BEST OF EASL

EASL-EASD-EASO Clinical Practice Guidelines for the management and treatment of NAFLD

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EASL – EASD - EASO

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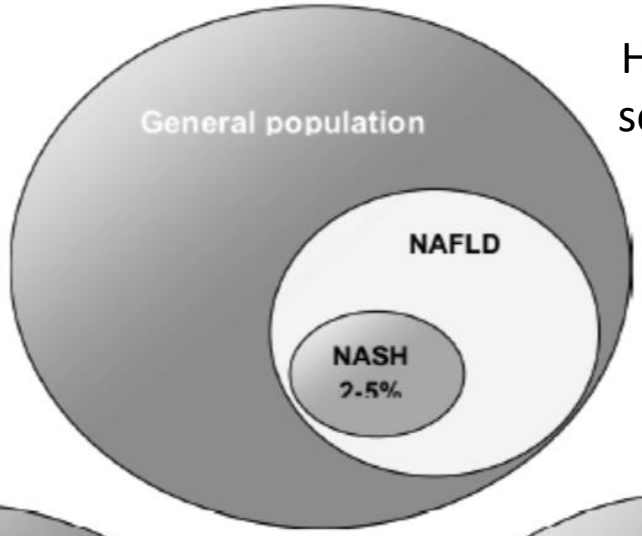
CPG – Plan of the presentation

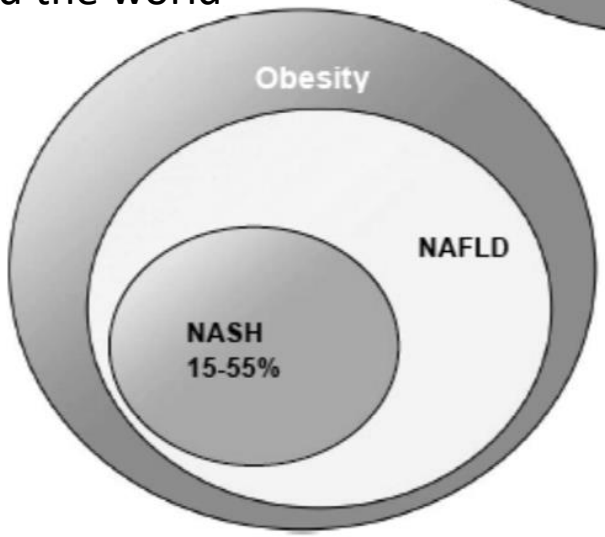
- Screening
- Genetics
- Non-invasive markers
- Liver biopsy
- Treatment

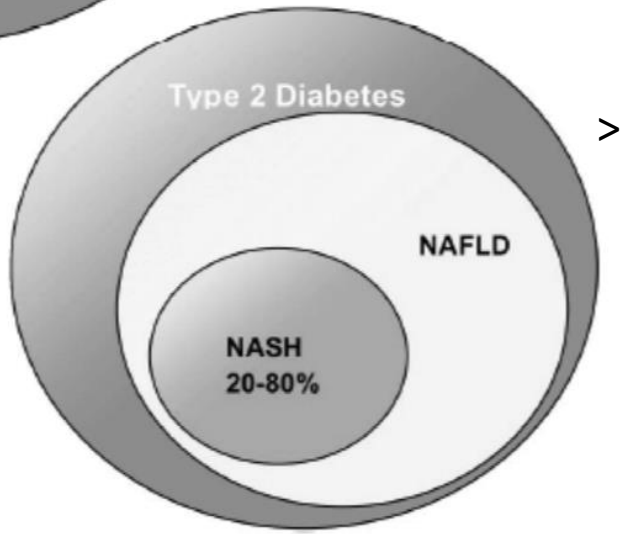
NAFLD - The dimension of the problem



Hepatologists only see the most severe cases (the tip of iceberg), and have a scarce idea of the global extent of disease

Obesity
1 billion persons overweight or obese around the world

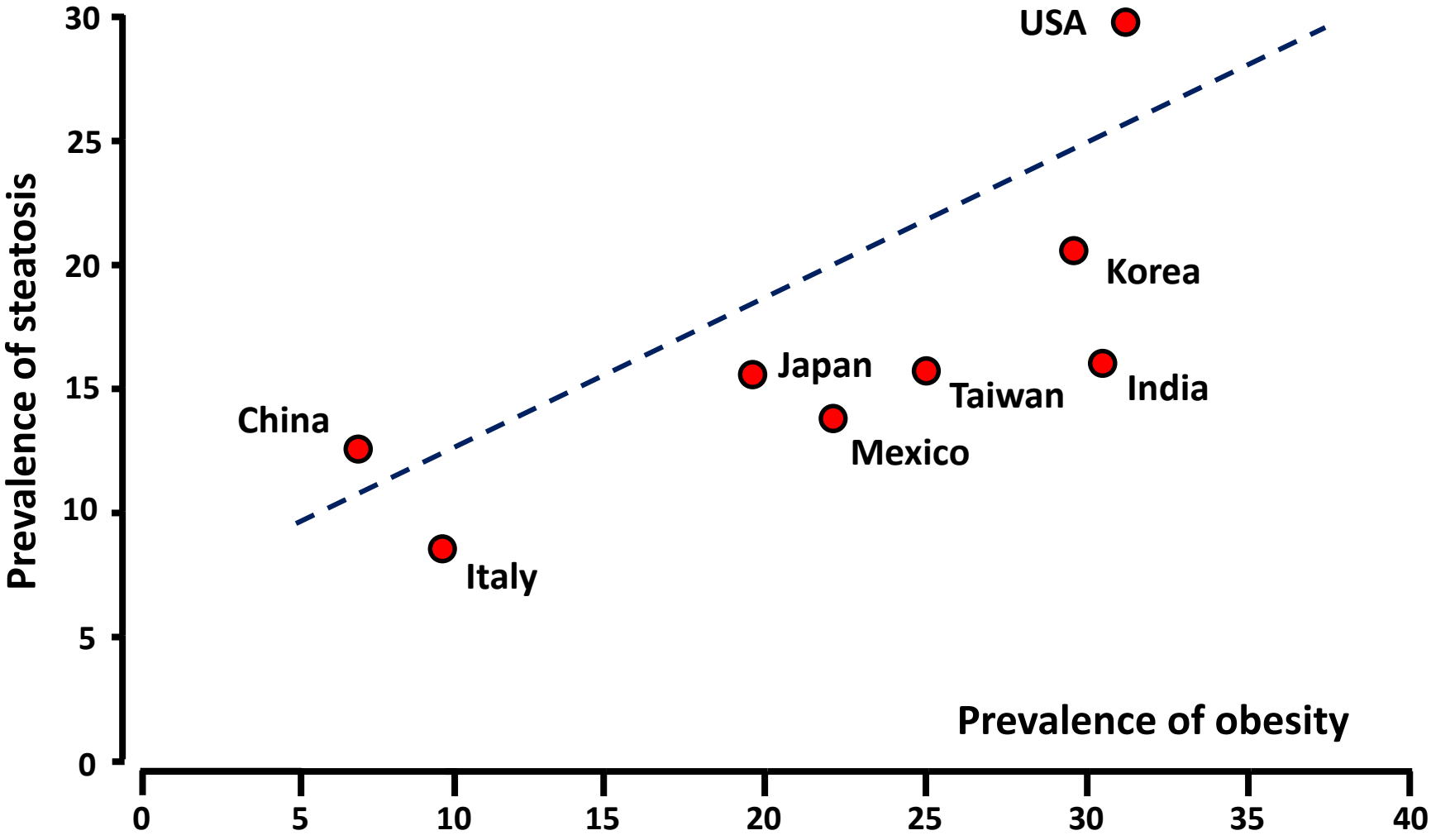




Diabetes
> 380 milion cases (550 in 2030)

BHALA *et al,* Curr Pharma Des 2013;19:5169-76

NAFLD is the most frequent liver disorder and its prevalence correlates with obesity



HILDEN et al, 1977; GROUND et al, 1982; BELLENTANI et al, 2000; CLARK et al, 2001; RUHL et al, 2004
BROWNING et al, 2004; ANGELICO et al, 2005; HAMAGUSHI et al, 2005; JIMBA et al, 2005; LIN et al, 2005
FAN et al, 2005; ZELBER et al, 2006; ZHOU et al, 2007; FAN et al, 2007; TARGHER et al, 2007; LAZO et al, 2008

NAFLD: whom to screen?

- Patients with IR and/or metabolic risk factors (i.e. obesity or metabolic syndrome [MetS]) should undergo diagnostic procedures for the diagnosis of NAFLD, which relies onthe demonstration of excessive liver fat (**A1**)
- Individuals with steatosis should be screened for secondary causes of NAFLD, including a careful assessment of alcohol intake. The interaction between moderate amounts of alcohol and metabolic factors in fatty liver should always be considered (**A1**)
- Other chronic liver diseases that may coexist with NAFLD should be identified as this might result in more severe liver injury (**B1**)

Diagnostic flow-chart in NAFLD

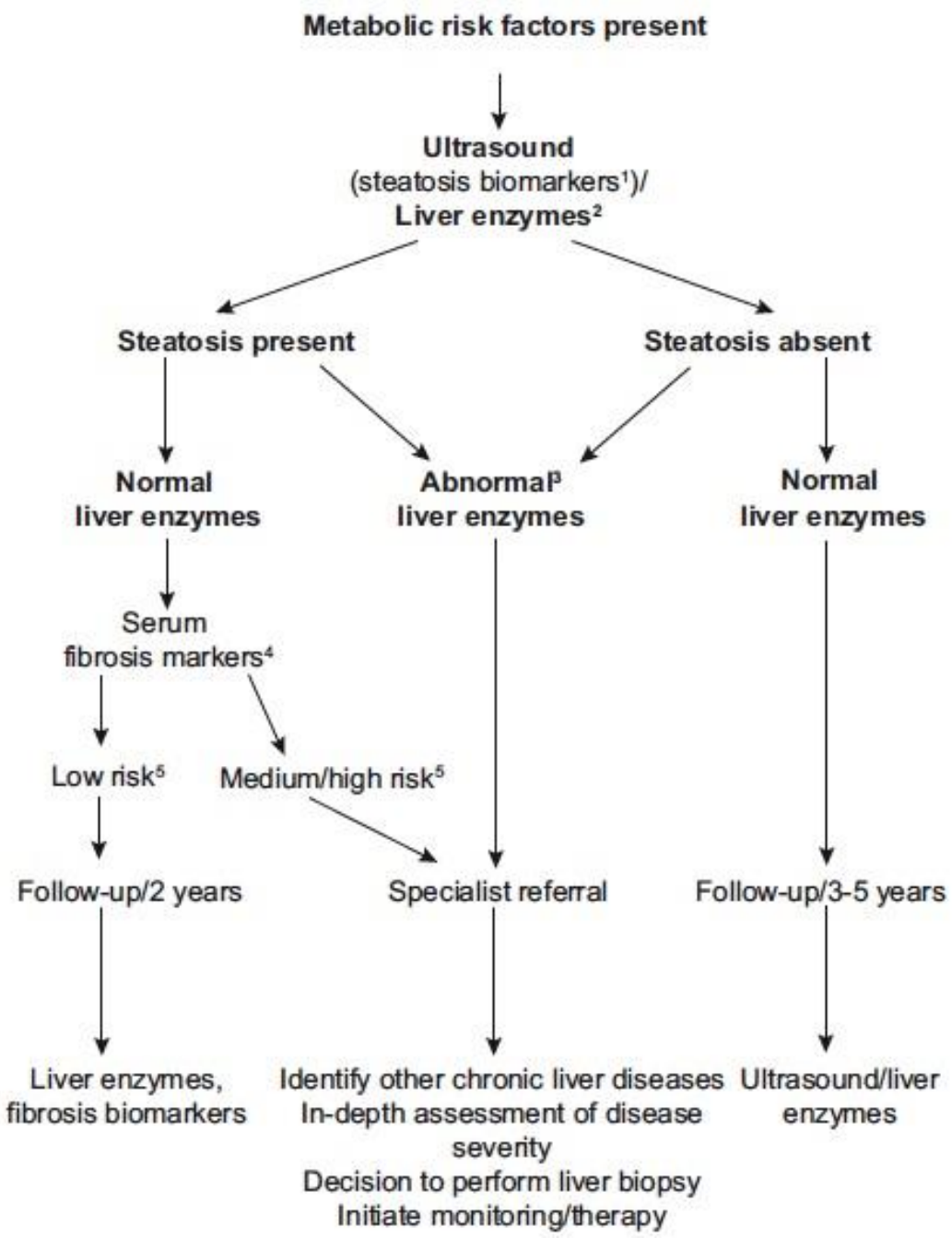
[1] Validated seatosis markers: Fatty Liver Index, SteatoTest, NAFLD Fat Score

