NAFLD and diabetes : the prespective friom the Hepatologist

Symposium Paris NASH June 30th- July 1st 2016

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faculté de médecine
Pierre et Marie CURIE

- Epidemiological links (and complexity)
- Disease burden
  - Screening ?
- Management : lifestyle vs. drugs

Follow-up fatty liver status and incident diabetes

Developement of Fatty Liver	OR : 2.5 (95% IC 1.5-4.1), p<0.001
Worsening of Fatty Liver	OR : 7.4 (95% IC 3.4-16.2), p<0.001
Resolution of Fatty Liver	OR : 0.95 (95% IC 0.46-1.6), p=0.9

Sung, JCEM 2013

- Epidemiological links (and complexity)
- Disease burden
  - Screening ?
- Management : lifestyle vs. drugs

Standardized Mortality Ratios in Type II Diabetes

n=7148, Verona Diabetes Study, 1987-1991

	SMR (95% CI)
All Causes	1.42 (1.35-1.5)
Diabetes	4.47 (1.23-1.44)
Cirrhosis	2.52 (1.96-3.2)
Cardiovascular	1.34 (1.23-1.44)
Malignancy	1.05 (0.94-1.17)
Respiratory	1.14 (0.91-1.42)

De Marco, Diabetes Care 1999

Impact of NAFLD on mortality in diabetic patients

Community based study i

Table 4. Multivariate Cox proportional hazard modeling for predictors of death in patients with diabetes mellitus

Variable	*P* value	HR	95% CI
Age (years)			
<50		1.0 (reference)	
50–60	0.22	2.2	0.6–7.9
60–70	0.005	5.8	1.7–19.7
>70	<0.001	12.9	3.6–46.3
Gender	0.96	1.0	0.6–1.8
Date of DM diagnosis	0.01	1.1	1.03–1.2
Smoker	0.45	1.2	0.7–2.2
Hypertension	0.61	1.2	0.7–2.0
Obesity	0.65	0.9	0.5–1.5
Hyperlipidemia	0.14	0.5	0.2–1.3
Earlier malignancy	0.03	2.4	1.1–5.3
CVD	0.02	2.8	1.2–6.7
IHD	0.01	2.3	1.2–4.4
NAFLD	0.03	2.2	1.1–4.2

no NAFLD
N=231)

F/u (yrs) 11.7 (5)

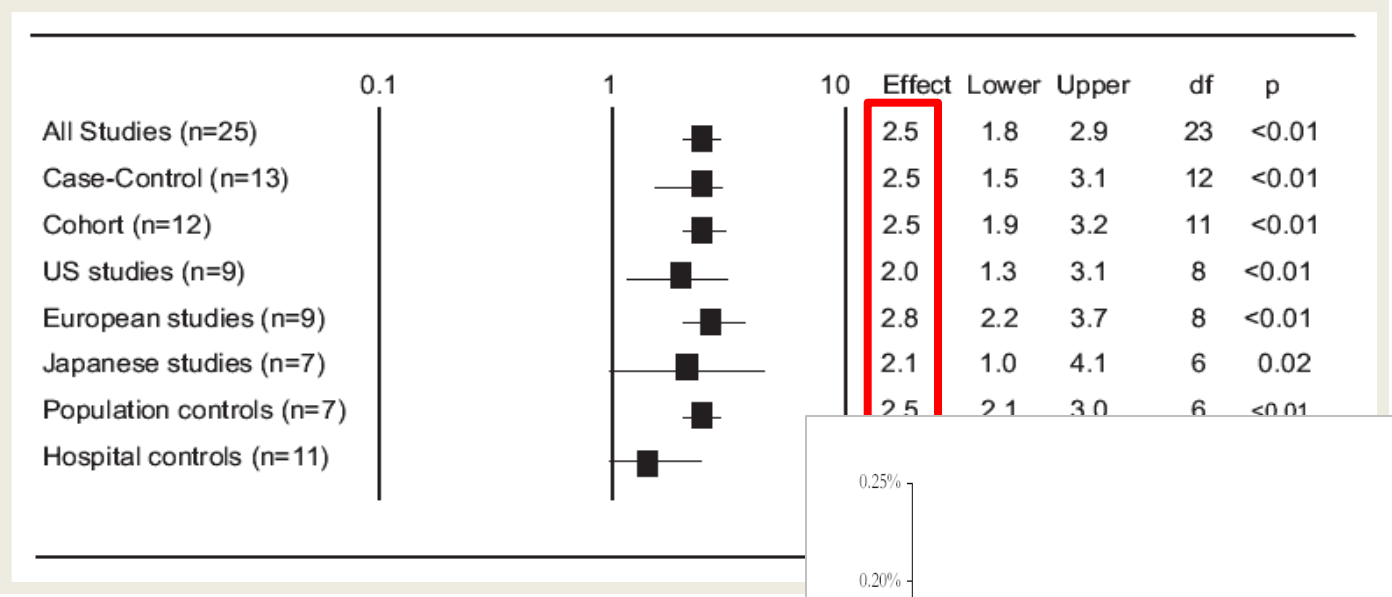
Liver–related dea 0

Malignancy 3 (18%)

