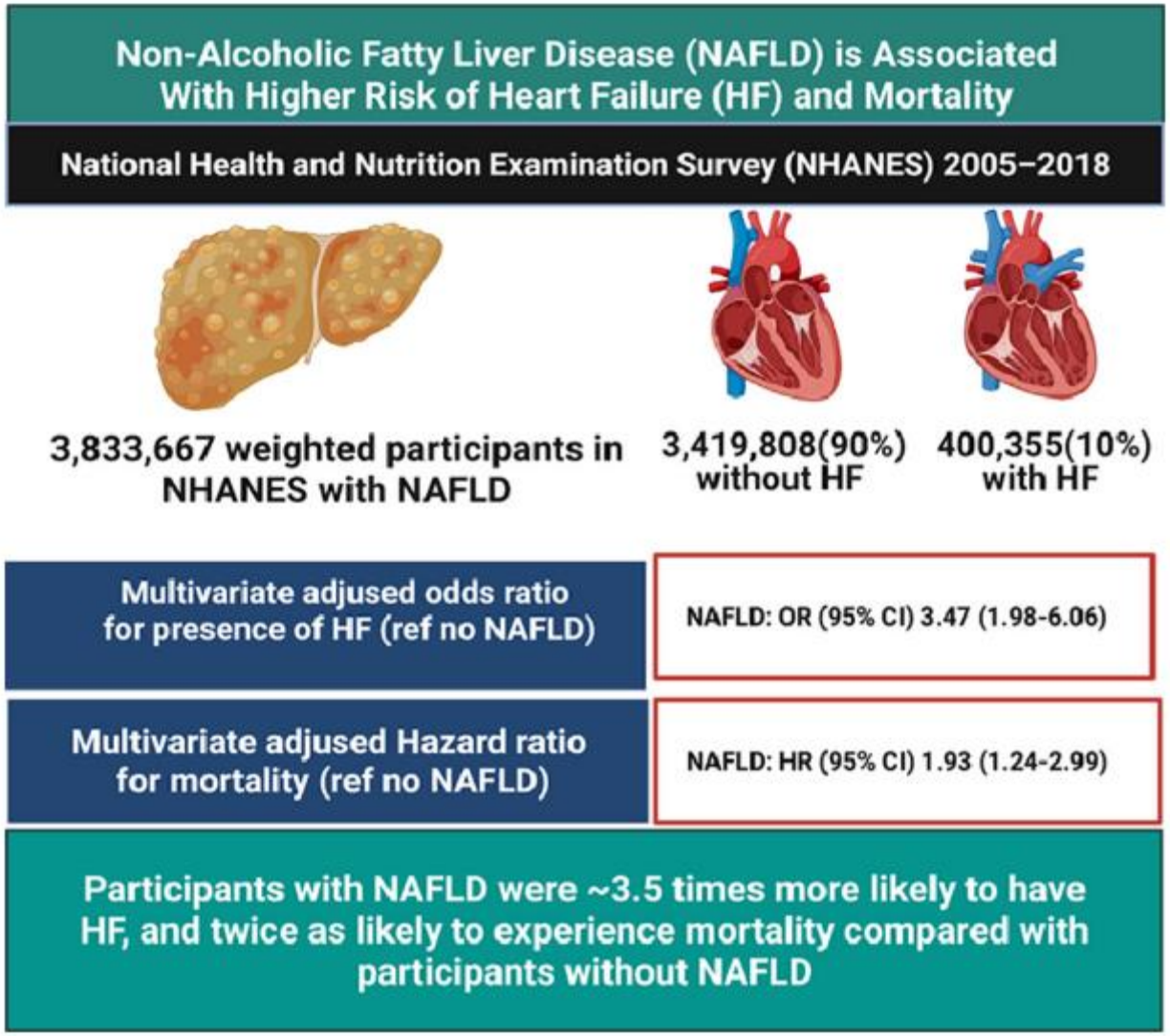
NAFLD

- Proinflammatory, oxidative
- valvular calcifications
- diastolic dysfunction
- left ventricular hypertrophy
- autonomic dysfunction

Arrhythmias

- Atrial fibrillation
- Prolonged QT
- Non sustained VT

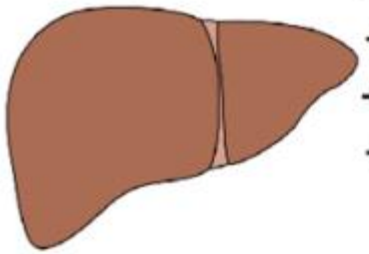
Non-Alcoholic Fatty Liver Disease, Heart Failure, and Long-Term Mortality: Insights From the National Health and Nutrition Examination Survey



Current Problems in Cardiology, 2022-12-01, Volume 47, Issue 12, Article 101333

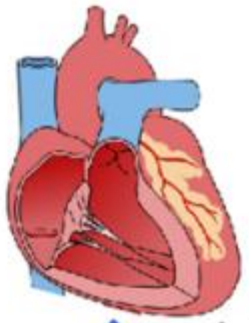
The Cardiovascular Link Between Liver Disease and HFpEF