[2] Liver enzymes: ALT AST, γGT

[3] Any increase in ALT, AST or γGT

[4] Serum fibrosis markers: NAFLD Fibrosis Score, FIB-4, Commercial tests (FibroTest, FibroMeter, ELF)

[5] Low risk: indicative of no/mild fibrosis; medium/high risk: indicative of significant fibrosis or cirrhosis

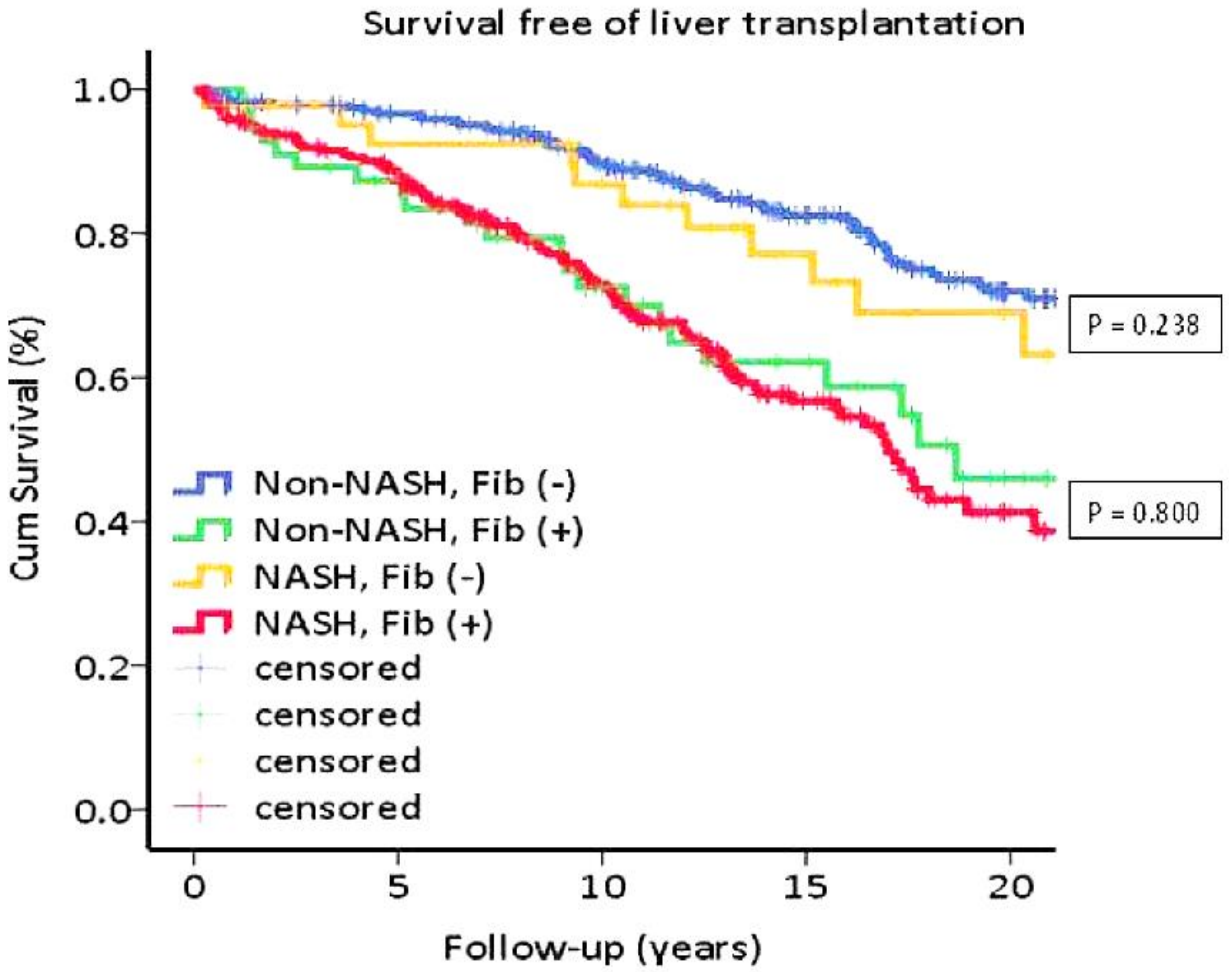


Non-invasive assays may increase the acceptability of an extensive screening strategy

Assay	Data required	Reference
Steato-Test	A2-macroglobulin, haptoglobin, ApoA1, bilirubin, GGT, glucose, TG, cholesterol, ALAT	Poynard et al, 2005
Fatty Liver Index	BMI, waist circumference, TG, GGT	Bedogni et al, 2006
NAFLD Fat Score	MS/T2D, insulin, AST, AST/ALT ratio	Kotronen et al, 2009

Fibrosis, not NASH, predicts survival

N=619 biopsy-proven NAFLD, FU 12.6 yrs



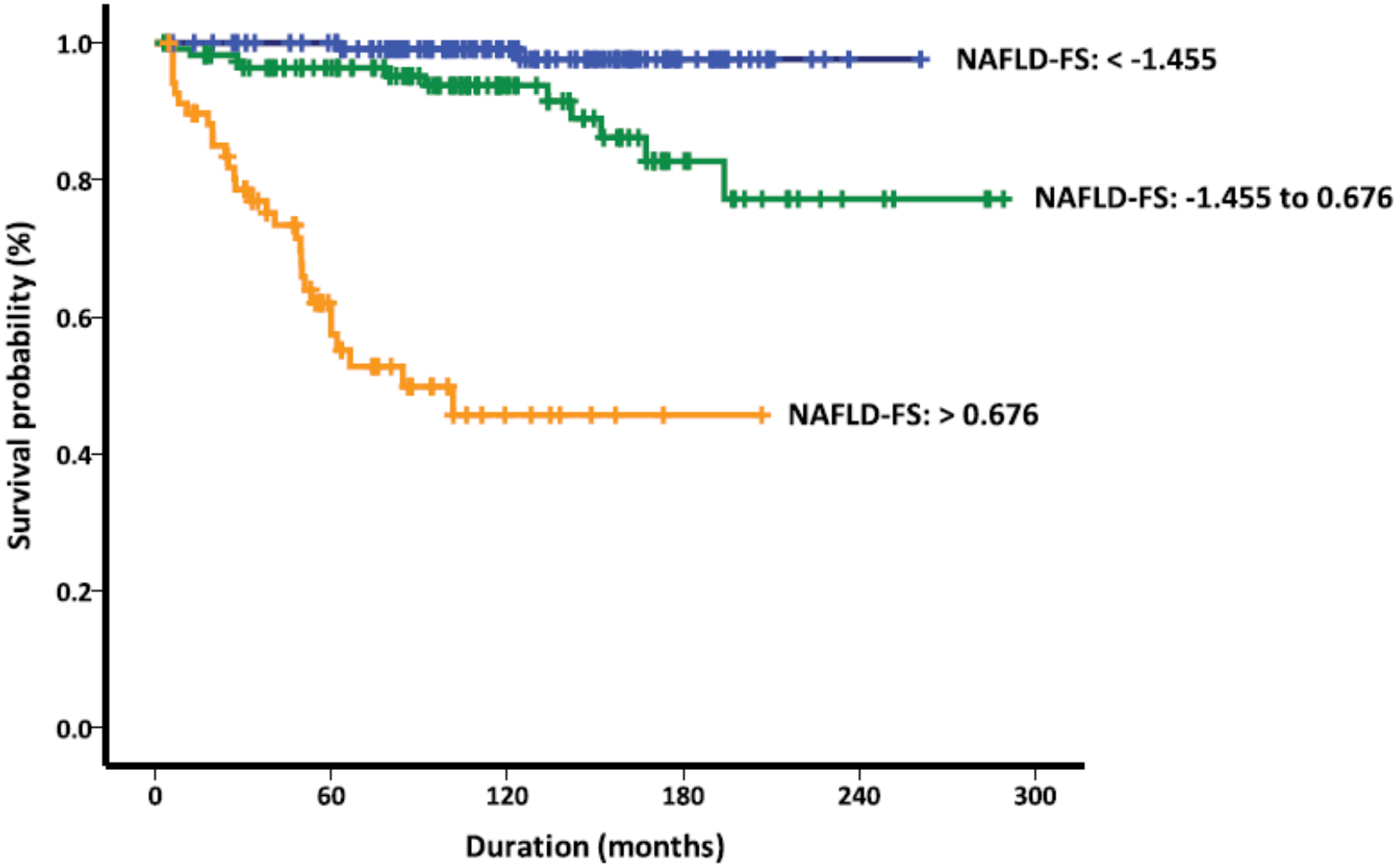
Causes of death: cardiovascular 38%, cancer 19%, cirrhosis 8%, HCC 1%

Independent predictors : fibrosis, diabetes, smoke, no statins

ANGULO *et al*, Gastroenterology 2015

Indirect markers of fibrosis predict mortality

N=320; NAFLD with advanced fibrosis (US, Australia, UK, Italy, Iceland)



-1.675 + 0.037 x age + 0.094 x BMI + 1.13 x hyperglycemia or diabetes (yes = 1, no = 0) + 0.99 x >AST/ALT ratio -0.013 x platelets (G/L) - 0.66 x albumin (g/dL)

ANGULO *et al*, Gastroenterology 2015

NAFLD screening must target the appropriate patients' population, use cost-effective assays, and lead to effective treatment

COMMENTARY

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease: disease mongering or call to action?

Elisabetta Bugianesi[1]

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease: is universal screening appropriate?

Christopher D. Byrne[1,2] · Giovanni Targher[3]

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease: guidelines, clinical reality and health economic aspects

Hermann Toplak[1] · Rudolf Stauber[2] · Harald Sourij[3]

Diabetologia 2016 (in press)

NAFLD screening and cost-effectiveness

Byrne & Targher (EASD):

- ….. any case finding strategy to diagnose NAFLD that focuses on the whole population of T2DM patients will be very expensive. Since the cost-effectiveness of any case finding strategy will improve with its implementation at a younger vs. older age, we consider that a targeted approach focussing on age stratification is sensible.

Toplak et al (EASO):

- ….. even if evidence-based and approved pharmacological treatment was available, it is questionable to what extent local health budgets may be able to offer it to the individual patient. This raises the additional importance of population strategies.

