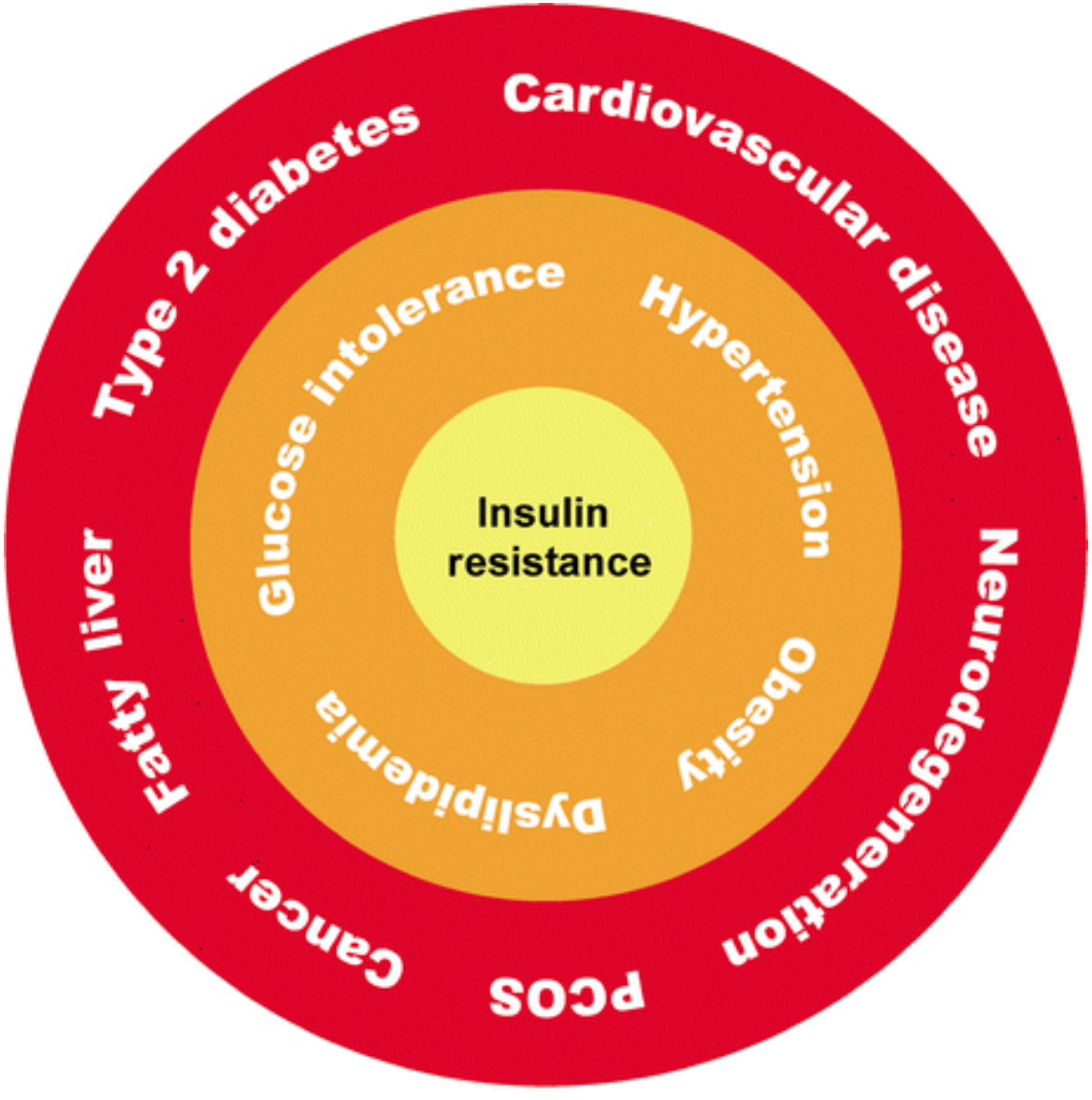
Dalla NASH alla sindrome metabolica: sintomatologia e quadro clinico

Steatosi epatica: malattia emergente
10 Maggio 2014 – Centro Analisi Monza

Elisabetta Bugianesi MD, PhD
Division of Gastro-Hepatology,
University of Turin, Italy.

Metabolic Syndrome: what is it?



Biddinger SB, Kahn CR. 2006.
Annu. Rev. Physiol. 68:123–58

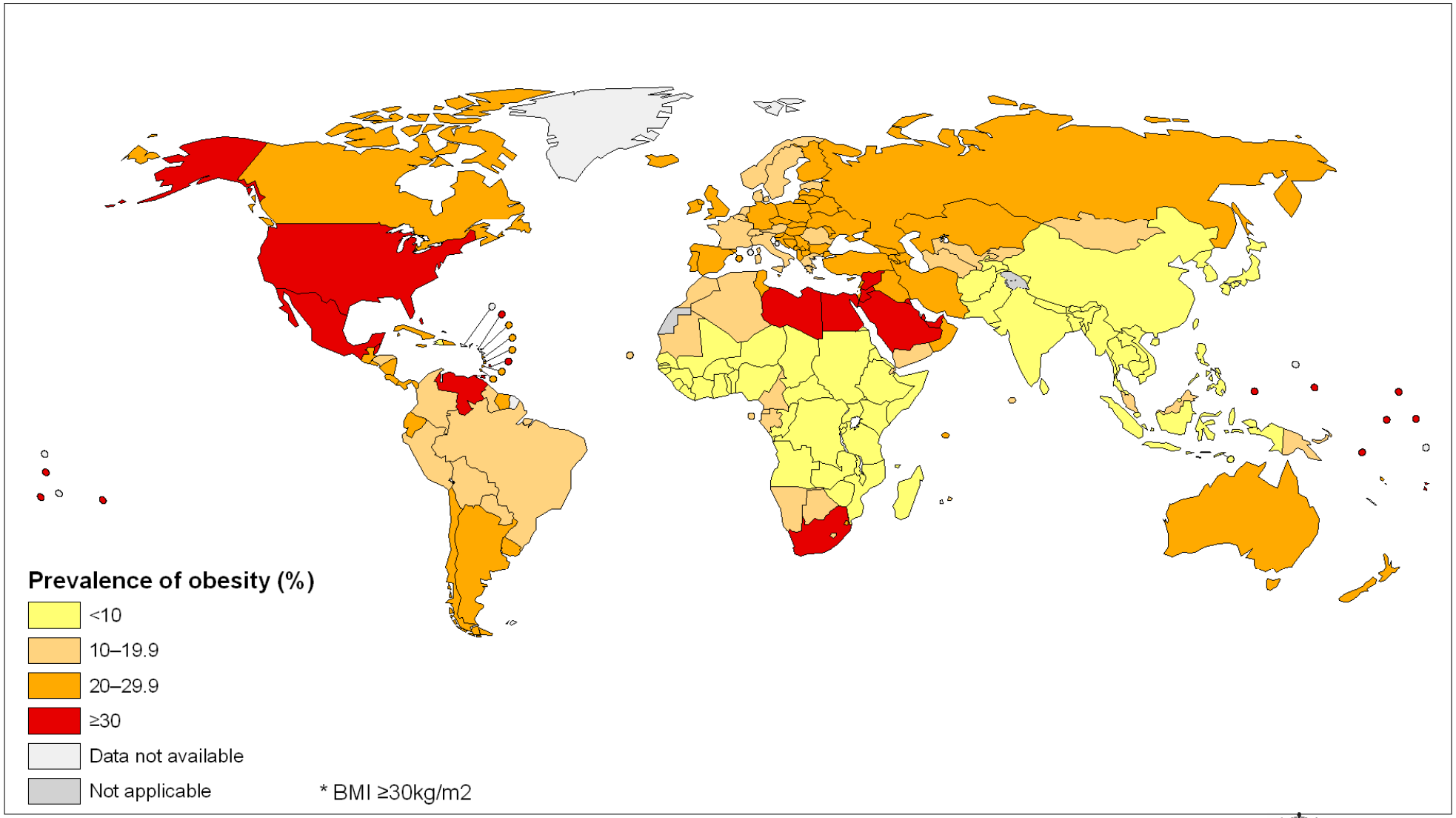
A Consensus Definition of the Metabolic Syndrome

Any 3 out of the following 5 criteria:

Measure	Categorical Cut Points
Elevated waist circumference	Population-specific definitions (>94 cm in males; >80 cm in females)
Elevated triglycerides (or on treatment)	>150 mg/dL (1.7 mmol/L)
Reduced HDL-C (or on treatment)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (or on treatment)	Systolic 130 and/or diastolic 85 mm Hg
Elevated fasting glucose (or on treatment)	>100 mg/dL

Alberti et al, Circulation. 2009 Oct 20;120(16):1640-5

Prevalence of obesity*, ages 20+, age standardized
Both sexes, 2008



Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

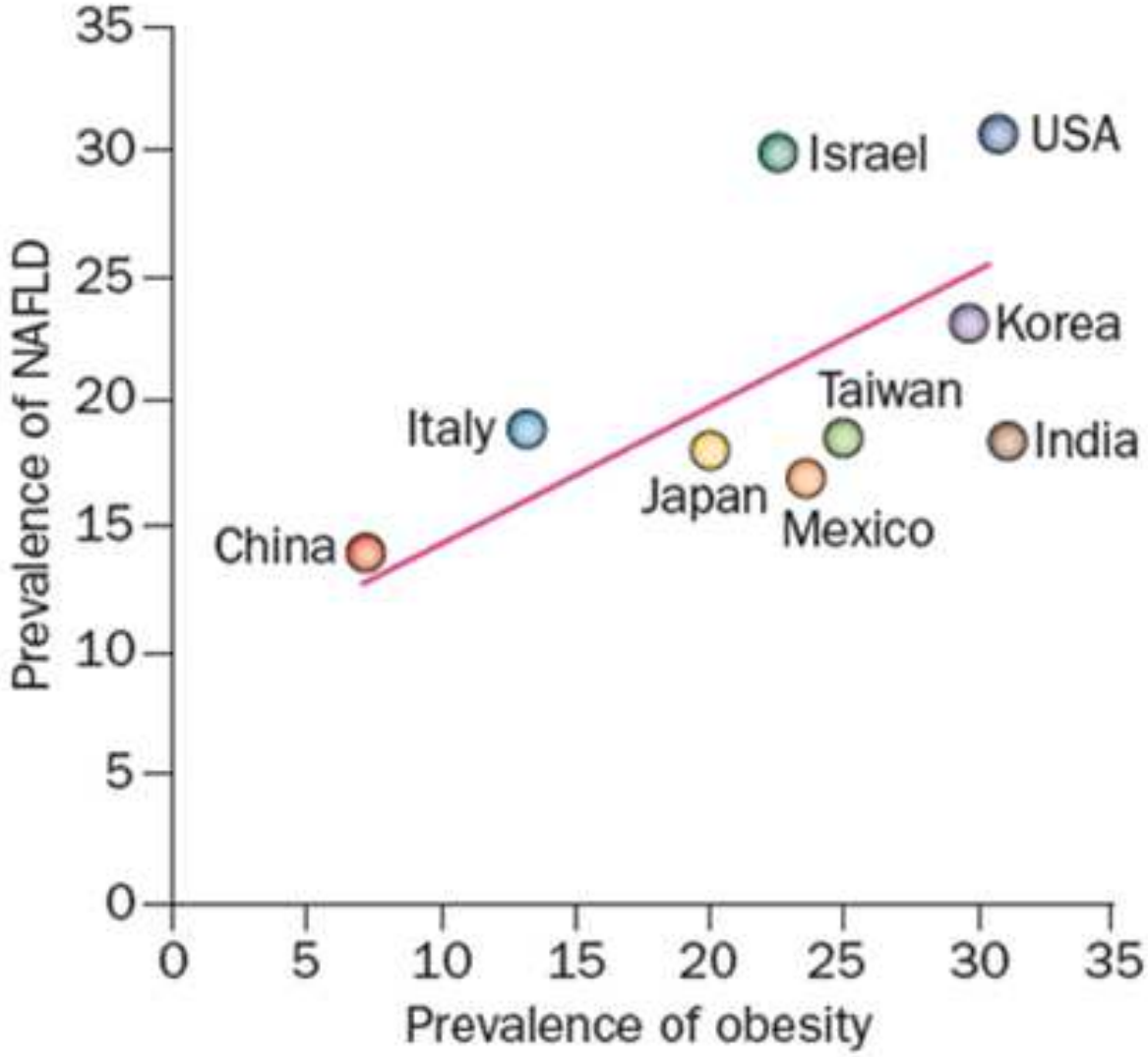
World Health Organization

Cause-specific mortality versus baseline BMI in the ranges 15–25 kg/m^2 and 25–50 kg/m^2

	15–25 kg/m^2		25–50 kg/m^2	
	Deaths	HR (95% CI)	Deaths	HR (95% CI)
Ischaemic heart disease	7461	1·22 (1·13–1·32)	10 783	1·39 (1·34–1·44)
Stroke	2964	0·92 (0·82–1·03)	3164	1·39 (1·31–1·48)
Other vascular disease	2648	0·84 (0·75–0·95)	3396	1·47 (1·39–1·56)
Diabetes	171	0·96 (0·59–1·55)	393	2·16 (1·89–2·46)
Kidney disease	197	1·14 (0·74–1·77)	217	1·59 (1·27–1·99)
Liver disease	489	0·69 (0·52–0·91)	603	1·82 (1·59–2·09)
Lung cancer	2959	0·71 (0·63–0·79)	2040	0·98 (0·88–1·09)
Upper aerodigestive cancer	685	0·49 (0·39–0·61)	471	0·98 (0·79–1·20)
Other specified cancer	6134	0·94 (0·87–1·02)	6190	1·12 (1·06–1·18)
Respiratory disease*	2426	0·31 (0·28–0·35)	1344	1·20 (1·07–1·34)
Other specified disease	2049	0·62 (0·54–0·71)	1823	1·20 (1·10–1·31)
External cause	2112	0·82 (0·71–0·95)	1720	1·19 (1·08–1·32)
Unknown cause†	4961	0·72 (0·66–0·79)	5349	1·22 (1·16–1·28)
All causes	35 256	0·79 (0·77–0·82)	37 493	1·29 (1·27–1·32)