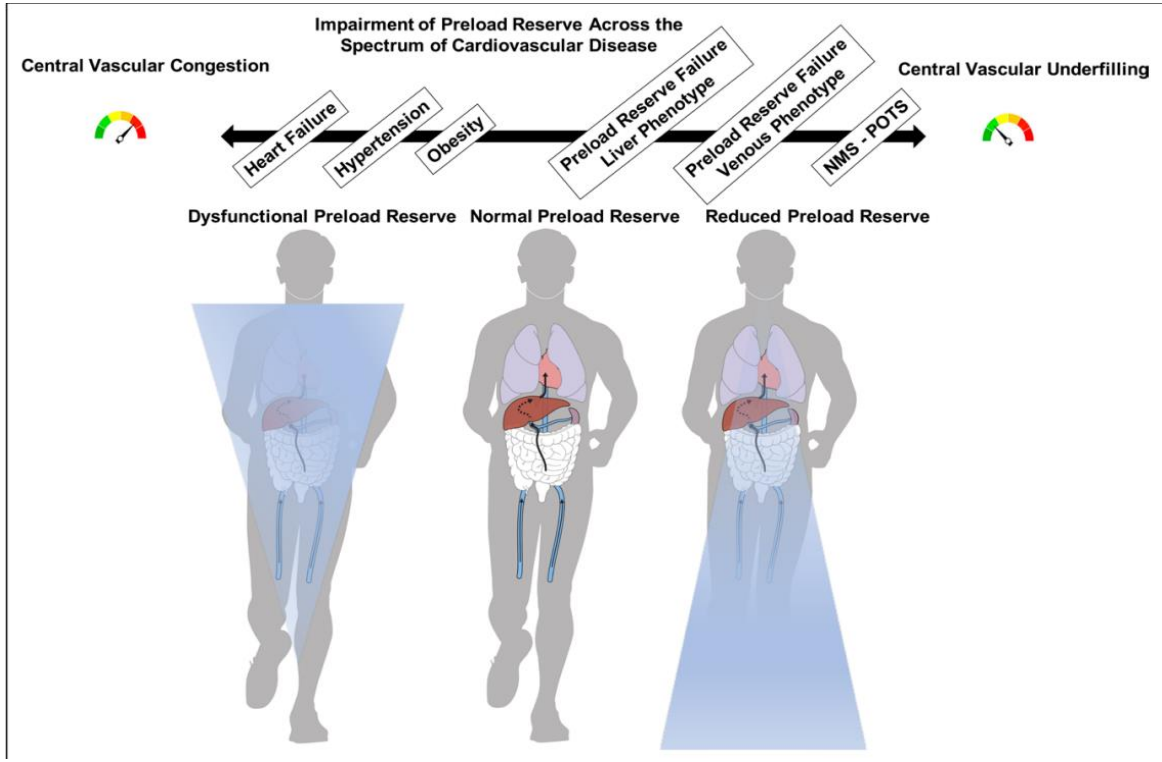
NAFLD

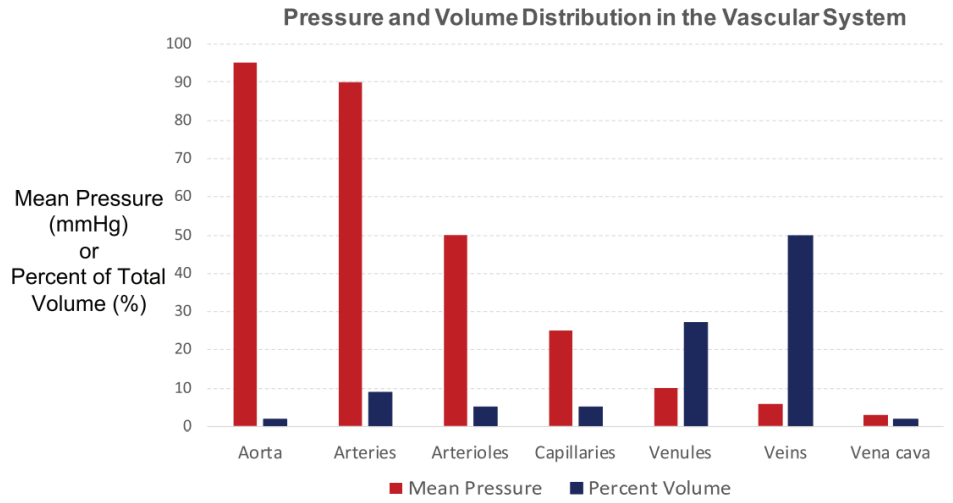


+ Diastolic dysfunction +
+ Atrial myopathy +
+ Limited exercise capacity +
+ High/normal cardiac output +
+ Systemic vasoconstriction +
+ Elevated sympathetic tone +
+ Chronotropic insufficiency +
+ Salt and water retention +
+ Portal hypertension +
+ Splanchnic vasodilation ?
? Limited preload reserve ?