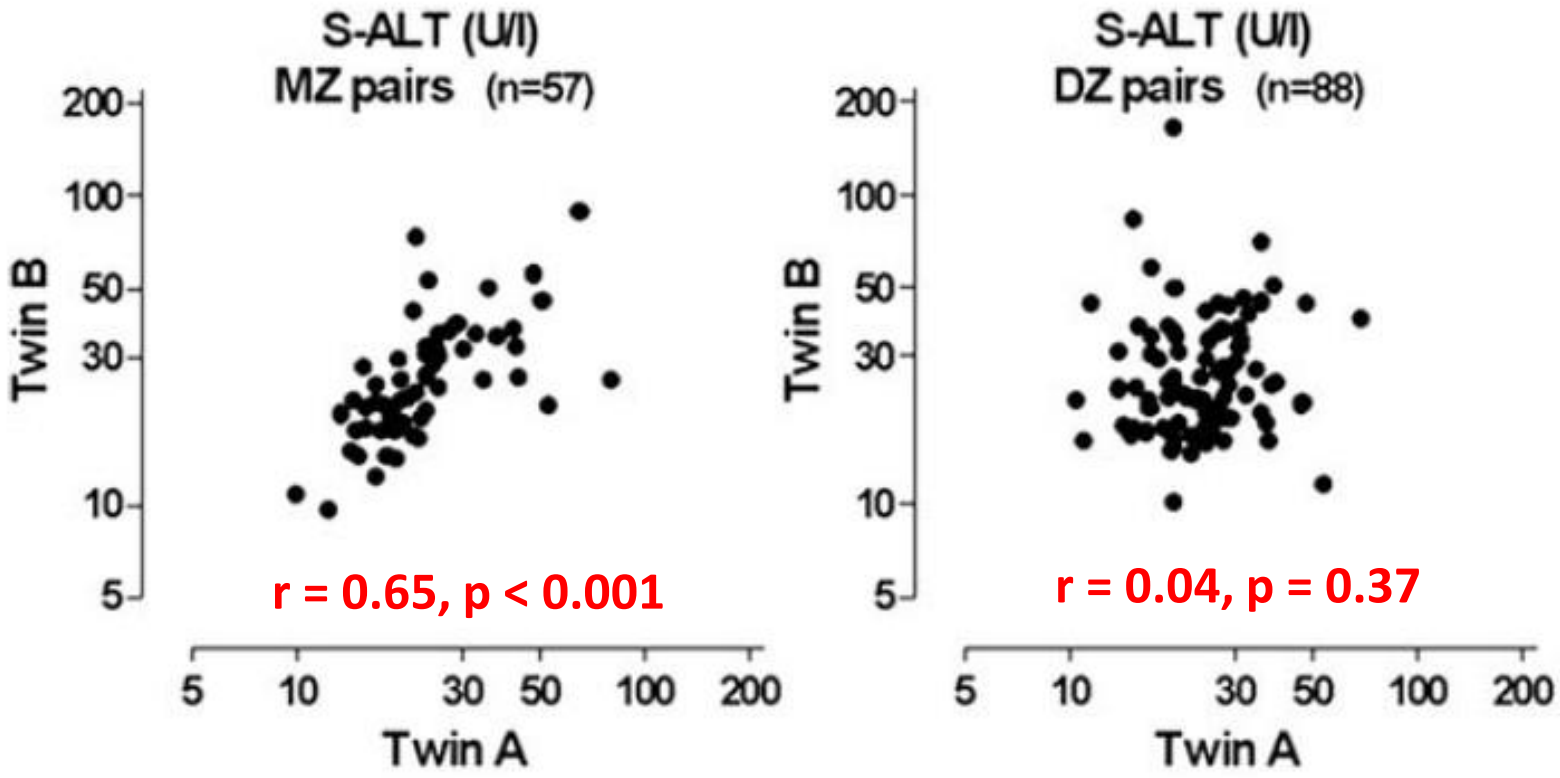
Bugianesi (EASL):

- …. we need to find a common ground where all the major players in the metabolic field can cooperate, sharing resources, clinical data and patient samples, to tackle this modern-day disease and translate 'disease mongering' into an effective way forward for the patients and for the healthcare systems.

Diabetologia 2016;59:1141-9

What about genes?

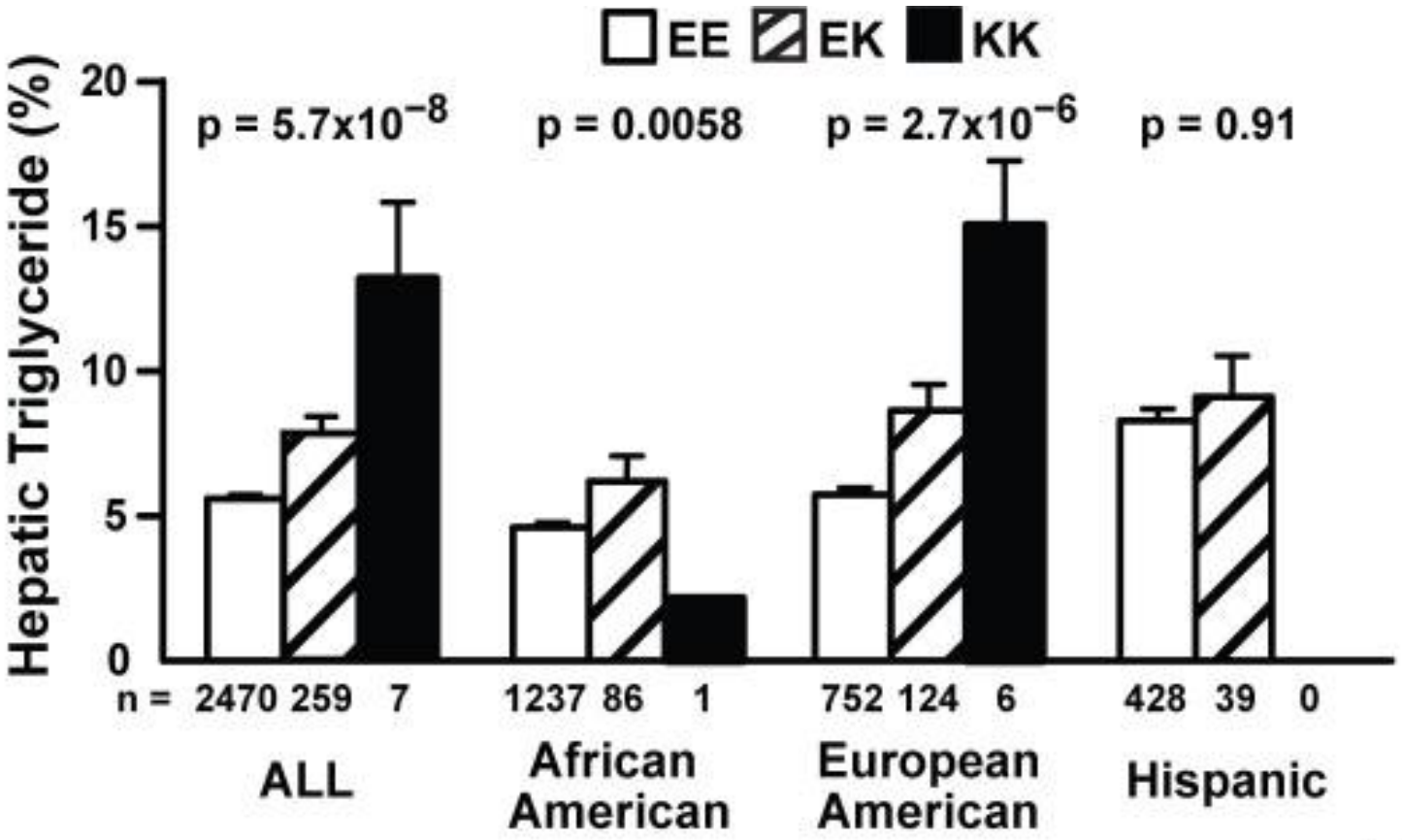
ALT levels are heritable



MAKKONEN *et al*, J Hepatol 2009;50:1035-42

Whole exome analysis for TG liver content

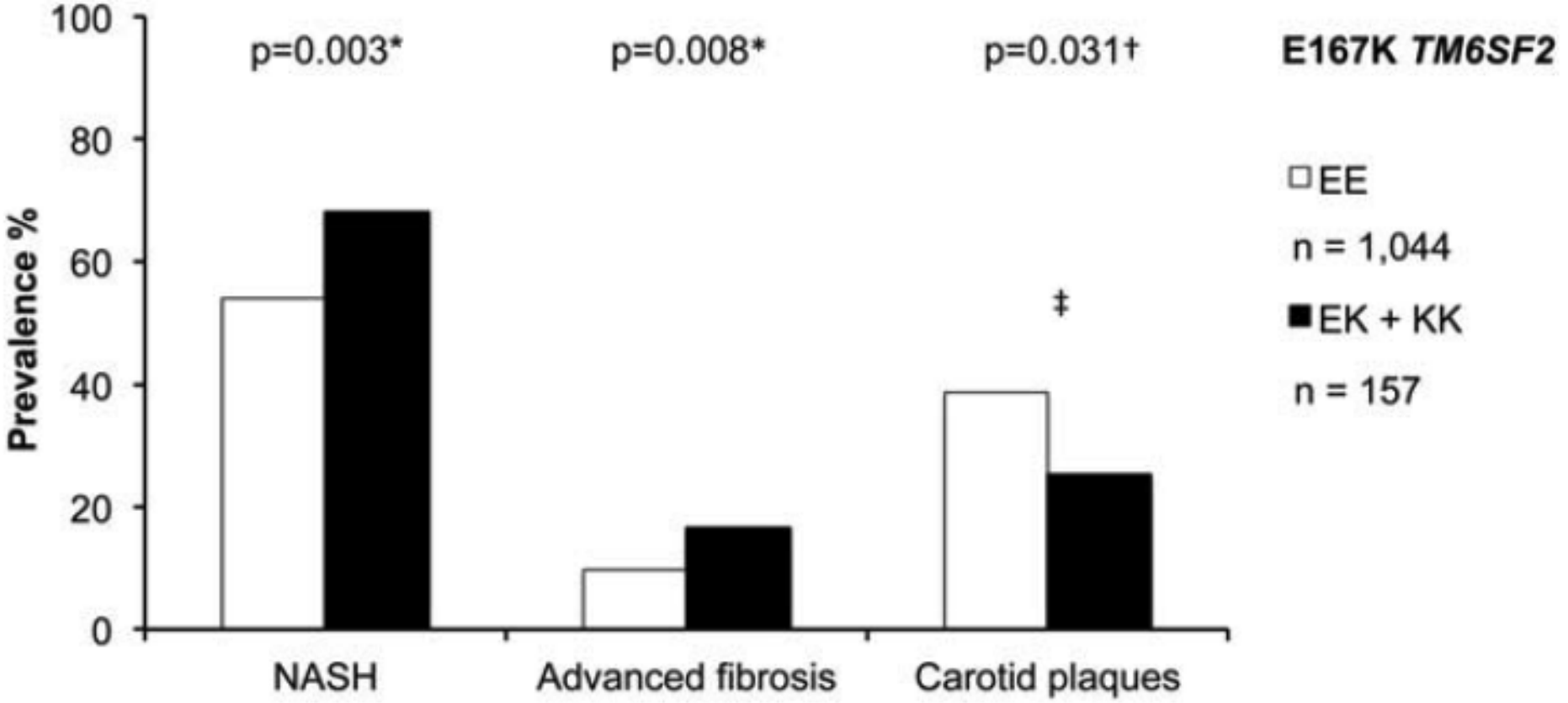
(The Dallas Heart Study, n=2,736)



167K (GLU→LYS) in *TM6SF2* is associated with increased ALT, but low total and LDL cholesterol and low TG (0.072 in European Americans)

