top ten in gastroenterologia

9ª EDIZIONE
2-3 MARZO 2018
BERGAMO Hotel Excelsior S. Marco
Piazza della Repubblica, 6

Sistema Socio Sanitario
Ospedale Papa Giovanni XXIII
Regione Lombardia
ASST Papa Giovanni XXIII

Cosa c'è di Nuovo

NAFLD

Stefano Fagiuoli
U.S.C. Gastroenterologia Epatologia e Trapiantologia
ASST Papa Giovanni XXIII - Bergamo

Fatty Liver

NAFLD:

- Excessive hepatic fat accumulation, associated with insulin resistance (IR)

DEFINITION

- Presence of steatosis in >5% of hepatocytes (Histology/NMR)

Nutrients **2013**, *5*, 4093-4114;

Nutritional Management of Insulin Resistance in Nonalcoholic Fatty Liver Disease (NAFLD)

Beth A. Conlon [1,*], Jeannette M. Beasley [1], Karin Aebersold [1], Sunil S. Jhangiani [2] and Judith Wylie-Rosett [1]

NAFLD

Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis.

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NAFLD

Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis.

NAFL

Presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is nominal.

Nutrients **2013**, *5*, 4093-4114;

Nutritional Management of Insulin Resistance in Nonalcoholic Fatty Liver Disease (NAFLD)

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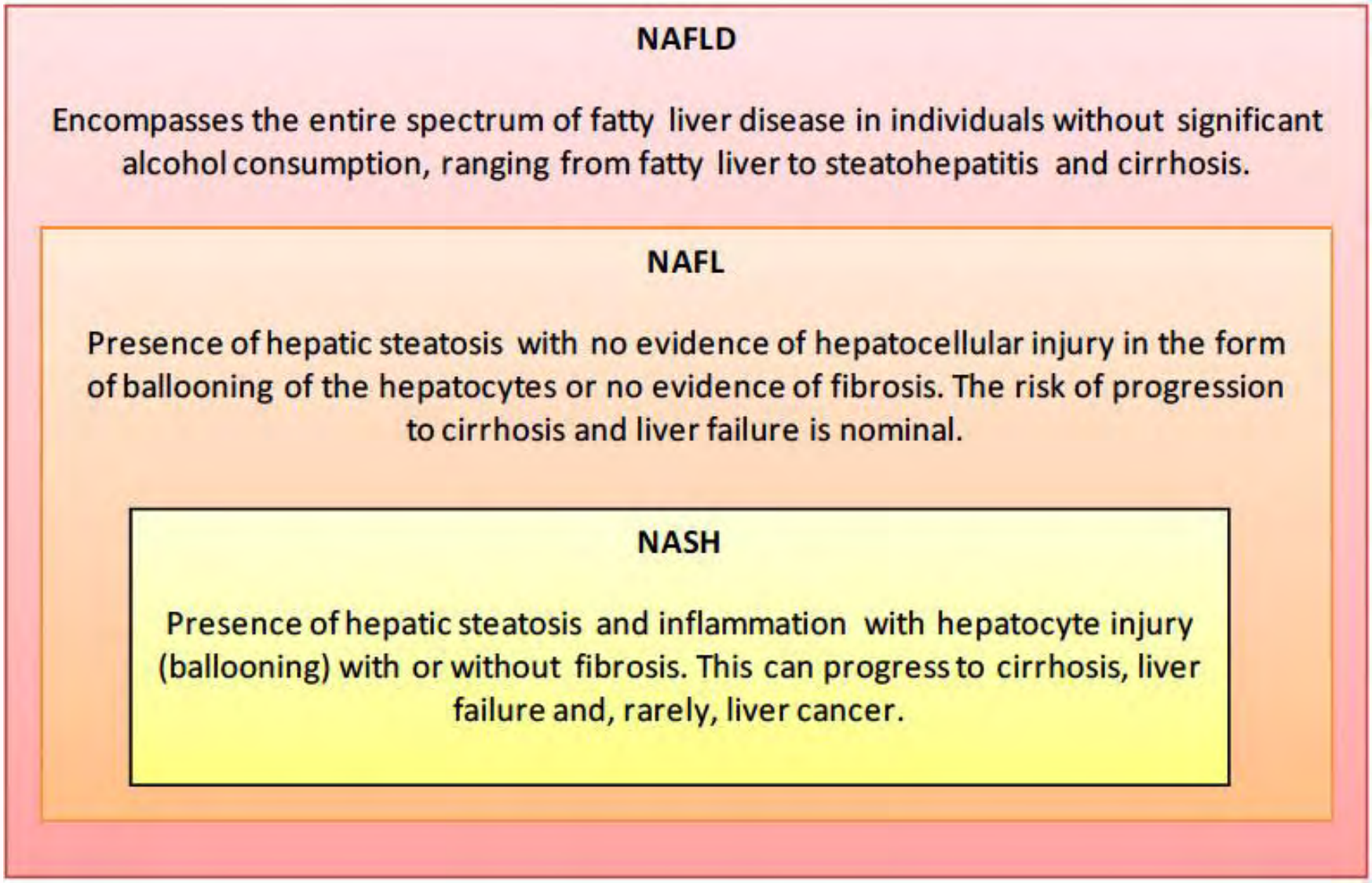


Fatty Liver

- The most common chronic liver disease in USA and Europa
- 10-24% incidence in general population
- Underestimated issue ?

NAFLD: epidemiology

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY VOLUME 15 | JANUARY 2018

Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention

Zobair Younossi[1,2], Quentin M. Anstee[3,4], Milena Marietti[5], Timothy Hardy[3,4], Linda Henry[1,2], Mohammed Eslam[6], Jacob George[6] and Elisabetta Bugianesi[5]

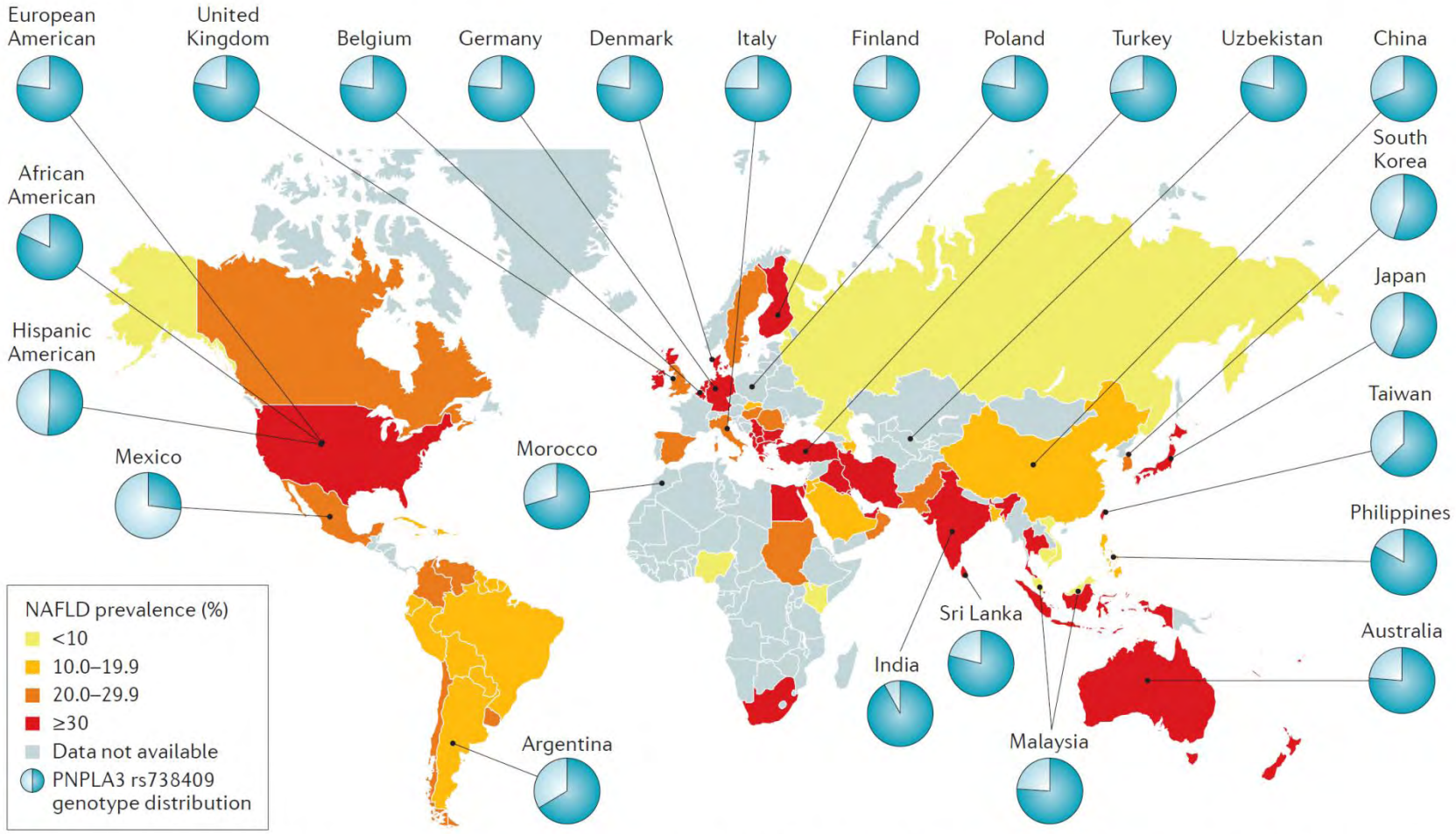


Figure 1 | **Worldwide estimated prevalence of NAFLD and distribution of *PNPLA3* genotypes.** *PNPLA3* is presented as minor allele frequency (light blue section of the pie chart).

Fatty liver, Metabolic Syndrome and Obesity

METABOLIC SYNDROME

- Present in 75% of type 2 diabetic (prevalence)
- Present in 60-70% of obese individuals

OBESITY

- NAFLD is present in 20% of obese patients
- 2-3% of the obese individuals present a picture of Cirrhosis

Diabetes Care Vol 27 N8 August 2004

Diagnosis of Metabolic Syndrome acc. With NCEP-ATP III G.L. (at least 3 factors)

Risk Factors	*Levels (adults)*
Abdominal obesity: Waist Circumference	**> 102 cm male** **> 88 cm female**
HDL Cholesterol	**< 40 mg/dL male** **< 50 mg/dL female**
Triglicerides	**≥ 150 mg/dL**
Arterial Pressure	**≥ 130/85 mmHg**
Fasting Glycemia	**≥ 110 mg/dL**

Diagnosis of Metabolic Syndrome acc. NCEP-ATP III L.G.
(at least 3 factors)

Proposed Definitions and Criteria of Metabolic Syndrome

Clinical Measure	NHLBI/AHA (2005)	WHO (1998)	EGIR	IDF (2005)
Insulin resistance	None *Any 3 of the following:*	IGT, IFG, T2DM, or lowered insulin sensitivity *PLUS any 2 of the following:*	Plasma insulin >75th percentile *PLUS any 2 of the following:*	None
Body weight	Waist circumference: Men: ≥102 cm Women: ≥88 cm	Waist-to-hip ratio: Men: >0.9 Women: >0.85; and/or BMI >30 kg/m²	Waist circumference: Men: ≥94 cm Women: ≥80 cm	Increased waist circumference *PLUS any 2 of the following:*
Triglycerides	TG ≥150 mg/dL or Rx for TG	TG ≥150 mg/dL	TG ≥150 mg/dL	TG ≥150 mg/dL or Rx for TG
HDL-C	Men: HDL-C <40mg/dL Women: <50 mg/dL; or Rx for reduced HDL-C	Men: HDL-C <35 mg/dL Women: <39 mg/dL	Men or women: HDL-C <39 mg/dL	Men: HDL-C <40 mg/dL Women: <50 mg/dL; or Rx for reduced HDL-C
Blood pressure	≥130 mmHg systolic or ≥85 mmHg diastolic; or Rx for HTN	≥140/90 mmHg	≥140/90 mmHg or Rx for HTN	≥130 mmHg systolic or ≥85 mmHg diastolic; or Rx for HTN
Glucose	≥100 mg/dL or Rx for glucose (includes diabetes)	IGT, IFG, or T2DM necessary	IGT or IFG (not diabetes)	>100 mg/dL fasting glucose (includes diabetes)
Other	None	Microalbuminuria	None	None

1976 - 77

2003

METABOLIC SYNDROME

INSULIN-RESISTENCE

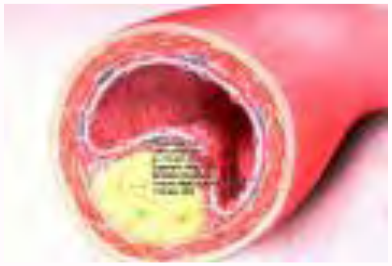
Glucose Intolerance

Obesity

Dislipidemia

Arterial Hypertension

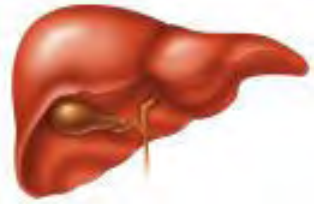
Risk Factors for Atherosclerosis



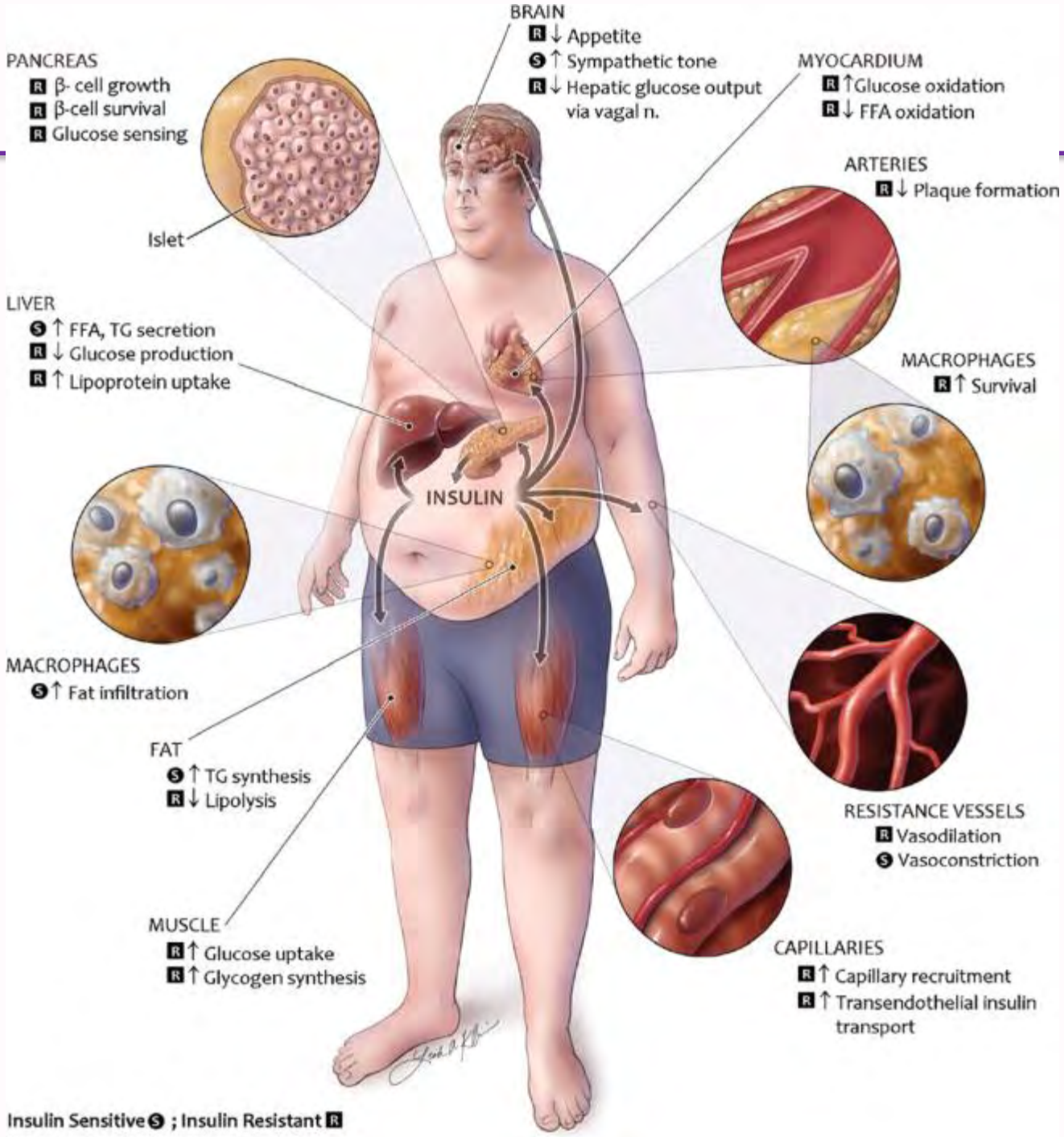
Risk Factors for NFLD

Cirrhosi

HCC



NASH



A systemic dysfunction

THE "OBESE MICROBIOTA"

INHERITED?

Kalliomaki et al., Am J Clin Nutr 2008;

Collado et al., Am J Clin Nutr 2010;

Turnbaugh et al, Nature 2009

DIET-INDUCED?

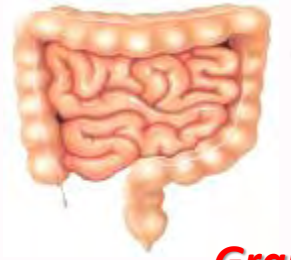
Hildebrandt et al, Gatroenterology 2009

De Filippo et al., PNAS 2010

AGING?

Claesson et al., Nature 2012

Contribution of Diet / Microflora to liver damage.



High Fat Diet

Gram(-) Bacteria

Endotoxins - bacterial translocation

Portal vein

Inflammasome

HCC

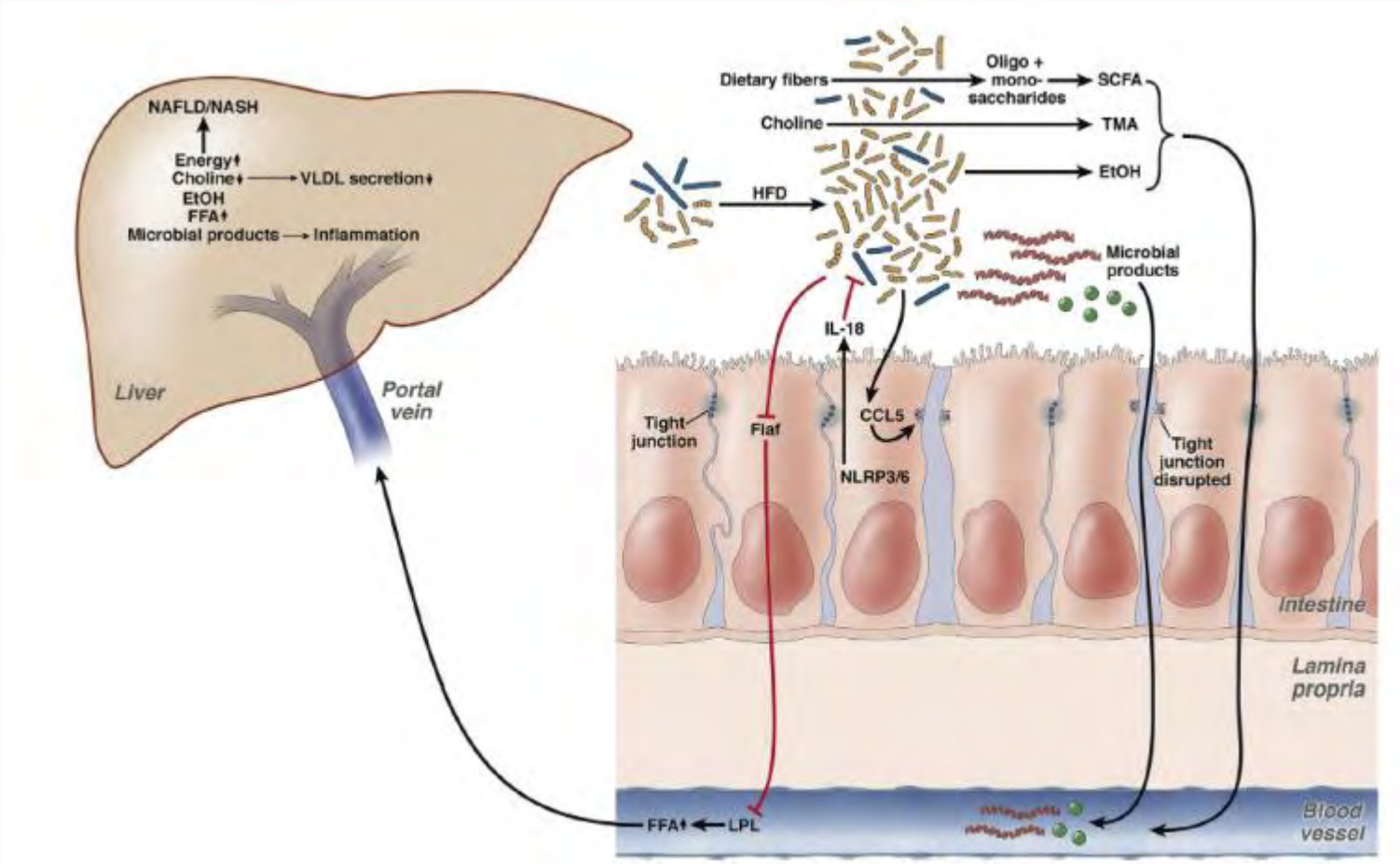
LIVER

De Minicis et al., Hepatology 2013

Gastroenterology 2014;146:1513–1524

Interactions Between the Intestinal Microbiome and Liver Diseases

Bernd Schnabl David A. Brenner



Effects of the intestinal microbiota on **NAFLD** and progression to steatohepatitis