Prospective Studies Collaboration: psc@ctsu.ox.ac.uk, LANCET 2009

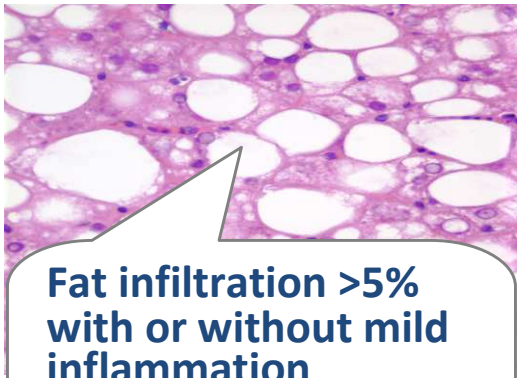
The prevalence of NAFLD as a function of the prevalence of obesity in various countries



Lazo et al. Semin. Liver Dis. 2008

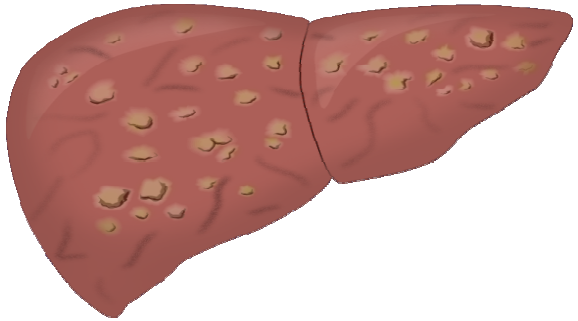
The Spectrum of NAFLD

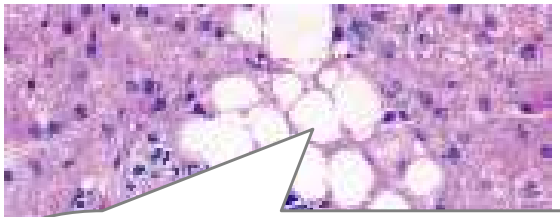
Fatty Liver



Fat infiltration >5% with or without mild inflammation

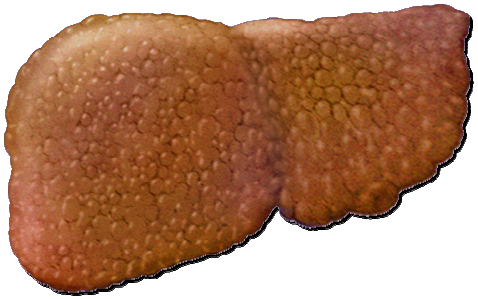
NASH

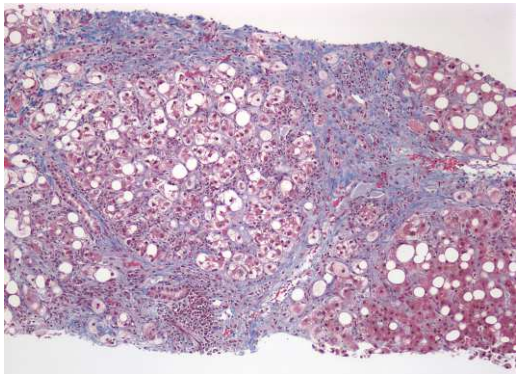




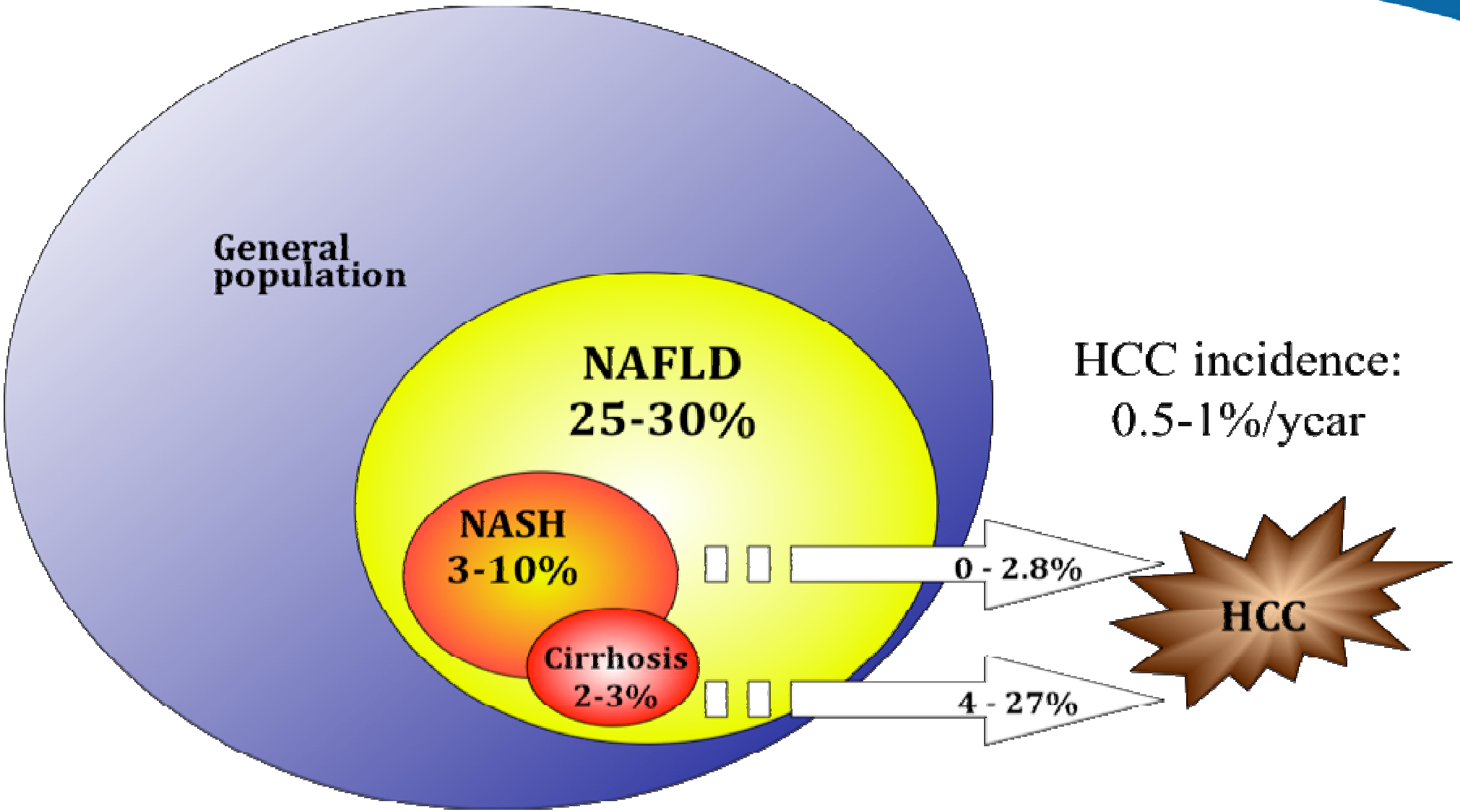
Steatosis + necro-inflammatory changes (ballooning degeneration, Mallory bodies, megamitochondria) and/or fibrosis