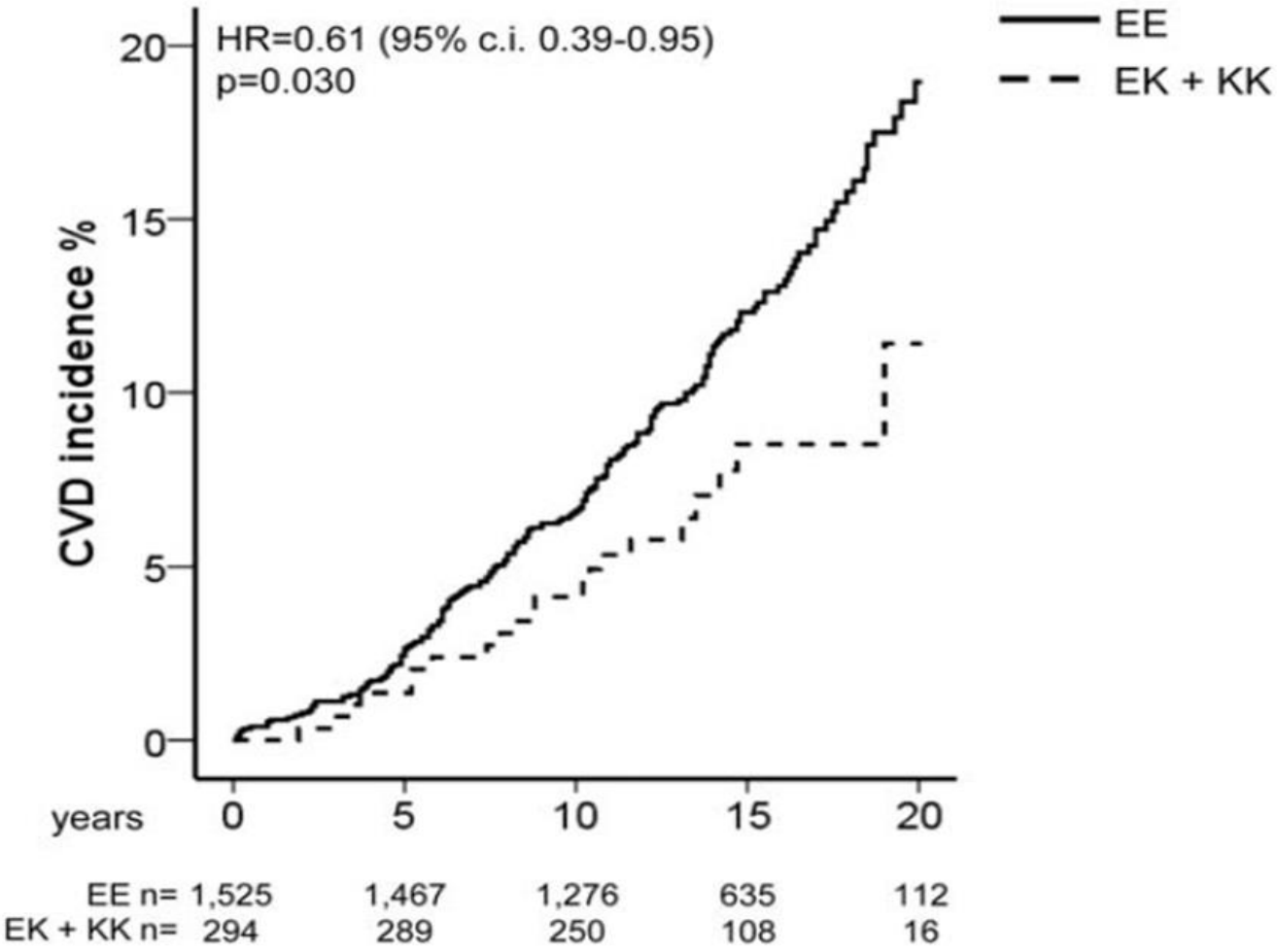
KOZLITINA *et al,* Nat Gen 2014;46:352-6

Associations between *TM6SF2* and clinical features in the Swedish Obese Subjects study



DONGIOVANNI *et al,* Hepatology 2015;61:506-14

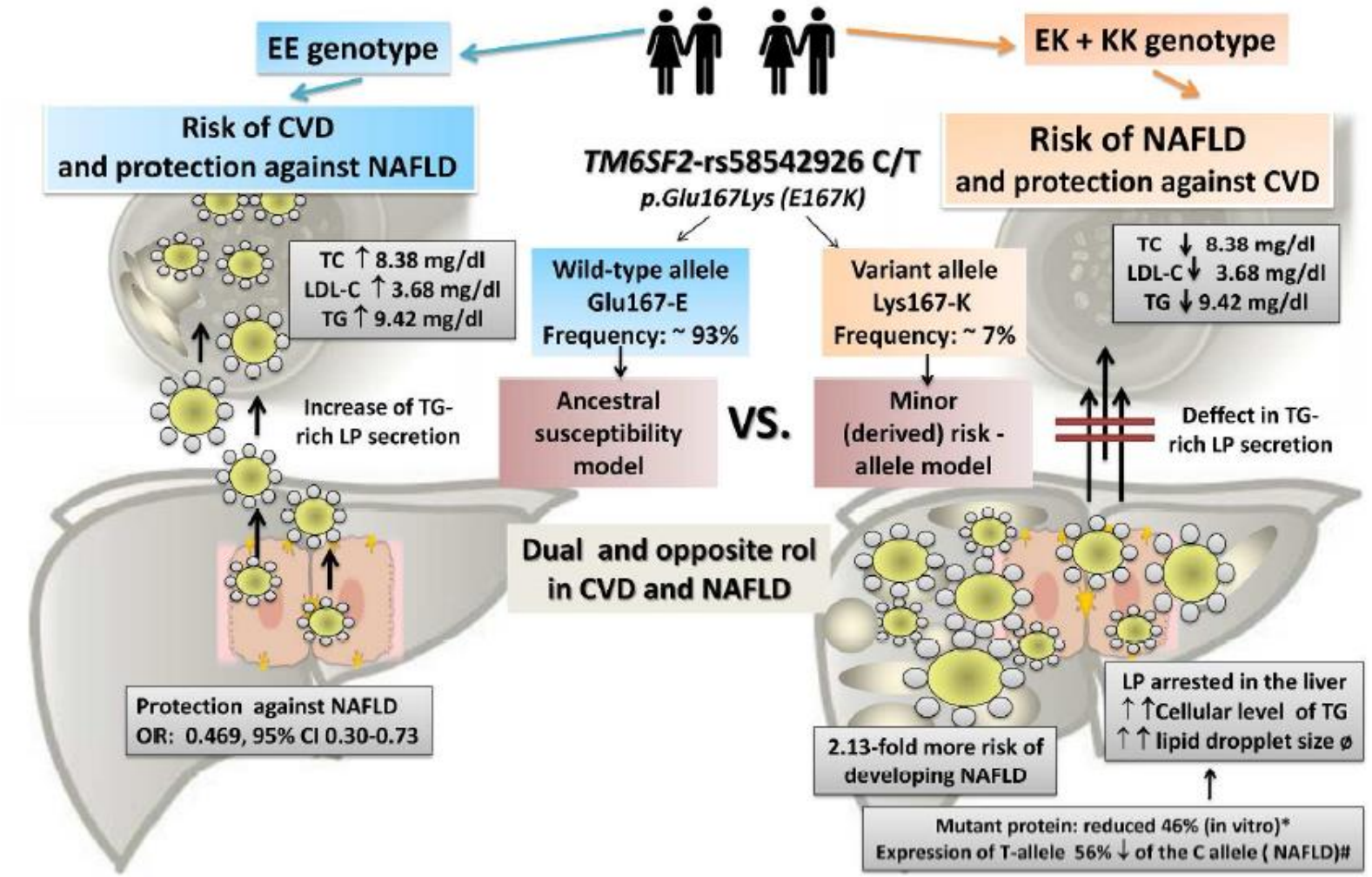
Association between *TM6SF2* and fatal and non-fatal CVEs in the Swedish Obese Subjects study



DONGIOVANNI *et al,* Hepatology 2015;61:506-14

Dual role of *TM6SF2* missense *rs58542926* variant

A meta-analysis



SOOKOIAN *et al,* Hepatology 2015;61:515-25

PIROLA & SOOKOIAN, Hepatology 2015 (in press)

PNPLA3 rs738409[G]

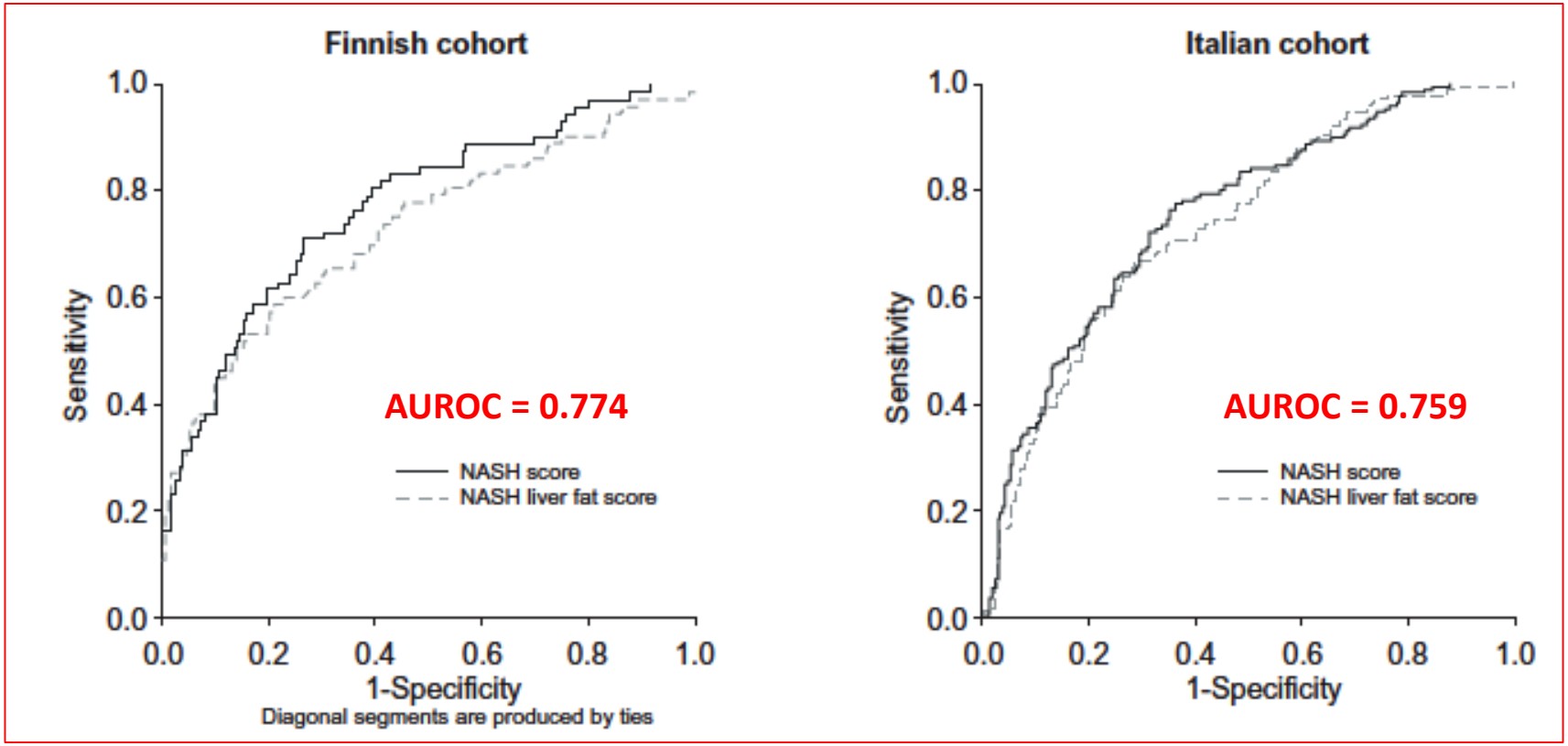
Patatin-like phospholipase domain-containing protein 3
aka **adiponutrin**

- Frequencies of the *PNPLA3 rs738409[G]* allele concordant with the relative prevalence of NAFLD in the three ancestry groups:
  - Hispanics = 0.49
  - European Americans = 0.23
  - African Americans = 0.17
- Associated with ALT and AST in Hispanics
- No association with BMI, insulin sensitivity indices, plasma TG or cholesterol (total, HDL, LDL)

ROMEO *et al,* Nat Gen 2008;40:1461-5

Predicting NASH (prevalence of ~5% in 45-74 year old Finnish) using a score including *PNPLA3* genotype, AST and insulin levels

$$-3.05 + 0.562 \times \textit{PNPLA3}\ \text{genotype}\ (\text{CC} = 1/\text{GC} = 2/\text{GG} = 3) - 0.0092 \times \text{fS-insulin}\ (\text{mU/L}) + 0.0023 \times \text{AST}\ (\text{IU/L}) + 0.0019 \times (\text{fS-insulin} \times \text{AST}).$$



HYYSALO *et al*, J Hepatol 2014;60:839-46

The effect of *PNPLA3* genotype on NAFLD-related HCC risk is independent of its role in fibrosis progression