GUT MICROBIOTA

1.5 kg of bacteria, >300.000 genes

8 bacterial divisions (superkingdoms)
95% genes identity

↓

1000-1500 species
98% genes identity

↓

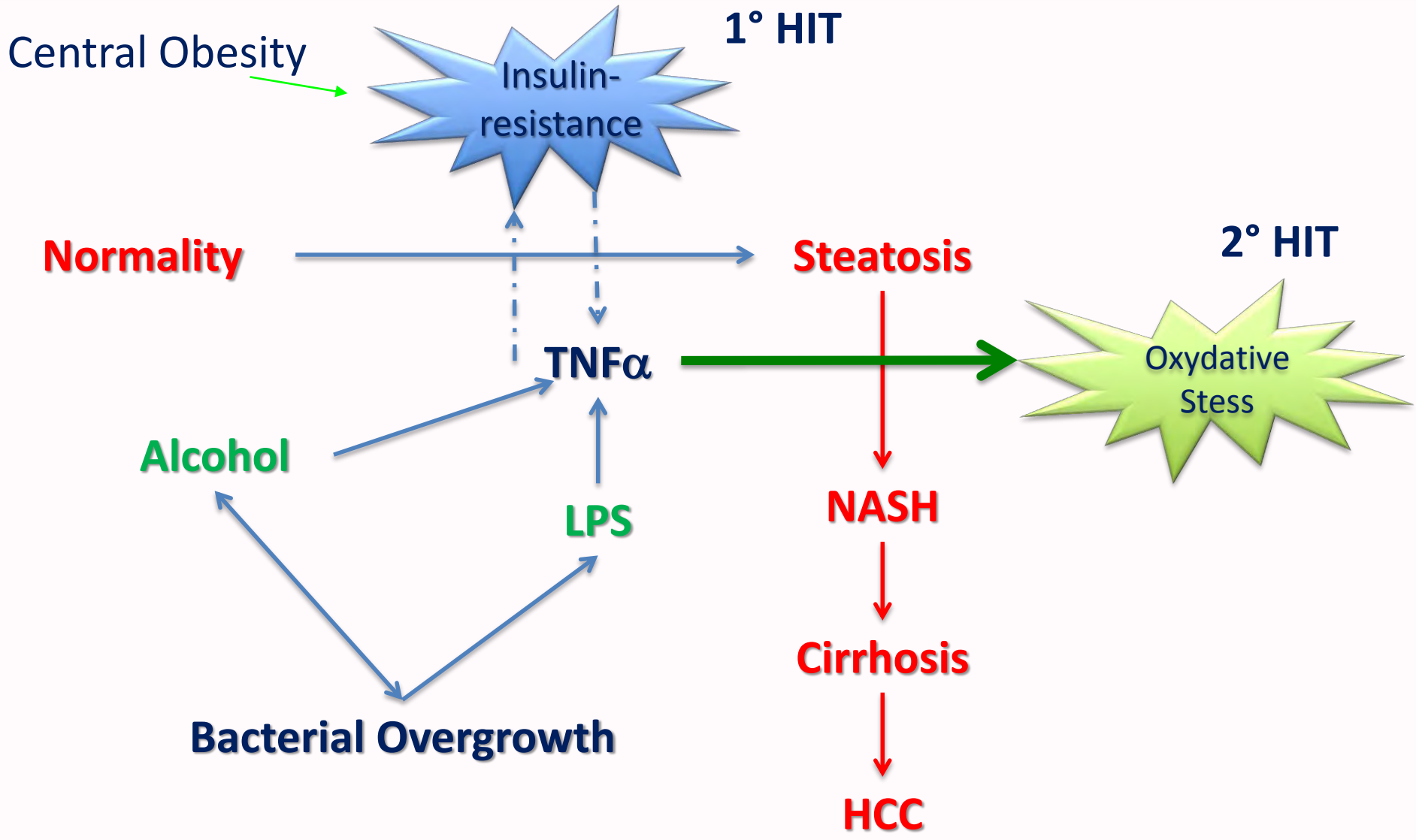
>10.000 strains
100% genes identity

↓

160 species constitute the core microbiota

Microbiome → **Metabolome**

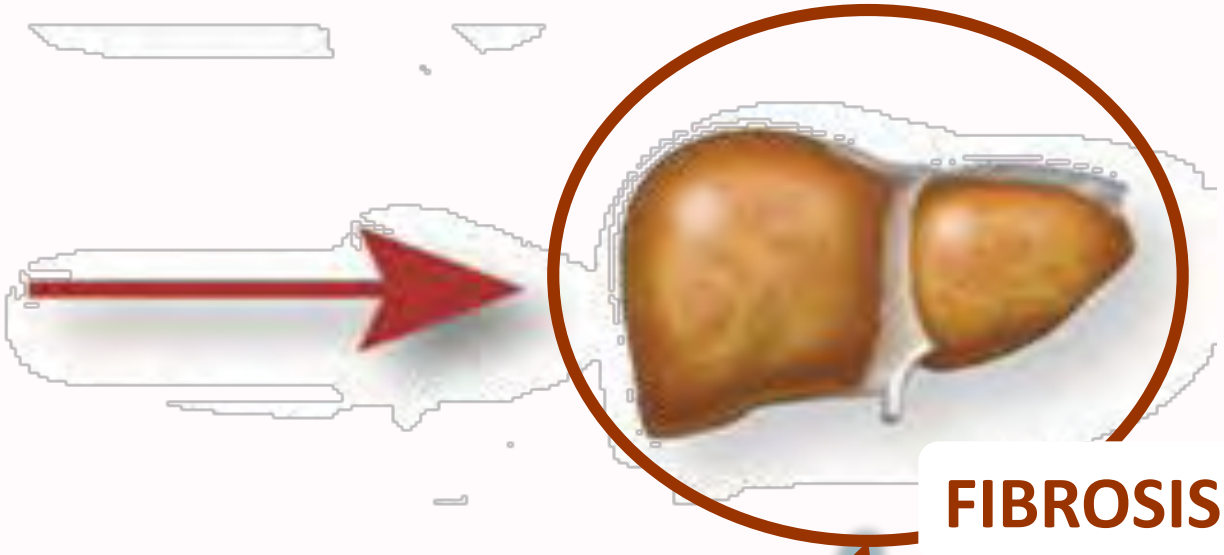
PATHOGENESI of NASH



The Oxydative Stress

Starter of the progression

STEATOSI



FIBROSIS

Oxydative Stress

- ROS accumulation
- Lipoperoxyidation and Hepatocyte Membrane Dysruption
- Hepatocyte Functional Loss

Inflammation

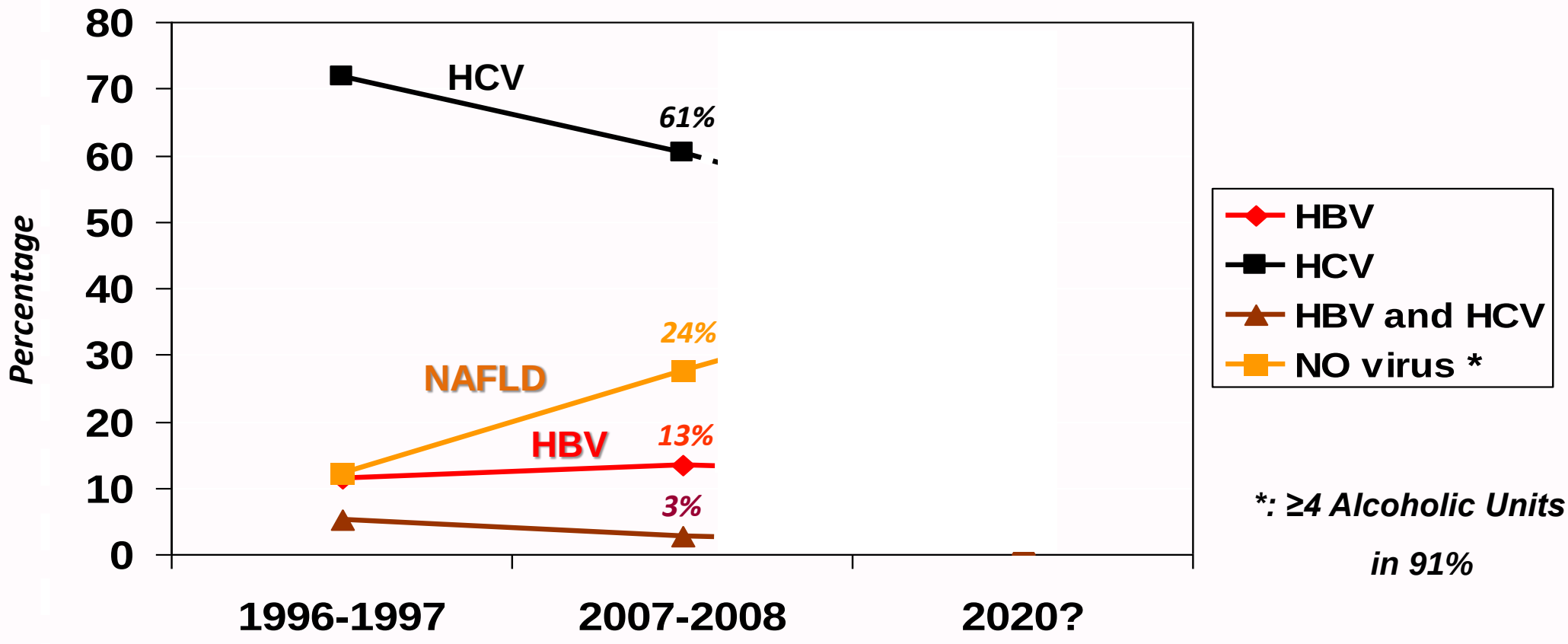
- Kupffer Cells Activation
- Tissue Necrosis

Immunitary System

- Activation and Proliferation of Stellate Cells
- Collagen Fibers Deposition

Changing aetiological factors of hepatocellular carcinoma and their potential impact on the effectiveness of surveillance.

(23 centres: 1733 HCC)



Stroffolini et al, Dig Liv Dis 2011

Non-Alcoholic Fatty Liver Disease (NAFLD)

Requirements for Definition of NAFLD:

- Evidence of Fatty Liver (imaging or Histology)
- Exclusion of secondarie Causes of Fat Accumulation

AASLD practice guideline, Hepatology 20012

Non-Alcoholic Fatty Liver Disease (NAFLD)

HEPATOLOGY, Vol. 55, No. 6, 2012

Table 2. Common Causes of Secondary Hepatic Steatosis

Macrovesicular steatosis

- Excessive alcohol consumption **(>21 drinks /week in men; >14 in women over a 2-year period prior to baseline liver histology)**
- Hepatitis C (genotype 3)
- Wilson's disease
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids)

Microvesicular steatosis

- Reye's syndrome
- Medications (valproate, anti-retroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (e.g., LCAT deficiency, cholesterol ester storage disease, Wolman disease)

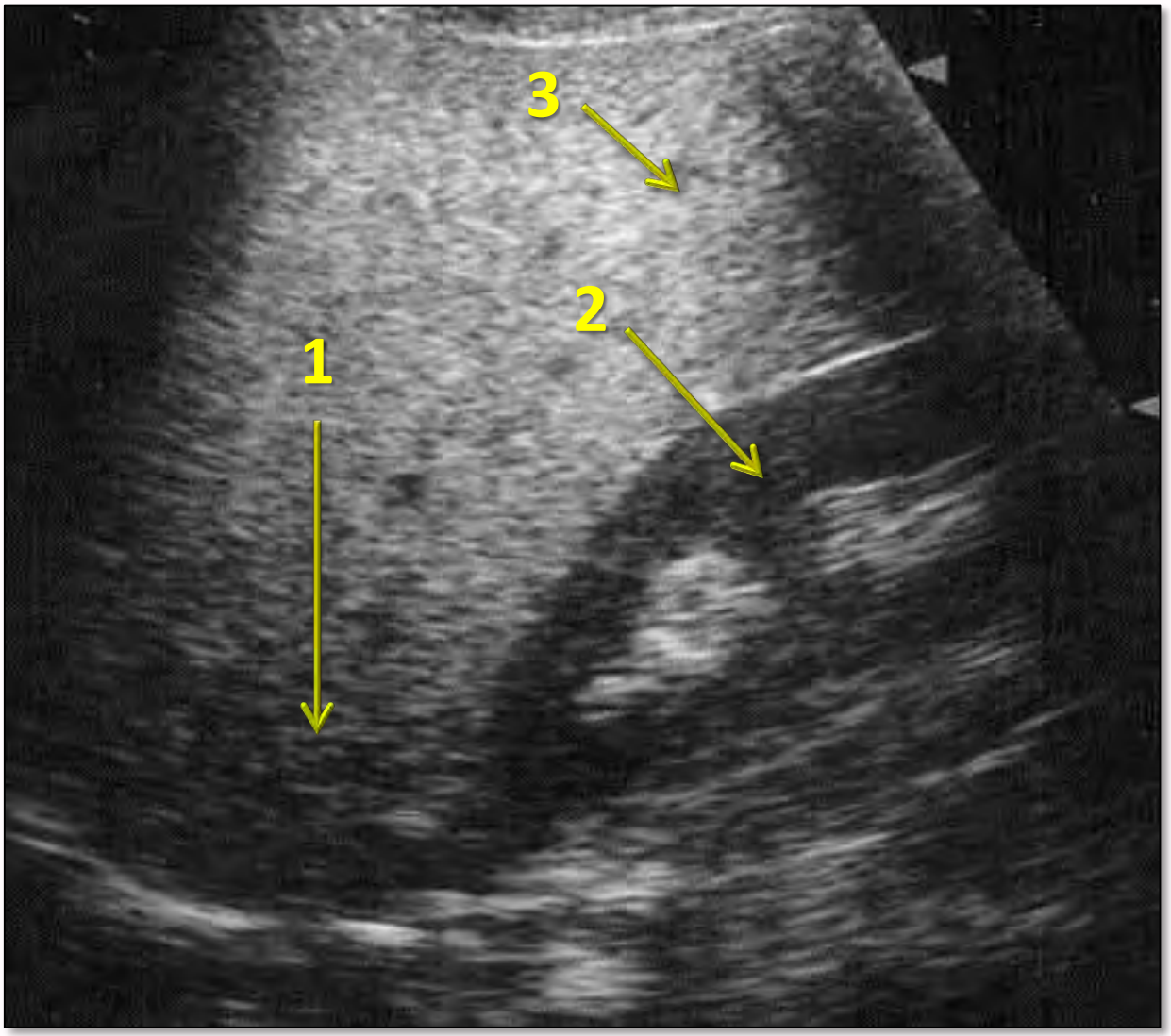
AASLD practice guideline, Hepatology 20012

US Criteria to graduate FL:

1. **Deep attenuation**

2. **Diffuse hyperechoic** echotexture **("bright liver")** compared with the kidney

3. **Poor visibility** of venous vessels, no expansion of the hepatic and portal vein diameters at deep breath



DIAGNOSIS OF FATTY LIVER:
THE FLI INDEX

www.fegato.it

	Predictors	logits
Triglicerydes (mg/dL)	200	5,049
BMI (Body Mass Index) (kg/m^2)	27	3,753
GGT (U/L)	45	2,733
Waist Circumference (cm)	98	5,194
Constant	**********	-15,745
Sum	**********	0,984

Fatty Liver Index (FLI) is **73**

Use this table for interpretation of FLI:

If FLI is ≥ 60 you have ≥ 85% probability of FL

If FLI is < 30 you have ≥ 86% probability of NON having FL

DIAGNOSIS OF FATTY LIVER:

http://nafldscore.com

NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

Age (years)	53
BMI (kg/m^2)	32
IGF/diabetes	☑
AST	56
ALT	58
Platelets (x10^9/l)	90
Albumin (g/l)	35
Score	1.900

< -1.455: predictor of **absence** of significant fibrosis (F0-F2 fibrosis)
≤ -1.455 to ≤ 0.675: indeterminate score
> 0.675: predictor of **presence** of significant fibrosis (F3-F4 fibrosis)

< -1,455 **=** *Absence of significant fibrosis*

> 0,675 **=** *Presence of significant fibrosis*

DIAGNOSIS OF FATTY LIVER:

HEPATOLOGY

HEPATOLOGY 2012;56:1751-1759

Histopathological Algorithm and Scoring System for Evaluation of Liver Lesions in Morbidly Obese Patients

Pierre Bedossa,[1] Christine Poitou,[2,3] Nicolas Veyrie,[4] Jean-Luc Bouillot,[4] Armand Basdevant,[2,5] Valerie Paradis,[1] Joan Tordjman,[2,3,*] and Karine Clement[2,3,*]

SAF score: Semiquantitative scoring

Steatosis *large or medium-sized lipid droplets*	
Activity *hepatocyte ballooning (0-2)* *lobular inflammation (0-2)*	
Fibrosis	
Total	

DIAGNOSIS OF FATTY LIVER:

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SAF score: Semiquantitative scoring					
Steatosis *large or medium-sized lipid droplets*	< 5%	5-33% *mild*	34-66% *moderate*	>67% *severe*	
	S0	**S1**	**S2**	**S3**	
Activity *hepatocyte ballooning (0-2) lobular inflammation (0-2)*					
Fibrosis					
Total					

DIAGNOSIS OF FATTY LIVER:

HEPATOLOGY
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	S0	**S1**	**S2**	**S3**	
Activity *hepatocyte ballooning (0-2) lobular inflammation (0-2)*	No Activity	Mild activity	Moderate activity	Severe activity	
	A0	**A1**	**A2**	**A3**	
Fibrosis					
Total					

DIAGNOSIS OF FATTY LIVER:

HEPATOLOGY
HEPATOLOGY 2012;56:1751-1759

Histopathological Algorithm and Scoring System for Evaluation of Liver Lesions in Morbidly Obese Patients

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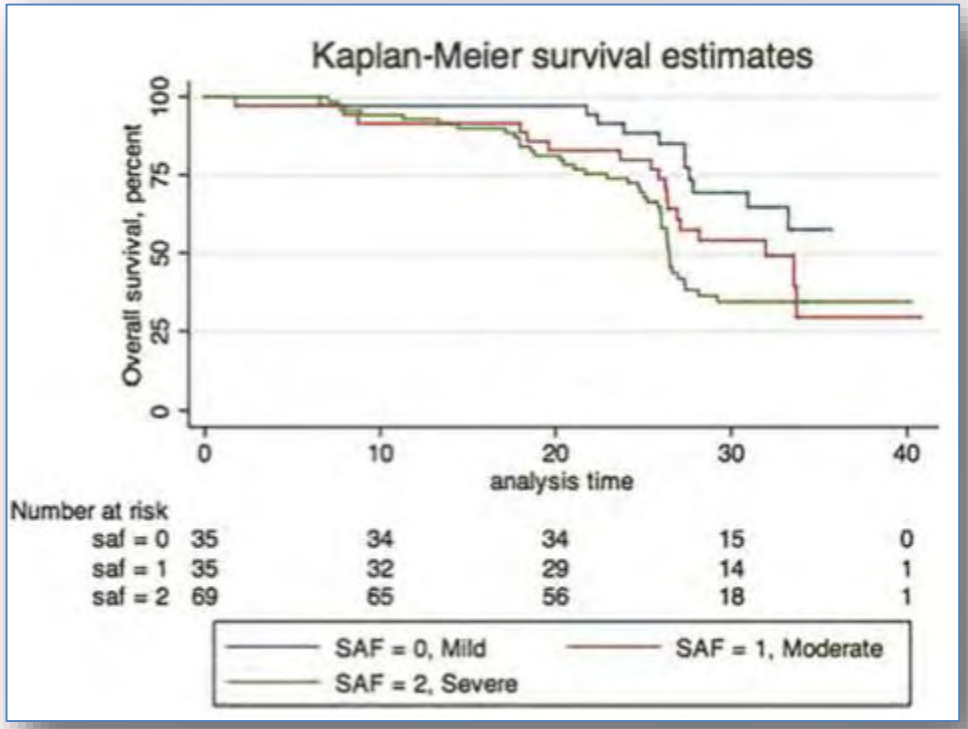
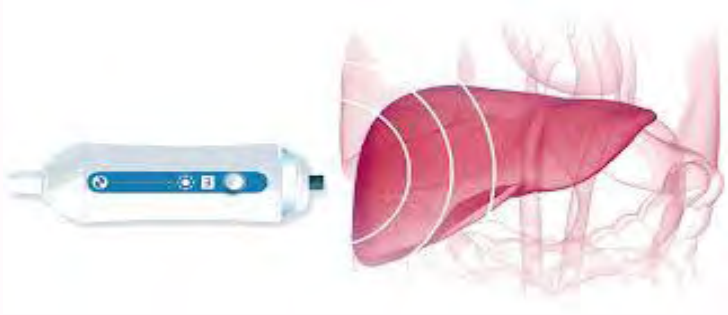
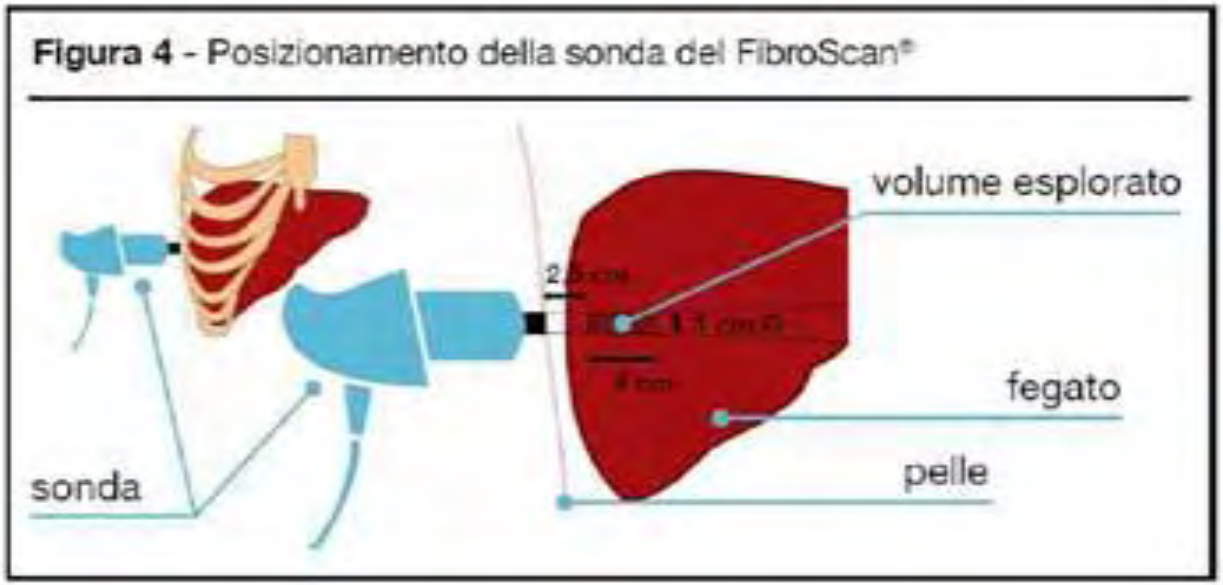


Author Conclusion:

- A severe **SAF score** is associated with increased mortality (41 years f-up)
- This is largely dependant on fibrosis stage

Hepatic Pulse Elastometry - Fibroscan®





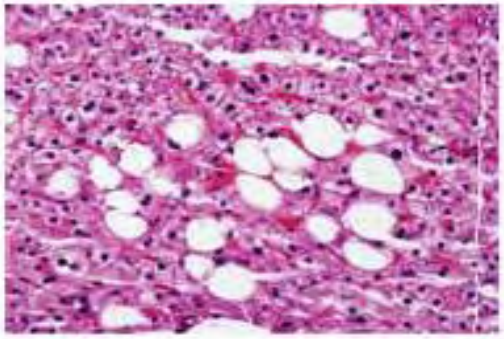
Azienda Ospedaliera Papa Giovanni XXIII Bergamo