- NAFLD i all mortality
- Increased nd neoplasia-related mortality

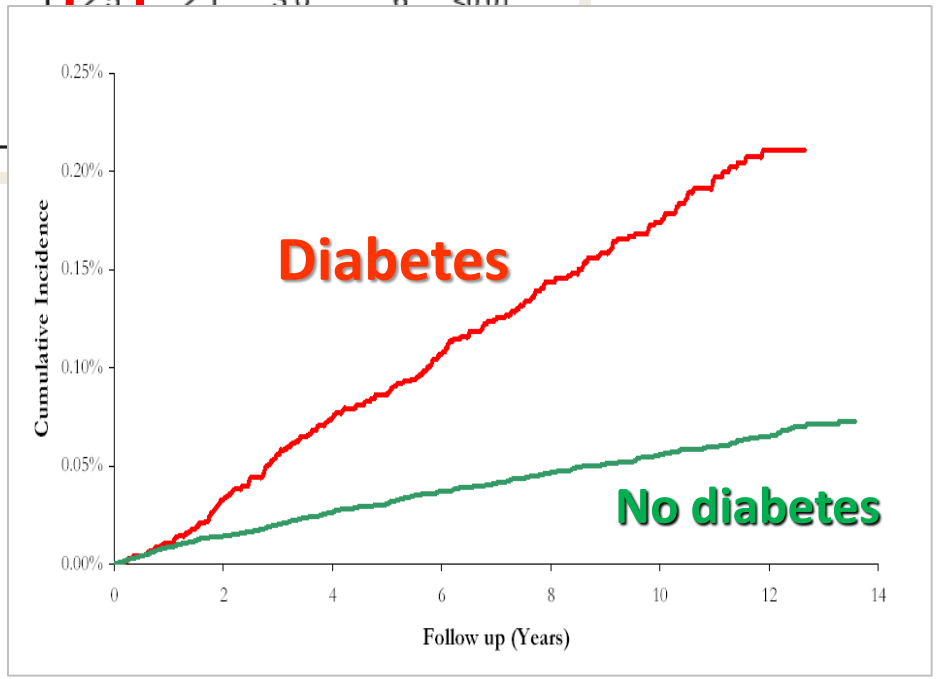
Adams, AM J Gastro 2010

NASH and HCC : Indirect evidence



El Serag, Clin Gastro Hepatol 2006

El Serag, Gastroenterology 2006



NAFLD is the most common risk factor in large population databases in the US

MarketScan

(2002-2008)

Condition	HCC (n=4406)	Controls (n=44060)
NAFLD/NASH	58.5 %	3.1 %
Diabetes	35.8 %	20.4 %
HCV	21.9 %	0.4 %
Alcohol	12.2 %	0.2 %
HBV	5.7 %	0.1 %

Prevalence HCC: 0.23%

Sanyal, CMRO 2010

SEER-Medicare database

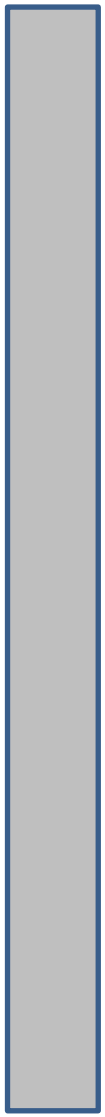
(1993-2005)

CHC (n=3649)	Controls (n=195953)
37.1 %	17.1 %
54.7 %	26.9 %
18.3 %	0.3 %
16.9 %	0.4 %
7.3 %	0.2 %

MS : independent risk factor (x2.13)

Welzel, Hepatology 2011

Diabetes in Pts with CLD (NAFLD)



?

First-recorded, experimental, evidence-based approach (for trying to find the truth)

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36 Then Gideon said to God, “If you will save
Israel by my hand, as you have
said, **37** behold, I am laying a fleece of wool
on the threshing floor. If there is dew on the
fleece alone, and it is dry on all the ground,
then I shall know that you will save Israel by
my hand, as you have said.”**38** And it was so.
When he rose early next morning and
squeezed the fleece, he wrung enough dew
from the fleece to fill a bowl with water[39].

Judges, 6,25:40

First-recorded, experimental, evidence-based approach (for trying to find the truth)

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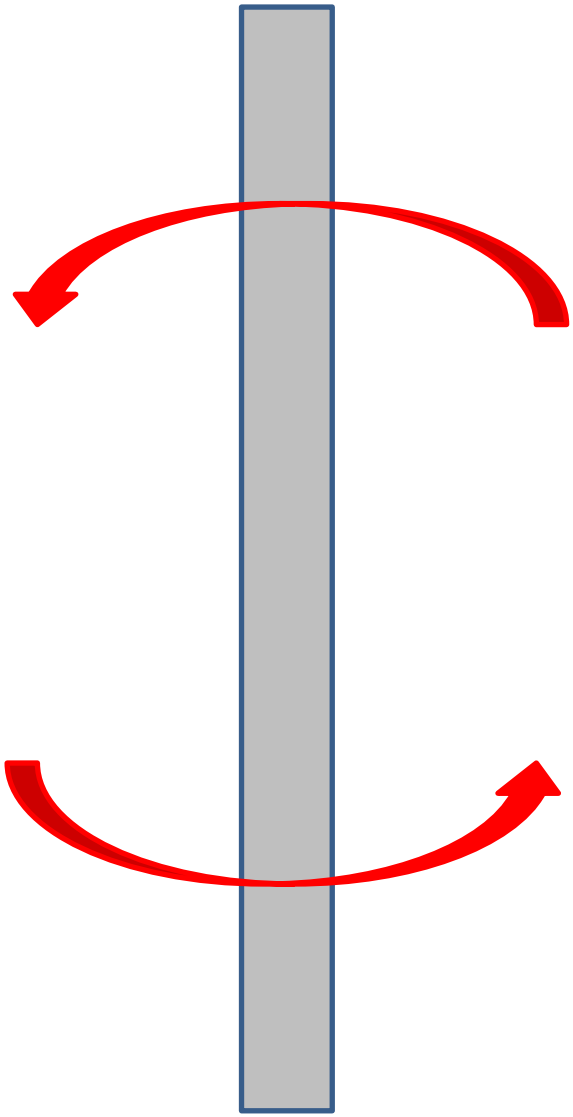
squeezed the fleece, he wrung enough dew
from the fleece to fill a bowl with water39.
Then Gideon said to God, “Let not your
anger burn against me; let me speak just
once more. Please let me test just once
more with the fleece. Please let it be dry on
the fleece only, and on all the ground let
there be dew.” 40 And God did so that night;
and it was dry on the fleece only, and on all
the ground there was dew.