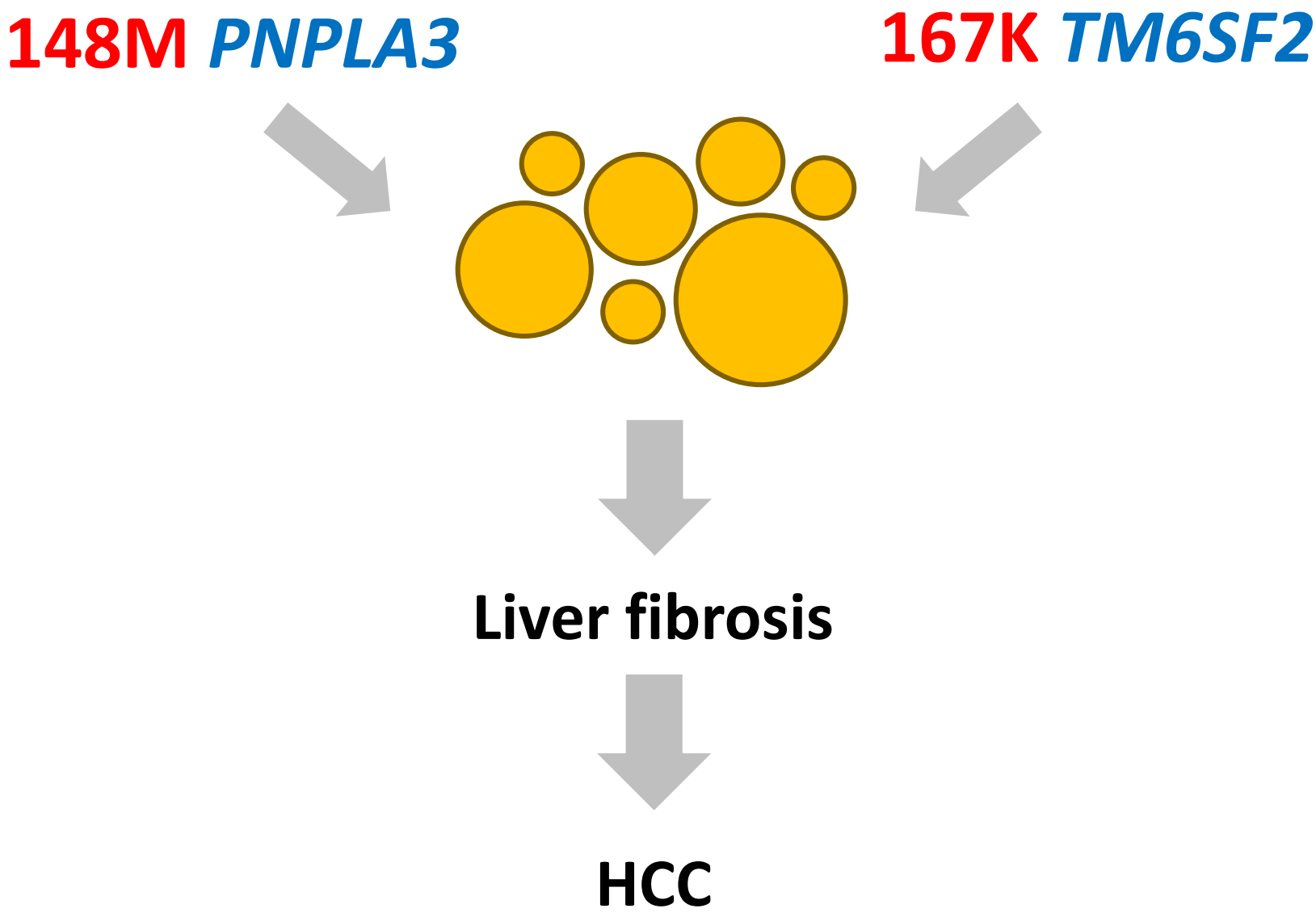
(n=100 NAFLD-HCC and 275 non-HCC controls; UK + Switzerland)

Variables	OR (95% CI)	*p* value
PNPLA3 rs738409 genotype	2.26 (1.23-4.14)	0.0082
Age	1.24 (1.17-1.32)	<0.0001
Sex (Male)	11.11 (4.17-33.33)	<0.0001
BMI	0.94 (0.87-1.02)	0.148
Diabetes	2.33 (0.93-5.81)	0.070
Cirrhosis	9.37 (3.82-23.00)	<0.0001

Additive model including age, gender, BMI, diabetes, and cirrhosis as covariates.

Carriage of each G allele is associated with a doubling of HCC risk

LIU *et al*, J Hepatol 2014;61:75-81


148M PNPLA3
167K TM6SF2
Liver fibrosis
HCC

NAFLD and genetics: conclusions

- Carriers of the *PNPLA3* I148M and the *TM6SF2* E167K variants have a higher liver fat content and increased risk of NASH. NAFLD due to these variants is not systematically associated with features of insulin resistance. Genotyping may be considered in selected patients and clinical studies but is not recommended routinely (**B2**)

- Although NAFLD is a risk factor for HCC, which may also develop in the pre-cirrhotic stage, and the risk is further increased by the presence of the *PNPLA3* rs738409 C>G polymorphism, no recommendation can be currently made on the timing of surveillance and its cost-effectiveness (**B1**)

Recommendations on screening

- US is the preferred first-line diagnostic procedure for imaging of NAFLD, as it provides additional diagnostic information (**A1**)
- Whenever imaging tools are not available or feasible (e.g. large epidemiological studies), serum biomarkers and scores are an acceptable alternative for the diagnosis of steatosis (**B2**)
- A quantitative estimation of liver fat can only be obtained by ^{1}H-MRS. This technique is of value in clinical trials and experimental studies, but is expensive and not recommended in the clinical setting (**A1**)

Recommendation for fibrosis

- Fibrosis biomarkers (combined or not with TE) can be used to **assess cases at low risk** of advanced fibrosis/cirrhosis and may help to spare unnecessary liver biopsies
- Identification of cases with advanced fibrosis or cirrhosis by non-invasive biomarkers and/or TE requires confirmation by liver biopsy
- Non-invasive biomarkers and /or TE are not validated for monitoring fibrosis progression
- Liver biopsy can be repeated every 5 years

Liver biopsy yes or no

- NASH has to be diagnosed by a liver biopsy showing steatosis + hepatocyte ballooning + lobular inflammation (A1)
- Biopsy is necessary to confirm the presence of advanced liver fibrosis or cirrhosis

The NAS score in NAFLD

- Not a diagnostic score
- Should only be used to evaluate disease severity once the diagnosis has been established (steatosis + ballooning + lobular inflammation)
- Little prognostic significance
- Duality NASH / no NASH is artificial for the pathologist:
  - A continuous histopathological spectrum
  - Dual classification does not consider special cases:
    - Advanced fibrosis with burnt-out steatosis
    - Steatofibrosis without ballooning or inflammation
- SAF is a reproducible, accurate and comprehensive alternative

Steatosis Activity Fibrosis

Steatosis (0-3): 0 = <5%, 1 = 5-33%, 2 = 33-66%, 3 = >66%

Activity (0-4): Ballooning (0-2) + Inflammation (0-2)

Fibrosis (0-4): 1a,b,c = perisinusoidal or periportal fibrosis, 2 = both perisinusoidal and periportal fibrosis, 3 = bridging fibrosis, 4 = cirrhosis

$$S_{0\text{-}3}A_{0\text{-}4}F_{0\text{-}4}$$

BEDOSSA *et al,* Hepatology 2012;56:1751-9

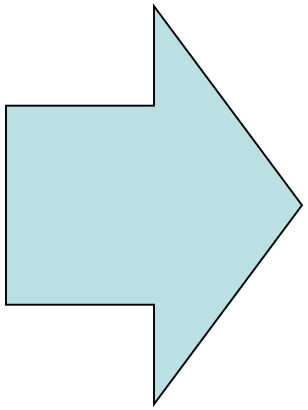
OGTT and HOMA-IR

- In all patients with NAFLD, screening for diabetes is mandatory using:
  - Fasting or blood random glucose
  - HbA1c
  - Standardized 75 g OGTT in high-risk patients
- In patients with T2DM, the presence of NAFLD should be ascertained, because T2DM is a risk factor of accelerated liver fibrosis progression
- HOMA-IR is a useful marker in cases without T2DM (but reference values must be established), in doubtful cases (e.g. lean patients), or to follow IR after implementing lifestyle changes

Management

Question to our Ethiopian
(but also non-Ethiopian…) friends:

What is the most effective measure to improve insulin resistance.....??



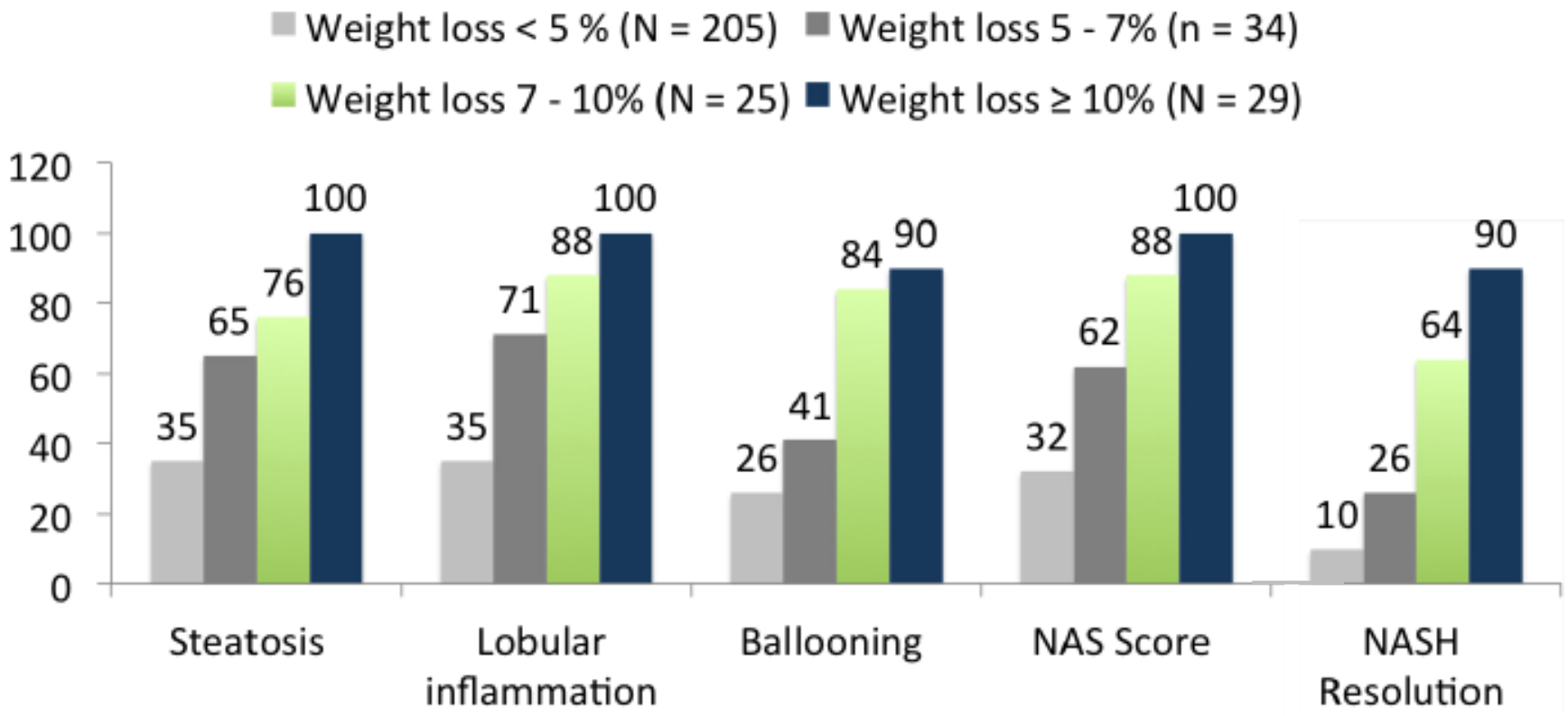
Area	Suggested intervention
Energy restriction	• 500-1000 kcal energy defect, to induce a weight loss of 500-1000 g/week • 7-10% total weight loss target • Long-term maintenance approach, combining physical activity according to the principles of cognitive-behavioural treatment
Macronutrient composition	• Low-to-moderate fat and moderate-to-high carbohydrate intake • Low-carbohydrate ketogenic diets or high-protein
Fructose intake	• Avoid fructose-containing beverages and foods
Alcohol intake	• Strictly keep alcohol below the risk threshold (30 g, men; 20 g, women)
Coffee drinking	• No liver-related limitations
Exercise/physical activity	• 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationery cycling) • Resistance training is also effective and promotes musculoskeletal fitness, with effects on metabolic risk factors • High rates of inactivity-promoting fatigue and daytime sleepiness reduce compliance with exercise