Regione Lombardia
ASL Bergamo

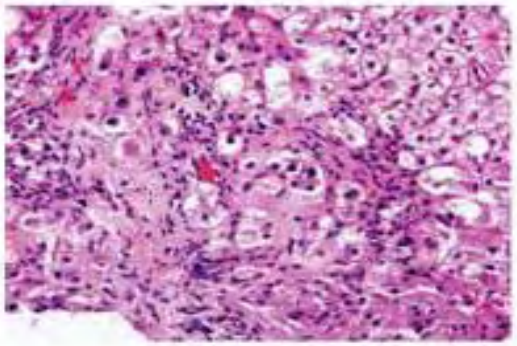
EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

- NASH has to be diagnosed by a liver biopsy showing steatosis, hepatocyte ballooning and lobular inflammation (**A1**)

Fatty Liver and Cryptogenic Cirrhosis



Fatty Liver



NASH

Fatty Liver

↓

NASH

↓

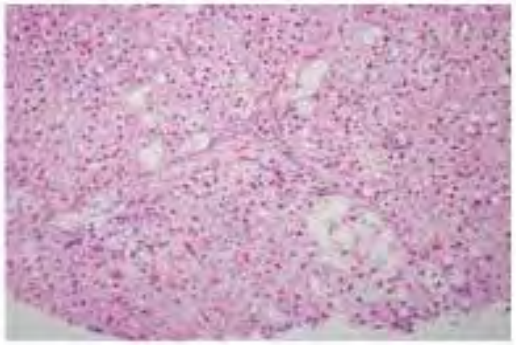
NASH
with Fibrosis

↓

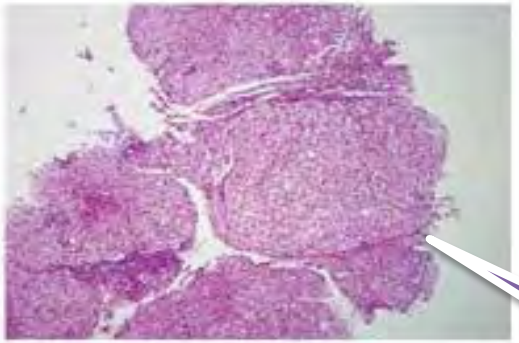
Cirrhosis

↓

Decompensated
Cirrhosis



NASH with Fibrosis



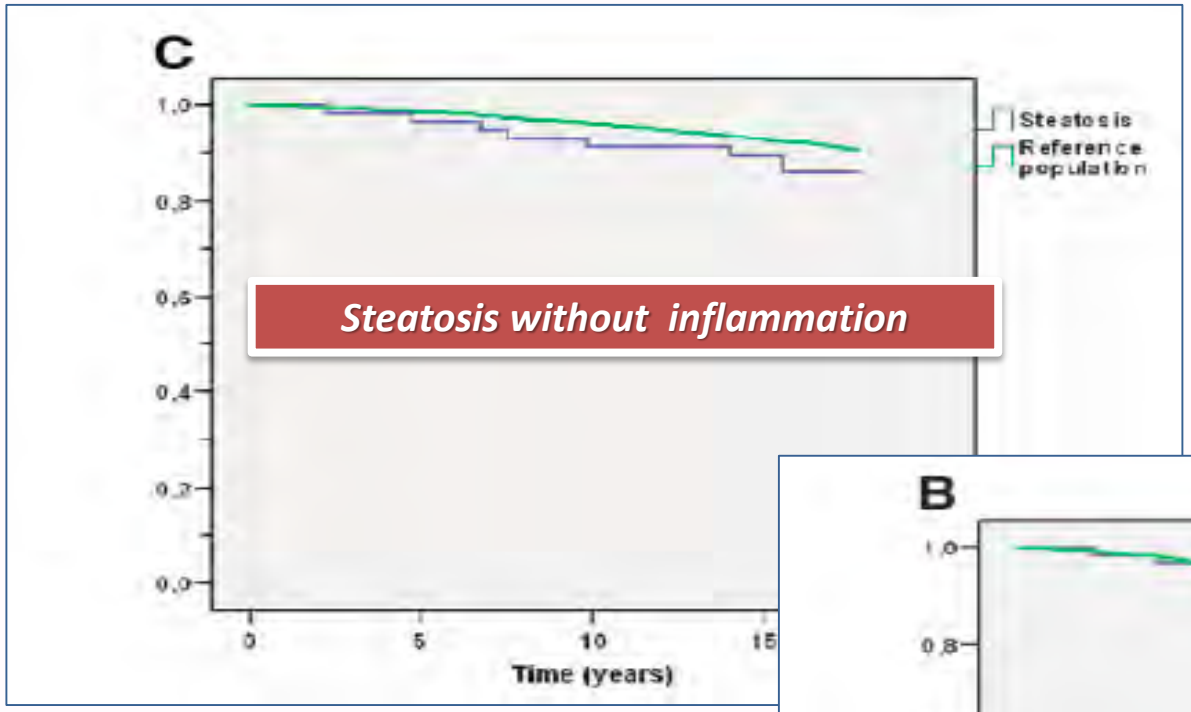
Cirrhosis

Disappearance of fat

Difficult Diagnosis

Maheshwari2006

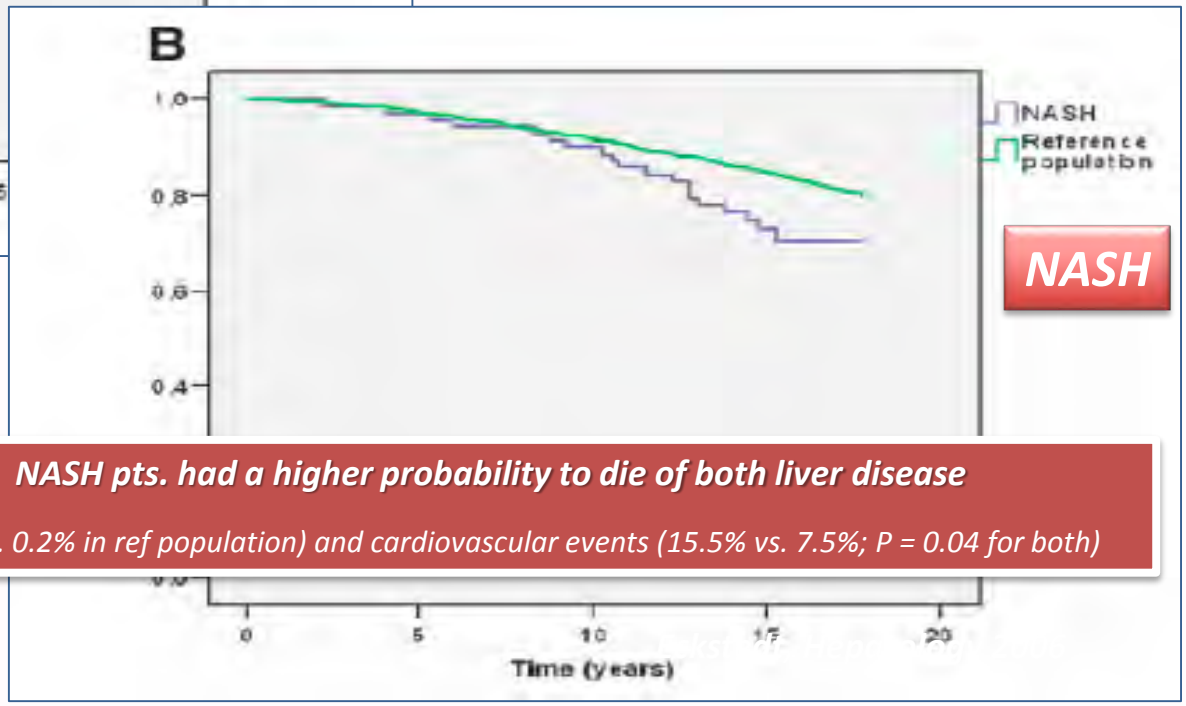
Survival in NAFL vs NASH



Steatosis without inflammation

129 NAFLD

Mean f-up, 13.7 yrs



NASH

Ekstedt, Hepatology 2008

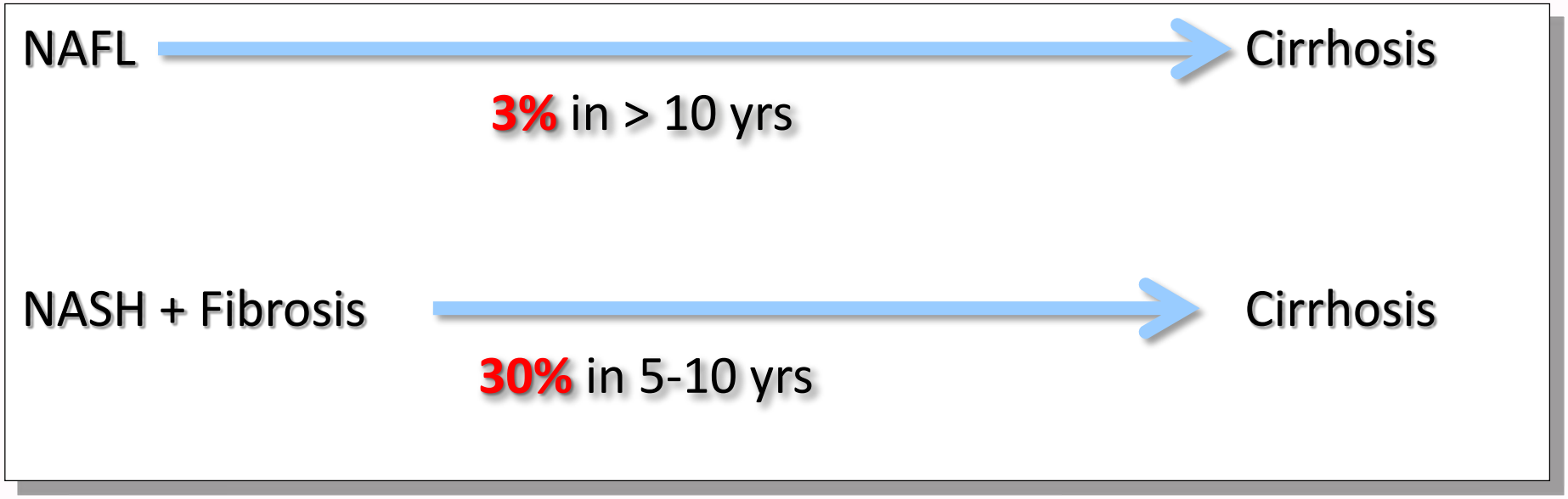
Soderberg, Hepatology 2010

NASH pts. had a higher probability to die of both liver disease

(2.8% vs. 0.2% in ref population) and cardiovascular events (15.5% vs. 7.5%; P = 0.04 for both)

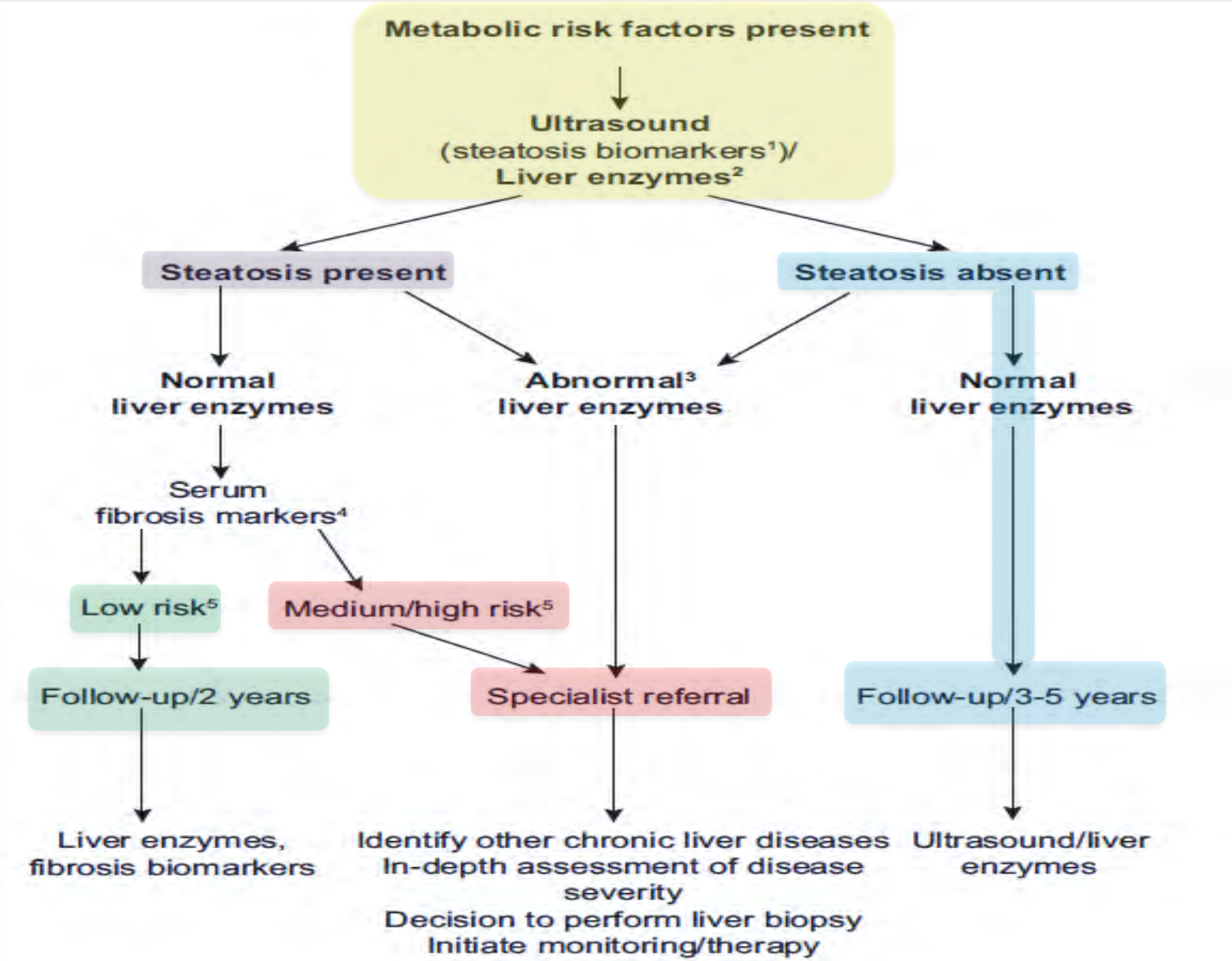
NASH ± fibrosis - Prognostic Implications

Progression to Cirrhosis more rapid compared with NAFLD



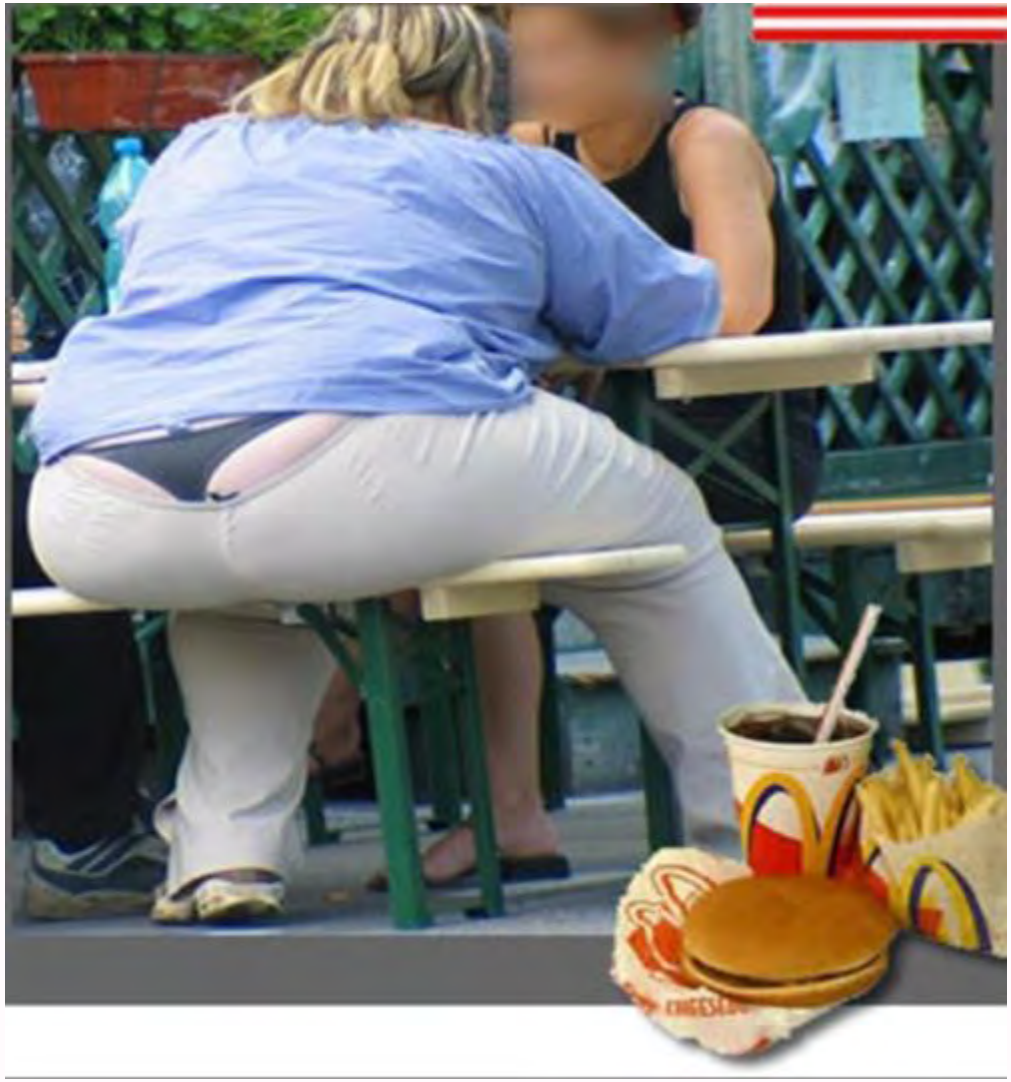
Matteoni et al. Gastroenterology 1999

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

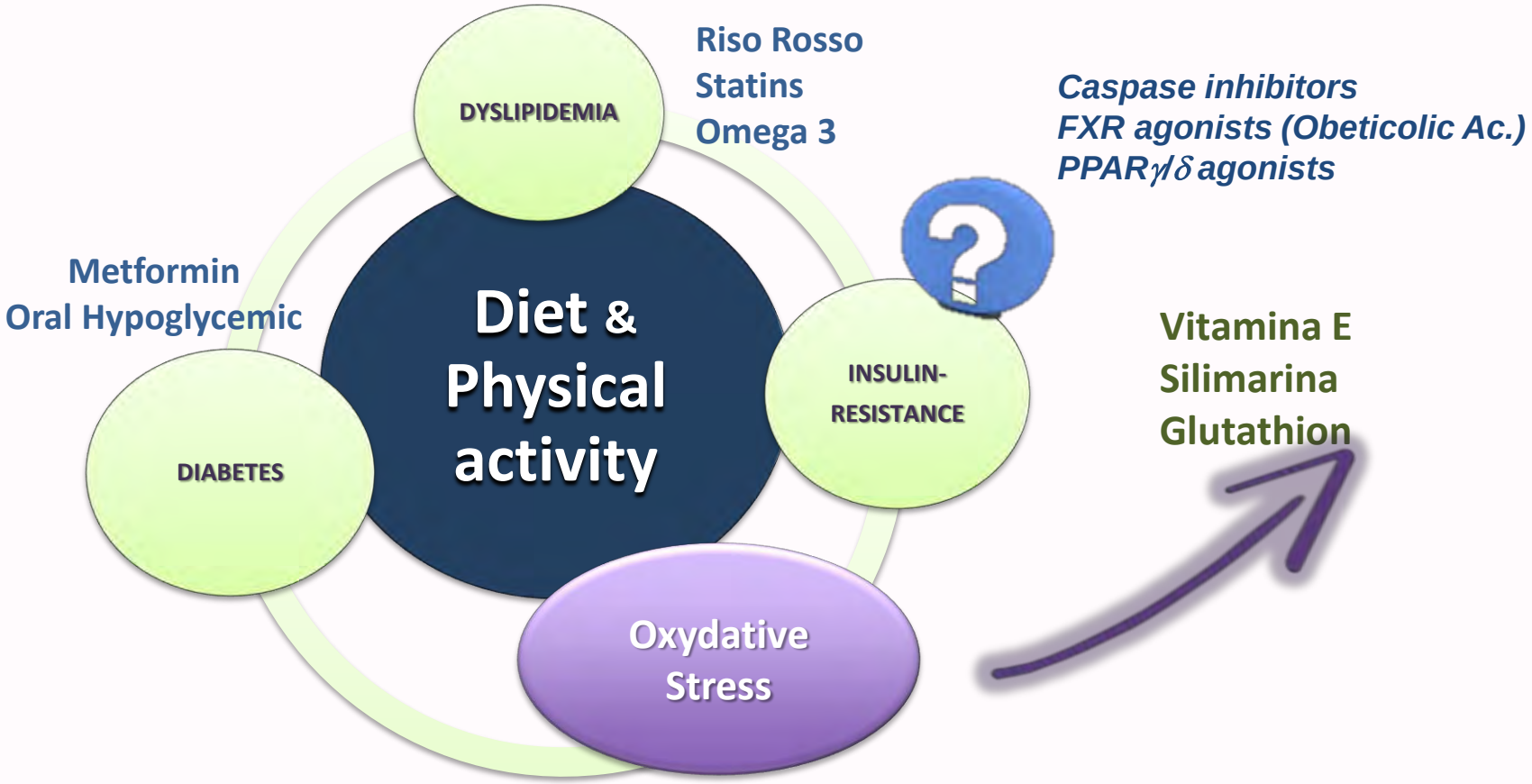


NAFLD: Treatment

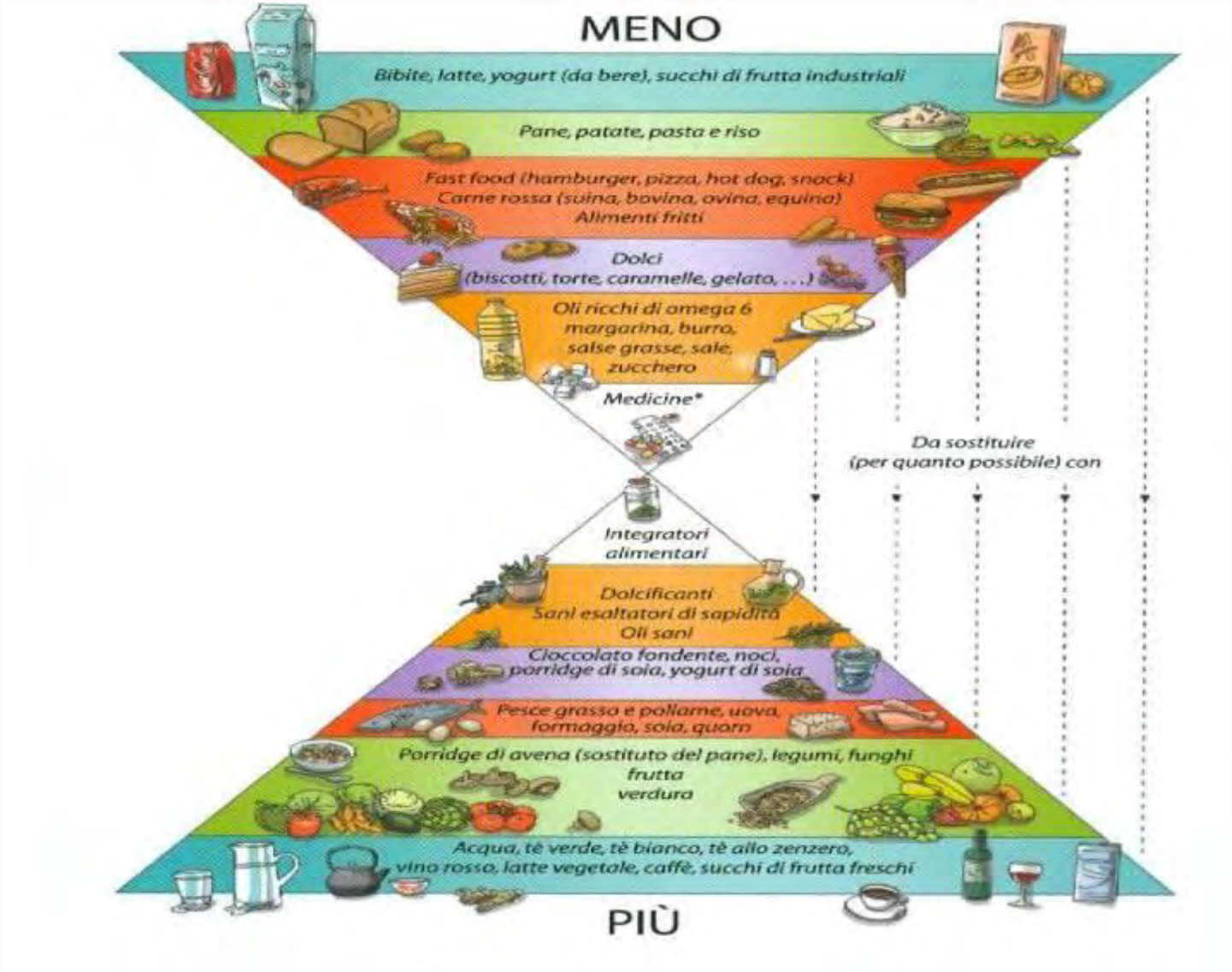
?