Diabetes in Pts with CLD (NAFLD)



CLD (NAFLD) in patients with diabetes

First records of CLDs in Scotland by diabetes status

Retrospective population-based cohort
Scottish Diabetes Register & National hospital cancer and death records
2004-2013; 40-89 years; 26 M Pt/years of F/u
97% mono diagnosis of CLD

Type of liver disease	Type 2 diabetes		No diabetes	
	Deaths	Hospital admissions	Deaths	Hospital admissions
Alcoholic liver disease	213	1773	2532	13345
Autoimmune liver disease	19	218	129	1925
Hemochromatosis	11	410	42	1966
Hepatocellular carcinoma	52	844	116	1932
Non-alcoholic fatty liver disease	327	2942	1435	8283
Viral liver disease	26	220	242	2515

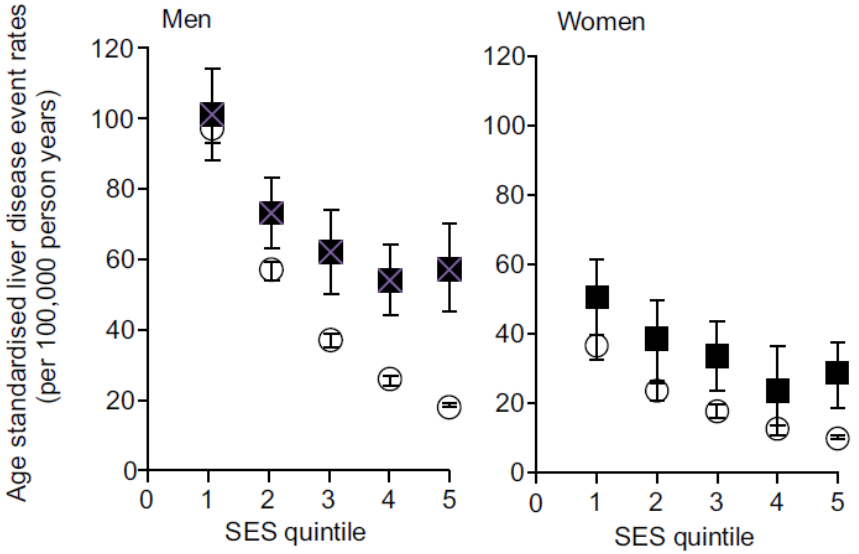
Wild, J Hepatol 2016

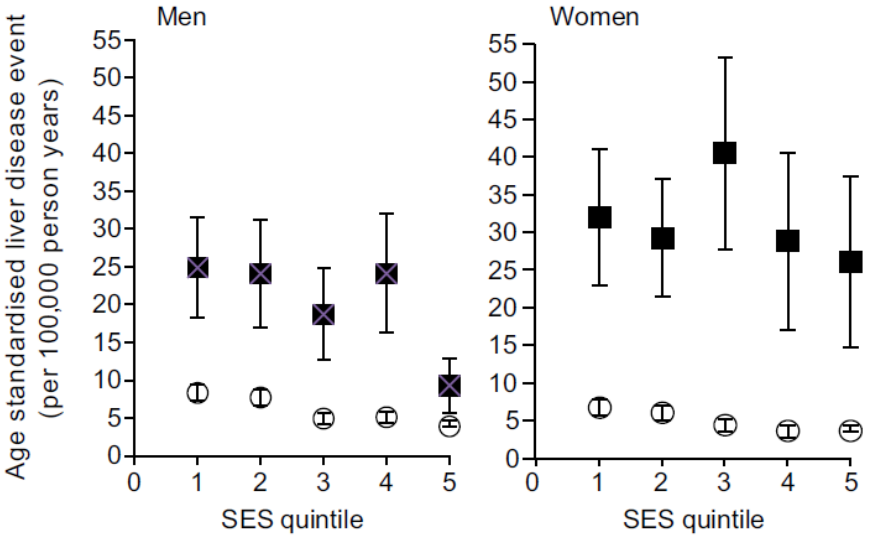
Sex-specific rate ratios in diabetes for CLDs

Type of liver disease	Men	Women
	Age and SES quintile adjusted	Age and SES quintile adjusted
Alcoholic liver disease*	1.38 (1.15-1.65)	1.57 (1.28-1.93)
Autoimmune liver disease	1.50 (1.12-2.01)	1.25 (1.04-1.49)
Hemochromatosis	1.67 (1.43-1.94)	1.60 (1.23-1.97)
Hepatocellular carcinoma	3.36 (2.97-3.81)	3.55 (3.02-4.17)
Non-alcoholic fatty liver disease*	3.03 (2.68-3.43)	5.11 (4.45-5.87)
Viral liver disease	1.28 (0.86-1.92)	2.20 (1.52-3.18)

Wild, J Hepatol 2016

Age-standardised incidence of hospital admission and deaths





Wild, J Hepatol 2016

Research Article

CrossMark

EASL JOURNAL OF HEPATOLOGY

Type 2 diabetes and risk of hospital admission or death for chronic liver diseases

Sarah H. Wild[1,*], Joanne R. Morling[1], David A. McAllister[1], Jan Kerssens[2], Colin Fischbacher[2], Julie Parkes[3], Paul J. Roderick[4], Naveed Sattar[5], Christopher D. Byrne[6,7], on behalf of the Scottish and Southampton Diabetes and Liver Disease Group, and the Scottish Diabetes Research Network Epidemiology Group[†]

and sex modified the association between T2DM and NAFLD. We suggest that there may be a role for targeted case finding of CLD and appropriate intervention in high risk populations including people with T2DM. The increasing global prevalence of T2DM can be expected to result in an increasing burden of all CLDs.

Not routine screening, but vigilance for chronic liver disease in patients with type 2 diabetes

Vincent Wai-Sun Wong[1,*], Naga Chalasani[2,*]

for NAFLD) at this time. We encourage health care providers taking care of diabetic patients to be vigilant for any signs and symptoms of chronic liver disease and refer the patients for further assessment and management.

Table 1. Wilson and Jungner classic screening criteria [16].

Factors	Criteria
Disease	The condition sought should be an important health problem.
	There should be a recognized latent or early symptomatic stage.
	The natural history of the condition, including development from latent to declared disease, should be adequately understood.
Setting	Facilities for diagnosis and treatment should be available.
Diagnosis	There should be a suitable test or examination.
	The test should be acceptable to the population.
	Case finding should be a continuing process and not a "once and for all" project.
Treatment	There should be an accepted treatment for patients with recognized disease.
	There should be an agreed policy on whom to treat as patients.
Cost-effectiveness	The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

Position Paper

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

A position statement on NAFLD/NASH based on the EASL 2009 special conference☆

Vlad Ratziu[a], Stefano Bellentani[b,*], Helena Cortez-Pinto[c], Chris Day[d], Giulio Marchesini[e]

Diagnostic strategies for NASH

Many individuals at risk for NAFLD/NASH seek medical attention outside the Hepatology clinics and therefore it is important to establish whether and in what settings screening or case finding [141] for NASH is deemed necessary (see "Case finding"). Conversely, when patients with suspected NAFLD/NASH are addressed for hepatological investigations, the procedures to be performed need to be need to be defined on an individualized basis (see "Individual diagnostic strategies in clinical practice"), in particular the indications for liver biopsy.