HFpEF

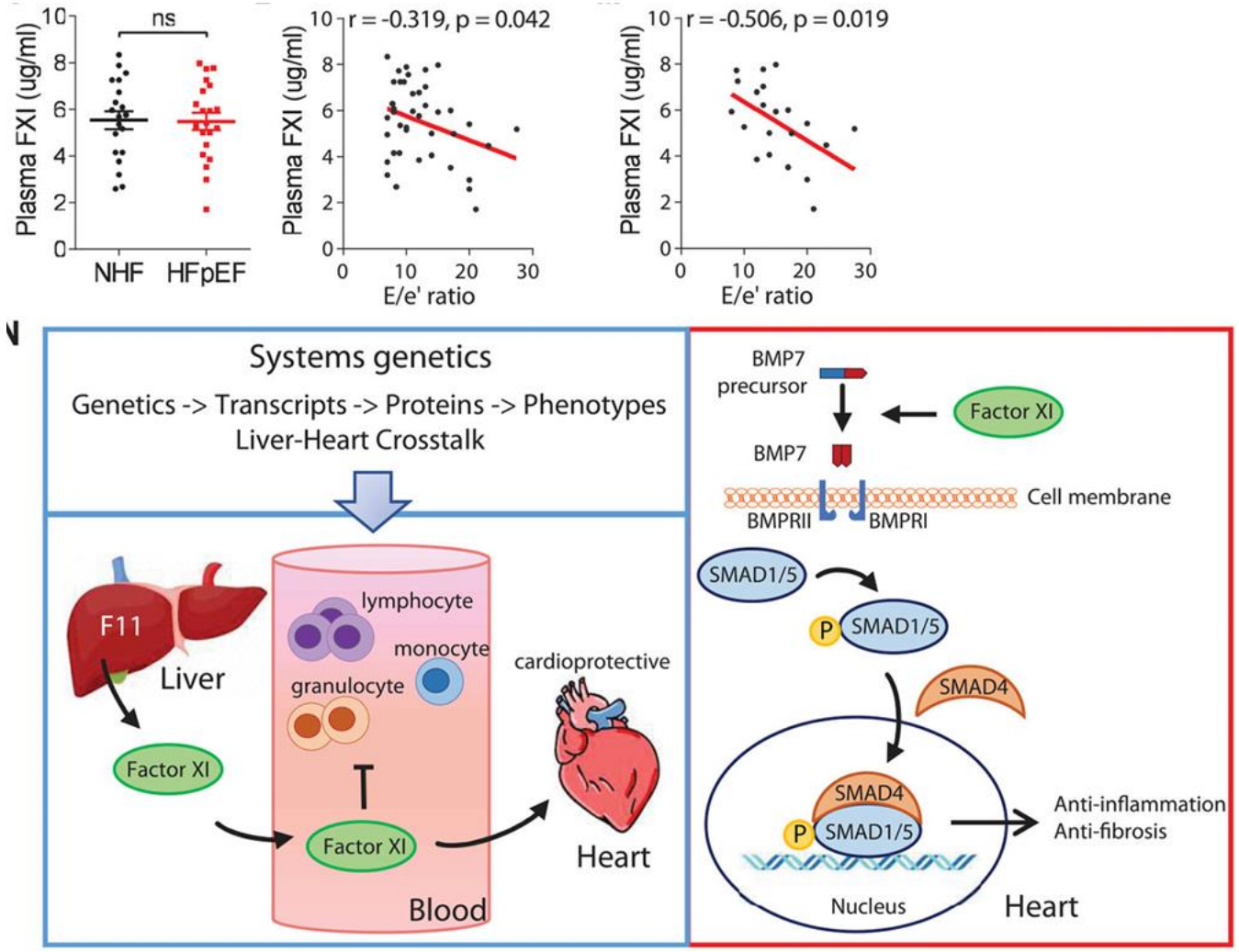






Circ Heart Fail. 2021;14:e007308

Liver-heart cross-talk mediated by coagulation factor XI protects against heart failure



Science. 2022 September 23; 377(6613): 1399–1406.