Cirrhosis

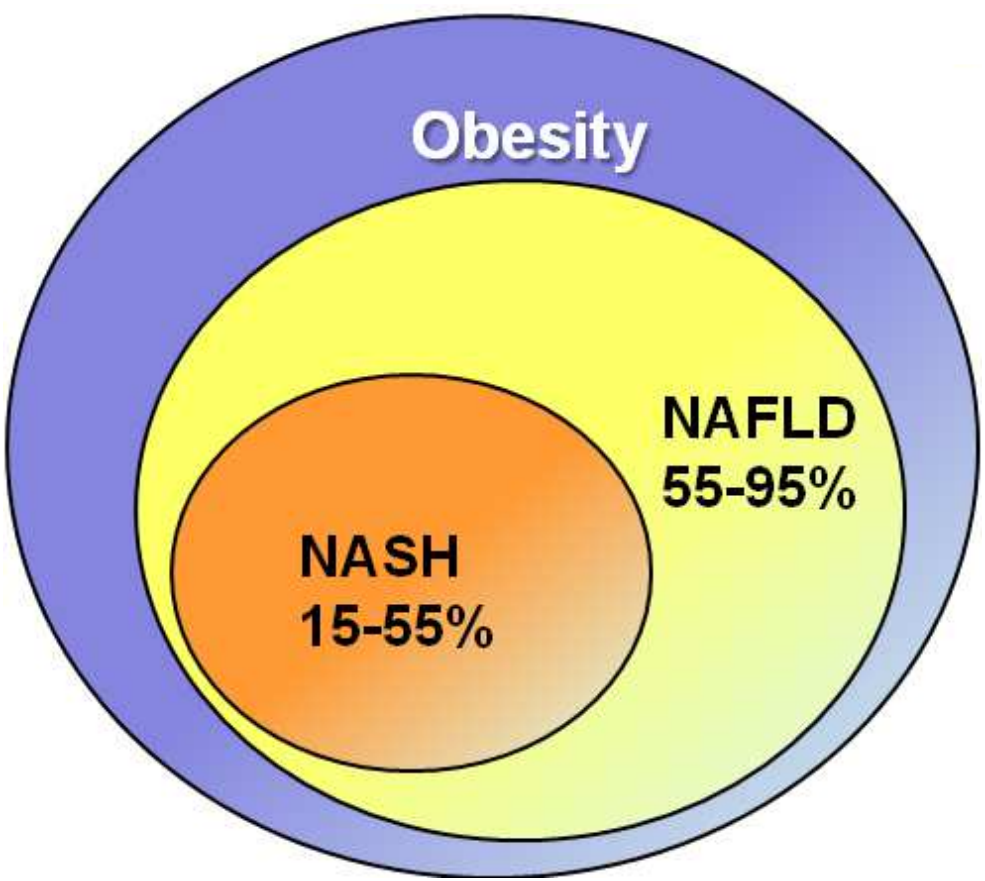


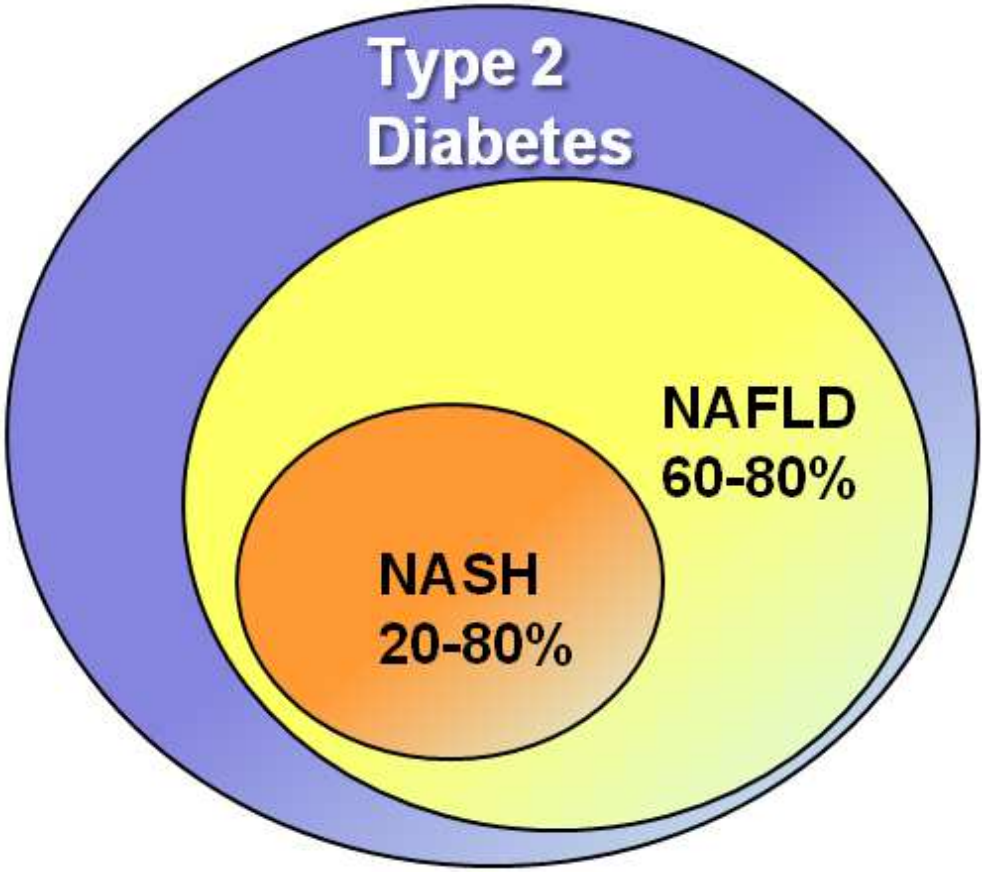


NAFLD/NASH: the burden of disease in the general population



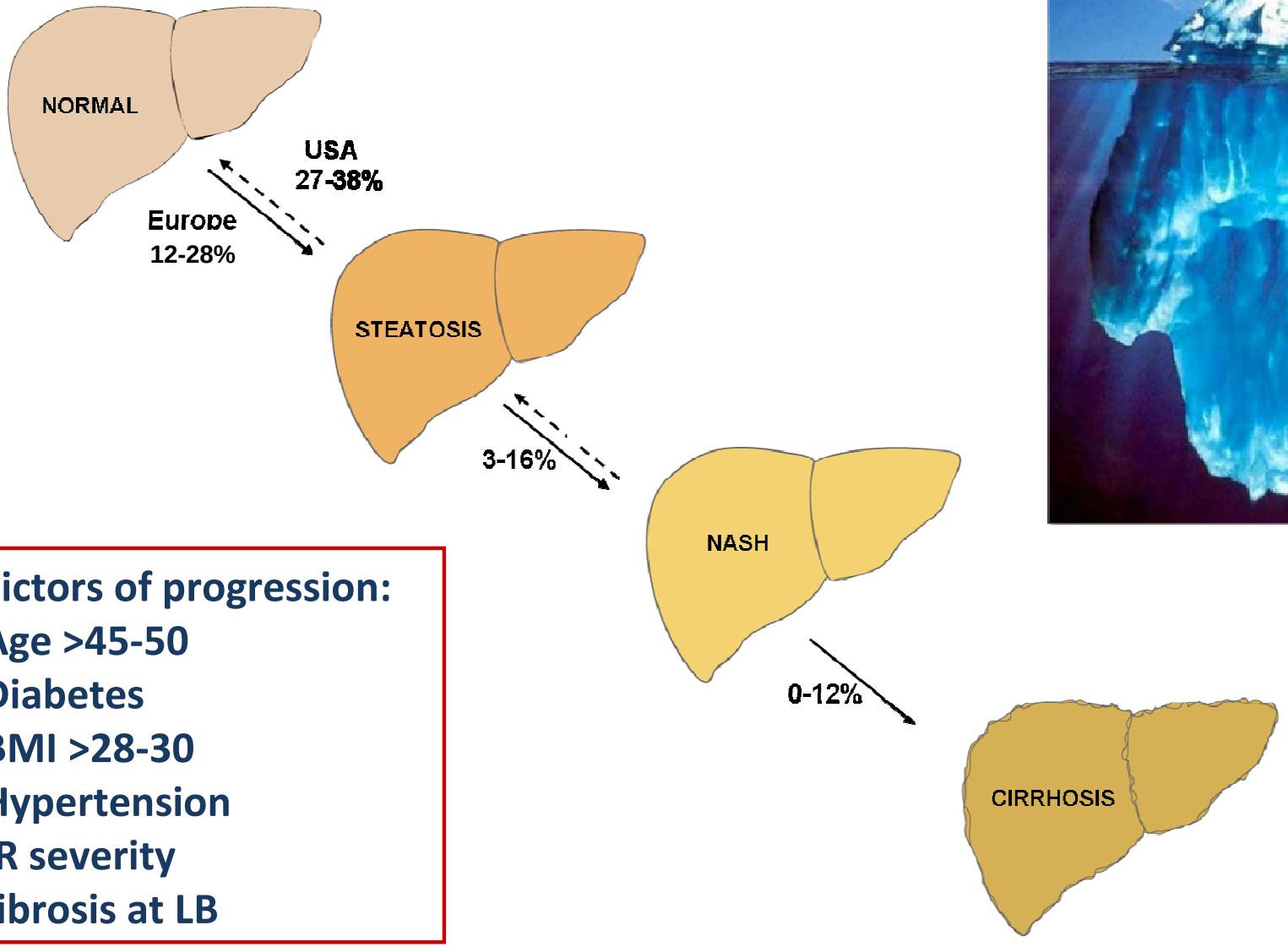
The average prevalence of NAFLD and NASH in high-risk groups

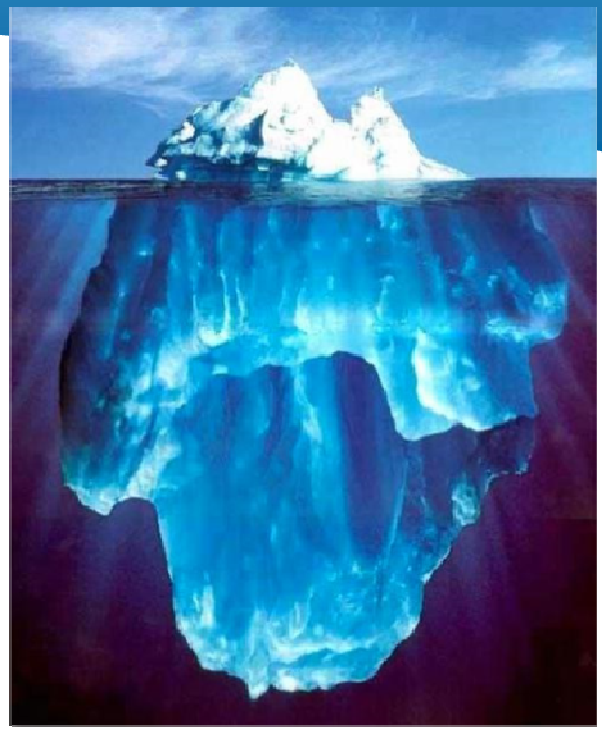




Bhala et al Curr Pharma Des 2013

Risk Stratification for progressive liver disease

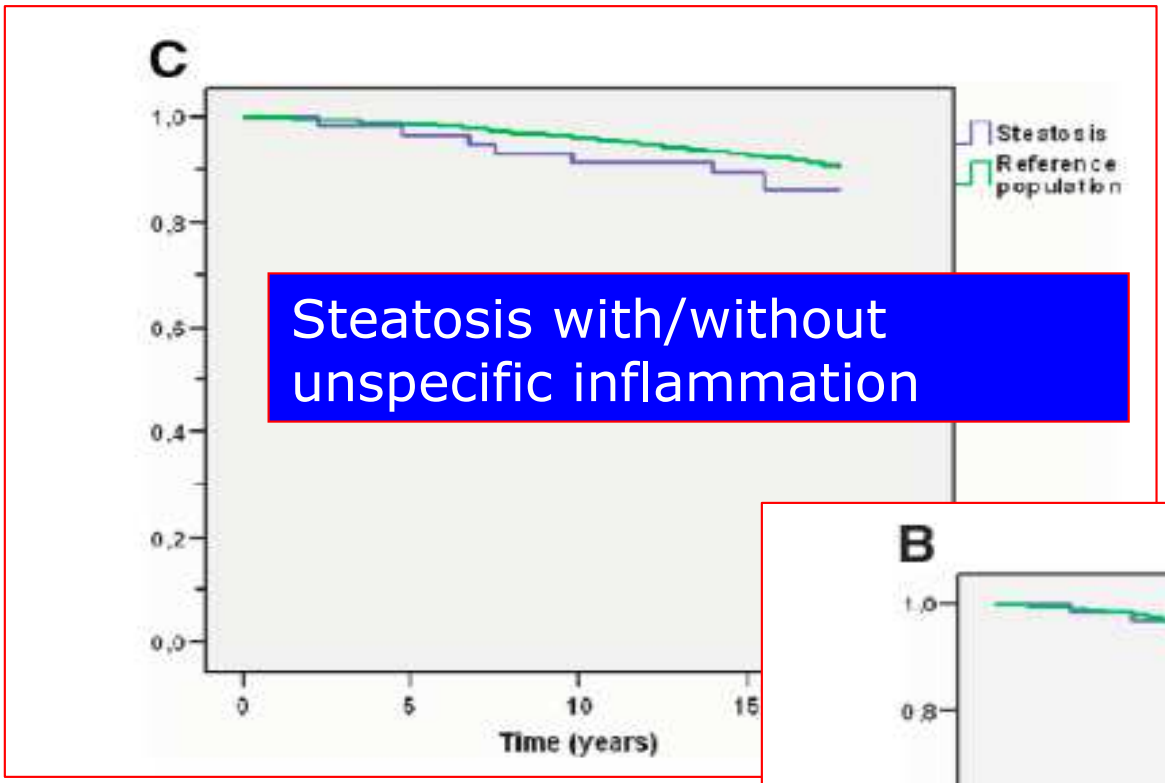




Predictors of progression:

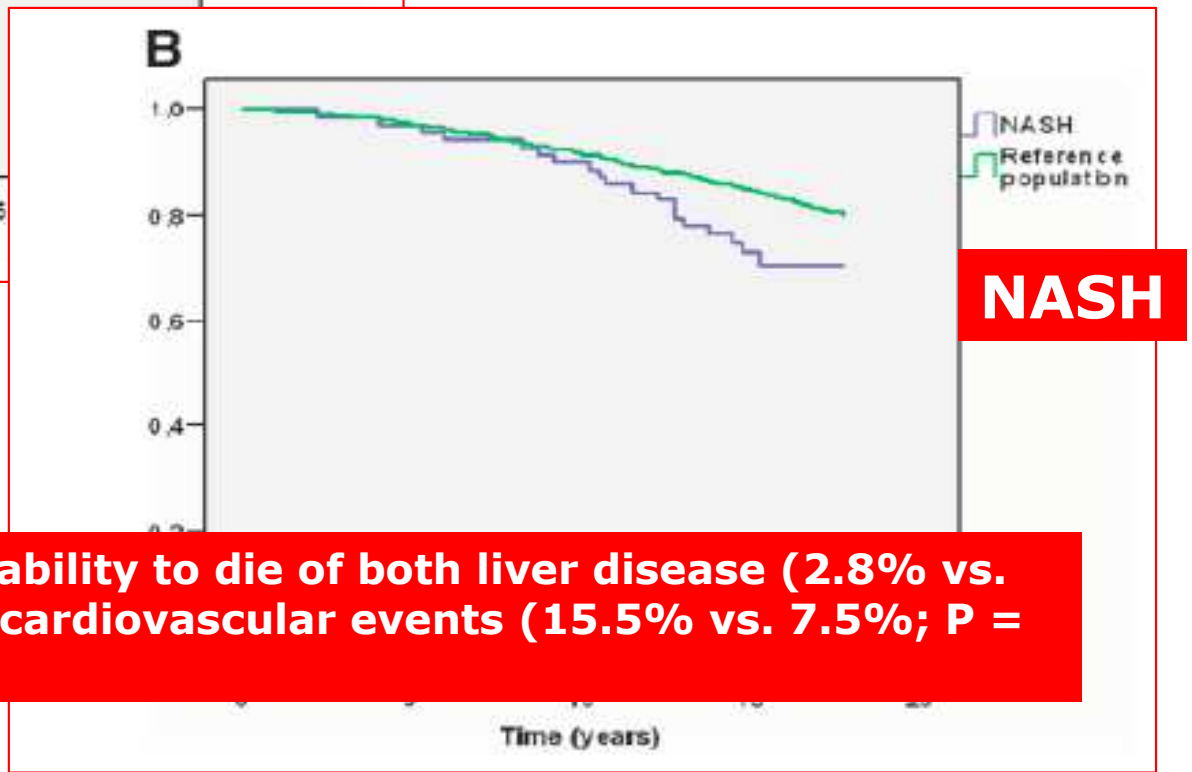
- ✓ Age >45-50
- ✓ Diabetes
- ✓ BMI >28-30
- ✓ Hypertension
- ✓ IR severity
- ✓ fibrosis at LB

Overall and liver-related mortality depends on NAFLD histology



Steatosis with/without unspecific inflammation

129 NAFLD
Mean f-up, 13.7 yrs

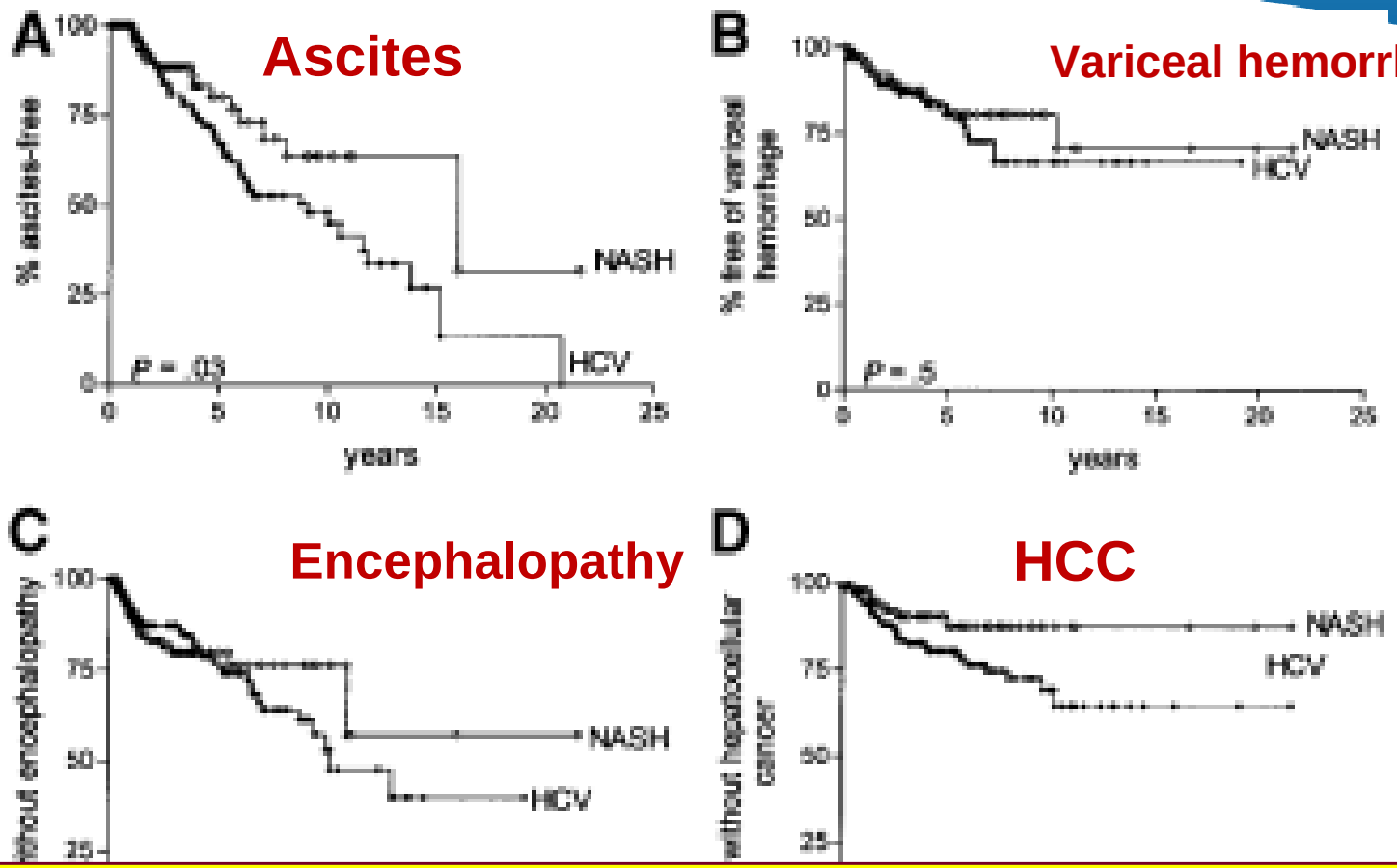


NASH

Ekstedt, Hepatology 2008

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)