Therapy of NAFLD in 2016

- Structured programs of lifestyle changes (healthy diet and habitual physical activity)
- If no NASH, only lifestyle changes
- In overweight/obese, weight loss of 7-10%
- Diet: avoid NAFLD-promoting nutrients (processed food, high fructose corn syrup-containing food)
- Favor the Mediterranean diet
- Aerobic exercise or resistance training, according to patients' preferences in order to maintain it in the long term

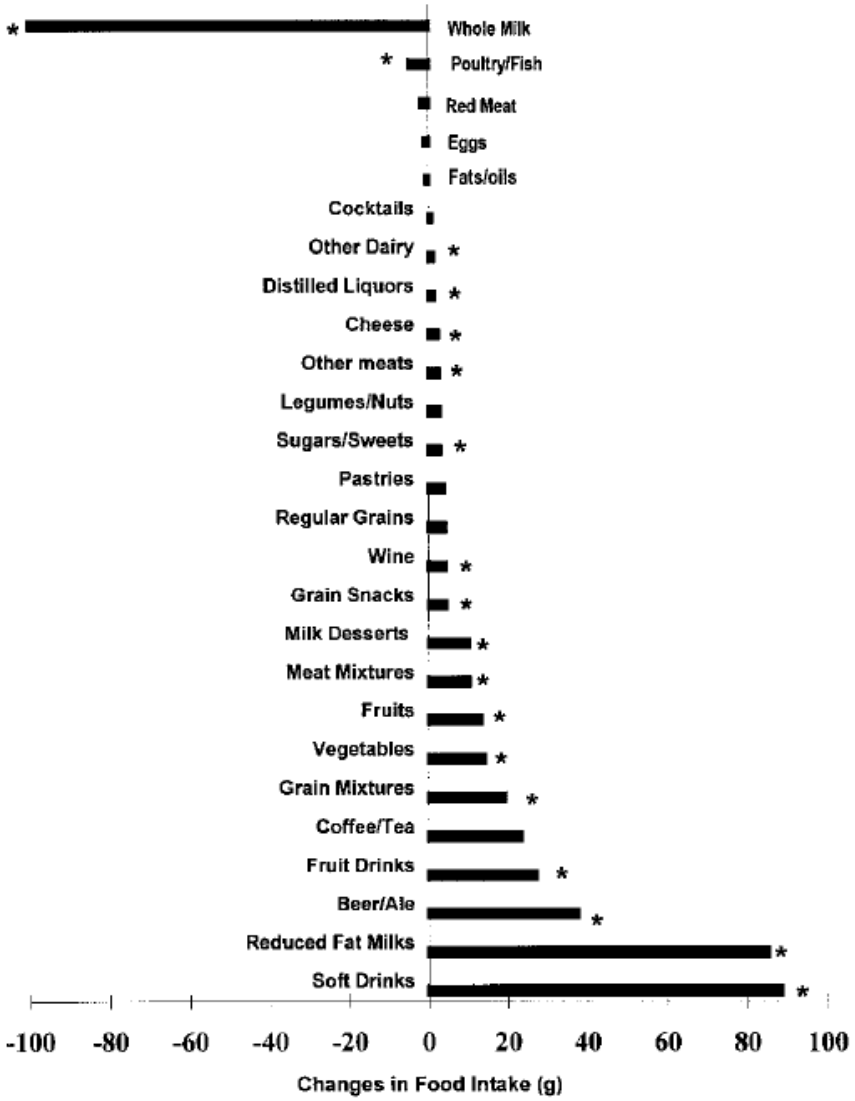
Body weight loss in non-cirrhotic NASH patients is associated with improved histology

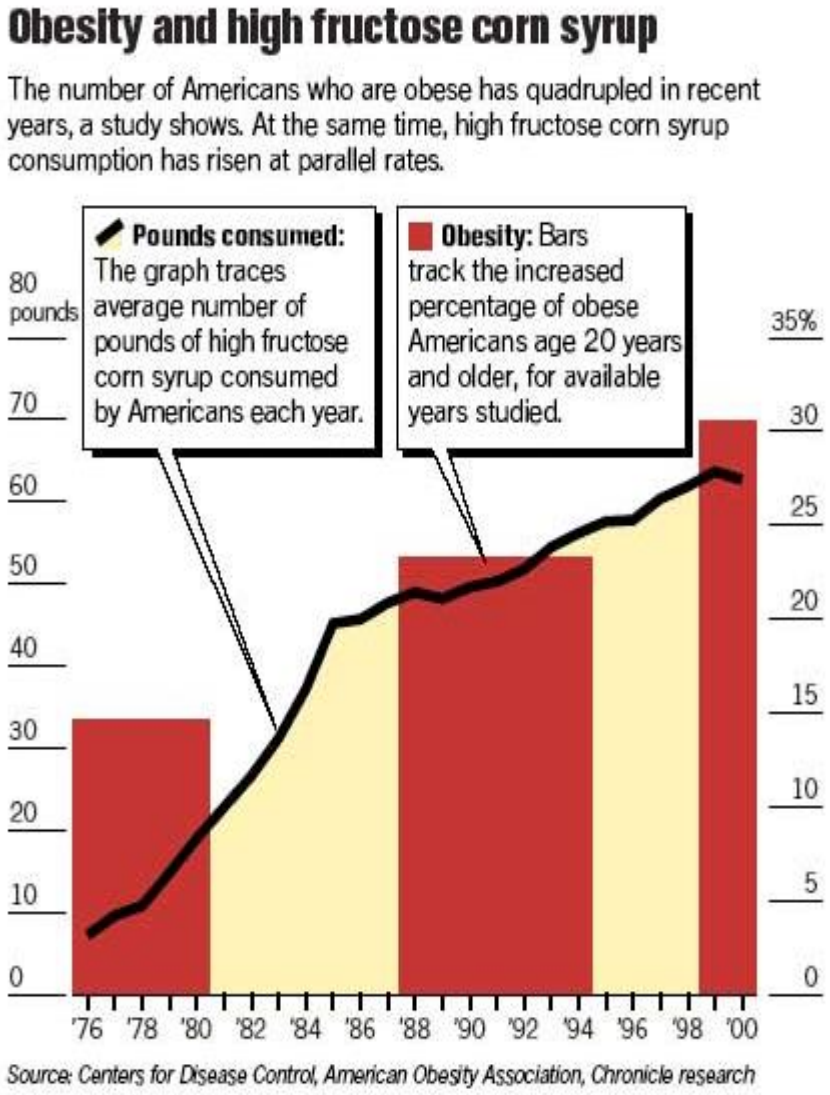
(n=293; 89% with paired liver biopsies; FU = 52 weeks; low-fat hypocaloric diet = -750 kcal)



VILAR-GOMEZ *et al,* Gastroenterology 2015;149:367-78.e5

Secular trends in specific food intake 1989-1996





CHANMUGAM *et al*, J Am Diet Assoc 2003;103:867-72

Soft drinks consumption and NAFLD

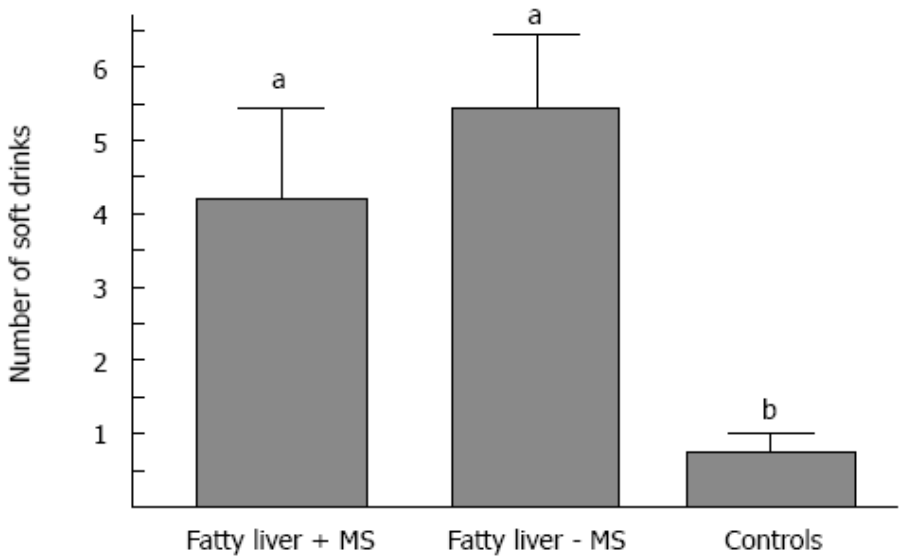


Table 1 Soft drink consumption linked with NAFLD

Dietary constituents	Controls (n = 30)	NAFLD (n = 31)	P value
Total energy intake (kcal)	2200 ± 600	2300 ± 500	0.300
Added sugar (g/d)	33.6 ± 12.6	75.6 ± 8.4	0.001
Percent of added sugar from soft drinks	8%	43%	0.001

- The primary dietary sources of fructose are high-fructose corn syrup and sucrose commonly used to sweeten beverages and processed foods
- Intake of soft drinks is 5-fold in NAFLD subjects compared to controls
- The consumption of soft drinks can increase the prevalence of NAFLD independently of the metabolic syndrome

NSEIR *et al,* World J Gastroenterol 2010;16:2579-88

Fructose and liver histology

(341 adults, NASH Clinical Research Network)

Association between fructose consumption and liver histology of NAFLD in different age groups

	Age < 48 yrs old				Age > 48 yrs old			
	Adjusted (Model 1)		Adjusted (Model 2)		Adjusted (Model 1)		Adjusted (Model 2)	
	OR [95% CI]	p-value	OR [95% CI]	p-value	OR [95% CI]	p-value	OR [95% CI]	p-value
Steatosis								
Fructose consumption								
< 7 servings	-	-	-	-	-	-	-	-
> = 7 servings	1.1 [0.6, 2.0]	0.72	1.0 [0.6, 1.9]	0.95	0.3 [0.1, 0.6]	0.0009	0.2 [0.1, 0.5]	0.0008
Lobular inflammation								
Fructose consumption								
< 7 servings	-	-	-	-	-	-	-	-
> = 7 servings	0.7 [0.4, 1.3]	0.24	0.9 [0.5, 1.8]	0.83	2.1 [1.0, 4.8]	0.07	2.5 [1.0, 6.2]	0.05
Ballooning								
Fructose consumption								
< 7 servings	-	-	-	-	-	-	-	-
> = 7 servings	1.3 [0.7, 2.3]	0.40	1.5 [0.8, 2.8]	0.19	2.1 [0.9, 4.5]	0.07	2.5 [1.0, 6.0]	0.05
Fibrosis								
Fructose consumption								
< 7 servings	-	-	-	-	-	-	-	-
> = 7 servings	2.5 [1.4, 4.4]	0.003	3.2 [1.7, 6.1]	0.0003	2.1 [0.1, 4.3]	0.05	3.2 [1.4, 7.4]	0.006

ABDELMALEK *et al,* Hepatology 2010;51:1961-71

Impact of physical activity on fibrosis: duration or intensity?