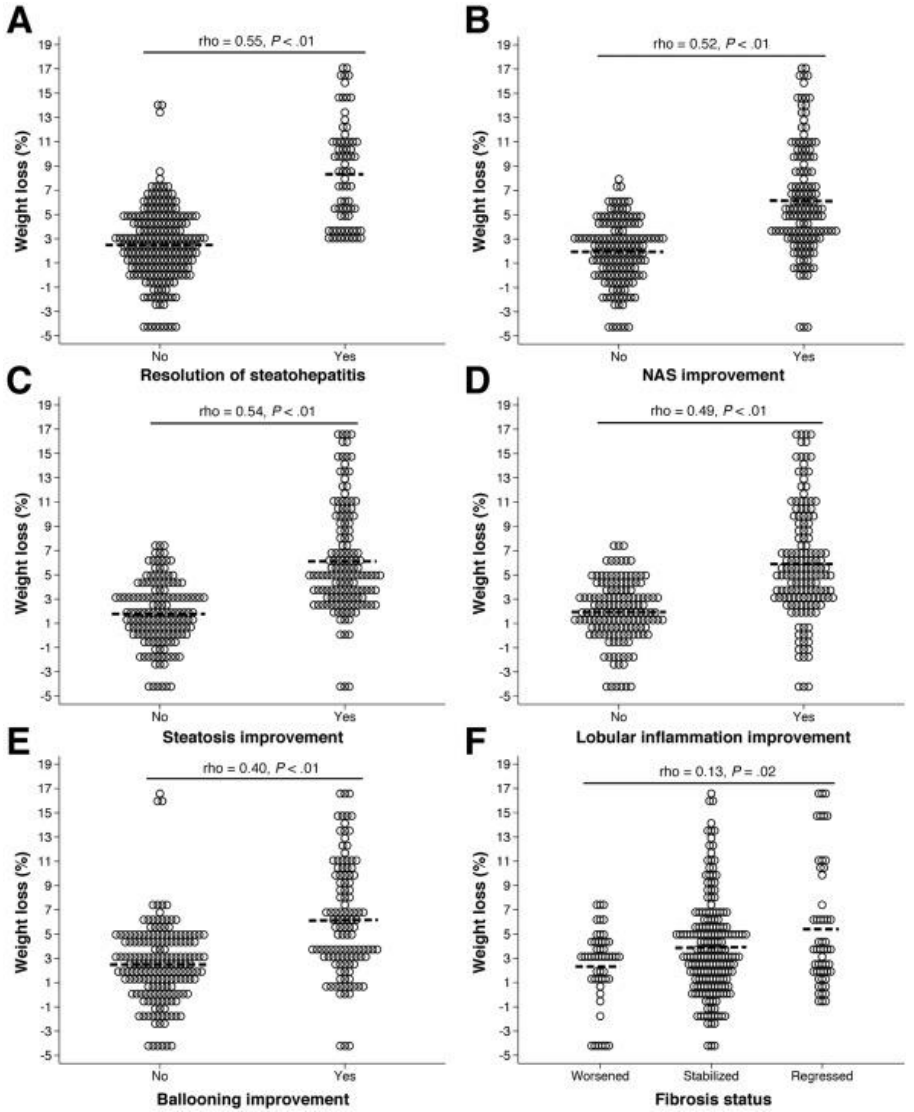
Multiethnic Genome-Wide Association Study Finds 7 Subgroups of NAFLD

Group	Genes	Steatosis	Cirrhosis	LDL	MI	TG	HDL	DM	BMI
Low lipoprotein out	*PTPRD PNPLA3 TM65F2*	↑	↑	↓	↓	↓	↓	↑	↓
High lipoprotein in	*APDE*	↑	↑	↓	↓	↓	↑	↑	↑
Low Lipid Burn	*FTO*	↑	--	↓	--	--	↓	↑	↑
Insulin	*INSR PNPLA2 GRB14 SRE6F1*	↑	--	↑	↑	↑	↓	↑	↓
Absorb	*MTTP*	↑	--	↑		↑	↑	↑	--
Glucose	*GCXR TRIB1*	↑	--	↑	↑	↑	↓	↓	↓
Divert	*MBOAT7 MARC1 TOR1B ADH1B GPAM*	↑	↑	↑	↑	↓	↑	↑	--
Epidemiology		↑	↑	↑	↑	↑	↓	↑	↑

BMI, body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; TG, triglycerides.

Du X, et al. Presented at: The Liver Meeting 2022: American Association for the Study of Liver Diseases (AASLD); November 4-8, 2022; Washington, DC/Virtual. Presentation 14.

Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis



Gastroenterology 2015;149:367–378

Ultra processed food

Mediterranean diet

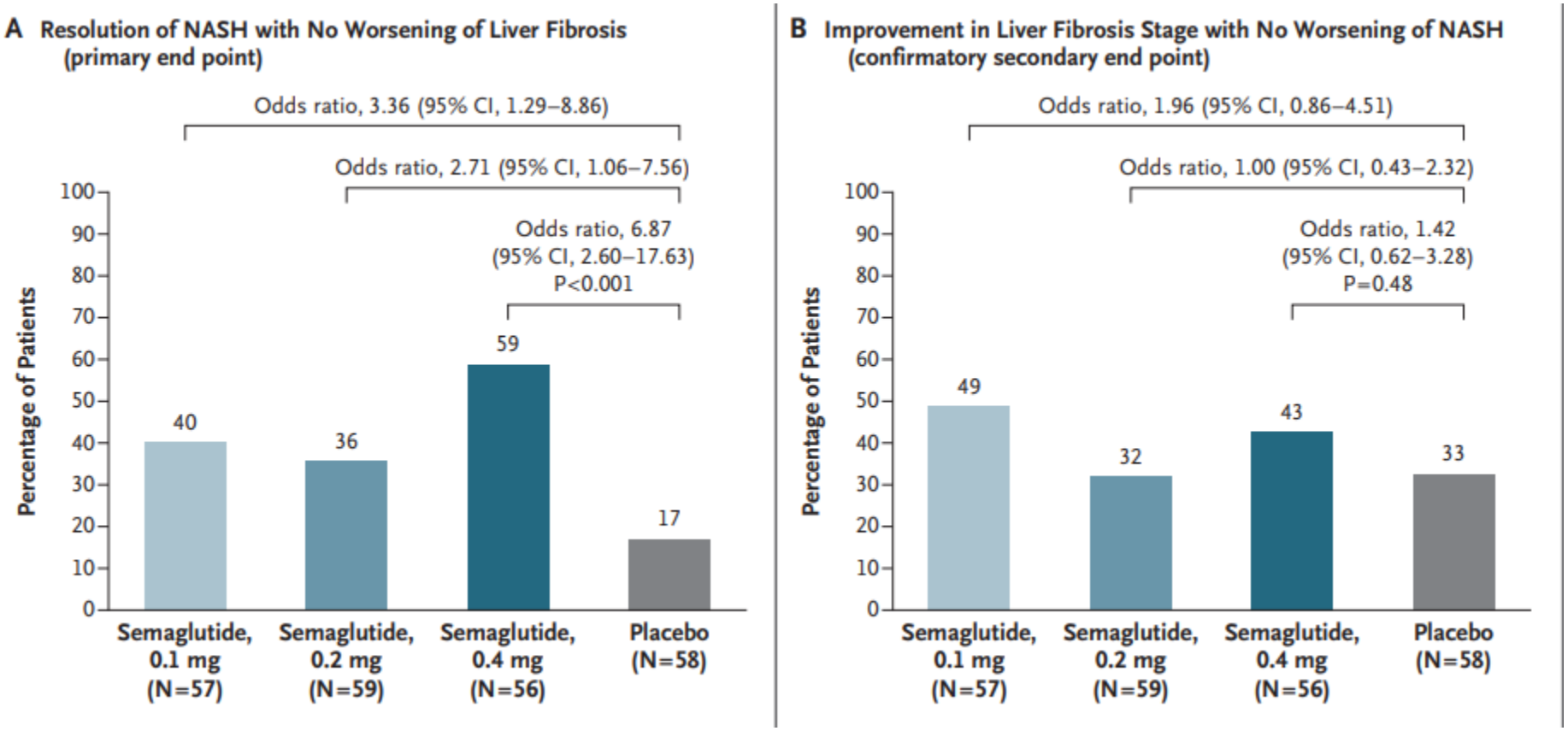
Social Determinants of Health and Association With Outcomes in Patients With MAFLD

Predictor	Mortality		Cirrhosis (FIB-4 < 3.25)		Cardiovascular Disease		Obesity-Related Cancer	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Disadvantage								
Quartile 1	Reference		Reference		Reference		Reference	
Quartile 2	1.33 (1.19, 1.50)	< .0001	1.08 (0.90, 1.30)	.40	1.16 (1.01, 1.34)	.034	1.25 (1.02, 1.53)	.031
Quartile 3	1.52 (1.36, 1.71)	< .0001	1.19 (0.99, 1.43)	.057	1.26 (1.09, 1.45)	.001	1.15 (0.93, 1.43)	.180
Quartile 4	1.66 (1.47, 1.87)	< .0001	1.27 (1.06, 1.53)	.010	1.20 (1.03, 1.39)	.017	1.27 (1.02, 1.58)	.029
Affluence								
Quartile 1	Reference		Reference		Reference		Reference	
Quartile 2	0.87 (0.78, 0.97)	.011	0.91 (0.77, 1.09)	.310	0.99 (0.86, 1.15)	.930	0.95 (0.77, 1.17)	.630
Quartile 3	0.69 (0.61, 0.77)	< .0001	0.82 (0.69, 0.98)	.026	0.94 (0.81, 1.08)	.380	0.97 (0.79, 1.19)	.750
Quartile 4	0.58 (0.52, 0.66)	< .0001	0.64 (0.53, 0.78)	< .0001	0.87 (0.76, 1.01)	.072	0.76 (0.61, 0.95)	.014

FIB-4, fibrosis 4.