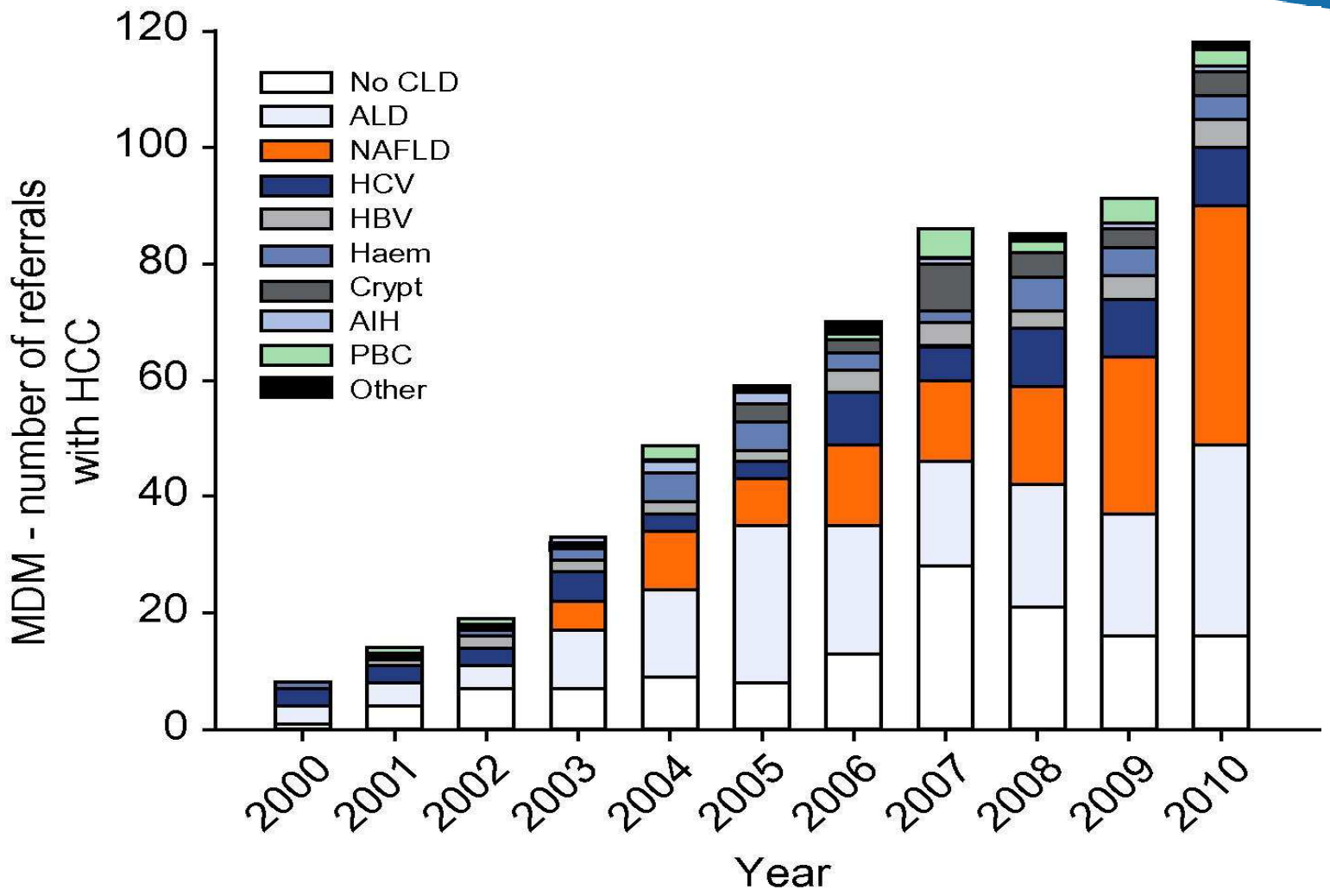
Long-term risks of developing complications of cirrhosis in NASH and HCV



Patients with NASH had a higher cardiac mortality (8/152 vs 1/150)

Sanyal, Hepatology 2006

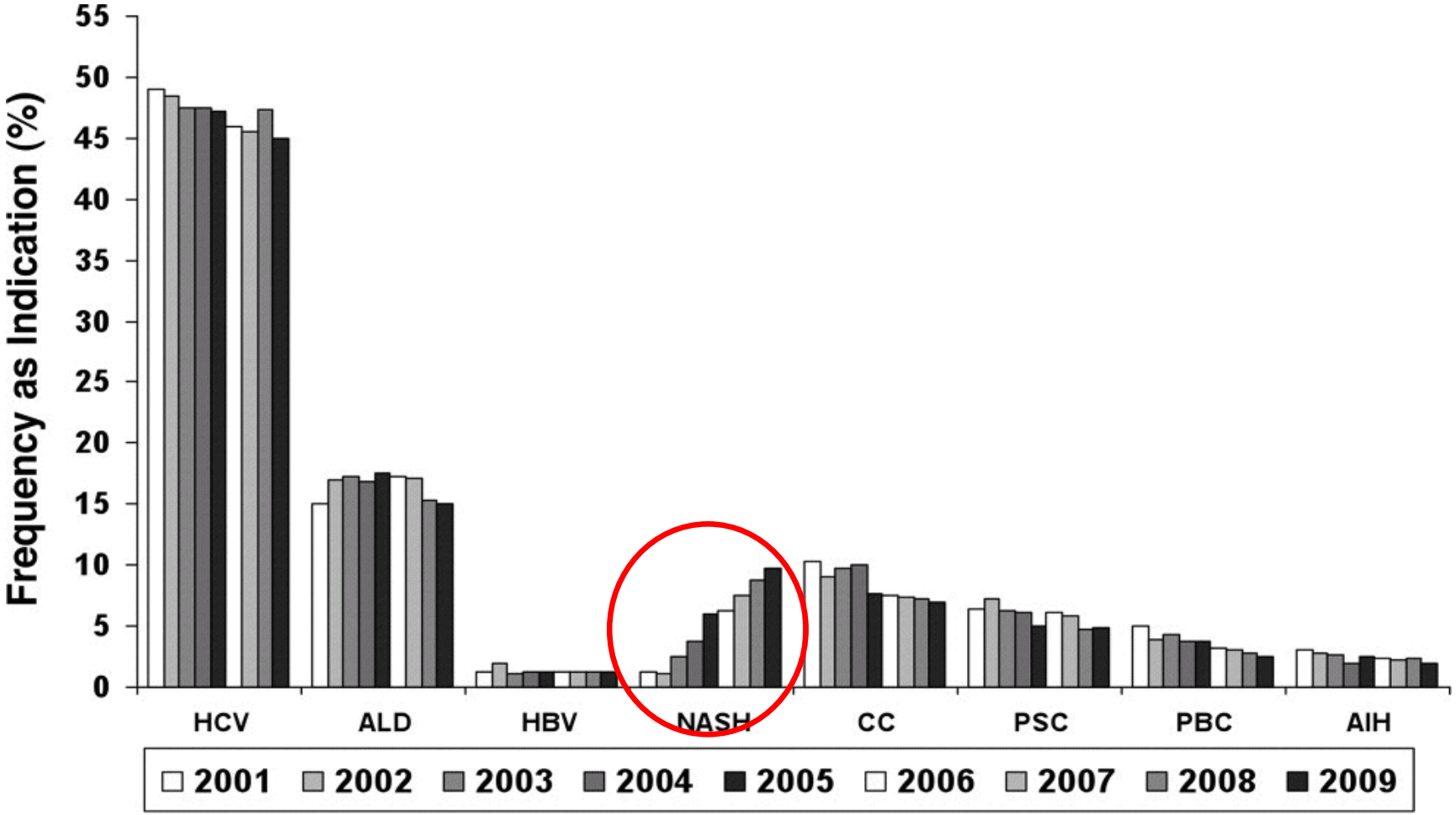
NAFLD is now the commonest cause of HCC in the North East UK



Patients with NAFLD associated HCC had a higher incidental presentation (38.2%) and lower prevalence of cirrhosis (77.2%).

Dyson et al J Hepatology 2013

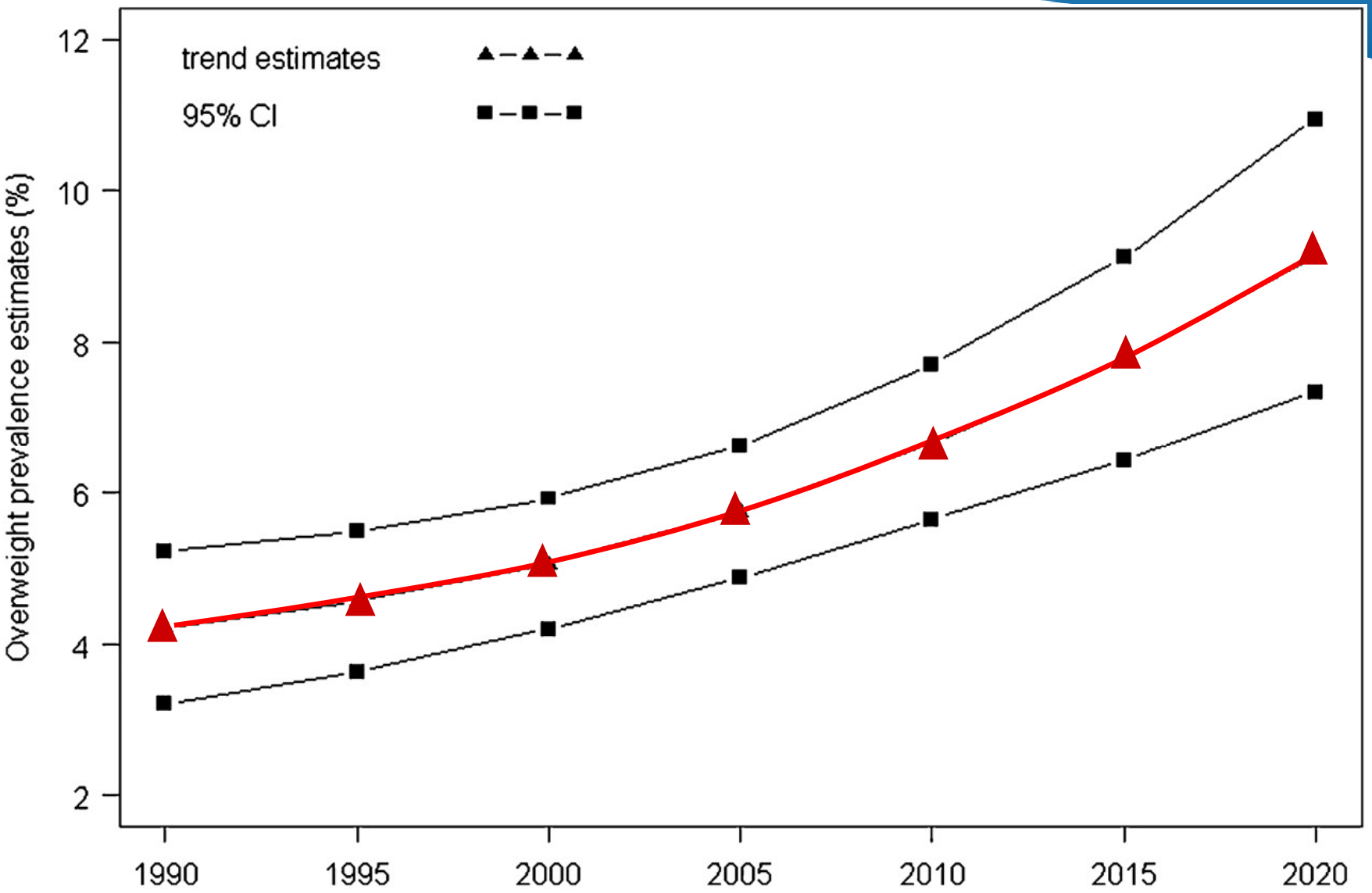
NASH is the 3rd most common indication for OLTx in the US and is the only indication increasing