Retrospective analysis of 813 biopsy-proven NAFLD (CRN) with physical activity record

No PA
n=438

Moderate PA
n=162

Vigourous PA
n=213

		Moderate target met		Vigorous target met	
	Odds	Minimum	More Extensive	Minimum	More extensive
NASH[a]	**Unadjusted**	1.01 (0.62, 1.66)	1.1 (0.56, 2.2)	**0.62 (0.42, 0.90)**	**0.57 (0.36, 0.90)**
	Adjusted	1.24 (0.73, 2.1)	1.46 (0.68, 3.1)	**0.65 (0.43, 0.98)**	**0.56 (0.34, 0.90)**
Advanced fibrosis[b]	**Unadjusted**	1.1 (0.65, 1.8)	1.1 (0.55, 2.0)	**0.53 (0.34, 0.82)**	**0.41 (0.23, 0.72)**
	Adjusted	1.2 (0.69, 2.1)	1.1 (0.53, 2.3)	0.75 (0.46, 1.2)	**0.53 (0.29, 0.97)**

Table 1. DHHS and USDA recommendations for physical activity in adults

	Moderate physical activity (minutes a week)	Vigorous physical activity (minutes a week)
Minimum targets	≥150	≥75
Targets for more extensive health benefits	≥300	≥150

KISTLER *et al,* Am J Gastroenterol 2011

Drug treatment

- **Insulin sensitizers**
  - **Metformin, Pioglitazone**
- **Cytoprotective/Antioxidants**
  - **UDCA, Vitamin E**
- **New treatments (?)**
  - **Debate on GLP-1, obeticholic acid & Elafibranor**

Agreed outcome:

NASH resolution, no worsening of fibrosis

Whom to treat

- Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher). Patients with less severe disease, but at high risk of disease progression (i.e. with diabetes, MetS, persistently increased ALT, high necroinflammation) could also be candidates to prevent disease progression (**B1**)

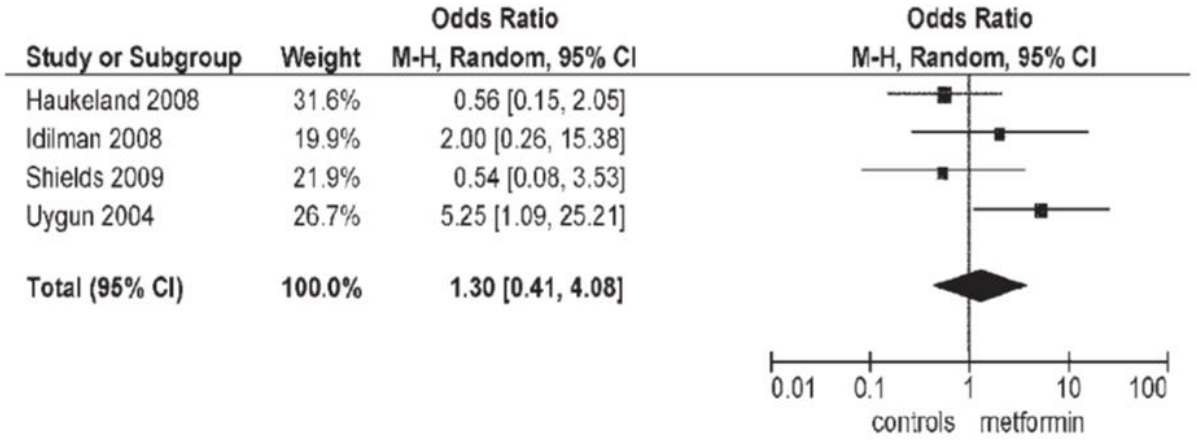
How to treat

- While no firm recommendations can be made, pioglitazone (most efficacy data, but off-label outside T2DM) or vitamin E (better safety and tolerability in the short-term) or their combination could be used for NASH (**B2**)
- The optimal duration of therapy is unknown; in patients with increased ALT at baseline, treatment should be stopped if there is no reduction in aminotransferases after 6 months of therapy; in patients with normal ALT at baseline, no recommendations can be made (**C2**)
- Statins may be confidently used to reduce LDL-cholesterol and prevent cardiovascular risk, with no benefits or harm on liver disease. Similarly *n*-3 polyunsaturated fatty acids reduce both plasma and liver lipids, but there are no data to support their use specifically for NASH (**B1**)

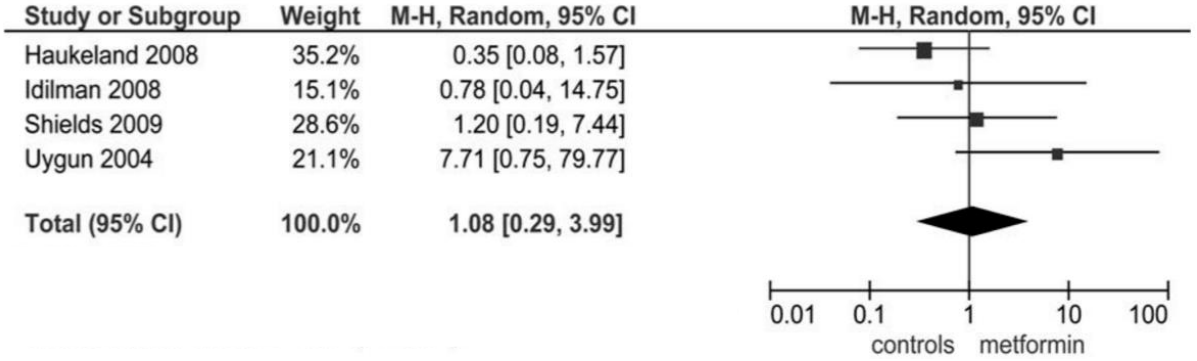
Role of bariatric surgery

By improving obesity and diabetes, bariatric (metabolic) surgery reduces liver fat and is likely to reduce NASH progression; prospective data have shown an improvement in all histological lesions of NASH, including fibrosis (**B1**)

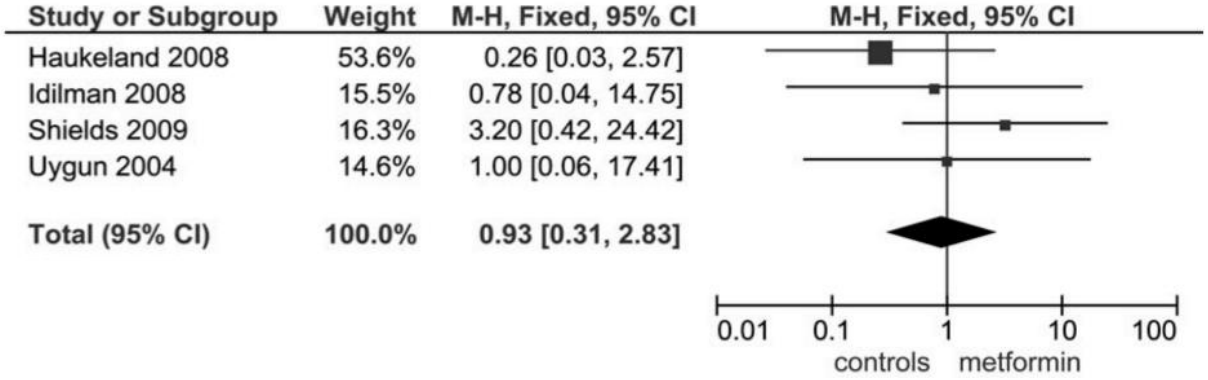
Metformin in NASH : R.I.P. ??



Steatosis



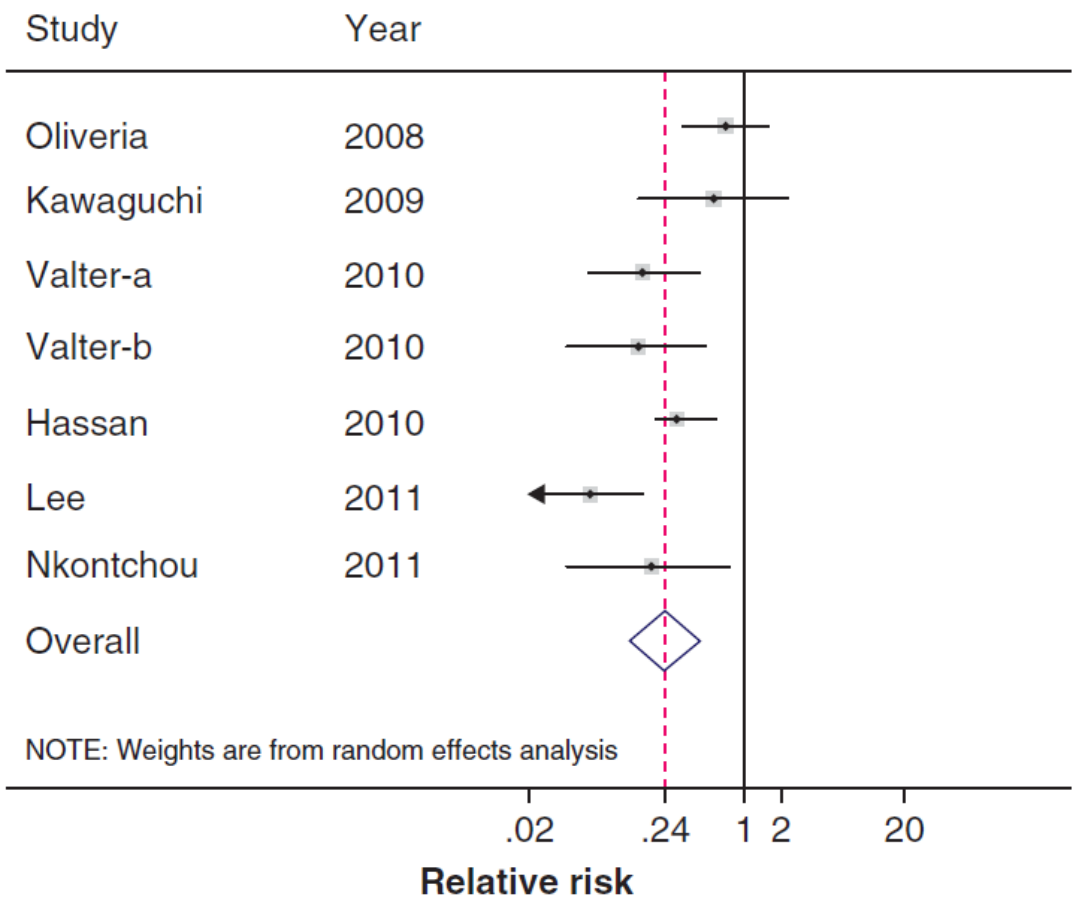
Inflammation



Fibrosis

MUSSO *et al,* Hepatology 2010;52:79-104

Pooled Relative Risks for HCC in diabetic patients treated with metformin: a meta-analysis



Significantly reduced risk of HCC in metformin users *vs.* nonusers in diabetic patients (RR 0.24, 95% CI 0.13 - 0.46)

ZHANG *et al,* Scand J Gastroenterol 2013;48:78-87

Glitazones in NAFLD

n	**10**	**26**	**32**	**31**	**80**
Glitazone regimen	Pioglitazone 30 mg + Vitamin E	Diet + Pioglitazone 45 mg	Rosiglitazone (4, then 8 mg)	Diet, exercise + Pioglitazone 30 mg	Pioglitazone 30 mg
Duration	**6 mo**	**6 mo**	**12 mo**	**12 mo**	**24 mo**
Study design	Pilot RCT	RCT	RCT	RCT	RCT
ALT	↓	↓	↓	↓	↓
Steatosis	↓	↓	↓	↓	↓
Inflammation	ND	↓	→	→	↓
Fibrosis	↓	→	→	↓	→
BW	→	+ 2.5 Kg	+ 1.5 Kg	+ 2.7 Kg	+ 4.7 Kg
Reference	Sanyal et al, CGH 2004	Belfort et al, NEJM 2005	Ratziu et al, Gastroenterology 2008	Aithal et al, Gastroenterology 2008	Sanyal et al, NEJM 2010