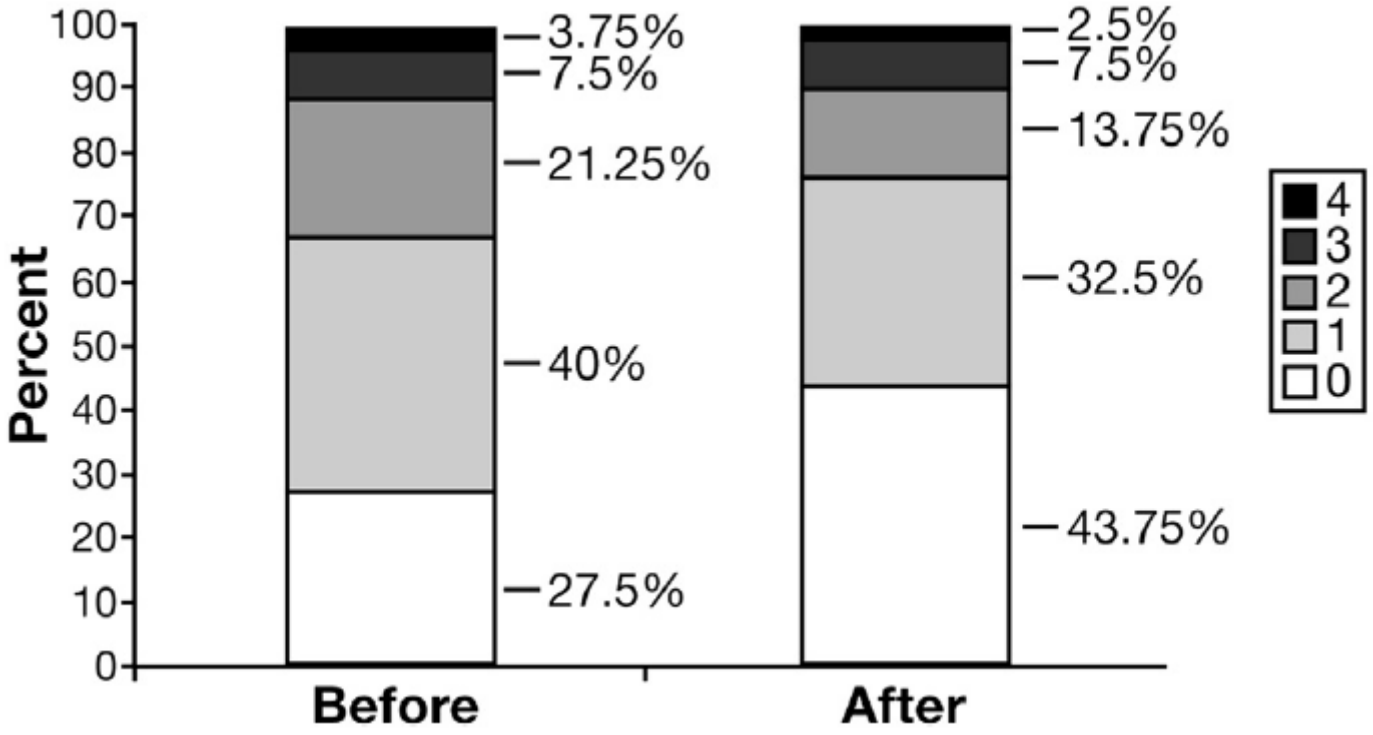
Song MW, et al. Presented at: The Liver Meeting 2022: American Association for the Study of Liver Diseases (AASLD); November 4-8, 2022; Washington, DC/Virtual. Abstract 110.

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis



N Engl J Med 2021;384:1113-24

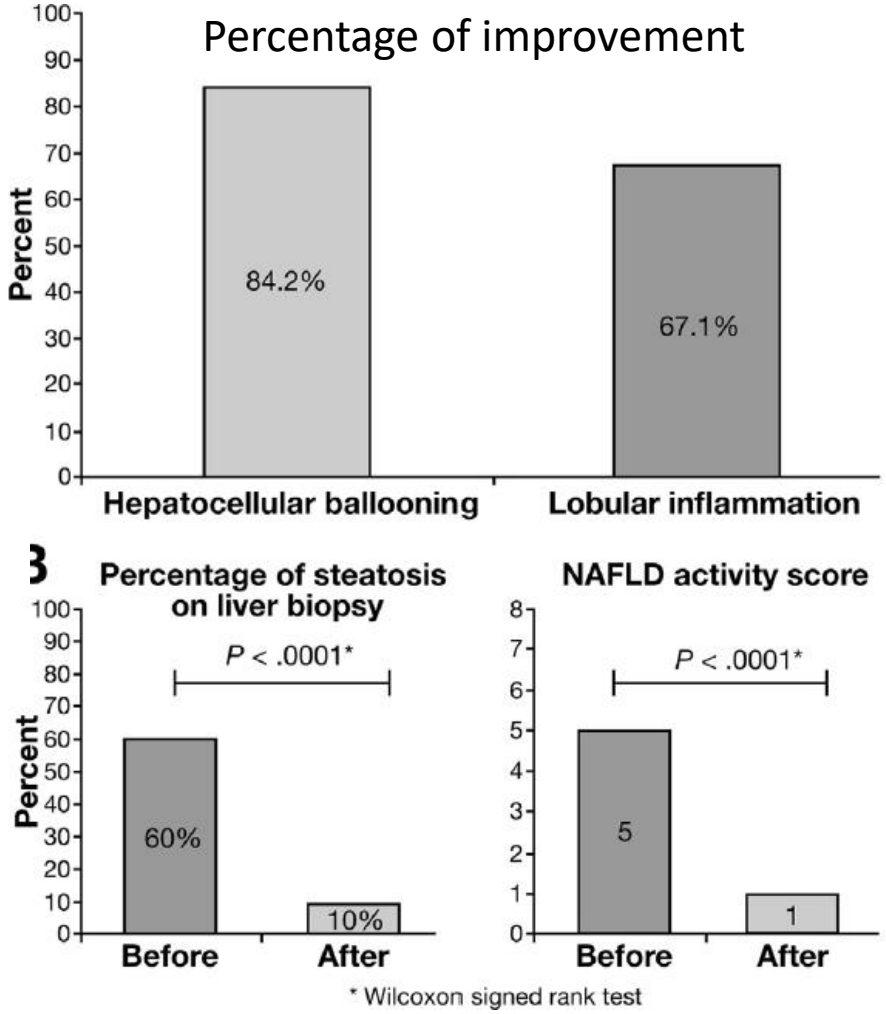
Bariatric Surgery Reduces Fibrosis of Nonalcoholic Steatohepatitis in Morbidly Obese Patients