Data Source: SRTR

Charlton Gastroenterology 2011

Global prevalence and trends of overweight and obesity among preschool children



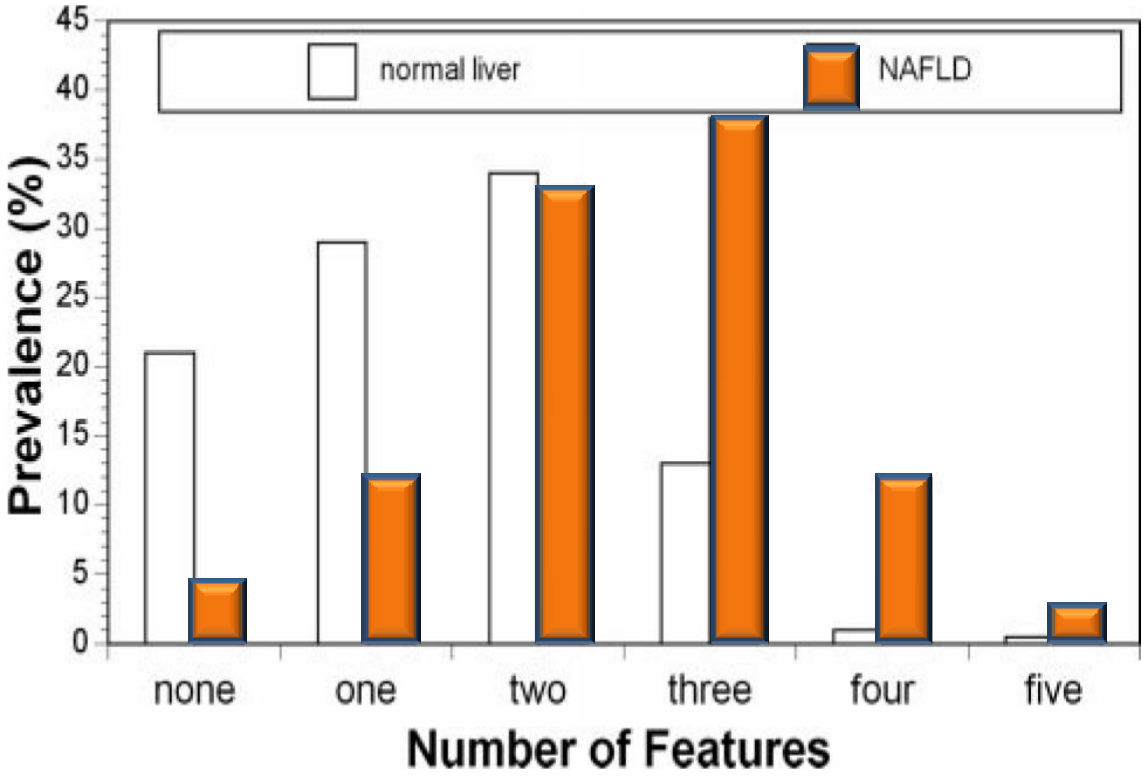
de Onis M et al. Am J Clin Nutr 2010

The burden of NAFLD in children

- ✓ Pediatric NAFLD prevalence by LFT or US in population-based studies 2.6–7.1% of children
- ✓ In overweight or obese children: from 8 to 42% (by ALT) or from 1.7 to 77% (by US)

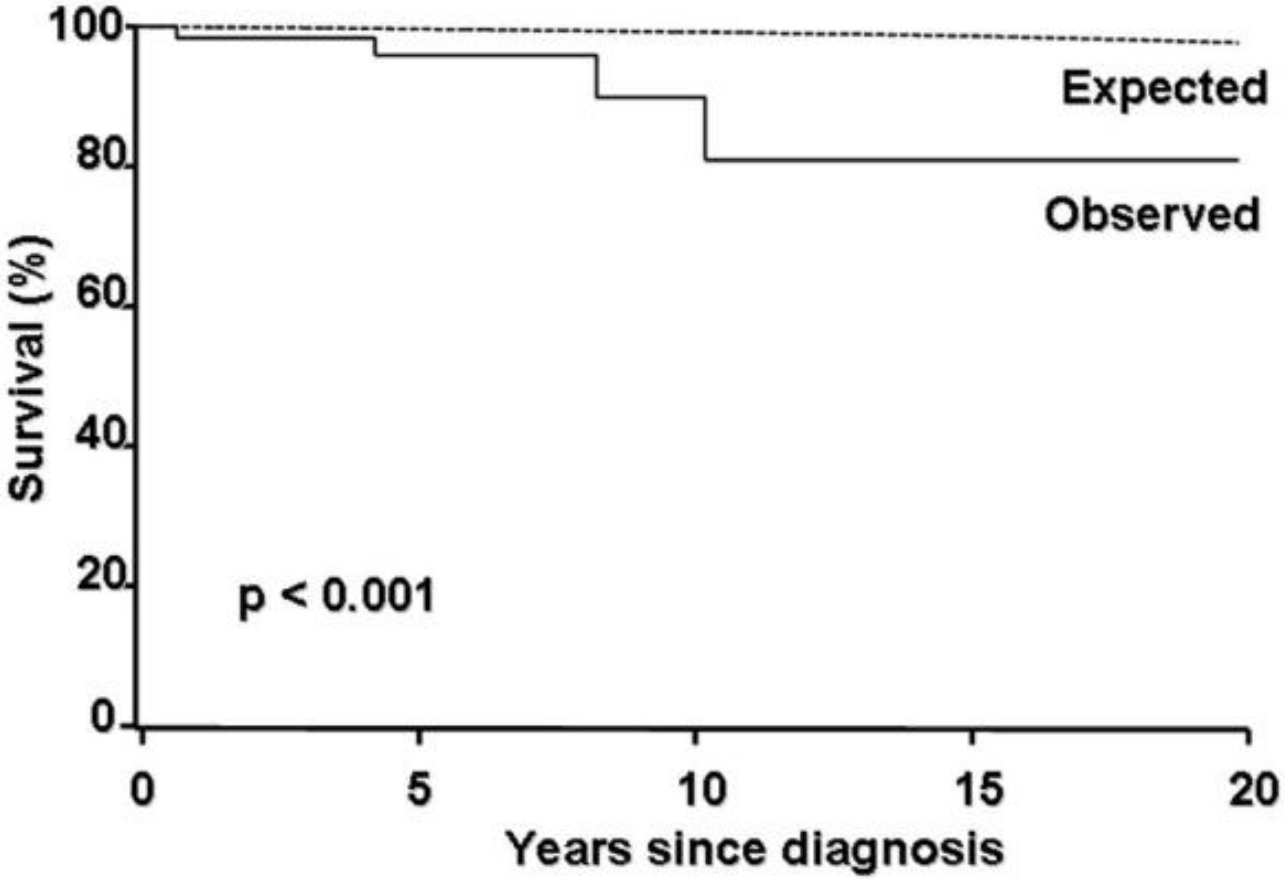
  Nobili J Hepatol 2013
- ✓ The prevalence of histological NAFLD:
  - 0.7% in 2–4 year old
  - 17.3% in 15–19 year old
  - 38% in obese

    Schwimmer et al. Pediatrics, 2006



Dixon et al, Gastroenterology, 2001

Kaplan-Meier survival curve of children with NAFLD as compared to the general United States population of same age and sex