Case finding

Screening or case finding of NASH [141] aims at diagnosing advanced liver disease, defined as NASH with bridging fibrosis or cirrhosis. Beyond the prognostic information it provides this may also change patient management including specific monitoring strategies, a stricter enforcement of diet and lifestyle measures, or the use of liver-targeted pharmacologic therapy.

Premises:

(1) In the general population, there are currently insufficient data on the prevalence of NASH, NASH-related mortality

fibrosis. In patients with both increased ALT anc
ultrasound (at higher risk for advanced liver dise
#3), liver biopsy could be the first-line procedure
sive independent validation of non-invasive meth
available.

3. Patients with chronic liver diseases other than N/
screened for metabolic risk factors, IR, and steat
sound. If all these are present, we suggest that
be performed to assess concurrent NAFLD, as c
invasive methods in patients with concurrent li
are lacking.
4. During elective surgical procedures, such as anti
gery (high risk of NASH and of unsuspected cirrho
lecystectomy (shared risk factors between
cholelithiasis), we suggest that a liver biopsy be

Individual diagnostic strategies in clinical practice

In patients referred for probable NAFLD to the hepat
biopsy should be performed based on an individuali
rather than rigid guidelines. Liver biopsy provides bo
and prognostic information on fibrosis and potential
sion. Liver biopsy should not be performed in p

Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

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

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

Introduction

The Clinical Practice Guidelines propose recommendations for the diagnosis, treatment and follow-up of non-alcoholic fatty liver disease (NAFLD) patients and are the product of a joint effort by the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO). They update a position statement based on the 2009 EASL Special Conference [1].

The data have been retrieved by an extensive PubMed search up to April 2015. The final statements are graded according to the level of evidence and strength of recommendation, which are adjustable to local regulations and/or team capacities (Table 1) [2]. In particular, screening for NAFLD in the population at risk should be in the context of the available resources, considering the burden for the national health care systems and the currently limited effective treatments. The document is intended both for practical use and for advancing the research and knowledge of NAFLD in adults, with specific reference to paediatric NAFLD whenever necessary. 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 providing evidence-based data, which also takes into consideration the burden of clinical management for the healthcare system.

Definition

NAFLD is characterised by excessive hepatic fat accumulation, associated with insulin resistance (IR), and defined by the presence of steatosis in >5% of hepatocytes according to histological analysis or by a proton density fat fraction (providing a rough estimation of the volume fraction of fatty material in the liver) >5.6% assessed by proton magnetic resonance spectroscopy (^{1}H-MRS) or quantitative fat/water selective magnetic resonance imaging (MRI). NAFLD includes two pathologically distinct conditions with different prognoses: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH); the latter covers a wide spectrum of disease severity, including fibrosis, cirrhosis and hepatocellular carcinoma (HCC) (Table 2).

The diagnosis of NAFLD requires the exclusion of both secondary causes and of a daily alcohol consumption ⩾30 g for men and ⩾20 g for women [1]. Alcohol consumption above these limits indicates alcoholic liver disease. The relationship between alcohol and liver injury depends on several cofactors (type of alcoholic beverage, drinking patterns, duration of exposure, individual/genetic susceptibility), rendering simple quantitative thresholds at least partly arbitrary. Specifically, patients consuming moderate amounts of alcohol may be still predisposed to NAFLD if they have metabolic risk factors. Of note, the overall impact of metabolic risk factors on the occurrence of steatosis appears to be higher than that of alcohol in these patients [3]. The definitive diagnosis of NASH requires a liver biopsy.

Received 4 November 2015; accepted 4 November 2015

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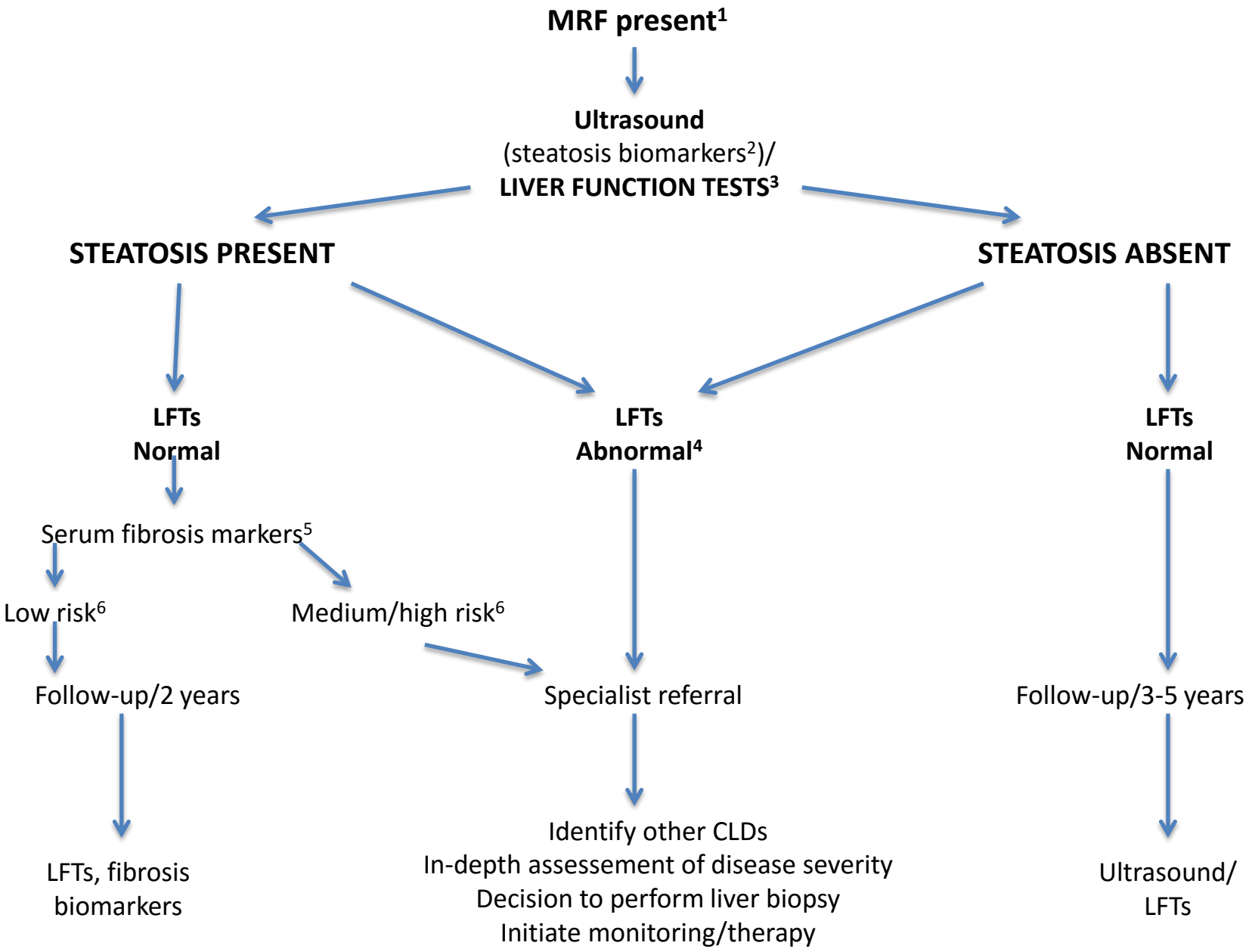
These Guidelines were developed by the EASL, EASD and the EASO, and are published simultaneously in the *Journal of Hepatology*, *Diabetologia* and *Obesity Facts*.