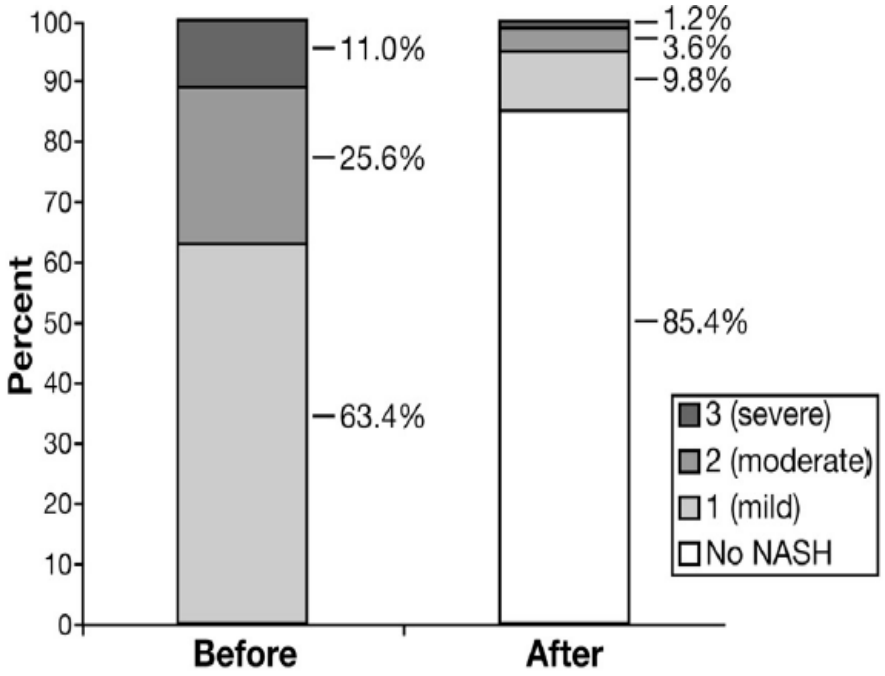
Distribution of fibrosis stage before and 1 year after surgery: Metavir score

Gastroenterology 2015;149:379–388

Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients



Change of histologic features 1 year after bariatric surgery.



Distribution of NASH inflammatory activity grade before and 1 year after surgery, according to the Brunt score

Gastroenterology 2015;149:379–388

Bariatric Surgery Impact in Patients With NAFLD

Study

- Multicenter retrospective cohort of patients with NAFLD

Patients

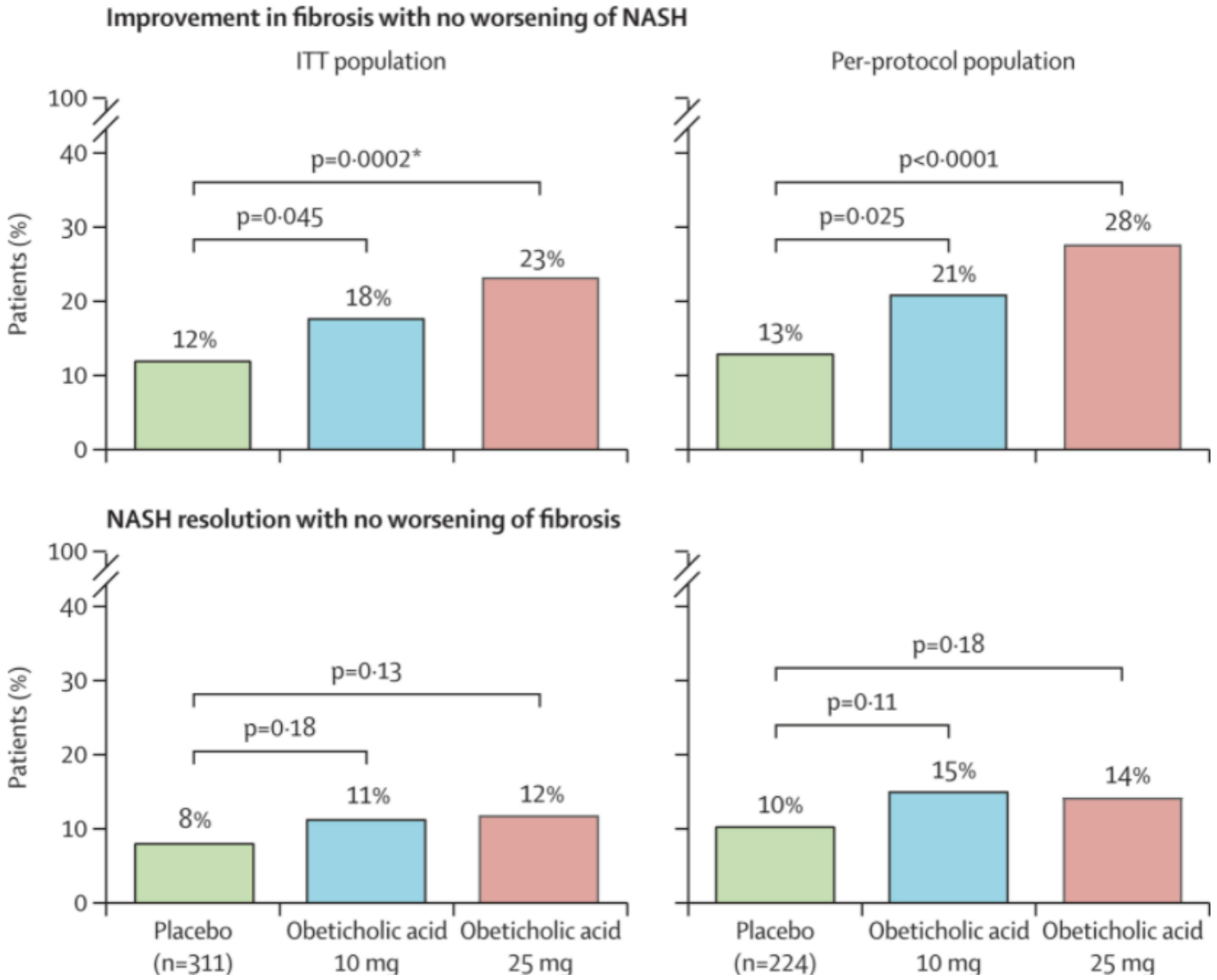
- 6123 patients with bariatric surgery matched 1:1 to patients without bariatric surgery for demographics by propensity scoring