Standardized mortality ratio: 13.6

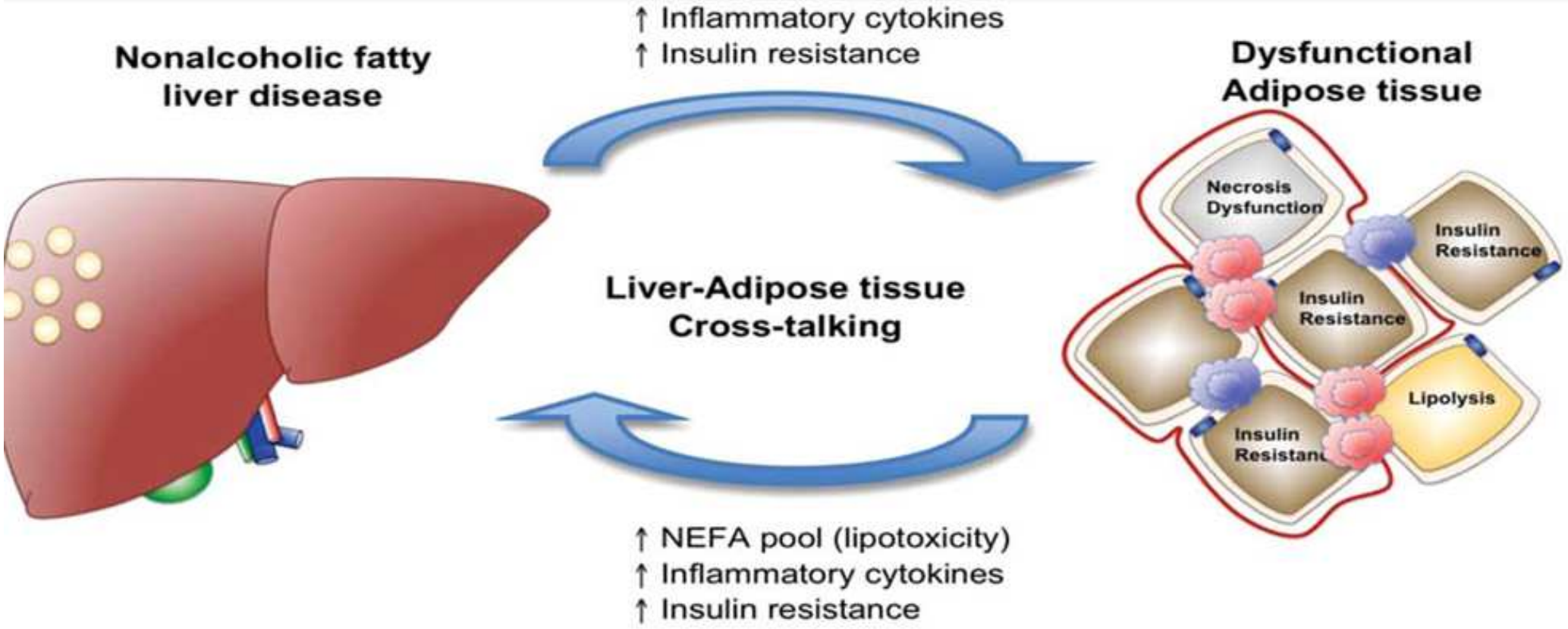
Feldstein et al Gut 2009

Mechanisms and clinical implications

The impact of the MS on NAFLD

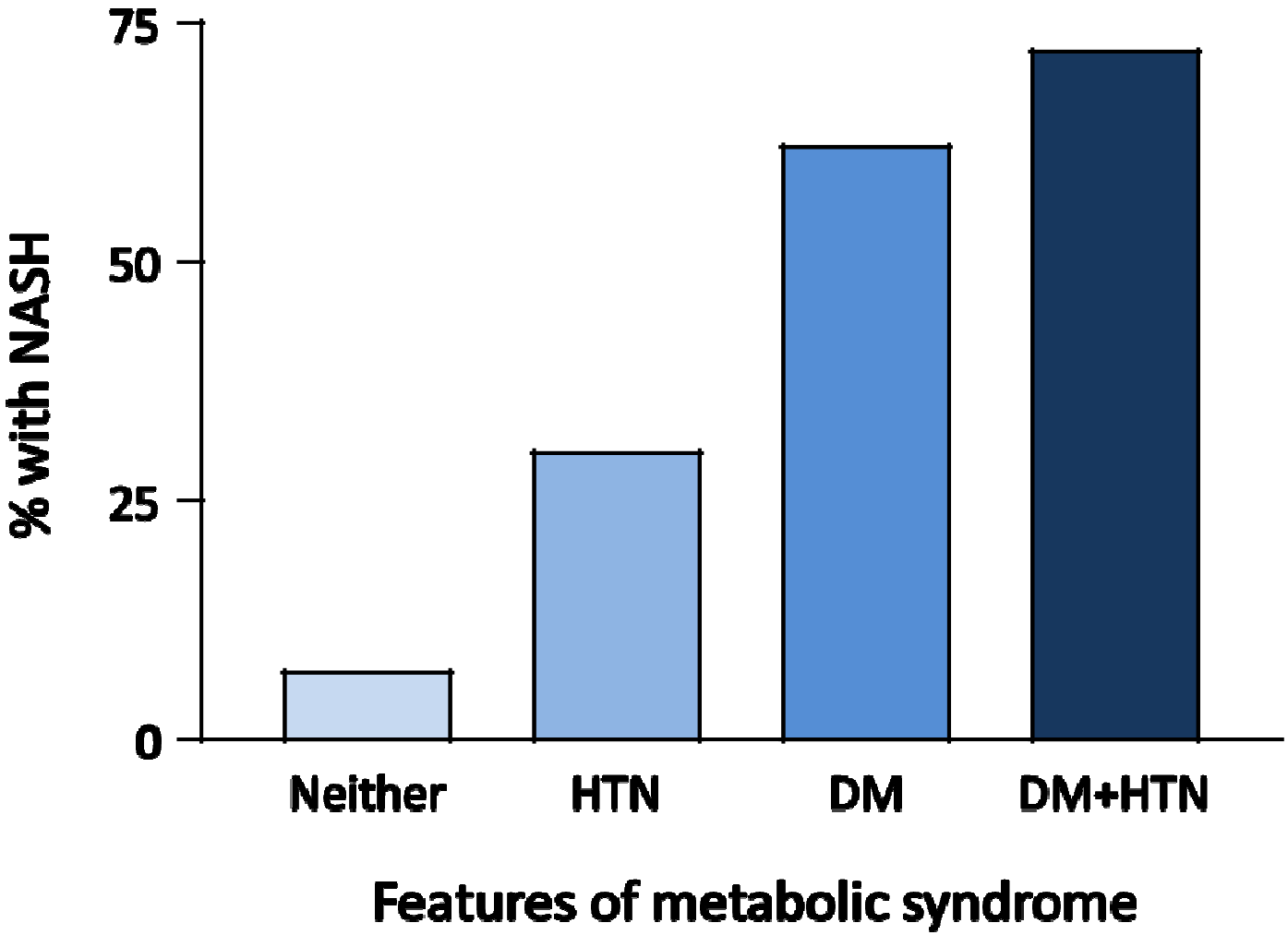
The impact of NAFLD on the MS

MS and NAFLD: Mechanisms of hepatic damage



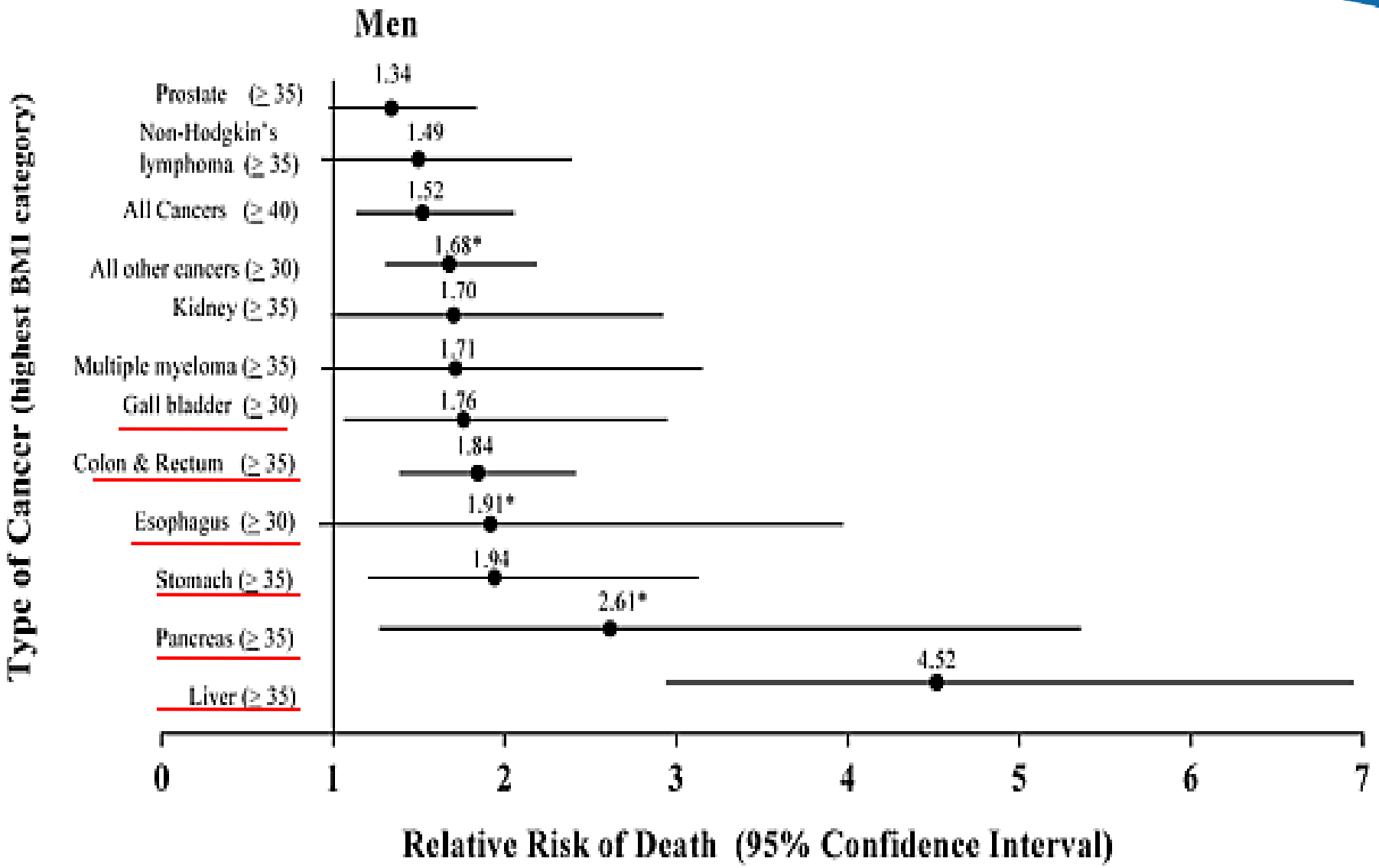
Armstrong et al, Hepatology 2014

The severity of NAFLD is associated with the severity of the metabolic syndrome in adults



Dixon et al, Gastroenterology, 2001

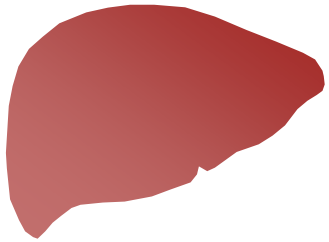
Obesity and MS increase the risk of HCC and GI cancers



Calle EE et al N Engl J Med 2003

A Fatty Liver overproduces glucose

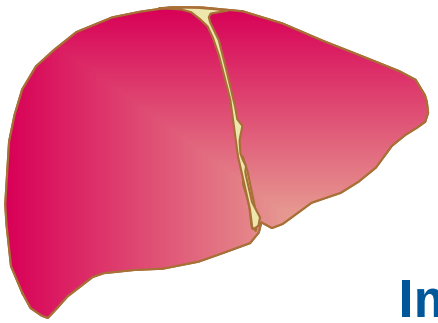
Normal



Normal Glucose

Normal insulin action

Insulin resistance

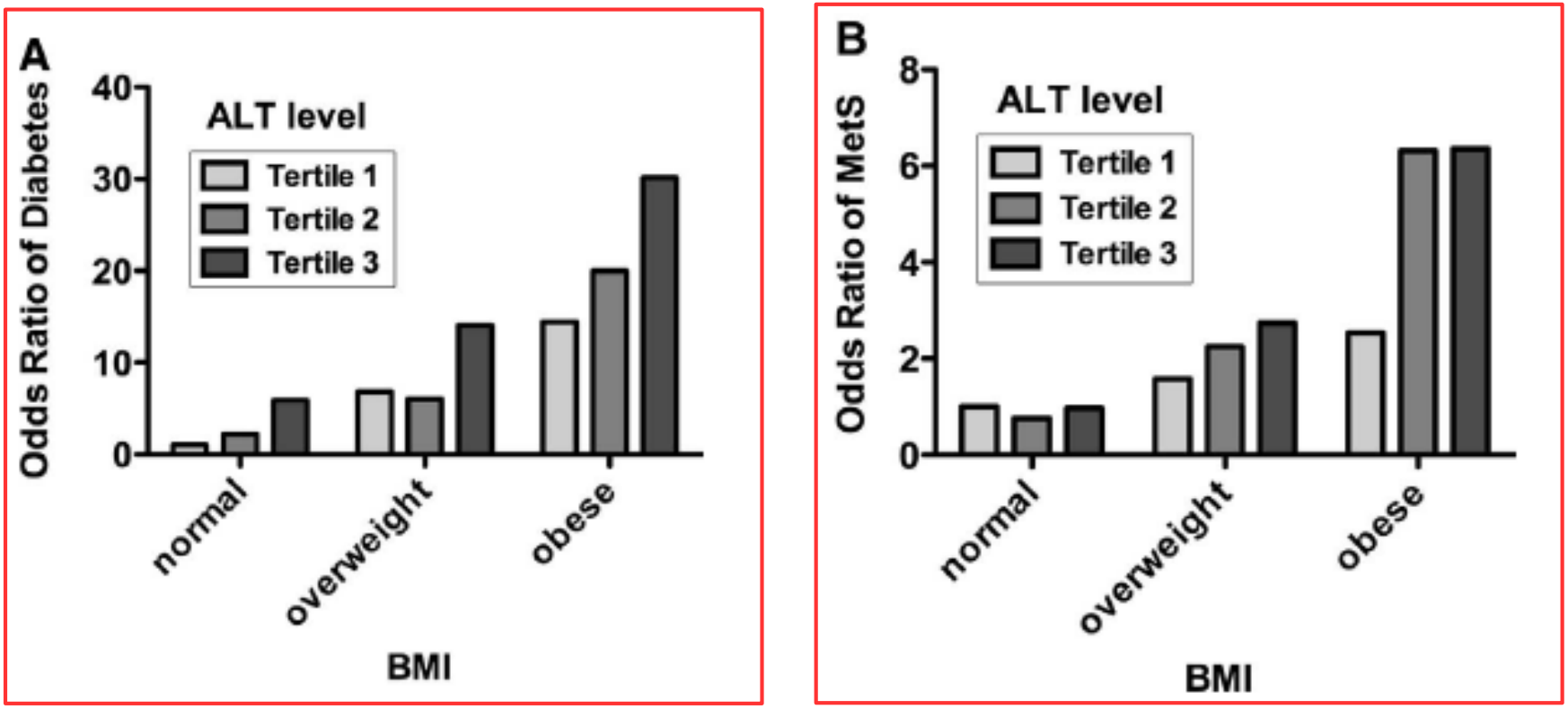


Glucose ↑ → **Insulin ↑↑** → **Glucose N↑ Insulin ↑**

Impaired insulin action to inhibit glucose production

Aminotransferase Levels predicts the 20-Year Risk of Metabolic Syndrome and Type 2 Diabetes

Framingham Offspring Heart study n = 2812, mean age 44 yrs.

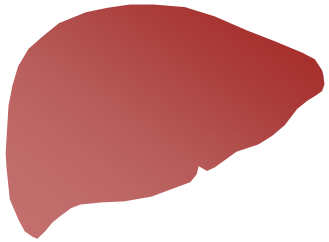


Over 20 yrs of f.u. per 1 standard deviation increase in log ALT level from baseline, increased odds of the development of:

1. Metabolic Syndrome (OR: 1.21,*P* < .001)
2. Diabetes (OR: 1.48; *P* < .0001).

A Fatty Liver overproduces lipids

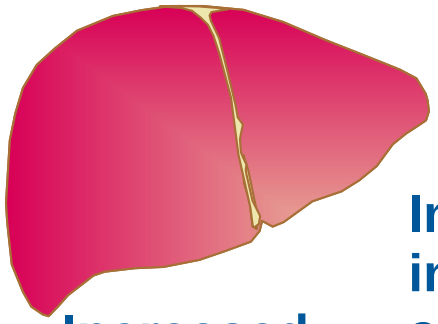
Normal



Normal insulin action

Normal S-TG

Insulin resistance

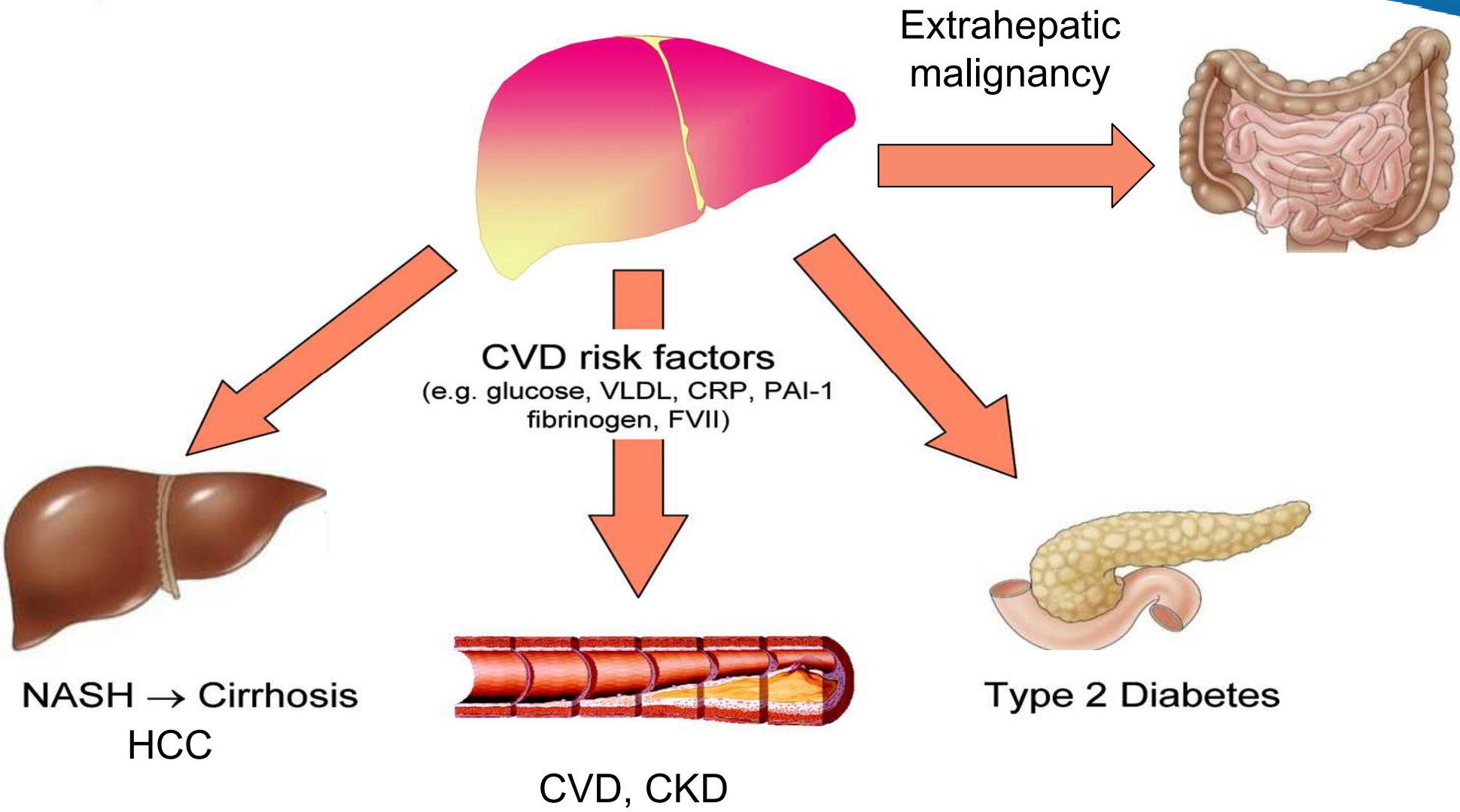


Increased liver fat

Impaired insulin action to inhibit VLDL production

S-Tg ↑ ➡ **HDLchol ↓** ➡ **TG ↑ HDLchol ↓**

NAFLD: RELATED OUTCOMES



Kotronen, Arterioscler Thromb Vasc Biol 2008

Diagnostic workup

History	Physical examination	Laboratory tests
Family occurrence of NAFLD and/or components of the metabolic syndrome	Height (m)	Blood cell count, total proteins and serum protein electrophoresis, PT, PTT, total bilirubin, AST, ALT, GGT, ALP
Alcohol consumption (< 20 g/day)	Weight (kg)	Lipid profile (total cholesterol, HDL-cholesterol, tryglicerides)
Diet	BMI (kg/m^2)	Fasting glucose and insulin
Physical activity	Waist circumference	Markers HBV, HCV
Body weight changes overtime	Arterial pressure	Autoantibodies including Celiac disease
Drugs	Hirsutism (women)	Serum iron, transferrin, ferritin
Exposure to toxins and chemicals	Enlarged liver	Alpha 1-antitrypsin
Changes of the menstrual cycle (PCOS)		Copper, ceruloplasmin
Night-time OSAS		TSH