The Treatment



Nutritional Attitude –
From the alimentary «piramid» to the alimentyary «hourglass»



K. Verburgh, La clessidra alimentare, Feltrinelli 2013

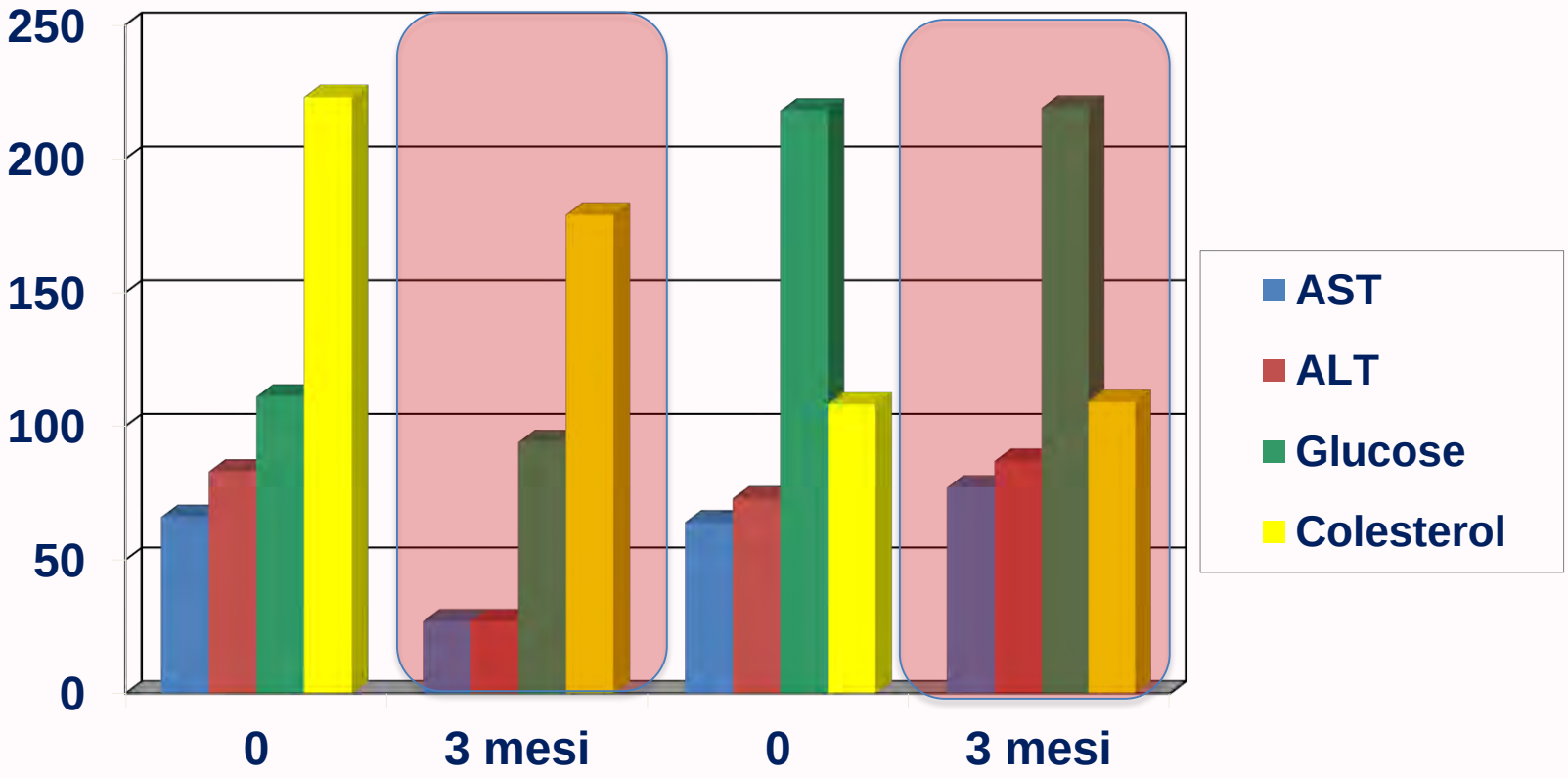
NAFLD: Physical Activity

- *Aerobic Activity (H/r 110 – 125)*
- *Frequency: at least 3 / Weeks*
- *Minimal Duration: 45-60 minutes*

Aim for ≈10% Weight loss

AASLD practice guideline, Hepatology 20012

Diet and Physical activity improve LFTs and Histology in obese patients



J Hepatol 1997

UDCA

AASLD recommendations

UDCA is not recommended for the treatment of NAFLD or NASH. (Strength – 1, Quality – B)

METFORMIN

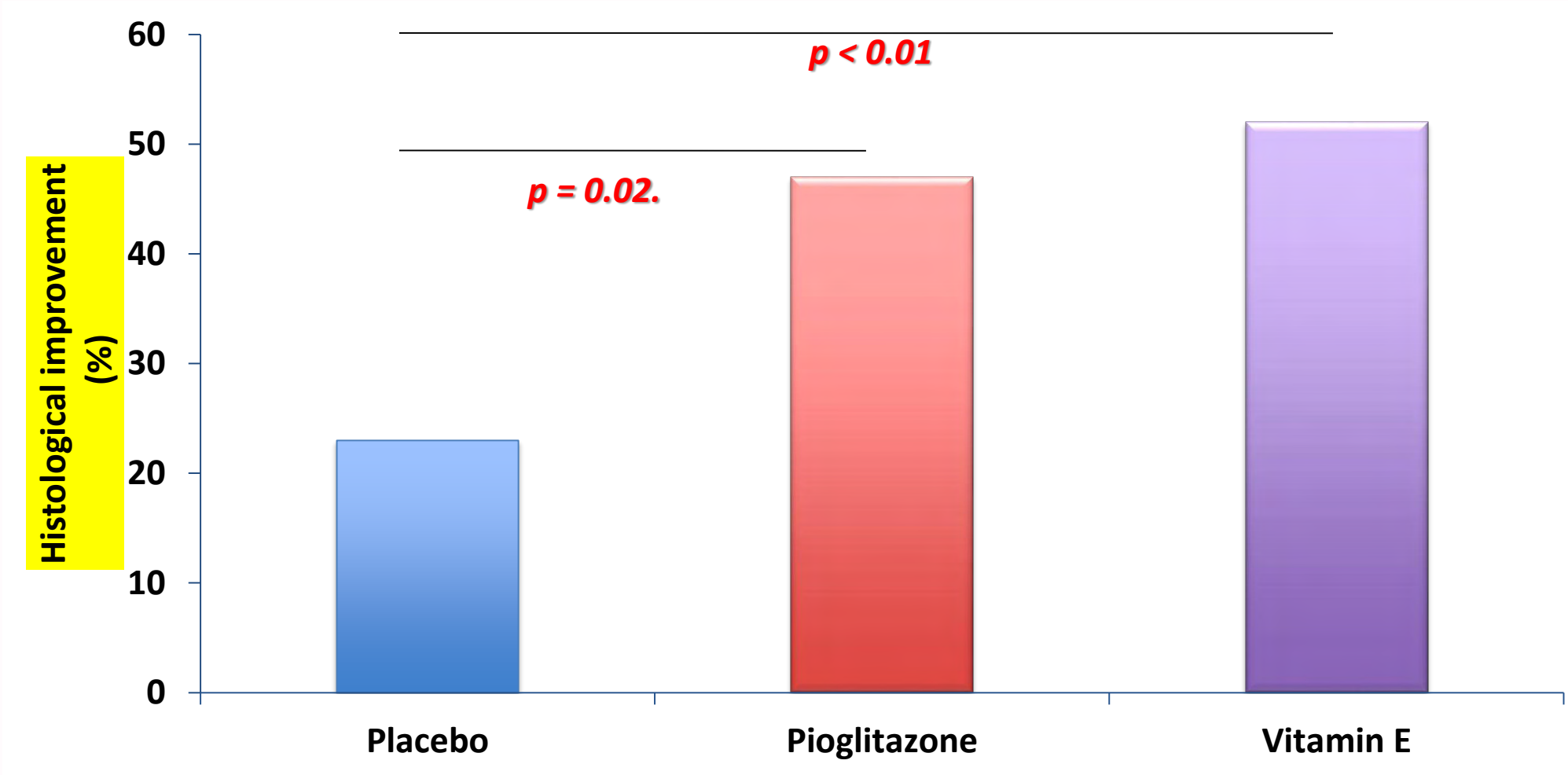
AASLD recommendations

Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH.

(Strength – 1, Evidence - A)

Pioglitazone, Vitamin E, or Placebo for NASH

Only «unbiased» Adult patients



Sanyal et al., NEJM 2010

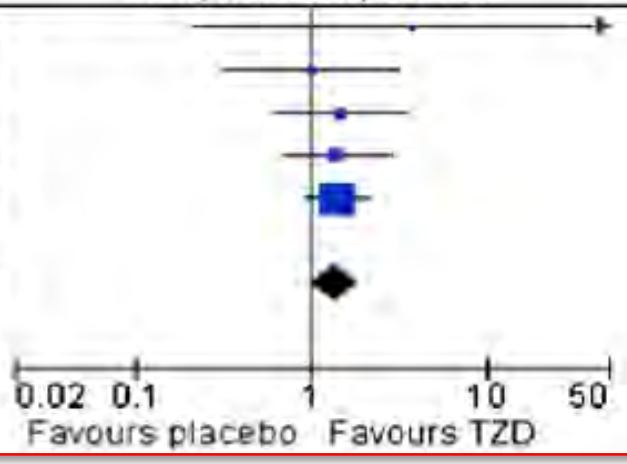
Role of thiazolidinediones in NASH

A systematic review and meta analysis.

Study or Subgroup	TZD Events	TZD Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Idilman 2008	2	11	0	8	1.2%	3.75 [0.20, 68.89]
Ratziu 2008	5	32	5	32	7.6%	1.00 [0.32, 3.12]
Aithal 2008	9	31	6	30	12.1%	1.45 [0.59, 3.58]
Belfort 2006	12	26	7	21	18.4%	1.38 [0.66, 2.88]
Sanyal 2010	35	80	26	83	60.7%	1.40 [0.93, 2.09]
Total (95% CI)		**180**		**174**	**100.0%**	**1.38 [1.01, 1.89]**
Total events	63		44			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.78$, df = 4 ($P = 0.94$); $I^2 = 0\%$

Test for overall effect: $Z = 2.01$ ($P = 0.04$)



Thiazolidinediones modestly improve histological variables including fibrosis and hepatocellular ballooning, but at the cost of significant weight gain.

Mahady et al., J Hepatol 2011

Recommendation

20. *Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH. However, it should be noted that majority of the patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic and that long term safety and efficacy of pioglitazone in patients with NASH is not established.* ***(Strength – 1, Evidence - B)***

VIT. E (α- tocopherol)

AASLD recommendations

Recommendation

Vitamin E (α-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population.

Strenght – 1, Quality - B

Statins

Table 3 Ef… liver disease

Author (yea…	…ults
Lewis et al.	
Athyros et …	
Maroni et a…	
Hatzitolios …	
Gomez-Dor…	
Athyros et …	
Kiyici et al.	
Foster et al.	
Browning […	
Georgescu …	…eatosis
Ekstedt et a…	…eatosis
Nelson et a…	
Kimura et a…	…eatosis, N-I

Recommendations

30. *Given the lack of evidence to show that patients with NAFLD and NASH are at increased risk for serious drug-induced liver injury from statins, statins can be used to treat dyslipidemia in patients with NAFLD and NASH.* ***(Strength – 1, Quality – B)***

31. *Until RCTs with histological endpoints prove their efficacy, statins should not be used to specifically treat NASH.* ***(Strength – 1, Quality – B)***

Lomonaco et al., Drugs 2013; Chalasani et al., Gastroenterology 2012

Effects of PUFA on LIVER FAT

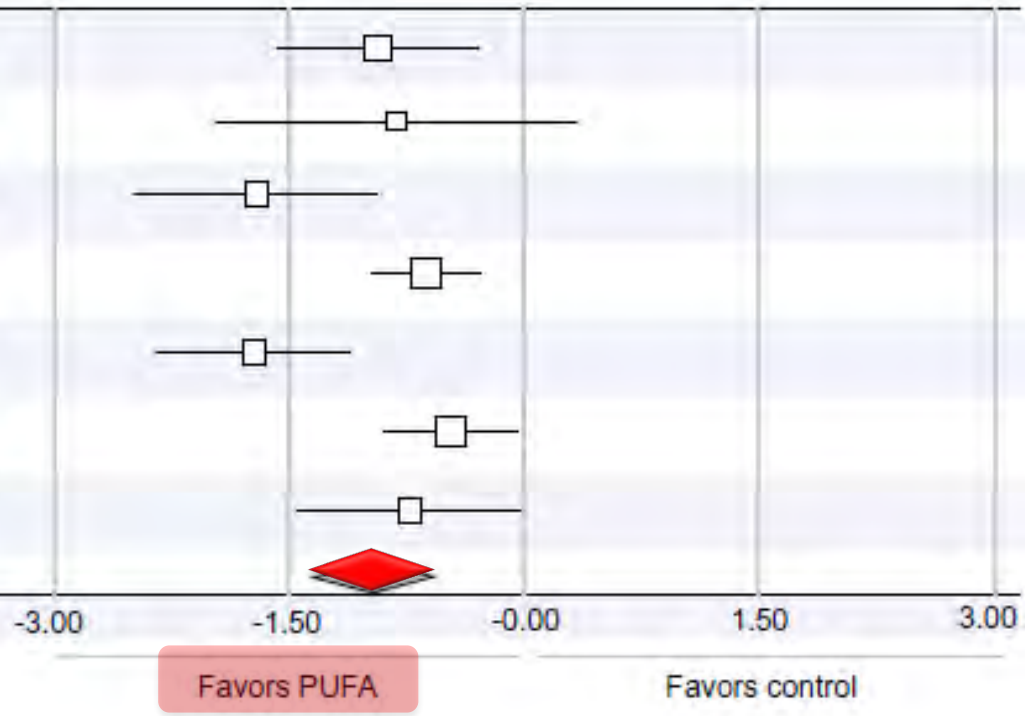
Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Omega-3 supplementation and non-alcoholic fatty liver disease: A systematic review and meta-analysis

Helen M. Parker[1], Nathan A. Johnson[1,3], Catriona A. Burdon[1], Jeffrey S. Cohn[2], Helen T. O'Connor[1,3], Jacob George[4,*]

Authors, year [Ref.]	Effect size		p
	Hedge's g	95% CI	
Capanni *et al.*, 2006 [45]	-0.938	-1.559, -0.316	0.003
Sofi *et al.*, 2010 [53]	-0.811	-1.948, 0.326	0.162
Spadaro *et al.*, 2008 [54]	-1.709	-2.460, -0.958	0.000
Zhu *et al.*, 2008 [48]	-0.626	-0.971, -0.281	0.000
Cussons *et al.*, 2009 [56]	-1.718	-2.326, -1.109	0.000
Tanaka *et al.*, 2008 [47]	-0.476	-0.894, -0.058	0.026
Chen *et al.*, 2008 [55]	-0.731	-1.441, -0.021	0.043
	-0.965	-1.348, -0.582	0.000



Effects of PUFA on AST/ALT

Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Omega-3 supplementation and non-alcoholic fatty liver disease: A systematic review and meta-analysis

Helen M. Parker[1], Nathan A. Johnson[1,3], Catriona A. Burdon[1], Jeffrey S. Cohn[2], Helen T. O'Connor[1,3], Jacob George[4,*]

AST

Authors, year [Ref.]	Effect size		p
	Hedge's g	95% CI	
Capanni *et al.*, 2006 [45]	-0.458	-1.060, 0.144	0.136
Sofi *et al.*, 2010 [53]	-0.517	-1.623, 0.590	0.360
Spadaro *et al.*, 2008 [54]	-0.477	-1.125, 0.172	0.150
Zhu *et al.*, 2008 [48]	0.363	0.023, 0.702	0.036
Hatzitolios *et al.*, 2004 [46]	-2.351	-3.137, -1.566	0.000
Cussons *et al.*, 2009 [56]	0.089	-0.291, 0.469	0.646
Tanaka *et al.*, 2008 [47]	-0.896	-1.368, -0.424	0.000
	-0.563	-1.158, 0.031	0.063

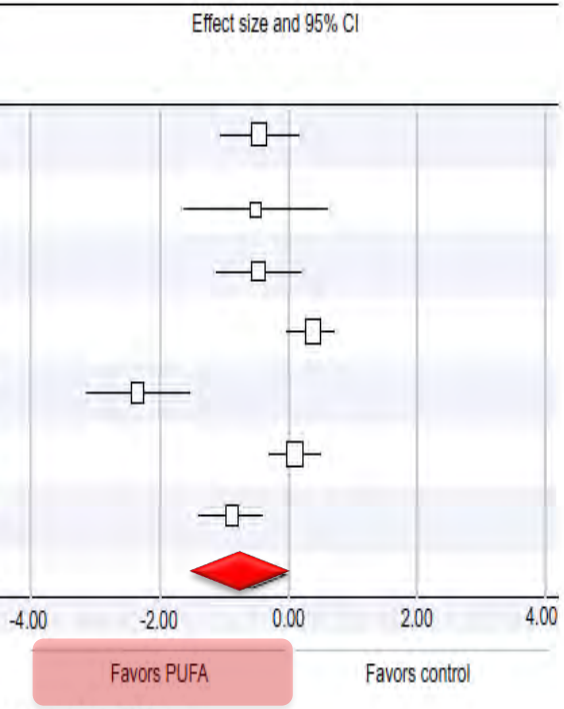


Fig. 3. Meta-analysis of effect of omega-3 supplementation on ALT using a random effects model.

AST

Authors, year [Ref.]	Effect size		p
	Hedge's g	95% CI	
Capanni *et al.*, 2006 [45]	-0.607	-1.214, 0.000	0.050
Sofi *et al.*, 2010 [53]	-2.859	-4.473, -1.245	0.001
Spadaro *et al.*, 2008 [54]	-0.439	-1.086, 0.207	0.183
Zhu *et al.*, 2008 [48]	0.435	0.094, 0.776	0.012
Hatzitolios *et al.*, 2004 [46]	-2.365	-3.154, -1.576	0.000
Tanaka *et al.*, 2008 [47]	-0.840	-1.303, -0.377	0.000
	-0.971	-1.815, -0.127	0.024

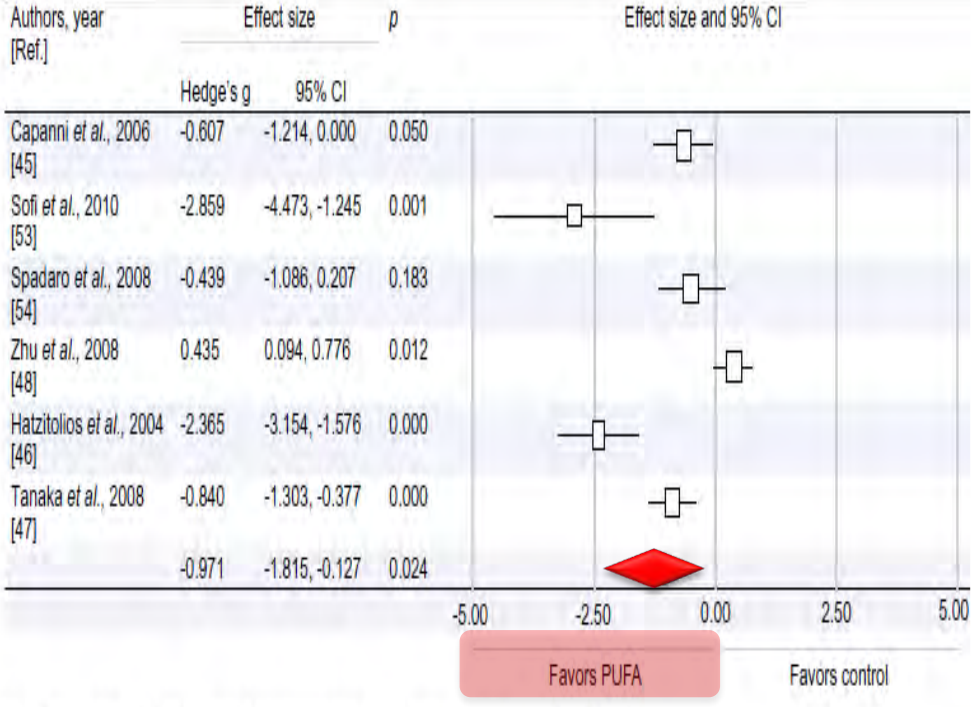


Fig. 4. Meta-analysis of effect of omega-3 supplementation on AST using a random effects model.