Abbreviations: ALT, alanine transaminase; BMI, body mass index; CAP, controlled attenuation parameter; CCR, chemokine receptor; CK-18, cytokeratin-18 fragments; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; ELF, enhanced liver fibrosis; F, fibrosis stage; FIB-4, fibrosis 4 calculator; FLI, fatty liver index; HbA1c, glycosylated haemoglobin A1c; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IR, insulin resistance; LDL, low-density lipoprotein; MetS, metabolic syndrome; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis; NPV, negative predictive value; OGTT, oral glucose tolerance test; PNHS, paediatric NAFLD histological score; PNPLA3, patatin-like phospholipase domain containing 3; PPAR, peroxisome proliferator-activated receptor; PPV, positive predictive value; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trials; SAF, steatosis, activity and fibrosis; T2DM, type 2 diabetes mellitus; TM6SF2, transmembrane 6 superfamily 2; UDCA, ursodeoxycholic acid; US, ultrasound.

Please cite this article in press as: , . EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2015.11.004

Recommendations

- All individuals with steatosis should be screened for features of MetS, independent of liver enzymes. All individuals with persistently abnormal liver enzymes should be screened for NAFLD, because NAFLD is the main reason for unexpectedly elevated liver enzymes (**A1**)
- In subjects with obesity or MetS, screening for NAFLD by liver enzymes and/or ultrasound should be part of routine work-up. In high risk individuals (age >50 years, T2DM, MetS) case finding of advanced disease (i.e. NASH with fibrosis) is advisable (**A2**)

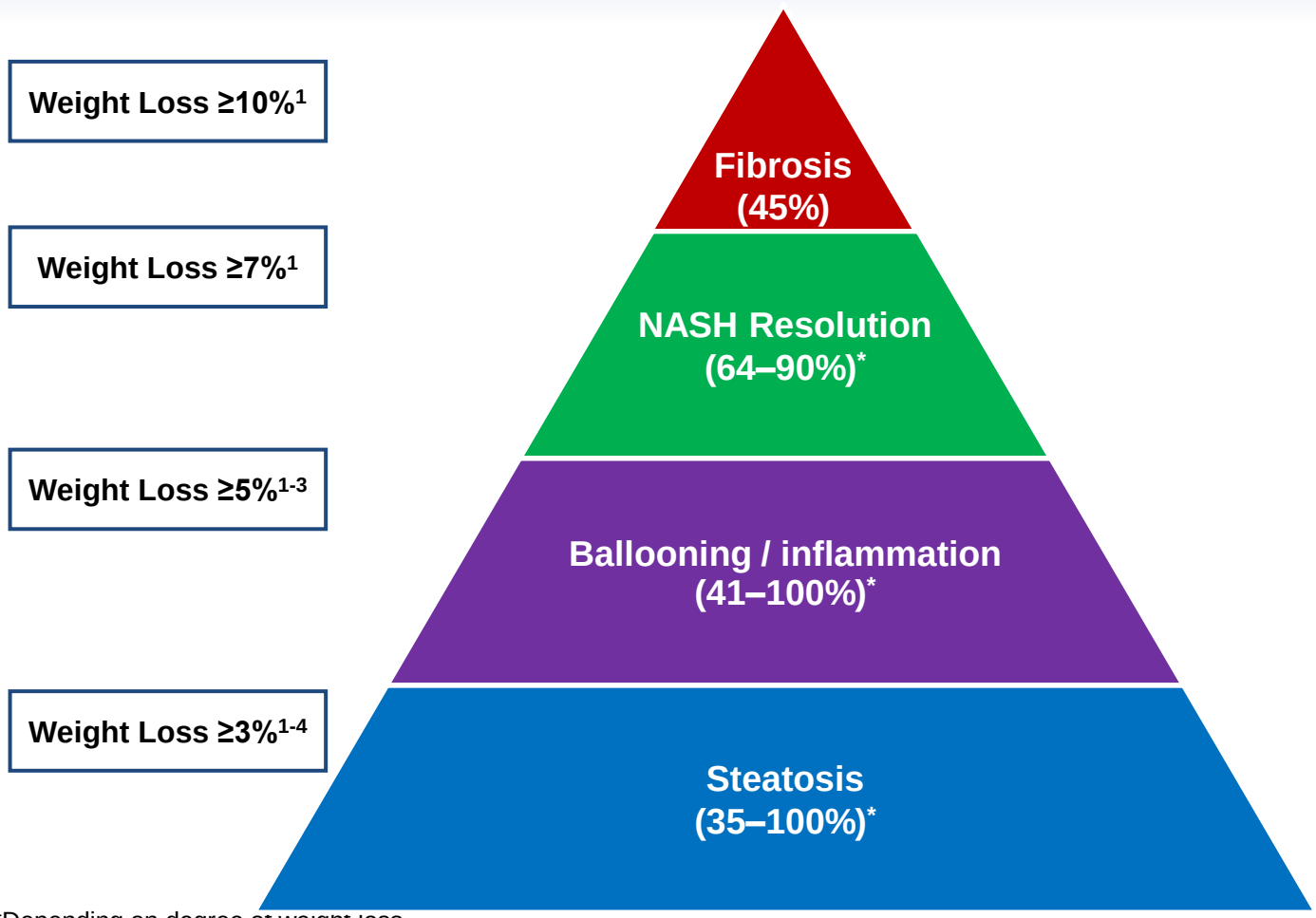


NASH CPG EASL 2016

- Epidemiological links (and complexity)
- Disease burden
  - Screening ?