Outcome	Risk Ratio* (95% CI)	*P* Value
Coronary artery intervention	0.60 (0.47, 0.78)	.01
Heart failure	0.57 (0.41, 0.78)	.05
Acute myocardial infarction	0.53 (0.28, 0.97)	.03
Cerebrovascular disease	0.70 (0.54, 0.93)	.01
Coronary artery interventions	0.62 (0.40, 0.95)	.02
Mortality	0.60 (0.38, 0.91)	.01

*Patients with bariatric surgery vs non-bariatric surgery.

Krishnan A, et al. Presented at: The Liver Meeting 2022: American Association for the Study of Liver Diseases (AASLD); November 4-8, 2022; Washington, DC/Virtual. Poster 2666.

Obeticholic acid for the treatment of non-alcoholic steatohepatitis



Lancet, The, 2019-12-14, Vol394, Issue 10215, Pages 2184-2196

The approach to NAFLD

Serology
US

- Elevated liver enzymes/Fatty liver
- R/O other causes of liver disease

NAFL score
Fibroscan

- Aggressively treat metabolic syndrome
- Stratify risk

Medical RX
Bariatric surgery
Clinical study

- Refer to liver clinic
- Clinical study
- Cirrhosis follow up R/O HCC and complications

Good and bad drugs for the liver

Good

- NSBB –Carvedilol – lower portal pressure and prevent deterioration in cirrhosis with portal HTN
- ACE, ARB
- GLP1 Agonists
- SGLT2 Inhibitors
- Metformine

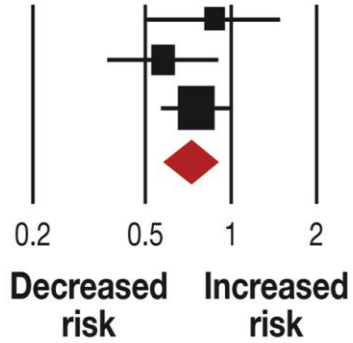
Safety concerns

- Amiodarone
- DDI
- Ritonavir+statins
- Atorvastatin+ clopidogrel
- **Alcohol !**

Statins

- Safe in Patients with Chronic Liver Disease
- Pharmacokinetics of Statins are Altered in Cirrhosis
  - Rosuvastatin and pravastatin –minimal liver metabolism
- Safe in Compensated Cirrhosis
- True Hepatotoxicity is Rare

Study name	Risk ratio	Lower limit	Upper limit	*P*-value	Statins	Placebo
Abraldes 2016	0.87	0.51	1.50	.63	17/69	22/78
Pollo-Flores 2015	0.58	0.37	0.91	.02	8/14	20/20
Abraldes 2009	0.76	0.57	1.02	.07	19/28	24/27
	0.73	0.59	0.91	.01	44/111	66/125



Bibliography

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  Arterioscler Thromb Vasc Biol. 2022;42:e168–e185. DOI: 10.1161/ATV.0000000000000153
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  Endocrine Practice 28 (2022) 528e562
- Nonalcoholic Fatty Liver Disease and the Heart JACC State-of-the-Art Review
  VOL. 73, NO. 8, 2019