Bariatric surgery

- Histological effects
  - ***Improves steatosis***
  - ***Improves NASH***
  - ***May improve fibrosis***

- Foregut bariatric surgery is not contraindicated in otherwise eligible obese individuals with NAFLD or NASH *(but without established cirrhosis).*

Chalasani et al., AGA-AASLD guidelines 2012

Farnesoid X Receptor Agonists (OBETICOLIC Acid)

***FXR** regulates bile acid metabolism through multiple mechanisms in both liver & Intestine*

***FXR** detects bile acid levels:*

LIVER:

- ↓ *bile acid synhesis*
- ↓ *bile acid uptake*
- ↑ *liver secretion*

INTESTINE

- ↓ *bile acid absorption*
- ↑ *secretion FGF15 e FGF19*

Net results:

↓ ***Overall bile acid leves***

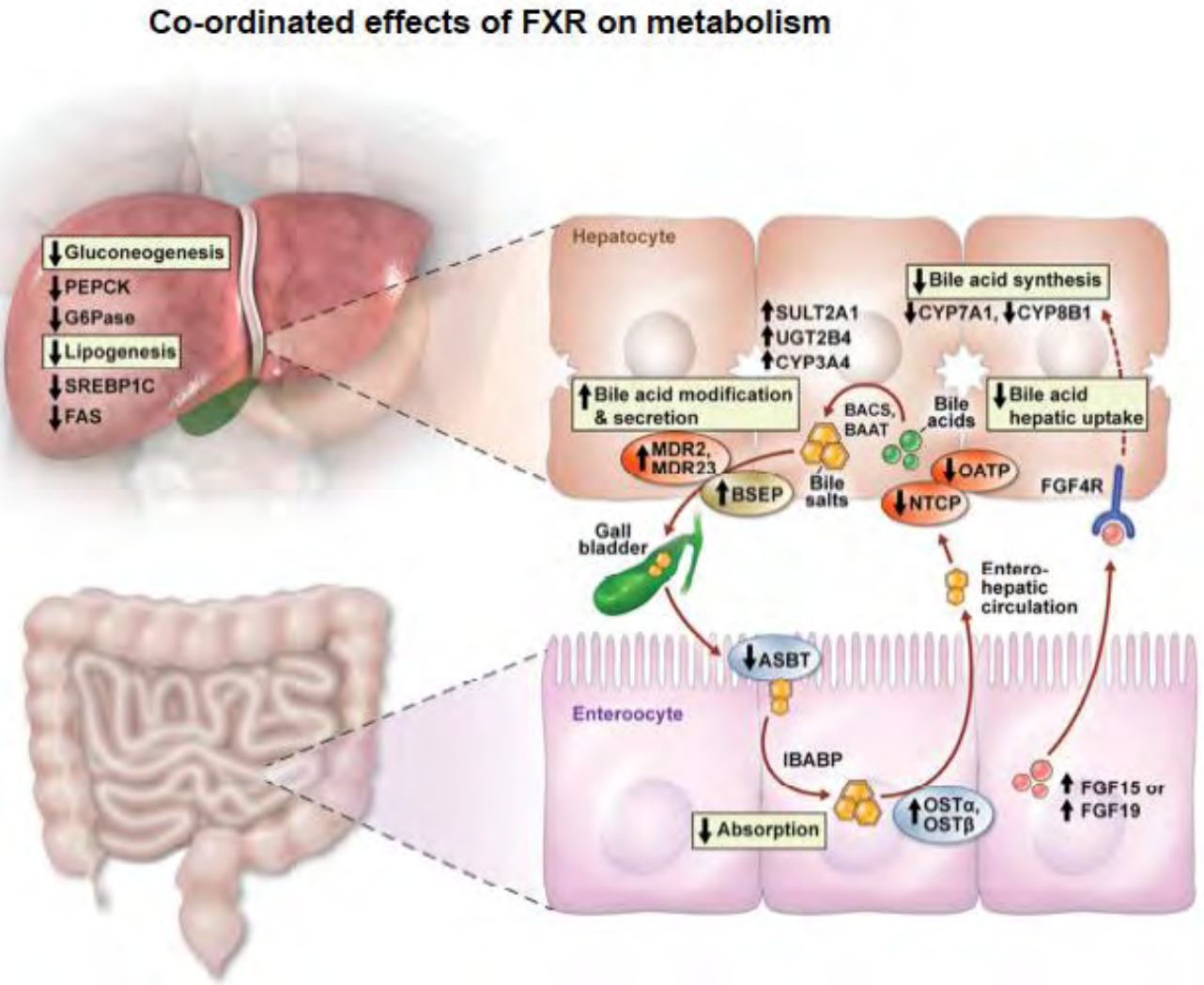


Figure adapted from Calkin and Tontonoz 2012).

Table 1. Summary of agents tested in nonalcoholic steatohepatitis

Benefit	Agent	Comment
Potential benefit	Pioglitazone	Improves components of the NAS score [12]. Increased risk of bladder cancer and MI [13,14].
	Vitamin E	Significant improvement in histological lesions [12]. However, may increase all-cause mortality [15].

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No clear benefit	Metformin	No effect on histology [16,17].
	Statins	
	Atorvastatin	No histological data, but improves liver enzymes and radiological steatosis [18,19].
	Simvastatin	No effect on histology or liver enzymes [20].
	UDCA	Histological data lacking, four RCTs showed no effect on liver enzymes [21].
	PUFAs	No histological improvement in activity [22▪▪], but reduction in steatosis radiologically [23].

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	PUFAs	No histological improvement in activity [22▪▪], but reduction in steatosis radiologically [23].
Unclear benefit	Angiotensin receptor blockers	Improvements in histology (necroinflammation and fibrosis) but study limited to seven patients [24].
	Pentoxyfylline	Improvement in NASH activity score, but not in fibrosis stage. Study limited to 55 patients [25].

Table 2. Novel agents currently being tested in, or completed, phase 2 trials*

Agent	Action	Effect on NASH pathogenesis
GS-9450	Caspase inhibition	Prevents apoptosis
GFT-505	Dual PPARα/δ agonist	Hepatic glucose utilization, lipoprotein metabolism and anti-inflammatory effects
Obeticholic acid	FXR agonist	Promotes insulin sensitivity, decreases hepatic gluconeogenesis and circulating triglycerides

Summary of treatments

- **For All** patients with NAFLD
  - ***Lifestyle advice***
- For patients with **NASH + T2DN**
  - **Metformin/Pioglitazone**
- For patients with **NASH + hypertension**
  - ***A2RBs + vitamin E / Omega 3***
- For **Hypercholesterolemic** + **NASH**
  - ***Low threshold for statins (HCC) / Omega 3***
- For **Obese** Patients with NASH
  - ***Bariatric Surgery / Omega3/ Vit E***
- For patients with **NASH only**:
  - *best evidence for:*
    - ***Antioxydants (Vitamin E, Astaxantine)***
    - ***Omega-3***

Role of new generation drugs !

- ***Caspase inhibitors***
- ***FXR agonists (Obeticolic Ac.)***
- ***PPARγ/δ agonists***

Not all NASH are borne equal.....

Grazie per l'attenzione

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Ospedale Papa Giovanni XXIII
Sistema Socio Sanitario
Regione Lombardia
ASST Papa Giovanni XXIII

Cosa c'è di Nuovo

NAFLD

Stefano Fagiuoli
U.S.C. Gastroenterologia Epatologia e Trapiantologia
ASST Papa Giovanni XXIII - Bergamo

Nutrients **2013**, *5*, 4093-4114;

Nutritional Management of Insulin Resistance in Nonalcoholic Fatty Liver Disease (NAFLD)

Beth A. Conlon [1,*], Jeannette M. Beasley [1], Karin Aebersold [1], Sunil S. Jhangiani [2] and Judith Wylie-Rosett [1]

NAFLD

Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis.

NAFL

Presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is nominal.

NASH

Presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure and, rarely, liver cancer.

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NAFLD: epidemiology

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY VOLUME 15 | JANUARY 2018

Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention

Zobair Younossi[1,2], Quentin M. Anstee[3,4], Milena Marietti[5], Timothy Hardy[3,4], Linda Henry[1,2], Mohammed Eslam[6], Jacob George[6] and Elisabetta Bugianesi[5]

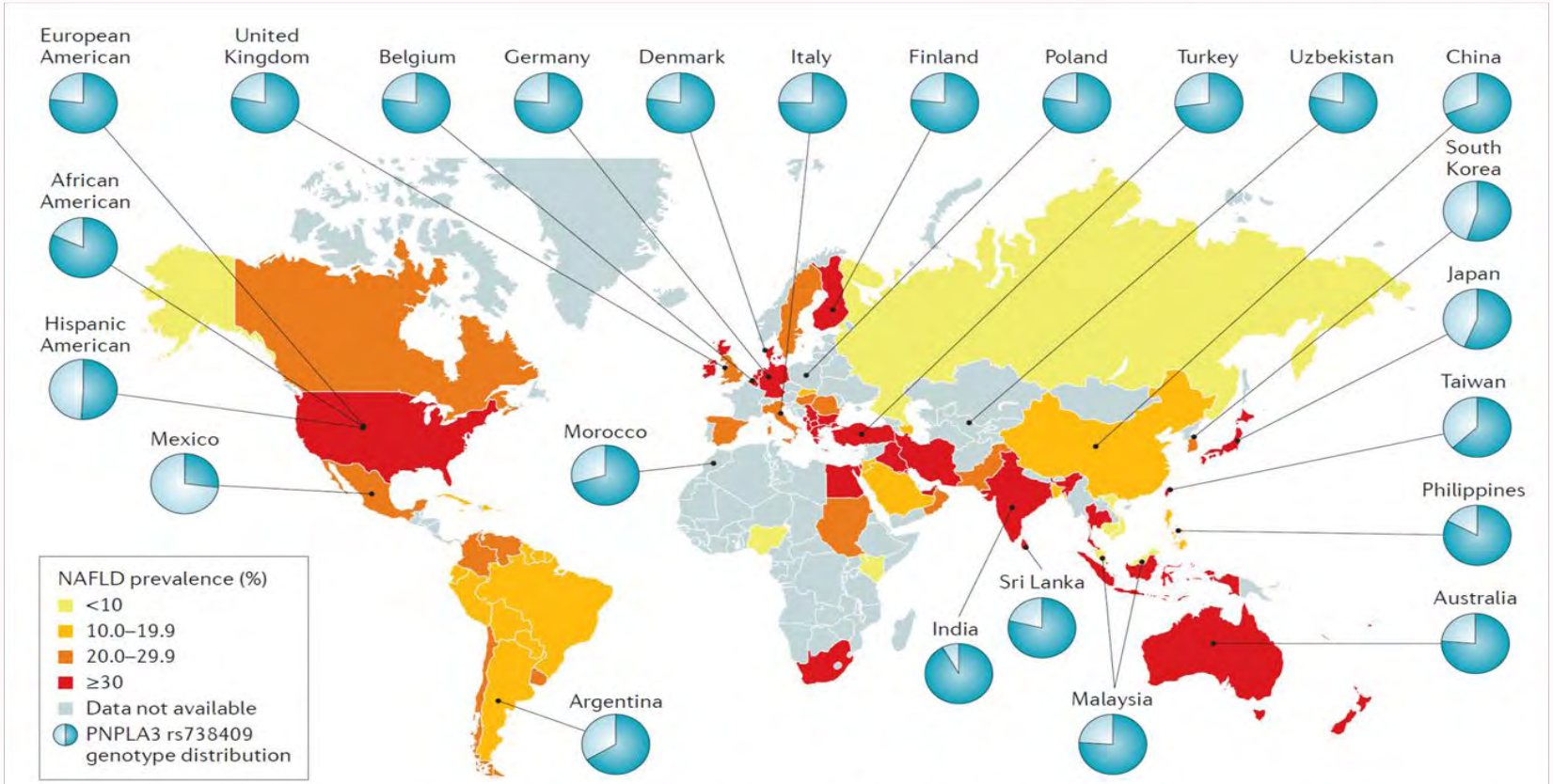

Figure 1 | **Worldwide estimated prevalence of NAFLD and distribution of *PNPLA3* genotypes.** *PNPLA3* is presented as minor allele frequency (light blue section of the pie chart).

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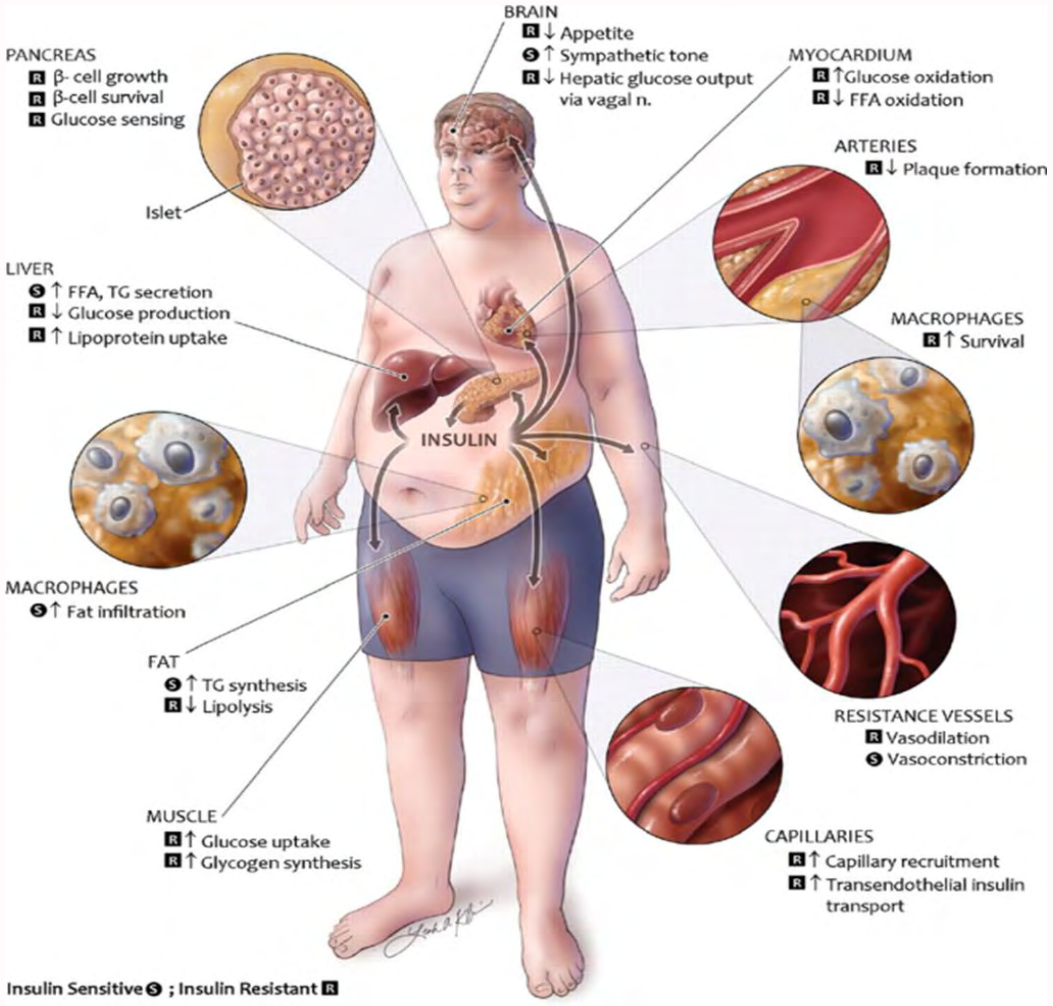
NASH



A systemic dysfunction

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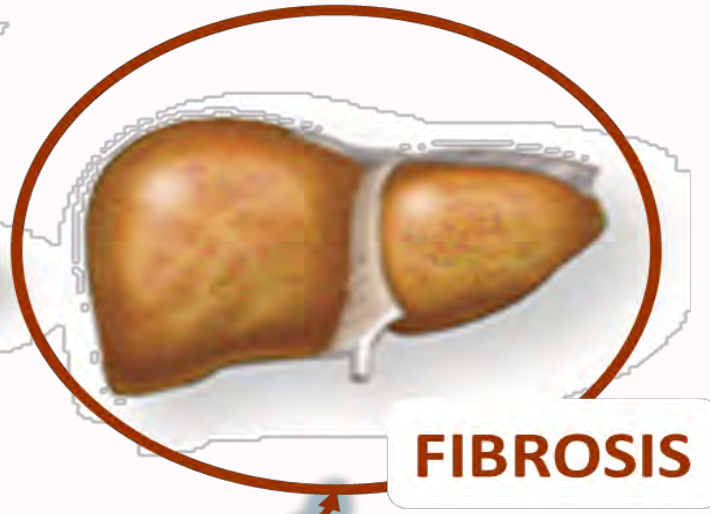
The Oxydative Stress

Starter of the progression

STEATOSI



FIBROSIS

Oxydative Stress

- ROS accumulation
- Lipoperoxyidation and Hepatocyte Membrane Dysruption
- Hepatocyte Functional Loss

Inflammation

- Kupffer Cells Activation
- Tissue Necrosis

Immunitary System

- Activation and Proliferation of Stellate Cells
- Collagen Fibers Deposition

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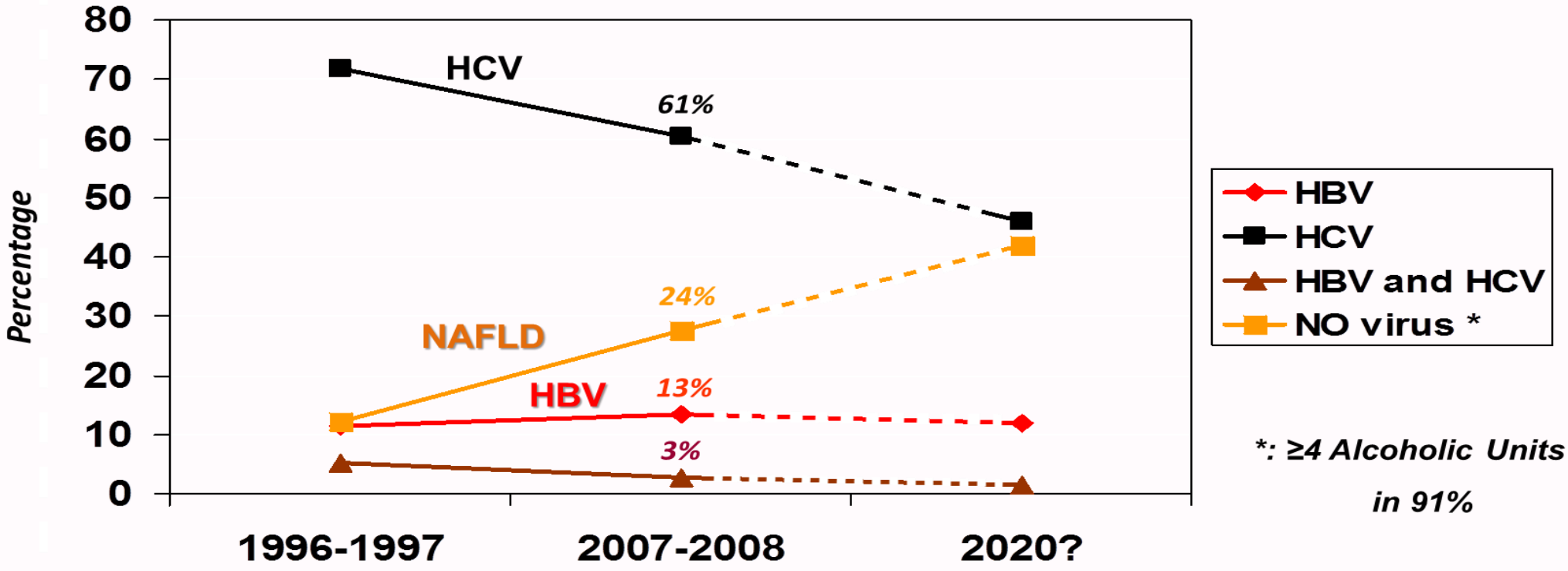
Changing aetiological factors of hepatocellular carcinoma and their potential impact on the effectiveness of surveillance.