➡ Management : lifestyle vs. drugs

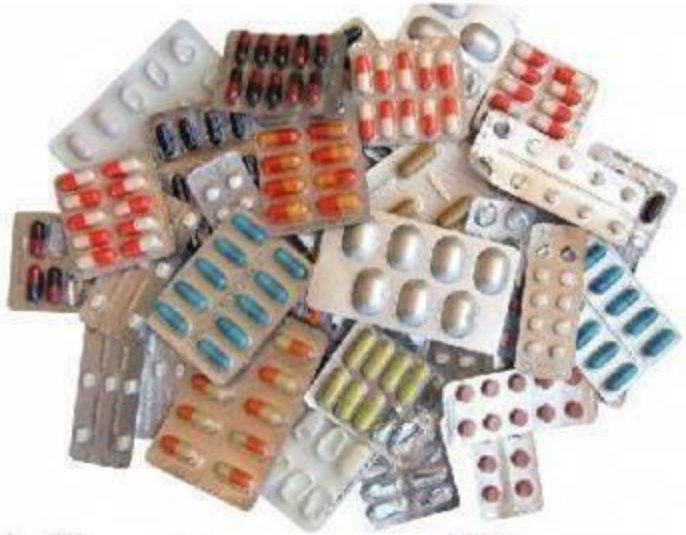
Weight loss pyramid



*Depending on degree of weight loss

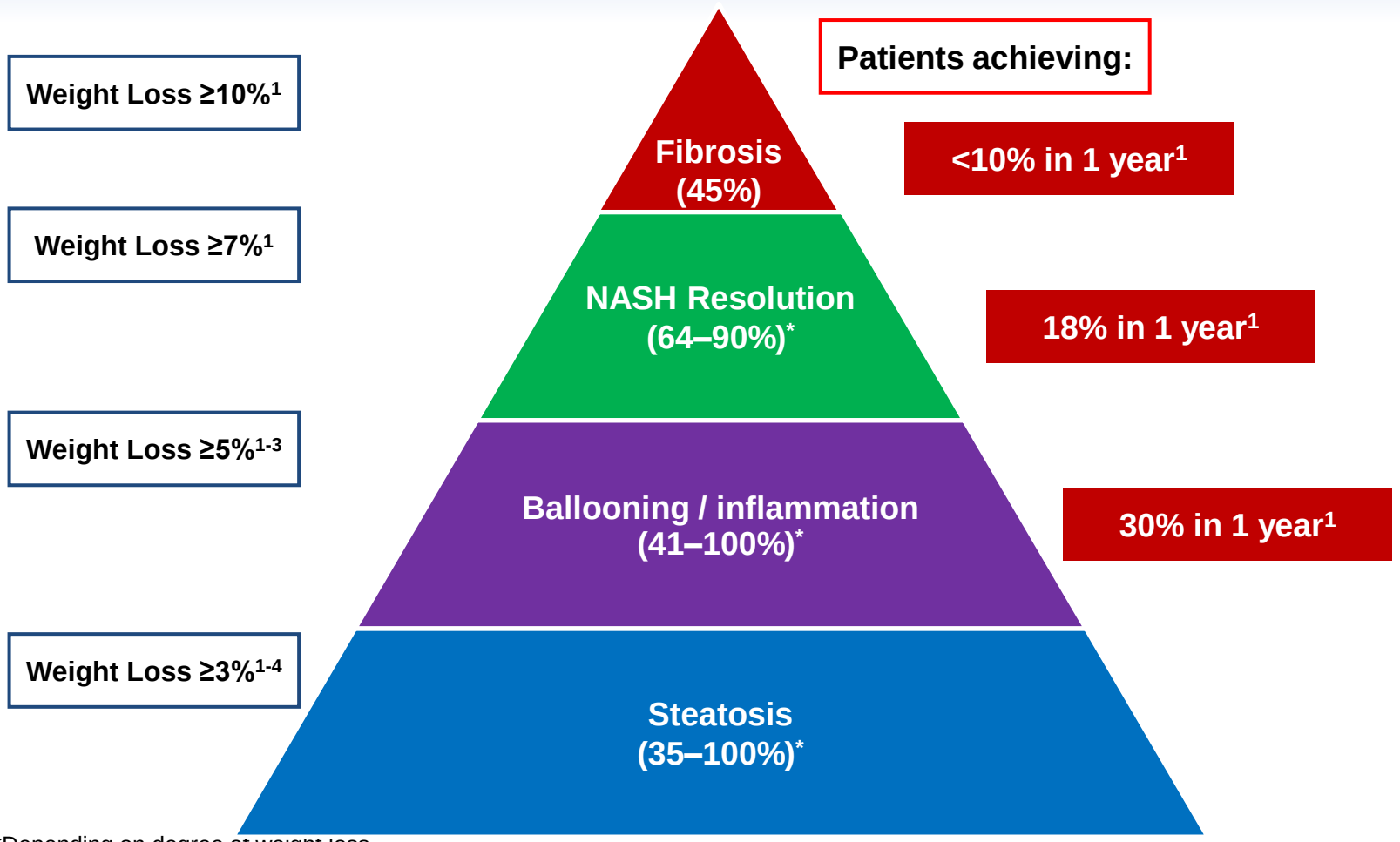
1 Vilar-Gomez E, et al. Gastroenterology. 2015;149:367-78. 2 Promrat K, et al. Hepatology. 2010;51:121-9
3 Harrison SA, et al. Hepatology. 2009;49:80-6. 4 Wong VW, et al. J Hepatol. 2013;59:536-42