Diagnosis of NAFLD and NASH

- NAFLD is the commonest diagnosis in patients with “incidental” abnormal LFTs (ALT/ALP/GGT)
  - BUT most patients with NAFLD (~80-90 %) have *normal* LFTs

Browning 2004, Wong 2013

- **Components of Metabolic Syndrome**
- **Ins**
- **Im**
  - –
  - –
  - –

Liver biopsy is the only reliable tool di diagnose NASH

- **Fatty Liver Index (Dyonisos)**
  - BMI, waist circumference, triglycerides and GGT
  - FLI > 60 PPV > 78%; FLI < 20 NPV > 91%.

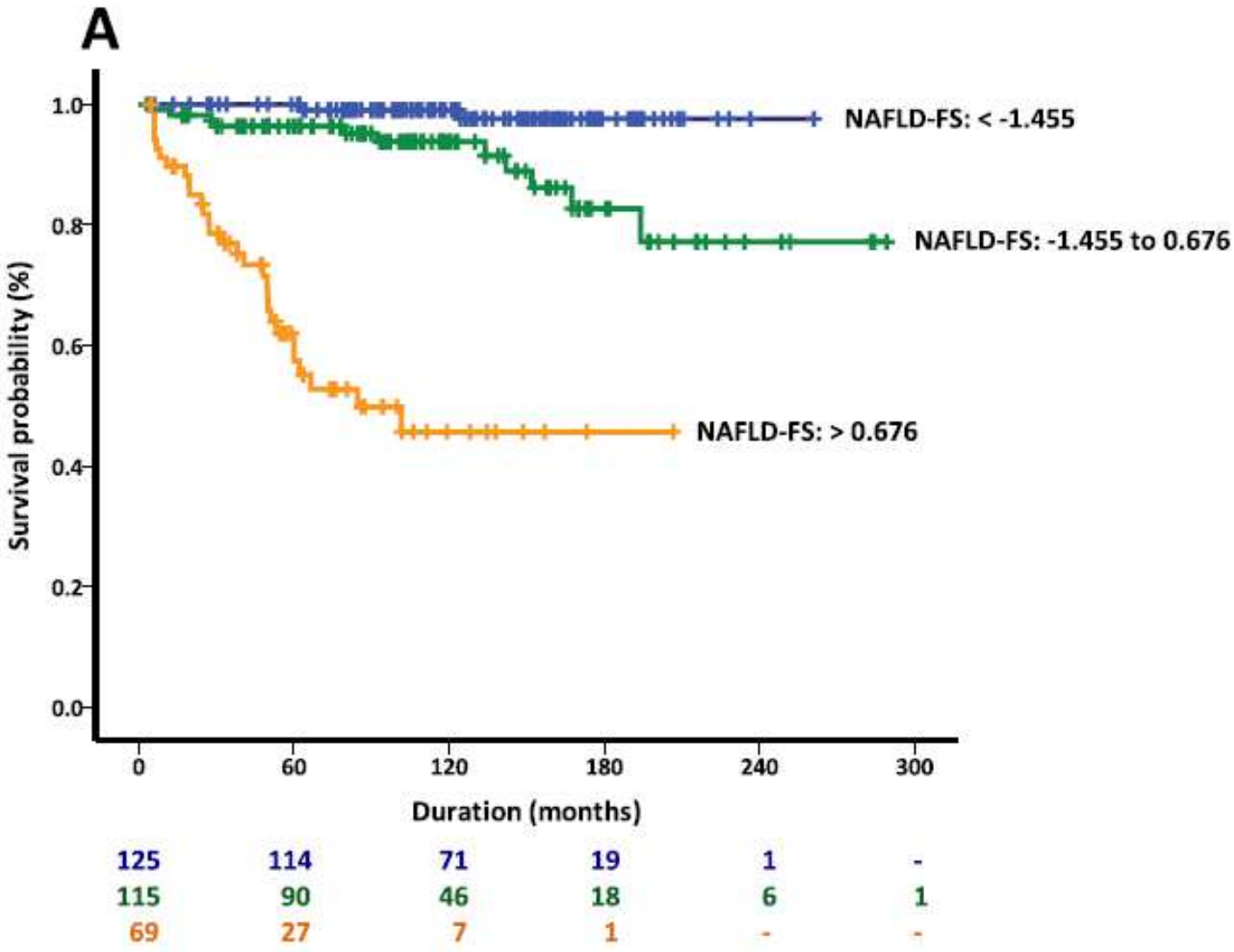
HEPATOLOGISTS CONSULTING ON LIVER BIOPSY IN NAFLD PATIENTS

Clinical Scores for the prediction of *fibrosis* in NASH

- **AST/platelet ratio index (APRI)**
  - AST (IU/L)/ (ULN) /platelet count ($x10^9$/L) x 100
- **FIB-4 score**
  - age x AST (IU/L)/platelet count ($x10^9$/L) x $\sqrt{}$ ALT (IU/L)
- **NAFLD Fibrosis Score (NFS)**
  - -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).
- **Commercial Panels including ELF Test and Fibrotest**
- *As the metabolic syndrome predicts the presence of steatohepatitis in patients with NAFLD, its presence can be used to target patients for a liver biopsy (AGA/AASLD guidelines)*

(Williams, Gastro 1988; Wai, Hepatology 2003; Harrison, Gut 2008; Vallet-Pachard, 2007; Bedogni, 2006)

NFS can predict liver related mortality



Angulo et al Gastro 2013

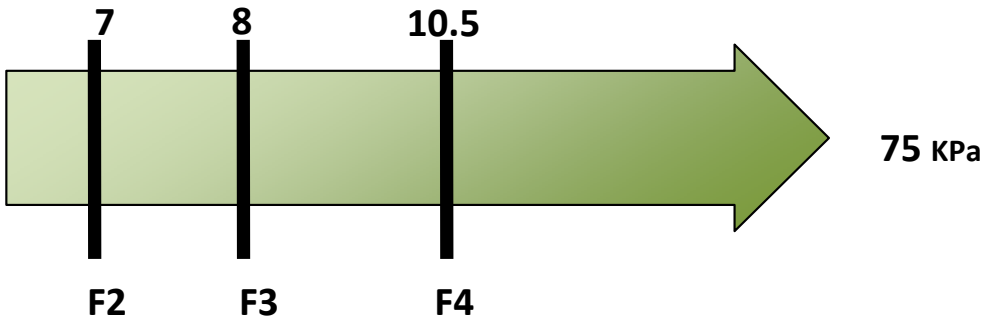
Imaging in NASH

1. Fibroscan®

- assessment of fibrosis measuring liver stiffness
- initial promising results in NAFLD *Wong, Hepatology 2010*

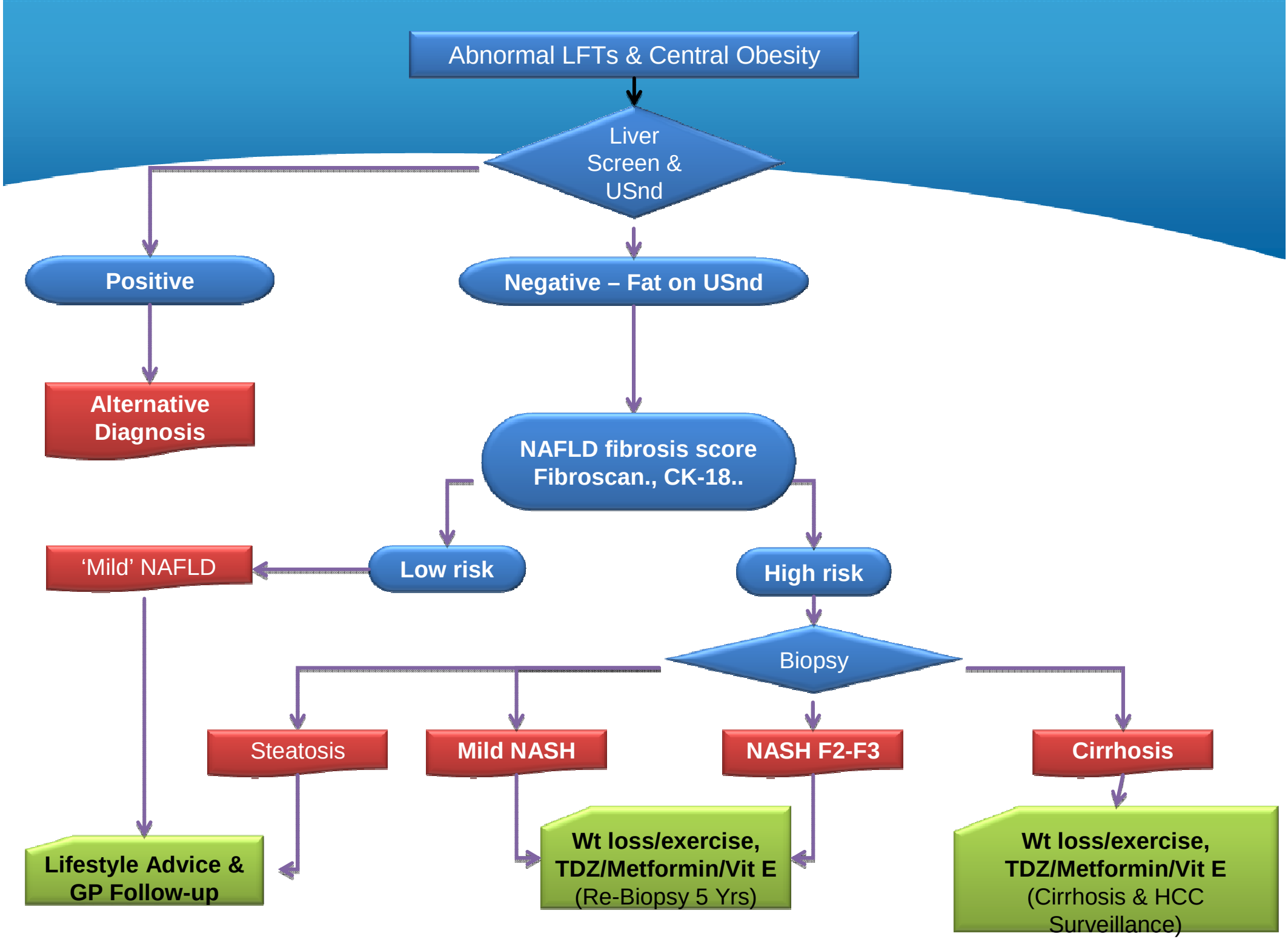
BUT

- Failure Rate ⟶ 25.5% if BMI≥ 30 and 2.6% if BMI < 30
- special XL probe for obese patients *De Ledinghen, J Hepatol 2009*
- caution in NAFLD => results may be influenced by steatosis *Gaia, J Hepatol 2011*