(23 centres: 1733 HCC)



**: ≥4 Alcoholic Units in 91%*

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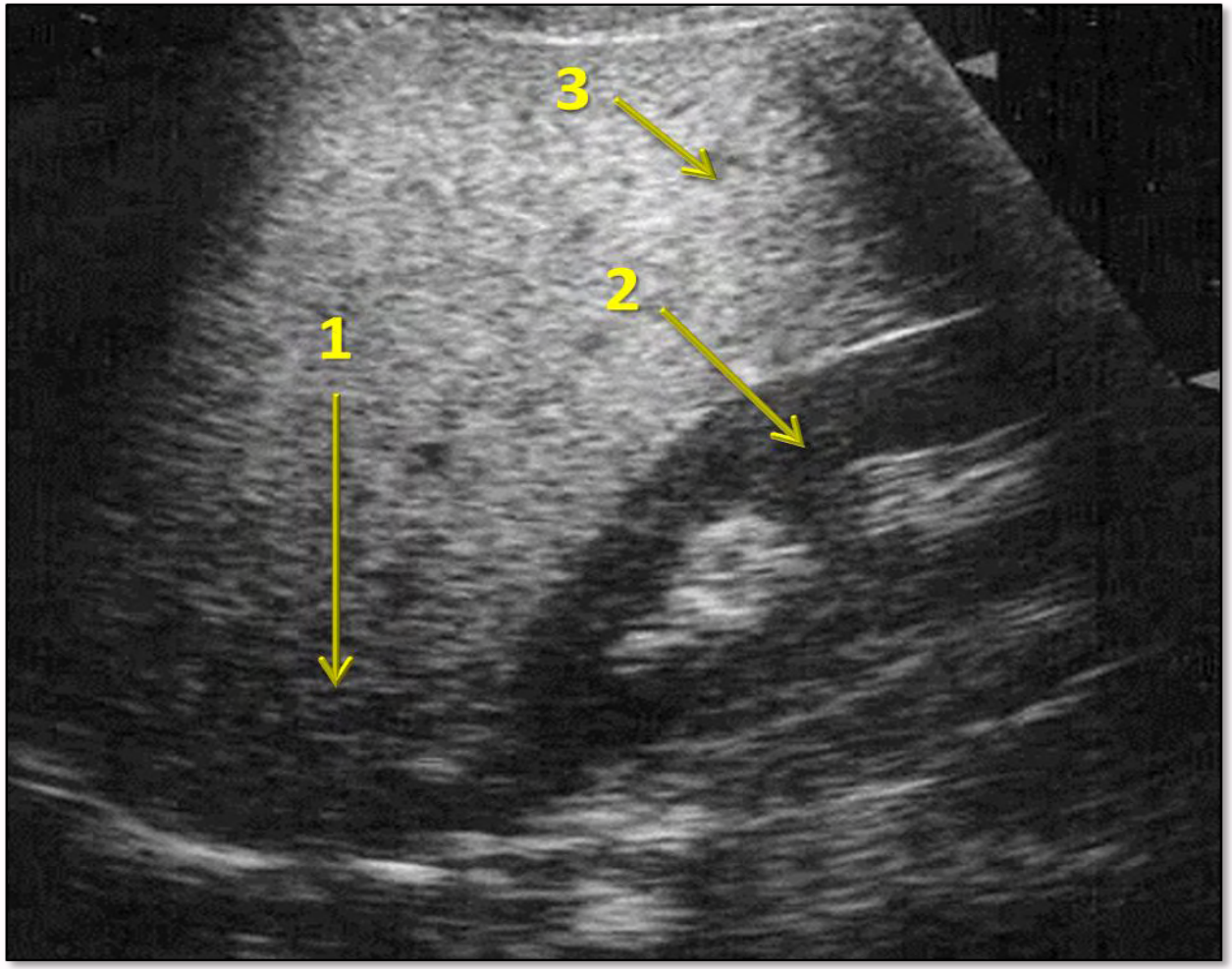
US Criteria to graduate FL:

1. **Deep attenuation**
2. **Diffuse hyperechoic** echotexture **("bright liver")** compared with the kidney
3. **Poor visibility** of venous vessels, no expansion of the hepatic and portal vein diameters at deep breath



Stroffolini et al, Dig Liv Dis 2011

The FL Index

	Predictors	logits
Triglicerydes (mg / dL)	200	5,049
BMI (Body Mass Index) (kg / m^2)	27	3,753
GGT (U / L)	45	2,733
Waist Circumference (cm)	98	5,194
Constant	**********	-15,745
Sum	**********	0,984
Fatty Liver Index (FLI) is	**73**	

Use this table for interpretation of FLI:
If FLI is > 60 you have > 85% probability of FL
If FLI is < 30 you have > 86% probability of NON having FL

SAF score

SAF score: Semiquantitative scoring

Steatosis *large or medium-sized lipid droplets*	< 5%	5-33% *mild*	34-66% *moderate*	>67% *severe*	
	S0	**S1**	**S2**	**S3**	
Activity *hepatocyte ballooning (0-2) lobular inflammation (0-2)*	No Activity	Mild activity	Moderate activity	Severe activity	
	A0	**A1**	**A2**	**A3**	
Fibrosis	None	Stage 1 *Perisinusoidal or Periportal*	Stage 2 Perisinusoidal and periportal	Stage 3 *Bridging fibrosis*	Stage 4 *Cirrhosis*
	F0	**F1**	**F2**	**F3**	**F4**
Total					

HEPATOLOGY

HEPATOLOGY 2012;56:1751-1759

Histopathological Algorithm and Scoring System for Evaluation of Liver Lesions in Morbidly Obese Patients

Pierre Bedossa,[1] Christine Poitou,[2,3] Nicolas Veyrie,[4] Jean-Luc Bouillot,[3] Arnaud Basdevant,[2,3] Valerie Paradis,[1] Joan Tordjman,[2,3*] and Karine Clement[2,3*]

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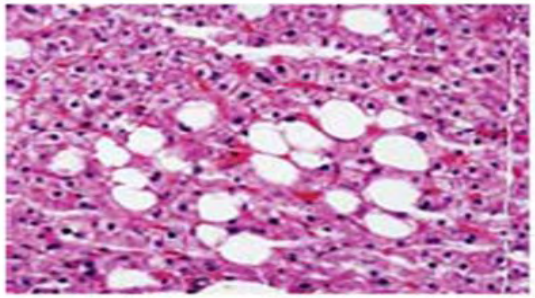
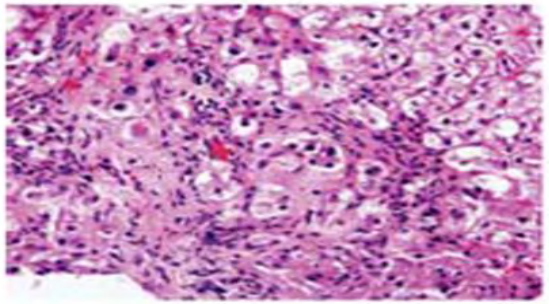
Fatty Liver and Cryptogenic Cirrhosis

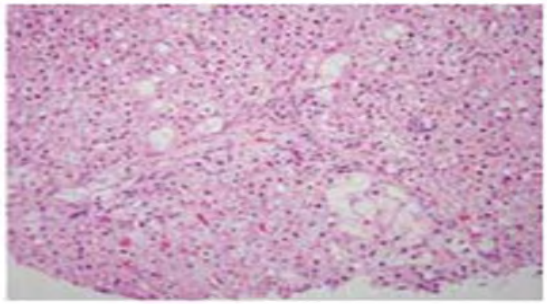


Fatty Liver

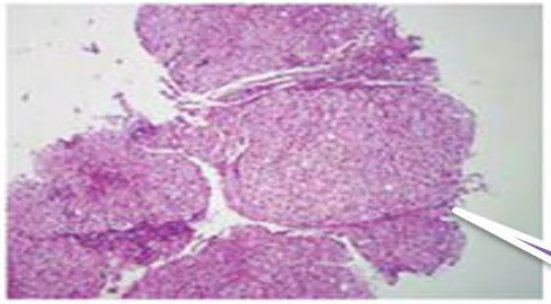


NASH

Fatty Liver
↓
NASH
↓
NASH with Fibrosis
↓
Cirrhosis
↓
Decompensated Cirrhosis



NASH with Fibrosis



Cirrhosis

Disappearance of fat

Difficult Diagnosis

Maheshwari2006

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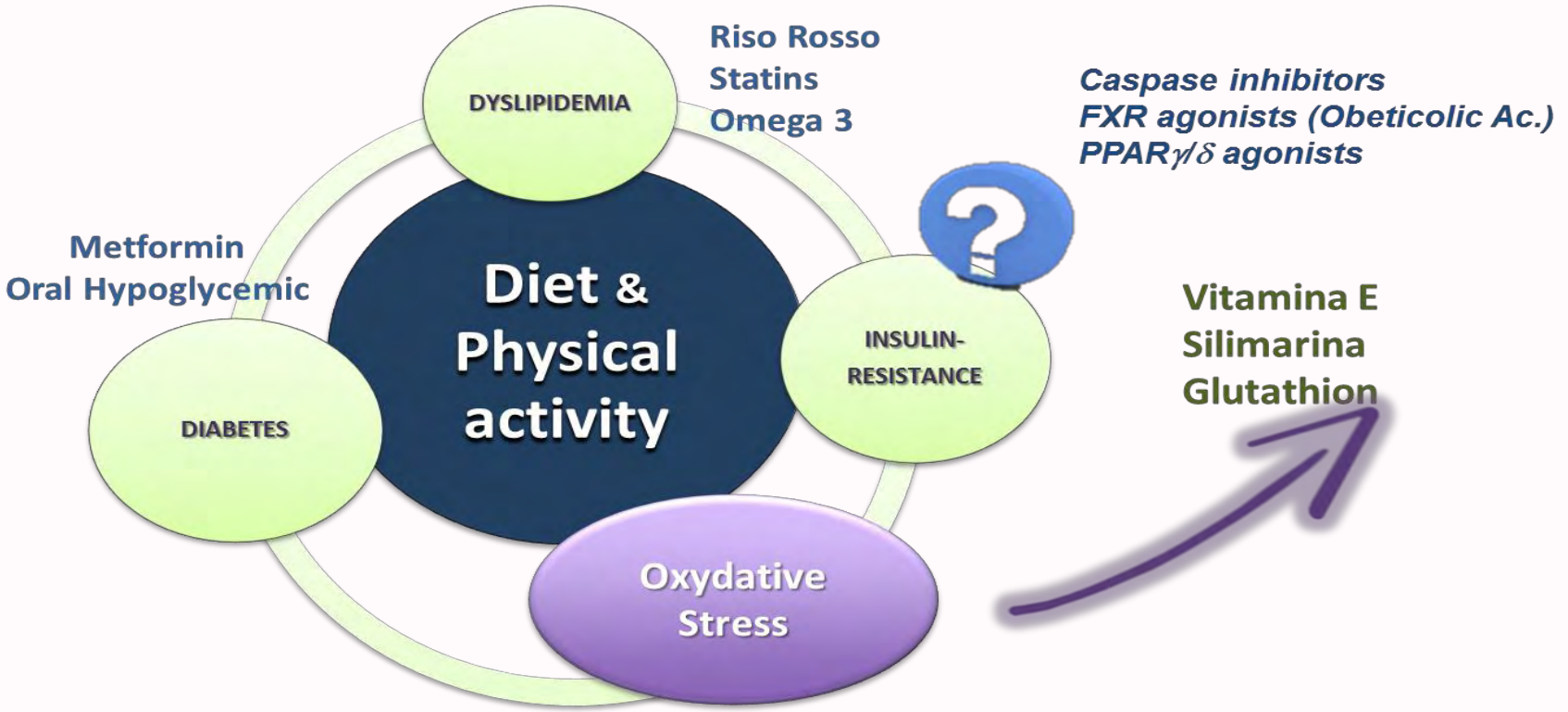
NAFLD

The Treatment



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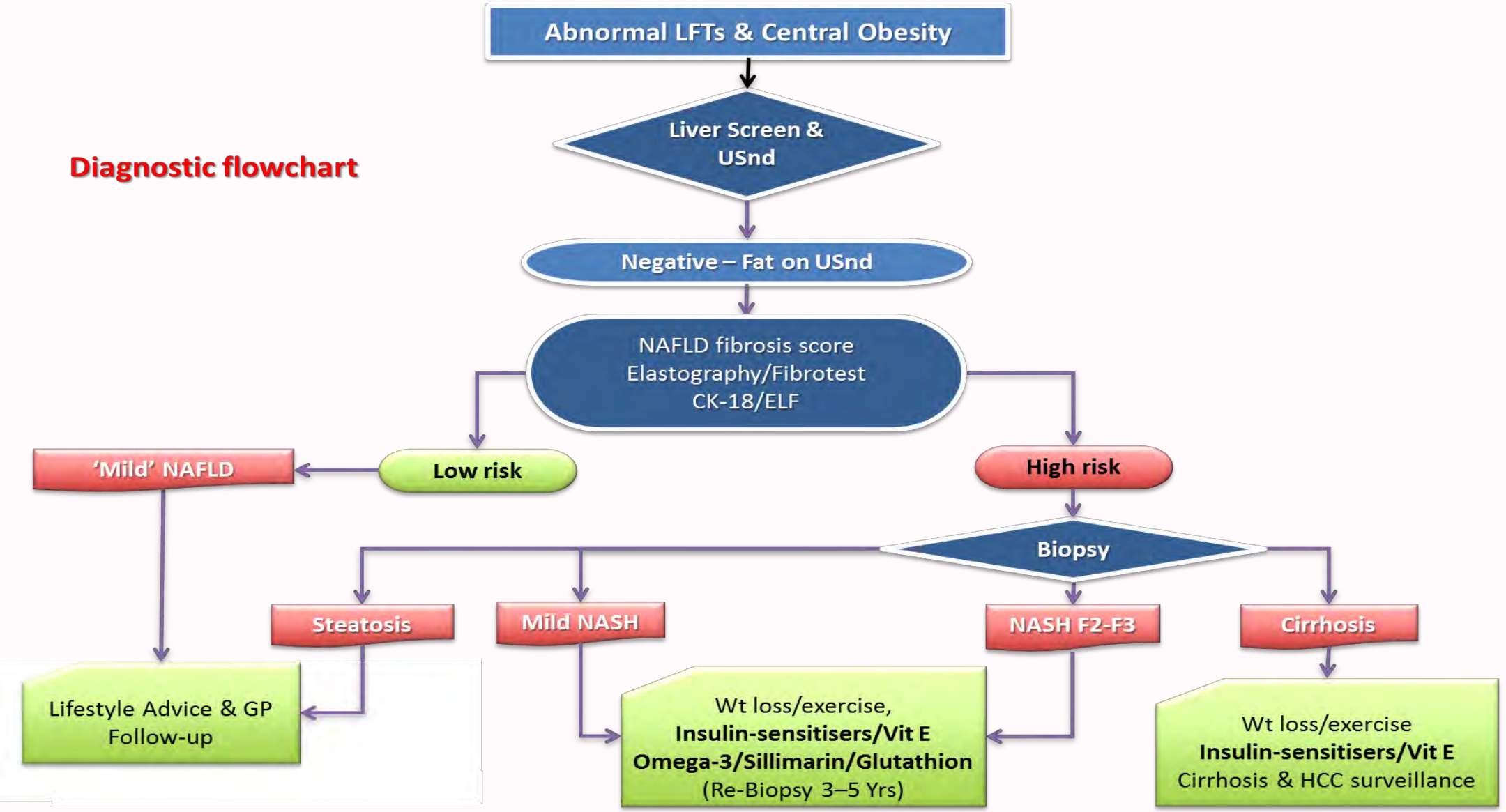
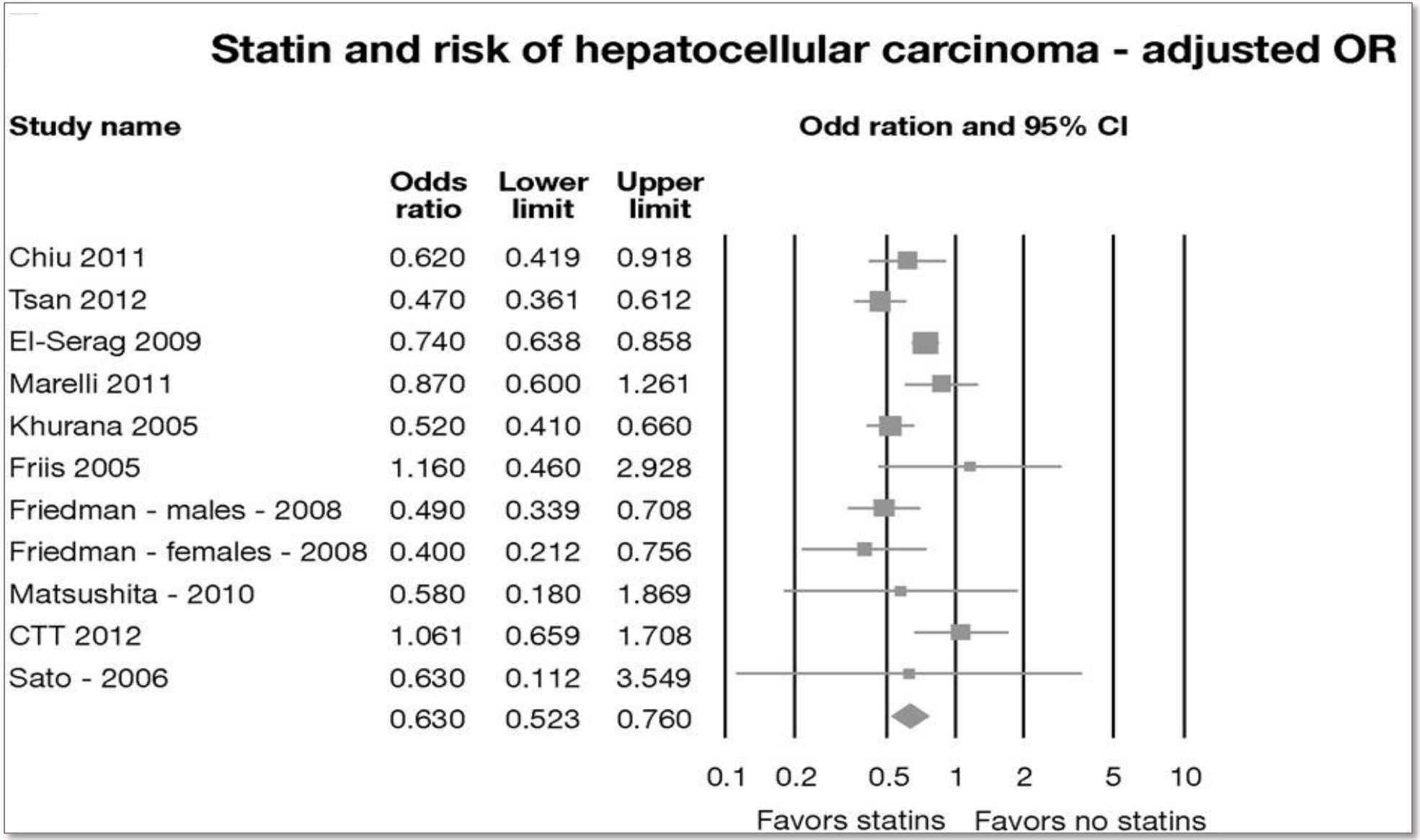
Diagnostic flowchart



Statins Are Associated with Reduced Risk of HCC

A Systematic Review and Meta-analysis

Singh et al., Gastroenterology 2013



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journal homepage: www.elsevier.com/locate/ejphar

Pulmonary, gastrointestinal and urogenital pharmacology

Silymarin ameliorates fructose induced insulin resistance syndrome by reducing de novo hepatic lipogenesis in the rat

Prem Prakash, Vishal Singh, Manish Jain, Minakshi Rana, Vivek Khanna, Manoj Kumar Barthwal, Madhu Dikshit*

Pharmacology Division, CSIR-Central Drug Research Institute, 1 M.G. Marg, Lucknow 226001, U.P. India

Table 2
Various parameters in chow and HFr fed rats and their modulation by silymarin treatment.

Parameters	Chow	HFr	HFr+Silymarin (mg kg^{-1})		
			30	100	300
Glucose (mg dl^{-1})	77 ± 5	100 ± 5[a]	94 ± 4	78 ± 3[b]	75 ± 4[b]
Insulin (μU ml^{-1})	15 ± 1	25 ± 3[a]	24 ± 4	15 ± 1[b]	14 ± 1[b]
Plasma triglyceride (mg dl^{-1})	90 ± 5	150 ± 15[a]	145 ± 6[a]	95 ± 7[b]	92 ± 5[b]
Hepatic triglyceride (nmole 100 mg^{-1} wet tissue)	4 ± 0.4	10 ± 0.5[a]	9 ± 0.2[a]	6 ± 0.8[b]	5 ± 0.9[b]
Uric acid (mg dl^{-1})	1.2 ± 0.1	2.4 ± 0.4[a]	2.3 ± 0.2[a]	1.4 ± 0.1[b]	1.4 ± 0.1[b]
Nonesterified fatty acid (mmole L^{-1})	0.35 ± 0.03	0.53 ± 0.04[a]	0.52 ± 0.04[a]	0.33 ± 0.04[b]	0.34 ± 0.06[b]
Alanine transaminase activity (U L^{-1})	25 ± 2	22 ± 2	20 ± 3	22 ± 5	23 ± 4
Aspartate transaminase activity (U L^{-1})	37 ± 5	34 ± 4	35 ± 3	30 ± 6	37 ± 2
Total bilirubin (mg dl^{-1})	0.37 ± 0.04	0.36 ± 0.04	0.34 ± 0.08	0.36 ± 0.05	0.32 ± 0.07
Direct bilirubin (mg dl^{-1})	0.23 ± 0.05	0.17 ± 0.03	0.2 ± 0.05	0.17 ± 0.03	0.17 ± 0.03
Liver wt/body wt ratio	0.036 ± 0.001	0.048 ± 0.002[a]	0.046 ± 0.002[a]	0.039 ± 0.002[b]	0.038 ± 0.001[b]
Spleen wt/body wt ratio	0.003 ± 0.0001	0.003 ± 0.0002	0.003 ± 0.0001	0.003 ± 0.0002	0.003 ± 0.004
Body wt (g)	410 ± 20	390 ± 25	410 ± 25	415 ± 10	395 ± 25

Values are Means ± S.E.M from thirty different rats.

[a] $P < 0.05$ vs. Chow.

[b] $P < 0.05$ vs. HFr.

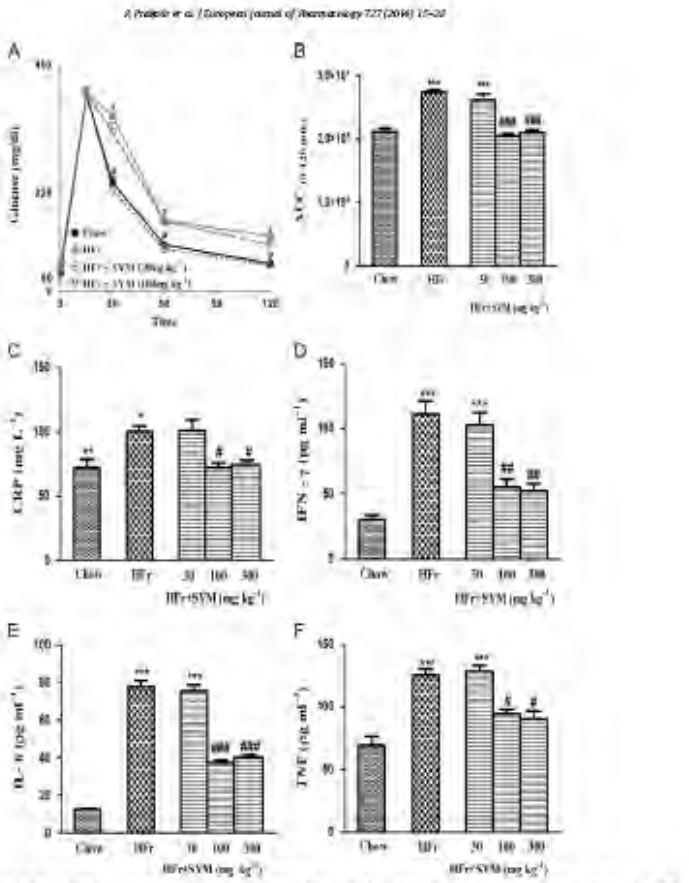


Fig. 1. Effect of silymarin on glucose utilization and inflammatory cytokines in fructose fed rats. Graph represents glucose tolerance test (A), area under the curve of the glucose response (B) and levels of inflammatory markers in plasma, such as, CRP (C), IFN-γ (D), IL-6 (E) and TNF (F), following HFr and silymarin treatment. Values are Mean ± S.E.M from two rats. *P < 0.05, **P < 0.01 and ***P < 0.001 in comparison to the normal chow fed animals; $ P < 0.05, $$ P < 0.01 and $$$ P < 0.001 in comparison to the high fructose fed, insulin resistant animals.