Insulin Sensitizers: a Meta-Analysis

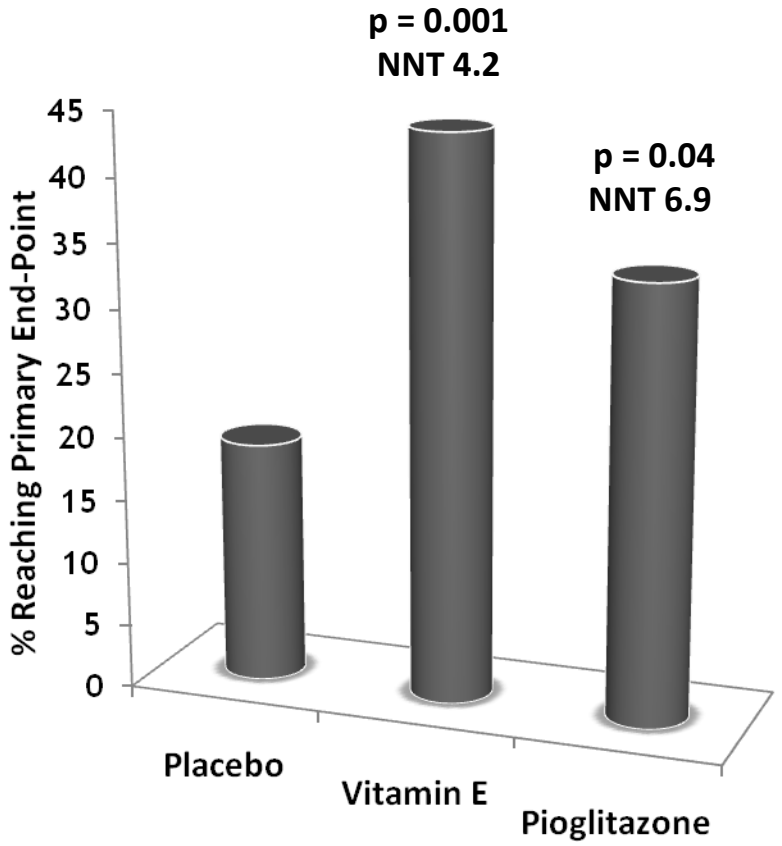
- 9 trials (5 using thiazolidinediones, 3 using metformin and 1 both)
- Compared with controls, glitazones improved steatosis, hepatocyte ballooning and ALT, but not inflammation or fibrosis
- In patients without diabetes, glitazones significantly improved all histological and biochemical outcomes, including fibrosis
- Metformin failed to improve any pooled outcome

RAKOSKI et al, Aliment Pharmacol Ther 2010; 32: 1211–21

The PIVENS Trial

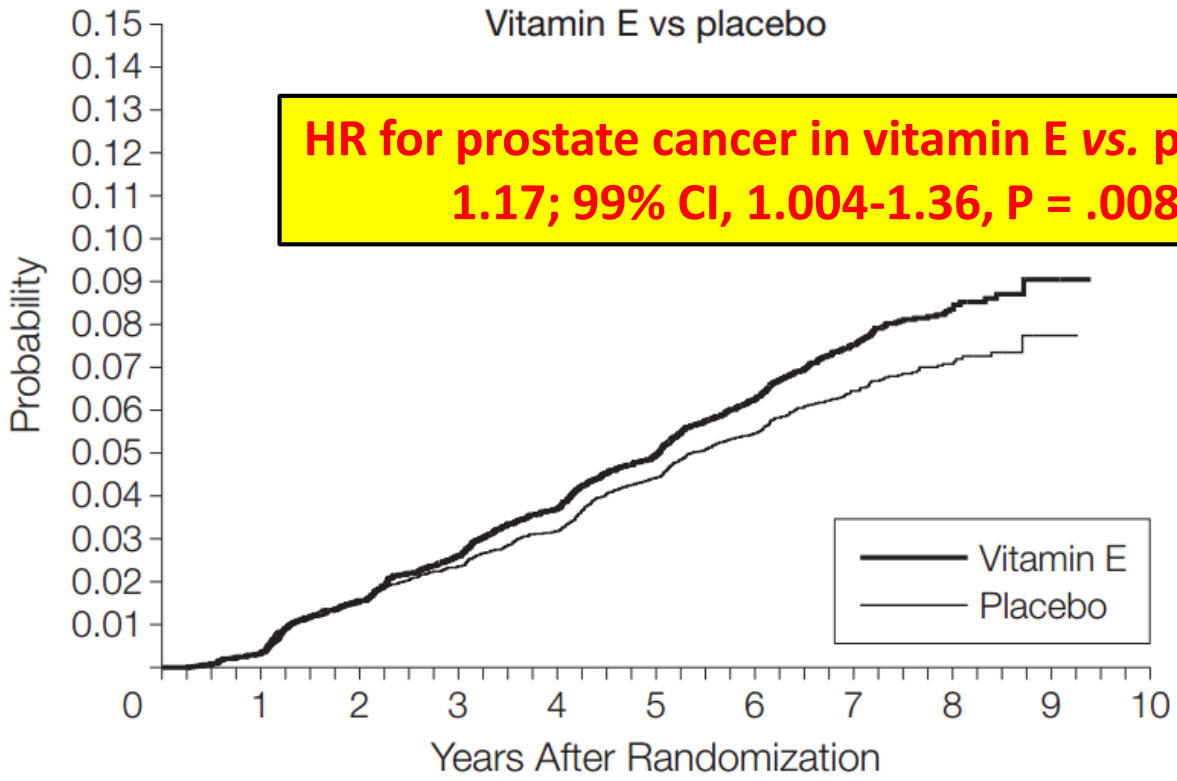
(n = 247 non-diabetic adults with NASH; primary outcome: histology)

- Interventions:
  - **30 mg Pioglitazone**
  - **800 IU Vitamin E**
  - **Placebo**
- Liver biopsy at 96 weeks
- Both agents improved steatosis and inflammation scores
- Only Vitamin E reduced ballooning
- Neither agent reduced fibrosis
- **Resolution of NASH in 30-40% of patients**



SANYAL *et al,* N Engl J Med 2010;362:1675-85

Dietary supplementation with vitamin E significantly increases the risk of prostate cancer among healthy men



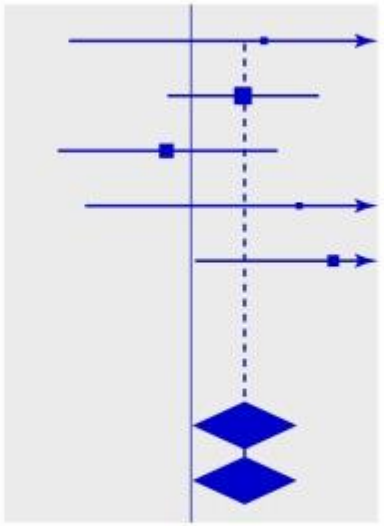
No. at risk									
Placebo	8565	8344	8081	7831	7471	6399	4044	1833	70
Cumulative cases	32	127	201	268	367	446	503	524	529
Vitamin E	8620	8397	8150	7839	7442	6394	4010	1821	50
Cumulative cases	29	135	223	314	415	512	586	614	620

KLEIN *et al,* JAMA 2011;306:1549-56

Vitamin E increases the risk of hemorrhagic stroke

A meta-analysis

Trial	No of events: Vitamin E group	No of events: Placebo group	Relative risk (95% CI)	Weight (%) (fixed effects)	Relative risk (95% CI)
HOPE 2000[14]	17/4761	13/4780		7.10	1.31 (0.64 to 2.70)
ATBC 2000[12]	108/14 238	89/14 281		48.61	1.22 (0.92 to 1.61)
WHS 2005[11]	44/19 937	48/19 939		26.25	0.92 (0.61 to 1.38)
WACS 2007[9]	15/4083	10/4088		5.47	1.50 (0.68 to 3.34)
PHS II 2008[13]	39/7315	23/7326		12.57	1.70 (1.02 to 2.84)
Pooled results					
Fixed effects model	223/50 334	183/50 414		100.00	1.22 (1.00 to 1.48)
Random effects model					1.22 (1.00 to 1.48)



Pooled relative risk 1.22 (1.00 to 1.48), P=0.045

SCHÜRKS *et al*, BMJ 2010;341:c5702

Lipid lowering agents

Fibrates (PPARα agonists)

- No benefit in two RCTs

Statins

- Definitely safe in NAFLD
- They improve LFTs

ATHYROS *et al,* Lancet 2010

- May reduce HCC risk

SIEGEL & EL-SERAG, Expert Rev Gastroenterol Hepatol 2013

- They can be used in NAFLD with dyslipidemia

CHALASANI et al, Hepatology 2012

- Increased risk of T2D?

Omega-3 PUFAs

- Reduce liver fat in meta-analysis

PARKER *et al,* J Hepatol 2012

GFT 505 (elafibranor, by Genfit), a dual PPAR δ/α agonist

- Improvement of ALAT, ASAT, γGT, ALP, insulin sensitivity and glucose homeostasis
- Decrease of plasma triglycerides and LDL-C, and increase of HDL-C levels
- Anti-inflammatory properties
- In October 2013, Data Safety and Monitoring Board (DSMB) concluded that GFT505 showed no safety issue
- In February 2014, the FDA granted Fast Track designation to GFT505 in NASH

- Phase 2b study (GOLDEN-505), after 52 weeks of 120 mg of elafibranor in non-cirrhotic patients:
  - Improvement of NASH
  - Improvement of fibrosis in responders
  - Improvement of serum biomarkers in parallel with NAS score

SANYAL *et al*, AASLD 2015

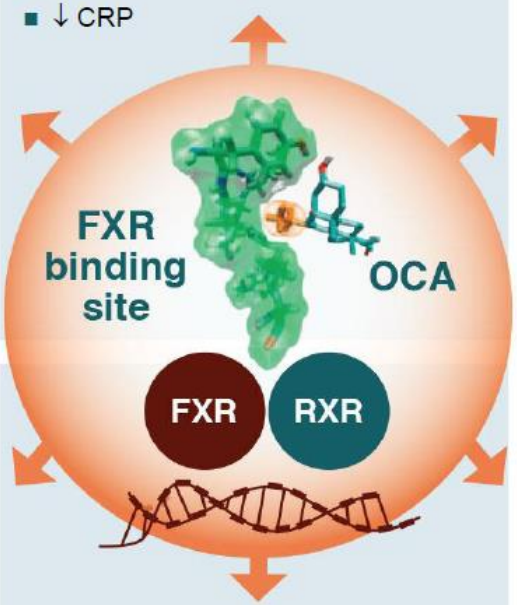
Bile acid receptor Farnesoid X receptor agonists (FXR) is central to several pathways

FIBROSIS

- ↓Stellate cell activation (α-SMA)
- ↑Stellate cell apoptosis (TIMP-1)
- ↓Fibrogenesis (TGF-β1)
- ↑Matrix degradation (MMP-2)

INFLAMMATION

- ↓ NF-κB
- ↓ TNFα, IL-1β, IL-17, IFN-γ
- ↓ CRP



ATHEROSCLEROSIS

- ↑Vasodilation (eNOS)
- ↓Inflammation (COX-2, iNOS)
- ↓Calcification (JNK)
- ↓Smooth muscle cell migration

LIPID METABOLISM

- ↓Triglyceride synthesis (SREBP-1c)
- ↑Triglyceride clearance (apoC-III)
- ↓HDL-C (SR-B1, CETP)
- ↑LDL-C (CETP)

GLUCOSE METABOLISM

- ↑ Insulin signaling (FGF19)
- ↑ Insulin sensitivity (IRS-1, IRS-2)
- ↑ Insulin production (KLF11, GLUT-2)
- ↓ Hepatic gluconeogenesis (PEPCK)

BILE ACID HOMEOSTASIS

- ↓ Bile acid synthesis (CYP7A1)
- ↓ Bile acid uptake (NTCP)
- ↑ Bile acid secretion (BSEP)
- ↓Bile acid absorption (ASBT)

In vitro/in vivo studies do not necessarily correlate with clinical response.

Conclusions

- For the EASL CPG, data were retrieved by an extensive PubMed search up to 04/2015
- The final statements are graded according to level of evidence and strength of recommendation, which are adjustable to local regulations and/or team capacities
- The document is intended both for practical use and for advancing the research and knowledge of NAFLD in adults
- The final purpose is to improve patient care and awareness of the importance of NAFLD, and to assist stakeholders in the decision-making process by evidence-based data, also considering the burden of clinical management for the healthcare system