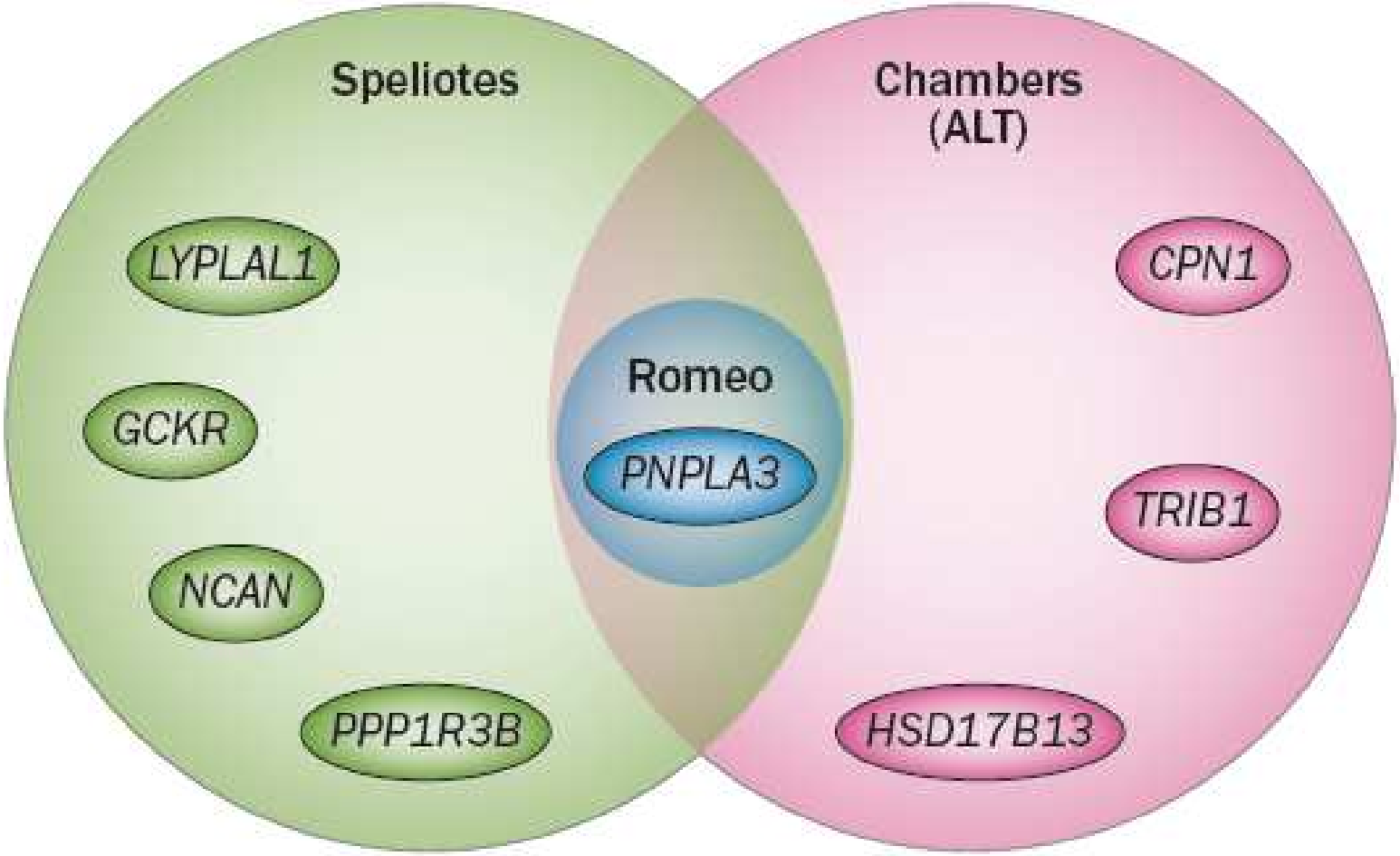


2. Acoustic radiation ARFI *Palmeri 2011*

3. Real time elastography *Ochi 2012*


Abnormal LFTs & Central Obesity
Liver Screen & USnd
Positive
Negative – Fat on USnd
Alternative Diagnosis
NAFLD fibrosis score Fibroscan., CK-18..
'Mild' NAFLD
Low risk
High risk
Biopsy
Steatosis
Mild NASH
NASH F2-F3
Cirrhosis
Lifestyle Advice & GP Follow-up
Wt loss/exercise, TDZ/Metformin/Vit E (Re-Biopsy 5 Yrs)
Wt loss/exercise, TDZ/Metformin/Vit E (Cirrhosis & HCC Surveillance)

Commonality between the largest GWAS in NAFLD.



Anstee, Q. M. & Day, C. P. Nat. Rev. Gastroenterol. Hepatol. 2013

THERAPY

We are what we eat...

Lifestyle Changes: Current Evidence

At present weight reduction through lifestyle modification with ***diet and exercise*** should be recommended because it:

- Improves cardiovascular risk profile
- Decreases the future development of diabetes
- Improves steatosis
- *Probably* improves inflammation (**requires 7-9% weight loss**)
- To date, little evidence that it improves fibrosis

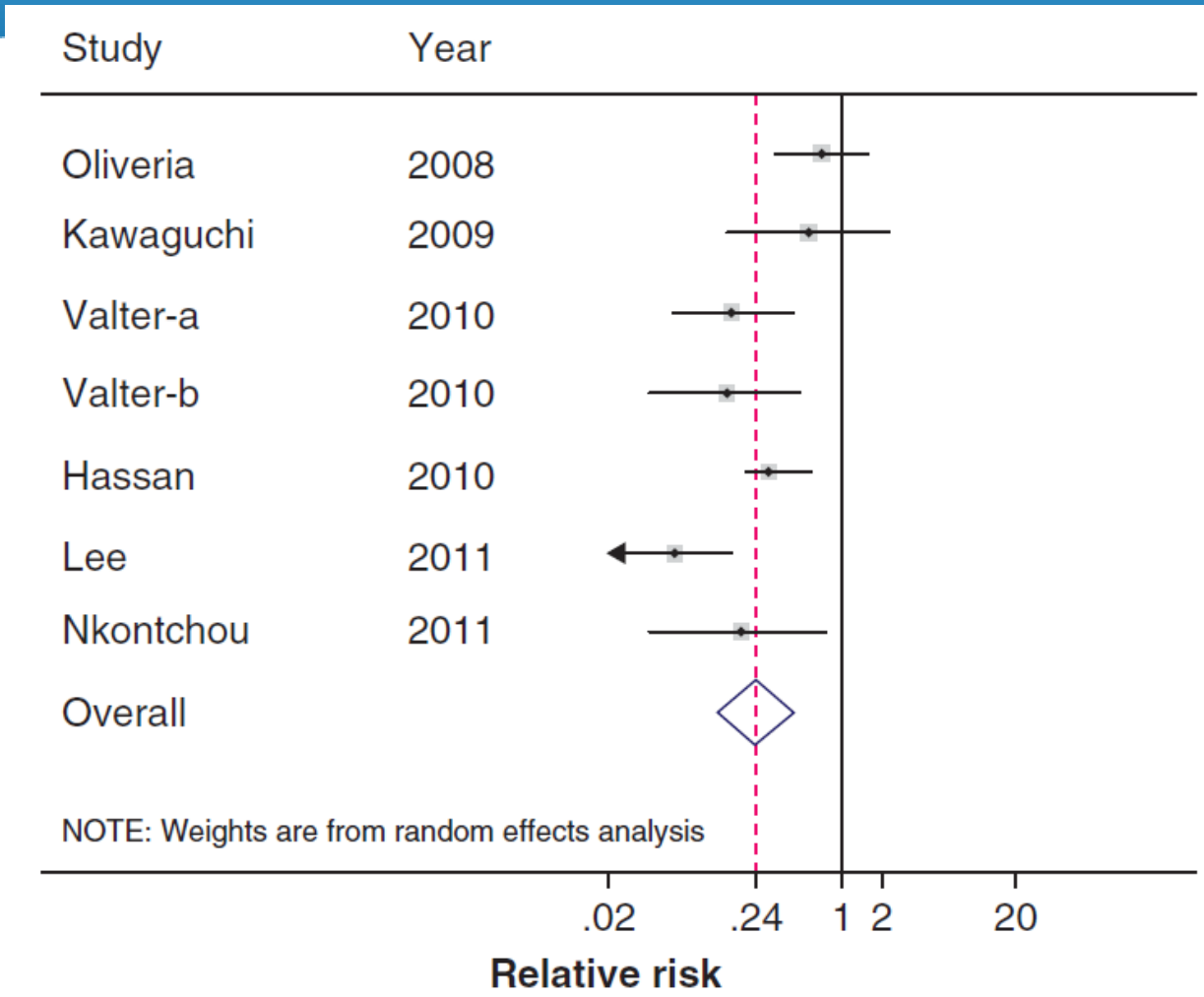
NAFLD pts lack confidence to exercise and have scarce readiness to lifestyle change ?

→ Need for behavioral counseling

Insulin sensitizers

- Metformin
  - Metformin drug-of-choice for obese T2DM (confers reduced mortality) also benefit on CVD prevention
  - Pilot data contradictory and recent RCT -ve
  - **But:** emerging evidence of anti-cancer effect 62%↓ HCC in diabetics *Zhang 2012, Chen 2013*
- Glitazones
  - Sound theoretical basis & encouraging pilot data
  - Recent large RCT *(in non diabetics)* negative for fibrosis but ↓NASH *Sanyal 2010*

Pooled Relative Risks for metformin treatment and the risk of HCC in diabetic patients.



Significantly reduced risk of HCC in metformin users versus nonusers in diabetic patients (Relative risk 0.24, 95% CI 0.13–0.46)

Zhang et al Scandinavian Journal of Gastroenterology. 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

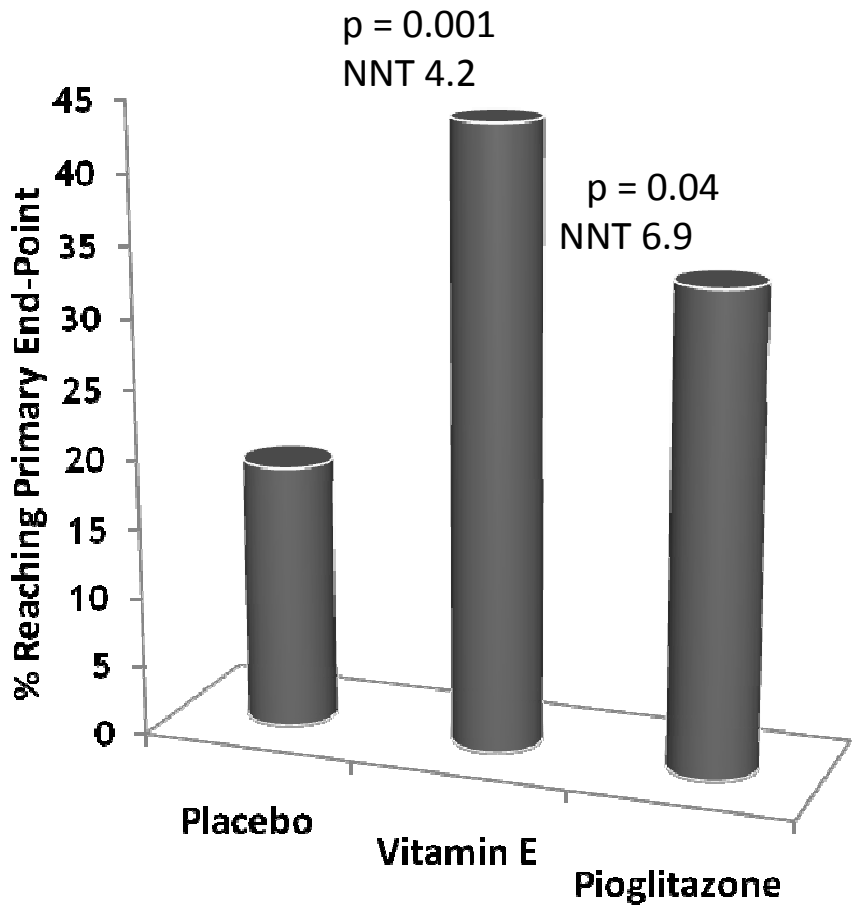
Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D., David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D., and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*

N ENGL J MED 362;18 NEJM.ORG MAY 6, 2010

'PIVENS' Trial

- 247 non-diabetic adults with NASH
  - **30mg Pioglitazone**
  - **800IU Vitamin E**
  - **Placebo**
- Liver biopsy at 96 Weeks
- Both agents improved steatosis & inflammation scores
- Only Vitamin E reduced ballooning
- Neither agent reduced fibrosis
- BUT resolution of NASH in 30-40% of patients treated



Lipid lowering agents

- Fibrates:
  - good theory - PPARα agonists
  - No benefit in two RCTs
- Statins
  - Definitely safe in NAFLD patients
  - Do improve LFTs *Athyros Lancet 2010*
  - May also ↓ HCC risk (OR: 0.63 [0.5-0.8]) *El-Serag 2009, Singh 2013*
- Omega-3 PUFAs
  - ↓ liver fat in meta-analysis *Parker 2012*

Conclusions

- The management of NAFLD patients is based on treatment of liver disease alongside the associated MS components → Lifestyle advice for all patients with NAFLD
- Pharmacologic therapy should be reserved only to NASH.
- EASL guidelines: 1–2 year course of therapy with glitazones or vitamin E, preferably associated with high-dose UDCA
- AGA-AASLD-ACG guidelines: pioglitazone and vitamin E in non-diabetic biopsy-proven NASH

However:

- Pioglitazone associated with weight gain and an increased risk of congestive heart failure, bone fractures, and bladder cancer
- High-dose vitamin E linked to increased all-cause mortality, hemorrhagic stroke and prostate cancer

Several promising agents awaiting RCT evidence

New PPARs - GFT 505 dual PPAR δ/α agonist

↓ intracellular TG (adipose tissue, liver), ↑ beta-oxidation

an international phase IIb RCT of GFT 505 ongoing

GLP-1 agonists – Liraglutide

↓ ALT and steatosis but NOT indep of ↓ weight and ↓ HbA1c

Armstrong 2012

Sylimarin/Sylibin

Initial promising results, no significant side effects but low bioavailability

Loguercio 2012

Modification of Gut Microbiota

Preliminary evidence from gut microbiota transplant in mice

Obeticolic acid

While UDCA no benefit **but** Urso + Vit E: encouraging pilot data

Lindor 2004, Dufour 2006

AT LEAST A COFFEE IS OK....

Thank you for your attention!

Acknowledgements:

Dr Ester Vanni
Dr Lavinia Mezzabotta
Dr Chiara Rosso
Dr Marilena Abate
Dr Silvia Carenzi
Dr Elena Gentilcore
Dr Alessandro Musso
Prof Antonina Smedile
Prof Mario Rizzetto