European Review for Medical and Pharmacological Sciences 2015; 19: 3118-3124

Effect of silymarin plus vitamin E in patients with non-alcoholic fatty liver disease. A randomized clinical pilot study

R. ALLER[1], O. IZAOLA[2], S. GÓMEZ[1], C. TAFUR[1], G. GONZÁLEZ[1], E. BERROA[1], N. MORA[1], J.M. GONZÁLEZ[1], D.A. DE LUIS[2]

[1]Svo. Gastroenterology, Hospital Clínico Universitario, University of Valladolid, Valladolid, Spain
[2]Center of Investigation of Endocrinology and Nutrition, Medicine School and Department of Endocrinology and Nutrition, Hospital Clínico Universitario, University of Valladolid, Valladolid

Table III. Biochemical and NAFLD-index in enrolled subjects (mean ± SD) (goup I: silymarin + vit E+ hypocaloric diet), group II (only hypocaloric diet).

	Group I (n = 18)		Goup II (n = 18)	
	Basal	After	Basal	After
Glucose mg/dl	93.1 ± 13	93.8 ± 12	129.9 ± 46	114.6 ± 47*
TG mg/dL	189.6 ± 84	185 ± 85	180.8 ± 68	170.9 ± 63
AST (IU/L)	35.6 ± 16	34.6 ± 16	41.6 ± 20	36 ± 11.8
ALT (IU/L)	56.4 ± 27	52.7 ± 26	70.8 ± 41	54.7 ± 18*
ALT/AST	1.5 ± 0.4	1.5 ± 0.3	1.7 ± 0.5	1.5 ± 0.4*
GGT (IU/L)	81.5 ± 68	46.2 ± 27*	80.5 ± 46	50.3 ± 27*
HOMA-IR	3.4 ± 2.2	3.4 ± 2.2	5.4 ± 4.1	4.9 ± 4*
FLI	86.2 ± 19	76.9 ± 20*	85.2 ± 18	77.5 ± 23*
LAP	4.3 ± 0.1	4.3 ± 0.1	4.2 ± 0.5	4.2 ± 0.6
NAFLD-FS	-1.6 ± 1.8	-2.1 ± 1.5*	-1 ± 1.9	-1.5 ± 2.1*

TG: triglycerides; AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. GGT: Gamma glutamyl transpeptidase; HOMA-IR: Homeostatic model assessment-insulin resistance; FLI: fatty liver index. LAP: liver accumulation product. NAFLD-FS: non alcoholic fatty liver disease-fibrosis score; *$p < 0.05$.

Conclusions

We have demonstrated that treatment whit silymarin associated with vitamin E and a hypocaloric diet ameliorate function hepatic test, and non-invasive NAFLD test, and this change is also present in patients without lost of 5 % of weight. Life style modification continues to be a valid treatment for these patients. In patients who fail to lose weight with diet, silymarin ca be a valid alternative therapeutic option particularly when other drugs are not indicated or have failed or as a complementary treatment associated with other therapeutic program's. However these results should be confirmed by prospective randomized clinical trials in the future.

Alimentary Pharmacology & Therapeutics

Review article: omega-3 fatty acids – a promising novel therapy for non-alcoholic fatty liver disease

G. S. MASTERTON*, J. N. PLEVRIS† & P. C. HAYES‡

Table 3. Summary of trial methodology

Study	Primar… diag…		Sample …				…utcome	Histology
Capanni *et al.*[94]	NAI…						…of the …rasound	No
Spadaro *et al.*[95]	NAI…						…of the …rasound, …ses	No
Tanaka *et al.*[96]	NASH	label					…e of the liver on ultrasound, transaminases, liver histology	Yes
Vega *et al.*[98]	Fatty liver on MR spectroscopy	Open label	No	No	No	N/A	Plasma and hepatic triglycerides	No
Itoh *et al.*[77]	Obesity	Single blind	Yes	No	No	Dietary advice only	Serum adiponectin	No

Statistically significant Improvement of :

- ***STEATOSIS*** *(Histo/US)*
- ***Triglycerides***
- ***Cholesterol***
- ***AST/ALT***

Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

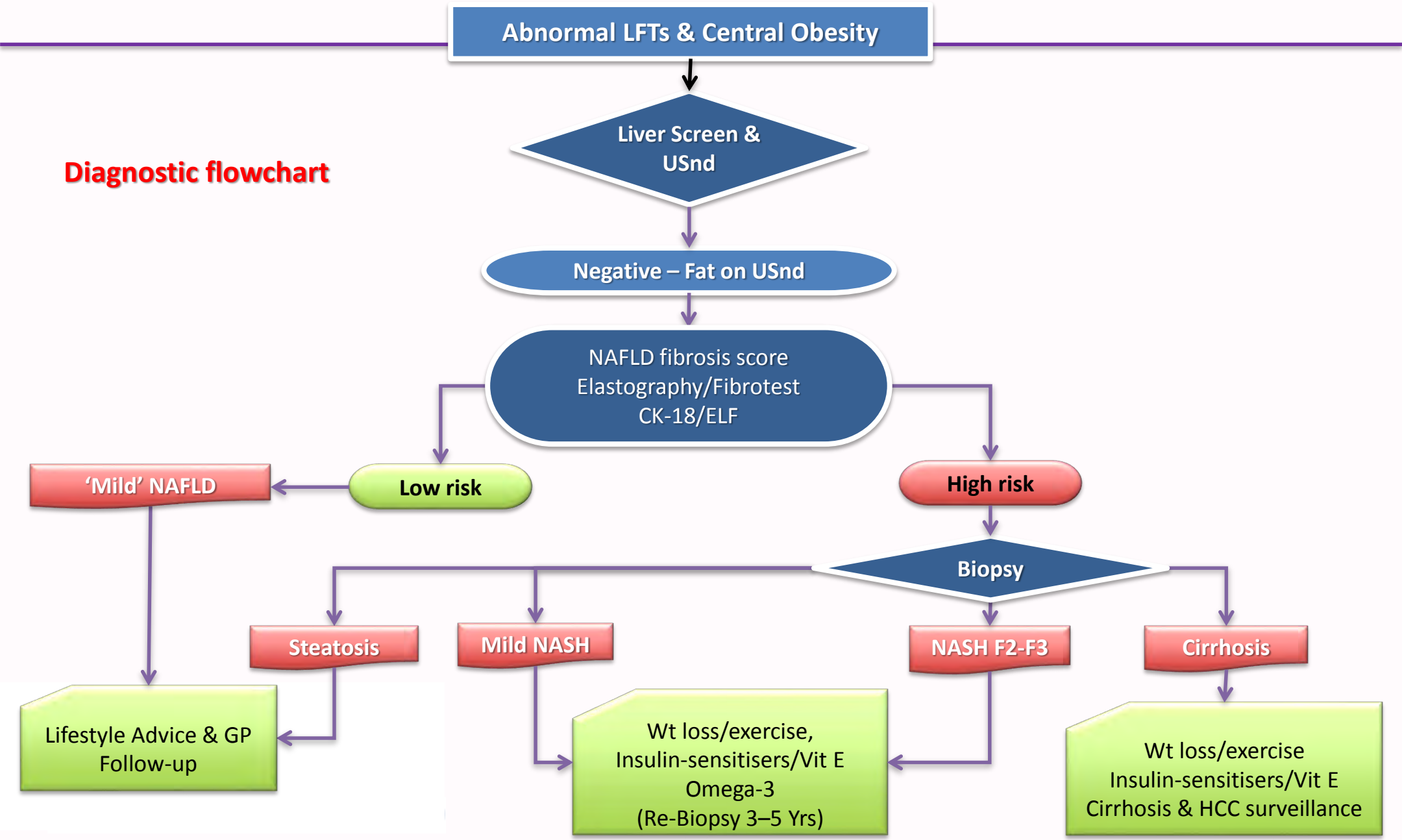
Omega-3 supplementation and non-alcoholic fatty liver disease: A systematic review and meta-analysis

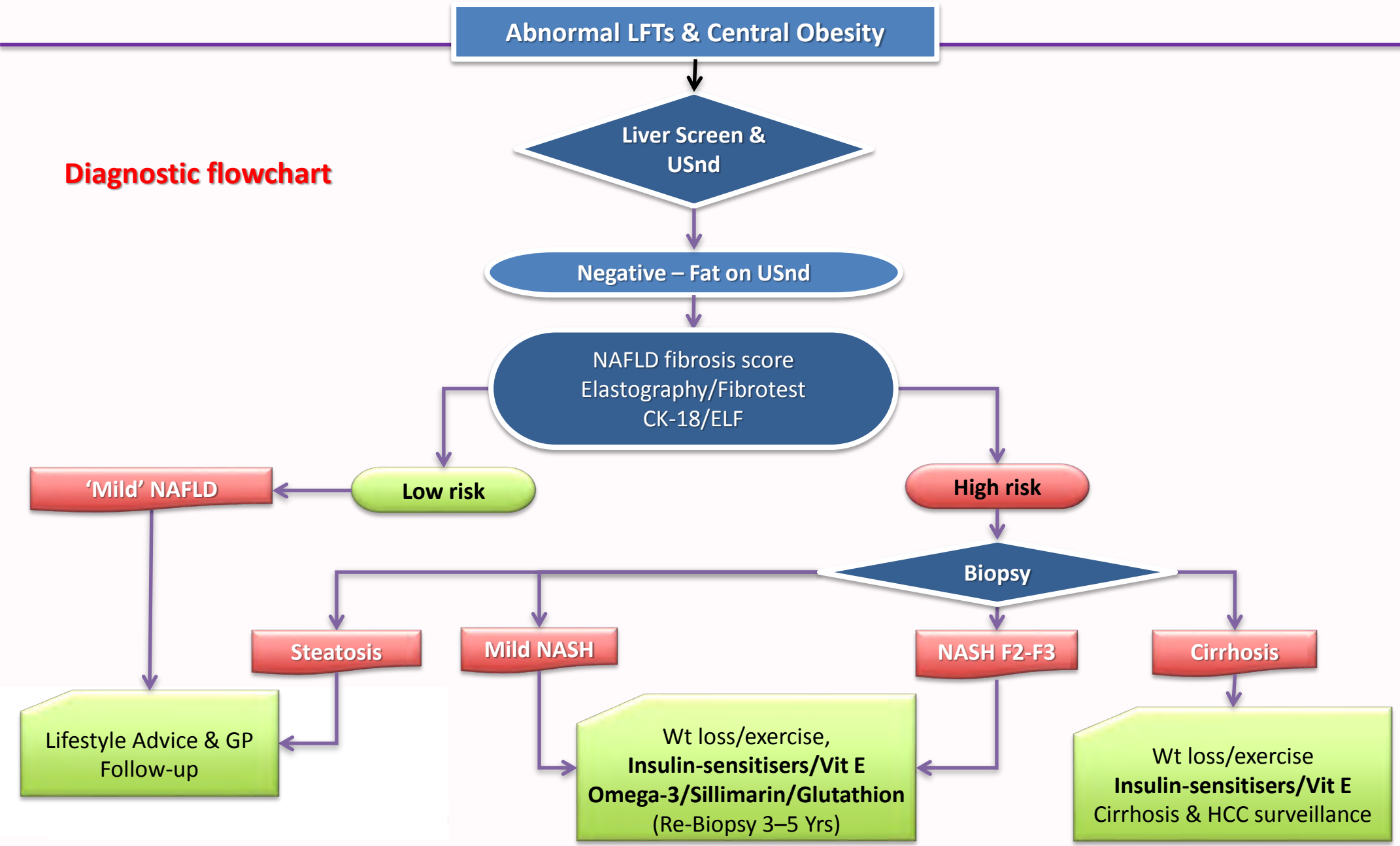
Helen M. Parker[1], Nathan A. Johnson[1,3], Catriona A. Burdon[1], Jeffrey S. Cohn[2], Helen T. O'Connor[1,3], Jacob George[4,*]

Key Points

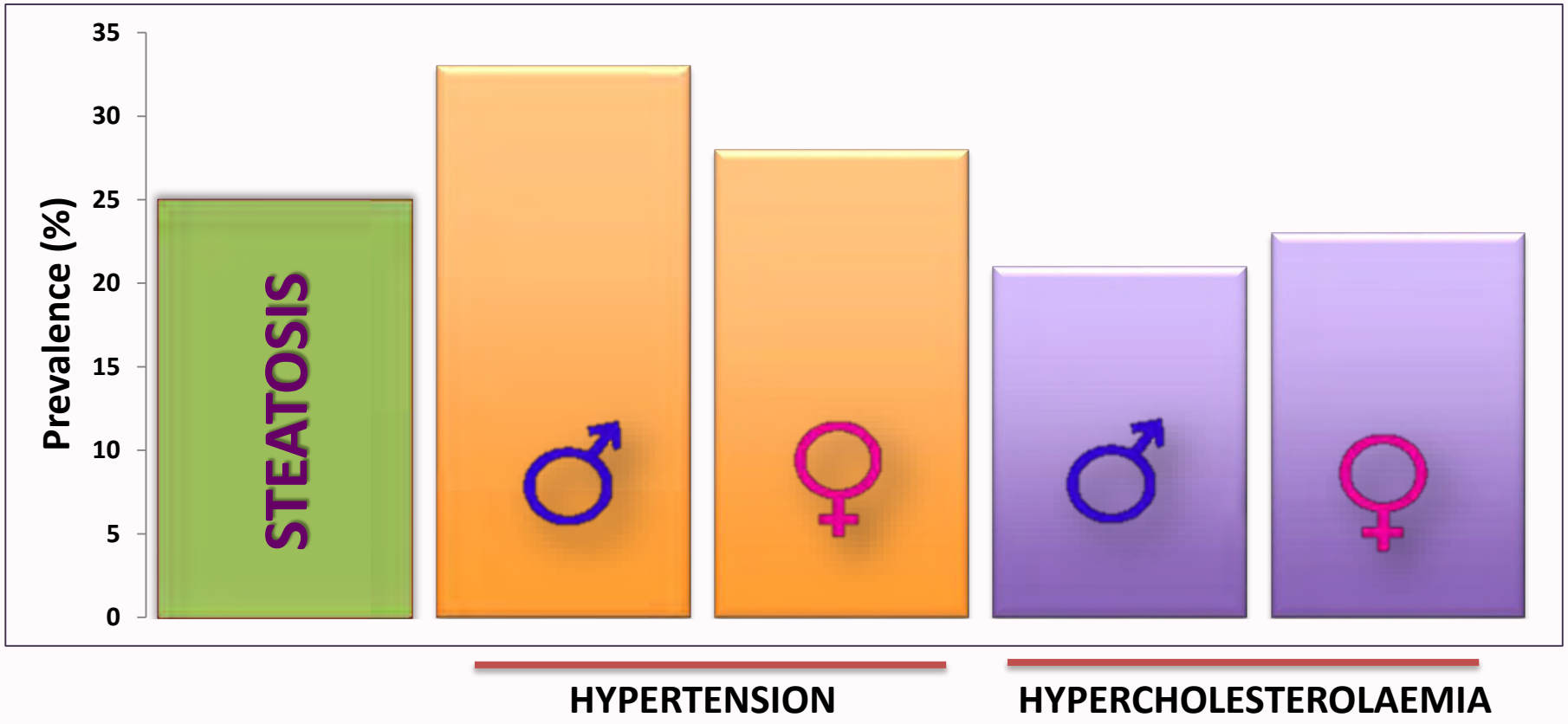
- Omega-3 supplementation decreases liver fat
- The optimal dose required has not been determined, but benefits are seen with ≥0.83 g/day of omega-3 supplementation

Diagnostic flowchart




Diagnostic flowchart
Abnormal LFTs & Central Obesity
Liver Screen & USnd
Negative – Fat on USnd
NAFLD fibrosis score
Elastography/Fibrotest
CK-18/ELF
Low risk
'Mild' NAFLD
High risk
Biopsy
Steatosis
Mild NASH
NASH F2-F3
Cirrhosis
Lifestyle Advice & GP Follow-up
Wt loss/exercise,
Insulin-sensitisers/Vit E
Omega-3/Sillimarin/Glutathion
(Re-Biopsy 3–5 Yrs)
Wt loss/exercise
Insulin-sensitisers/Vit E
Cirrhosis & HCC surveillance

Prevalence


Prevalence (%)
35
30
25
20
15
10
5
0
STEATOSIS
♂
♀
♂
♀
HYPERTENSION
HYPERCHOLESTEROLAEMIA

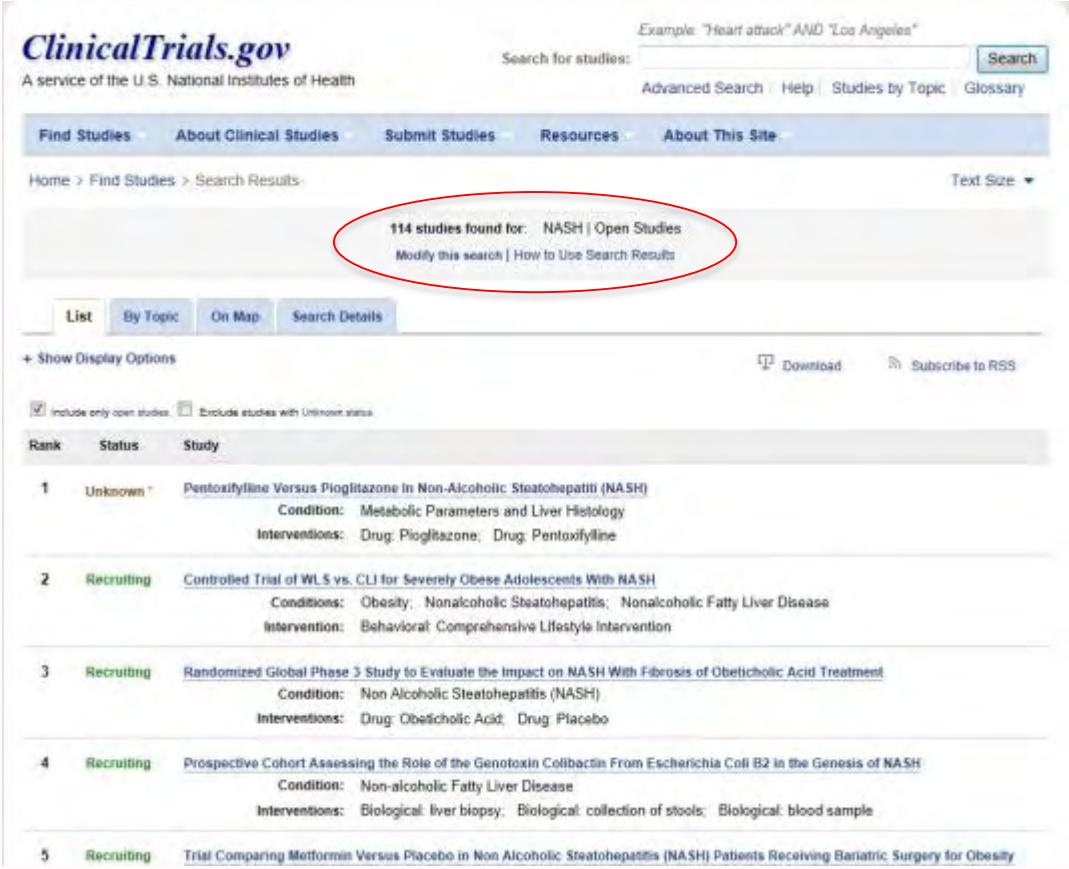
The Treatment

- ✓ **Removal of the cause**
- ✓ **Life style adjustments**
- ✓ **Pharmacological Approach**

- **To modify the pathogenetic factors implicated in NAFLD** *(insulin resistance, adipous tissue accumulation, lipid peroxidation)*
- **to prevent liver disease progression**

Il trattamento

Clinicaltrials.gov 29/10/2015



- Ac.obeticolico (ac. biliare di sintesi)
- Losartan (antifibrotico)
- Simtuzumab (antifibrotico)
- Liraglutide (insulino-sensibilizzante)
- Cenicriviroc (anti-infiammatorio)
- Armamchol (modulatore metabolico)
- GFT 505 (insulino-sensibilizzante)
- Microbioma intestinale

NAFLD: epidemiology

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY VOLUME 15 | JANUARY 2018

Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention

Zobair Younossi[1,2], Quentin M. Anstee[3,4], Milena Marietti[5], Timothy Hardy[3,4], Linda Henry[1,2], Mohammed Eslam[6], Jacob George[6] and Elisabetta Bugianesi[5]

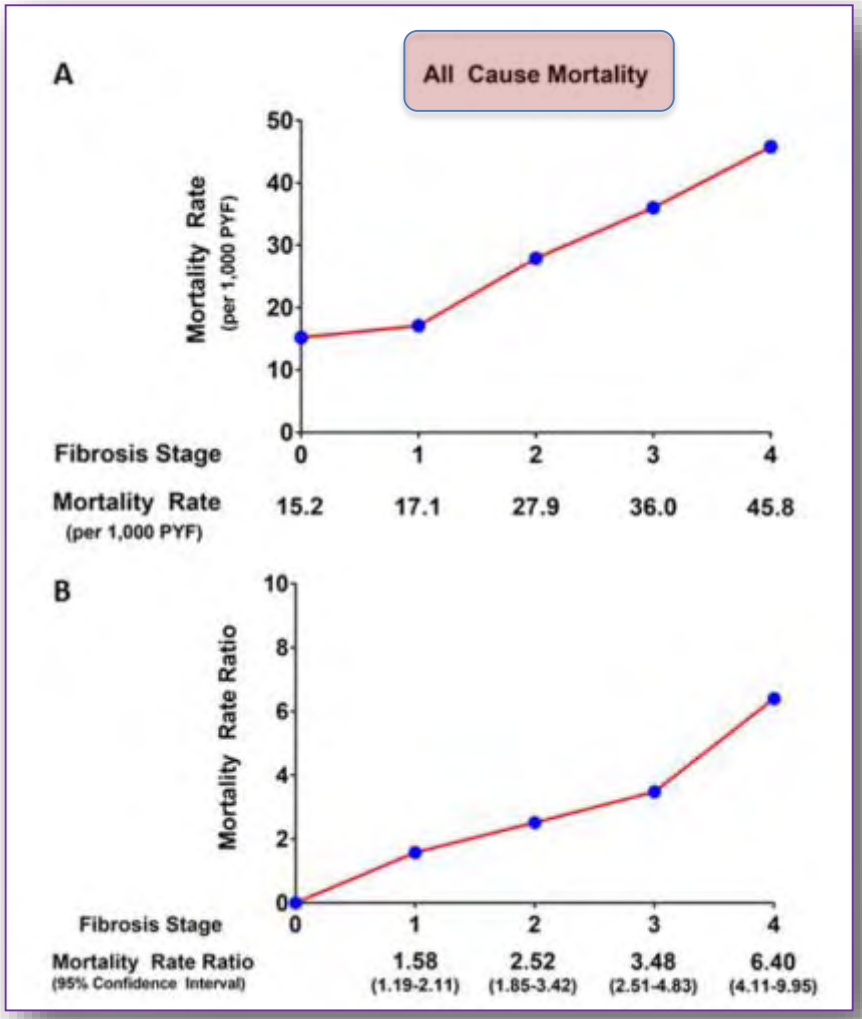
Box 1 | **Causes of NAFLD in individuals who are lean**