Slide courtesy of S. Harrison



Choice is Yours

Weight loss pyramid



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Slide courtesy of S. Harrison

Gastroenterology 2015;149:367–378

CLINICAL—LIVER

Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis

Eduardo Vilar-Gomez,[1,2] Yadina Martinez-Perez,[1] Luis Calzadilla-Bertot,[1] Ana Torres-Gonzalez,[1] Bienvenido Gra-Oramas,[3] Licet Gonzalez-Fabian,[3] Scott L. Friedman,[4] Moises Diago,[5] and Manuel Romero-Gomez[2]

Table 2. Improvement of Histologic Outcomes Across Different Categories of Weight Loss at the End of Treatment

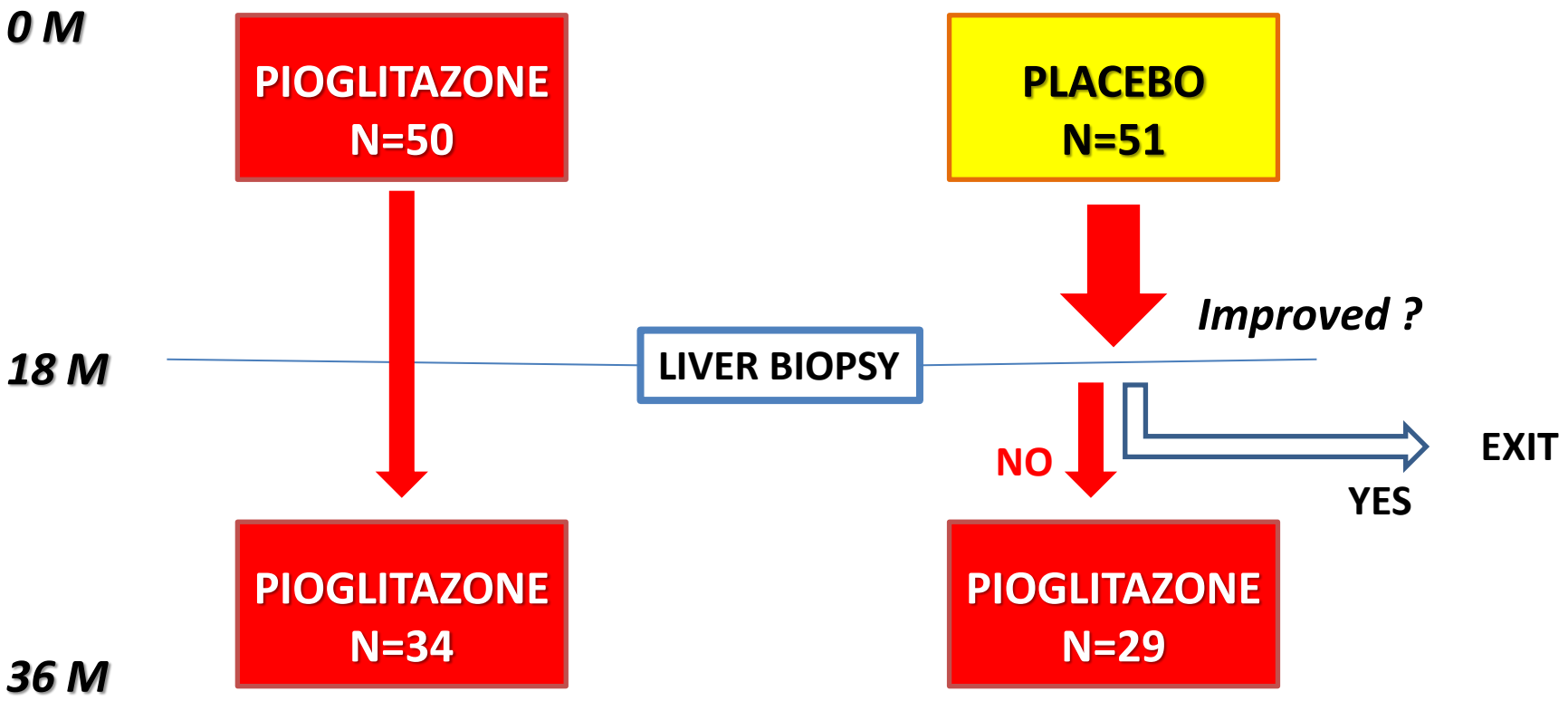
Variables	Overall (n = 293)	WL <5 (n = 205)	WL = 5–6.99 (n = 34)	WL = 7–9.99 (n = 25)	WL ≥10 (n = 29)	*P* value
Weight loss, %	3.8 ± 2.7	1.78 ± 0.16	5.86 ± 0.09	8.16 ± 0.22	13.04 ± 6.6	—
Resolution of steatohepatitis[a]	72 (25)	21 (10)	9 (26)	16 (64)	26 (90)	<.01

« …among patients with weight loss btw 7-10%, the presence of female sex, fasting glucose levels >5.5 mmol/l, many ballooned cells at baseline and a BMI >35 kg/m² clearly reduced the probability of steatohepatitis resolution. »

Vs.