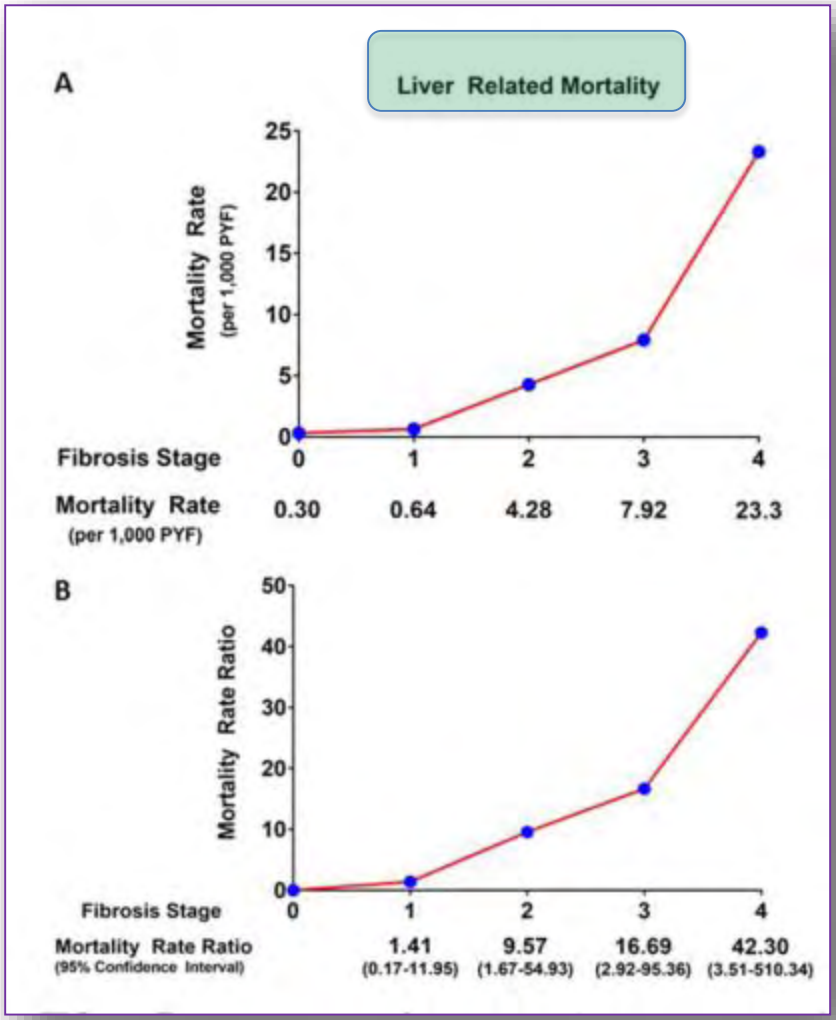
- Environmental causes
  - High-fructose and/or high-fat diet
  - Dual aetiology fatty liver disease (concomitant obesity and excess alcohol intake)
- Metabolically obese, normal-weight phenotypes
- Congenital and acquired lipodystrophy
  - Such as associated with highly active antiretroviral therapy for HIV
- Genetic causes
  - *PNPLA3* variants
  - Congenital defects of metabolism (familial hypobetalipoproteinaemia, lysosomal acid lipase deficiency)
- Endocrine disorders
  - Such as polycystic ovary syndrome, hypothyroidism or growth hormone deficiency
- Drug-related causes
  - Such as amiodarone, methotrexate or tamoxifen
- Other causes
  - Jejunoileal bypass, starvation or total parenteral nutrition

HEPATOLOGY VOL. 65, NO. 5, 2017

Increased Risk of Mortality by Fibrosis Stage in Nonalcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis

Parambir S. Dulai,[1,2] Siddharth Singh,[1,2] Janki Patel,[1] Meera Soni,[1] Larry J. Prokop,[3] Zobair Younossi,[4] Giada Sebastiani,[5] Mattias Ekstedt,[6] Hannes Hagstrom,[7] Patrik Nasr,[6] Per Stal,[7] Vincent Wai-Sun Wong,[8] Stergios Kechagias,[6] Rolf Hultcrantz,[7] and Rohit Loomba[1,2]

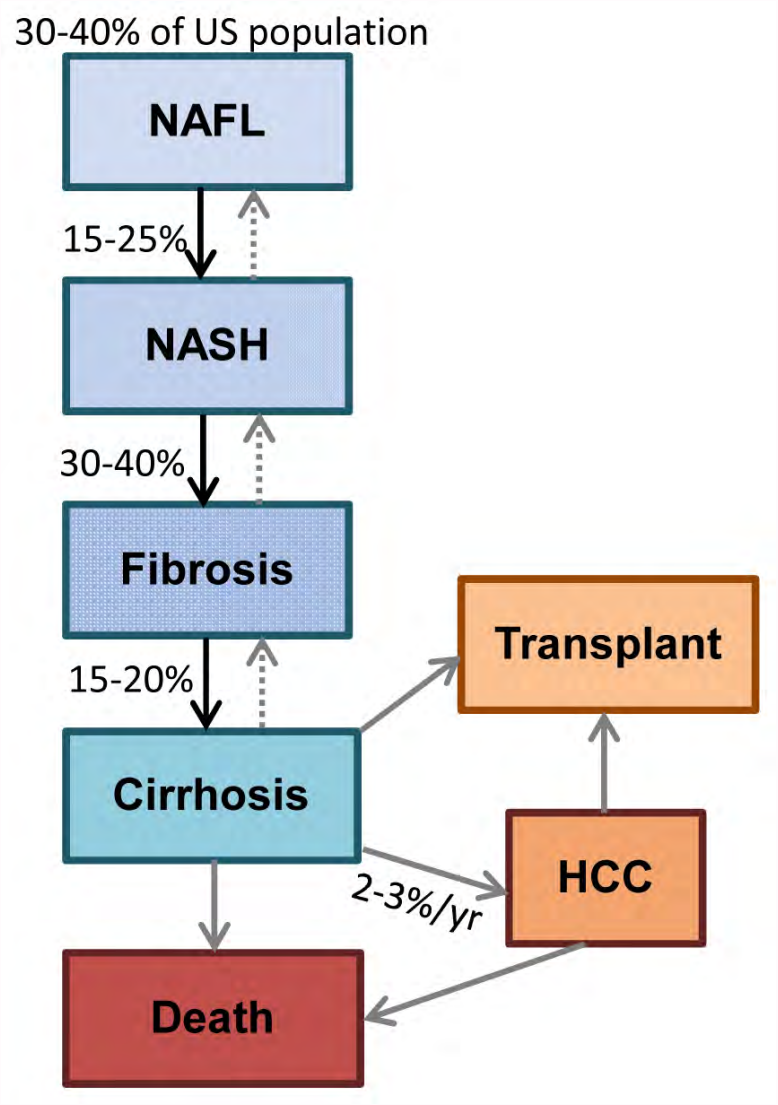




Mayo Clin Proc. 2015 September ; 90(9): 1233–1246.

Recommendations for Diagnosis, Referral for Liver Biopsy, and Treatment of NAFLD and NASH

Erin K Spengler, Rohit Loomba



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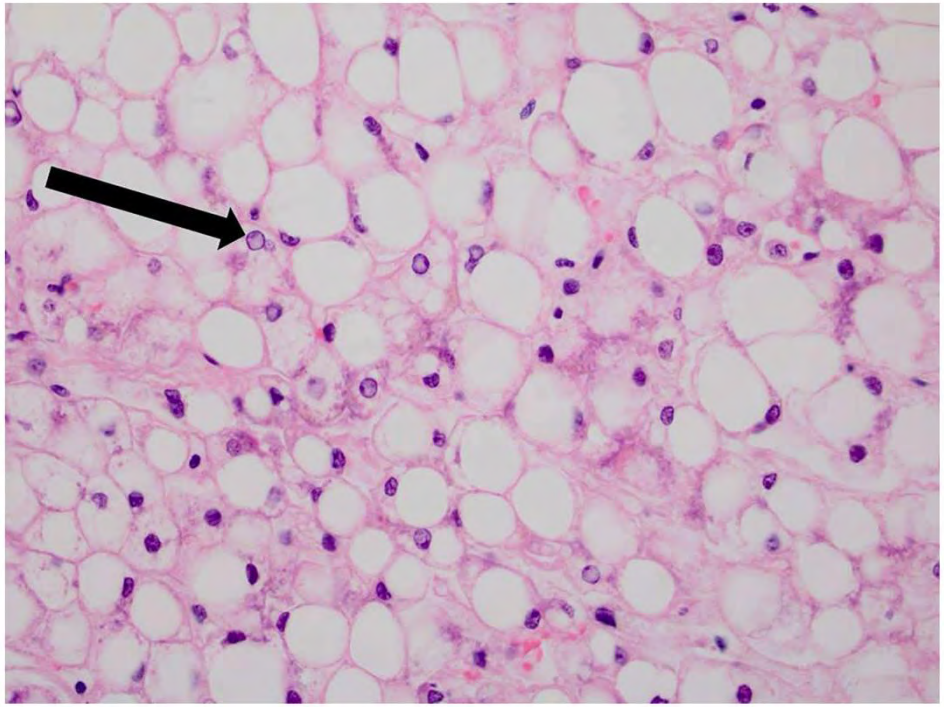
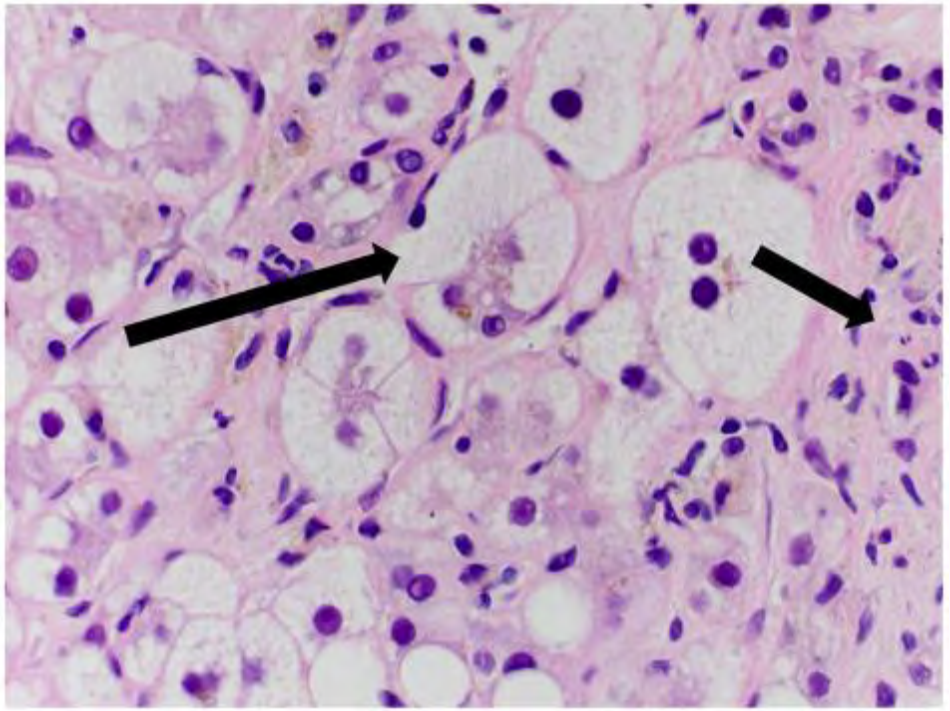


A. 40x H&E image of NAFL Note the severe fatty change, numerous glycogenated nuclei (arrow) and lack of inflammation or balloon degeneration



B. 60x H&E image of NASH In addition to significant steatosis, there is evidence of ballooned hepatocytes (long arrow) and mixed inflammation including neutrophils (short arrow).

Mayo Clin Proc. 2015 September ; 90(9): 1233–1246.

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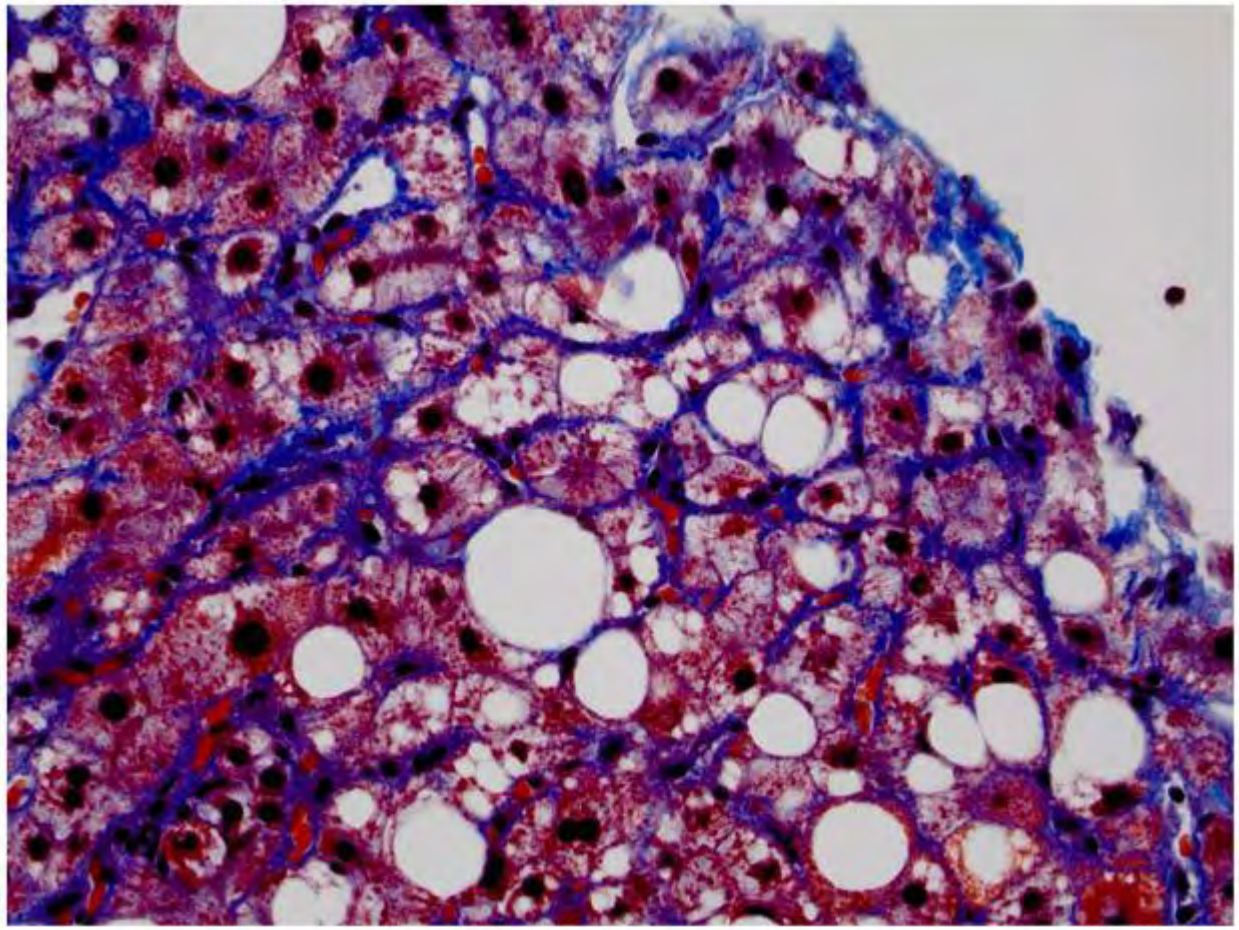

40x Klatskin trichrome stain image of NASH On this Klatskin stain the sinusoidal fibrosis characteristic of NASH is evident (zone 3).

Mayo Clin Proc. 2015 September ; 90(9): 1233–1246.

Recommendations for Diagnosis, Referral for Liver Biopsy, and Treatment of NAFLD and NASH

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Medication	Indications	Contraindications	Limitations	Side Effects
Pioglitazone	Primary treatment of biopsy-proven NASH in patients with or without DM Treatment of DM in NAFLD patients	Symptomatic heart failure	May increase risk of bladder cancer	Weight gain, bone loss, GI upset, fatigue, lower extremity edema
Vitamin E	Primary treatment of biopsy-proven NASH in patients without DM	History of prostate cancer, bleeding disorder	May increase all-cause mortality, risk of prostate cancer Not tested in patients with DM	Increased risk of bleeding and hemorrhagic stroke
Metformin	Treatment of DM and insulin resistance in NAFLD patients	Renal failure	Not a primary treatment for NASH	Diarrhea, lactic acidosis, GI upset
Obeticholic acid	Primary treatment of biopsy-proven NASH in DM and non-DM patients	Not currently commercially available	Not FDA approved or available outside of clinical trials Long-term safety is not known	Pruritus, hypercholesterolemia
Statin	Treatment of hyperlipidemia in NAFLD patients	Excessive alcohol use, hypersensitivity to statin class	Not a primary treatment for NASH	Myalgias, GI upset, mild transaminitis, rare liver injury or myopathy

Mayo Clin Proc. 2015 September ; 90(9): 1233–1246.

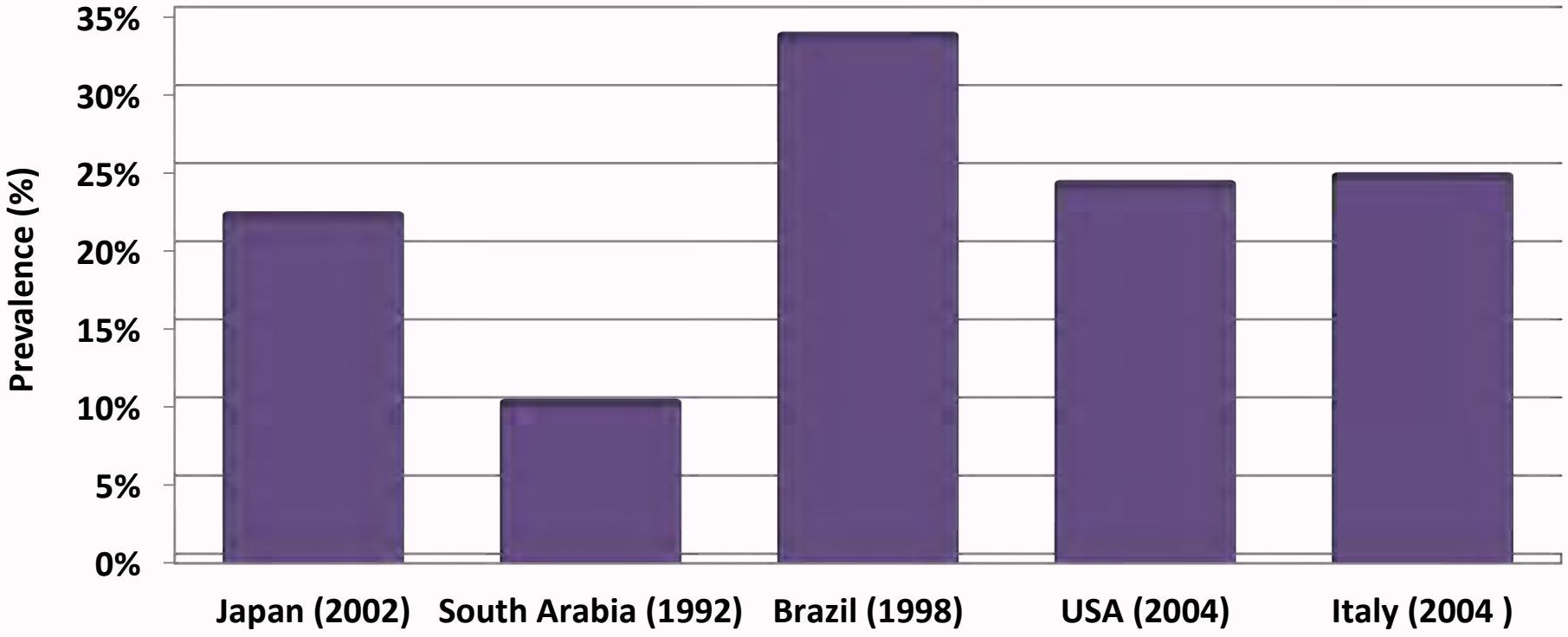
Recommendations for Diagnosis, Referral for Liver Biopsy, and Treatment of NAFLD and NASH

Erin K Spengler, Rohit Loomba

Recommended Management of Patients with NAFLD[a]

1. Recommend lifestyle modification:
   - a. Weight loss of at least 5–10% of total body weight
   - b. Aerobic exercise 3–5 times a week
   - c. Minimization of alcohol use (no more than 1 drink/day for women, or 2 drinks/day for men)
2. Assess cardiovascular risks: lipid profile, fasting glucose and/or Hgb A1c, waist circumference, BMI
3. Manage comorbidities, including: diabetes, dyslipidemia, hypertension, cardiovascular disease
4. Discontinue medications that may worsen steatosis: corticosteroids, amiodarone, methotrexate, tamoxifen, estrogens, tetracyclines, valproic acid
5. Obtain baseline liver evaluation, including: liver ultrasound, CBC, liver panel (AST, ALT, bilirubin, alkaline phosphatase), INR and creatinine
6. Consider referral for liver biopsy, if:
   - a. Patient has risk factors for NASH and advanced fibrosis, including diabetes[b] and/or metabolic syndrome
   - b. Patient has findings concerning for cirrhosis, such as thrombocytopenia, AST>ALT or hypoalbuminemia
   - c. Patients is undergoing cholecystectomy or bariatric surgery and intraoperative biopsy is low risk
7. Consider pharmacotherapy if patient has biopsy-proven NASH without cirrhosis and no absolute contraindications
8. Obtain appropriate screening if patient has known cirrhosis:
   - a. Right upper quadrant ultrasound every 6 months for HCC screening (refer to AASLD guidelines)
   - b. EGD screening for esophageal varices (refer to AASLD guidelines)
   - c. Referral to transplant center when appropriate (refer to AASLD guidelines)

Prevalence


Prevalence (%)
35%
30%
25%
20%
15%
10%
5%
0%
Japan (2002)
South Arabia (1992)
Brazil (1998)
USA (2004)
Italy (2004)