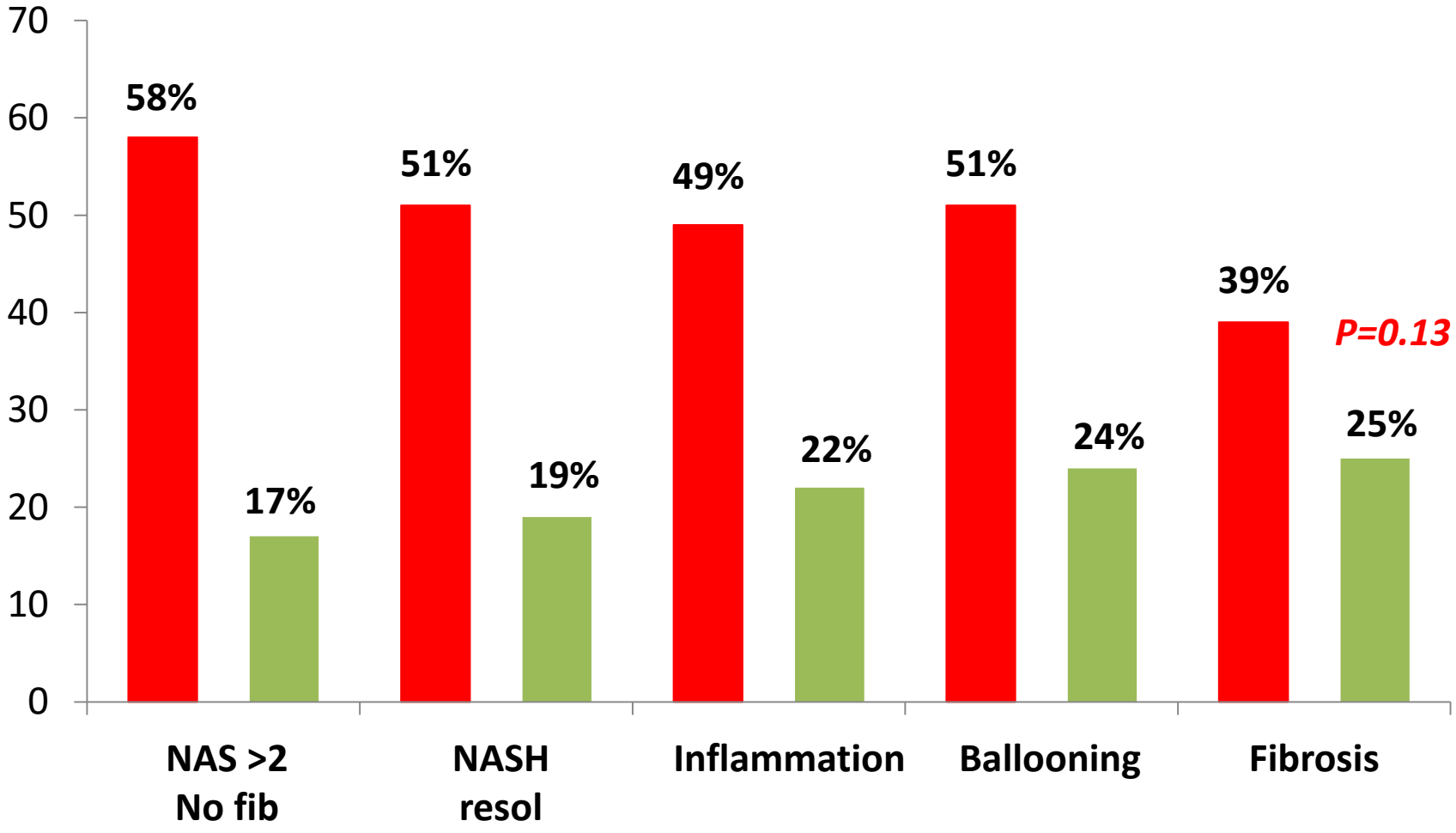
Short and long-term pioglitazone for NASH

- Histologically confirmed NASH
- OGTT: pre-diabetes or diabetes only
- Pioglitazone (30 mg/d then 45 mg/d) vs. placebo



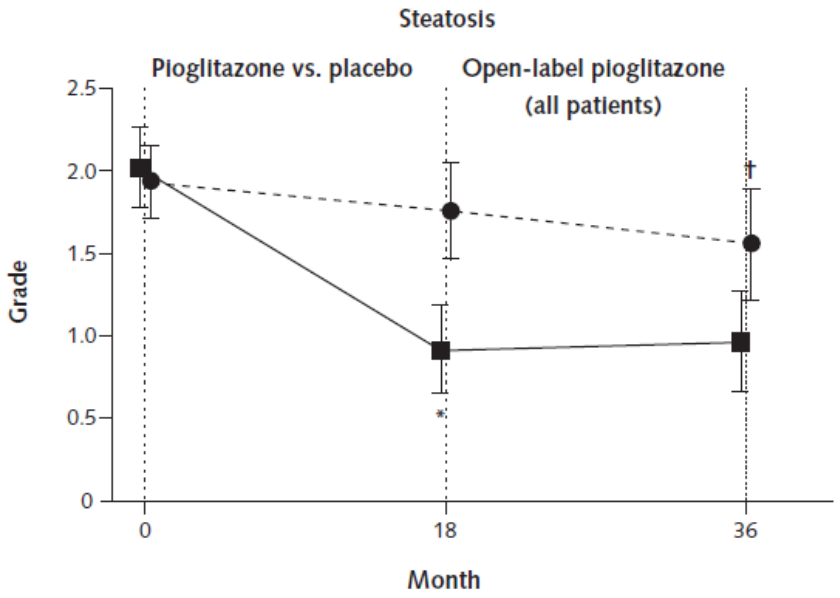
Cusi, Ann Intern Med 2016

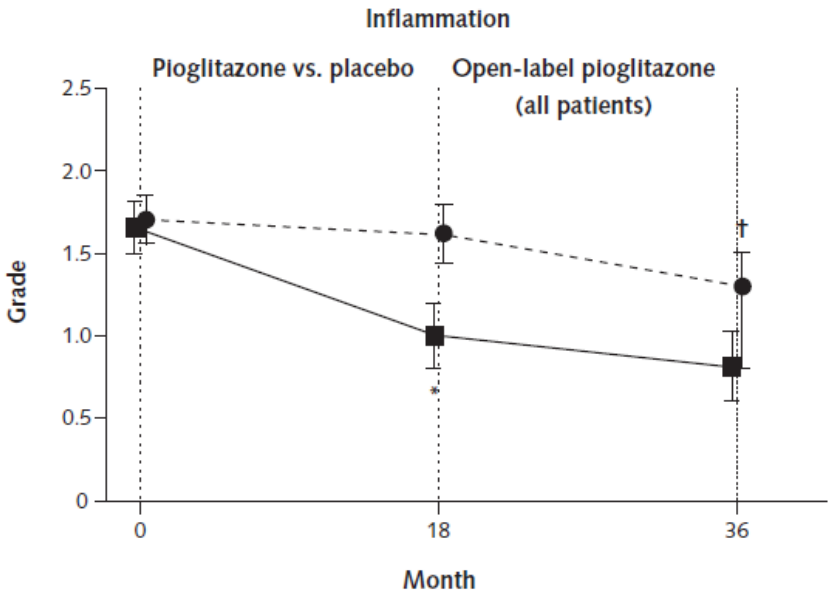
Histological improvement at 18 months

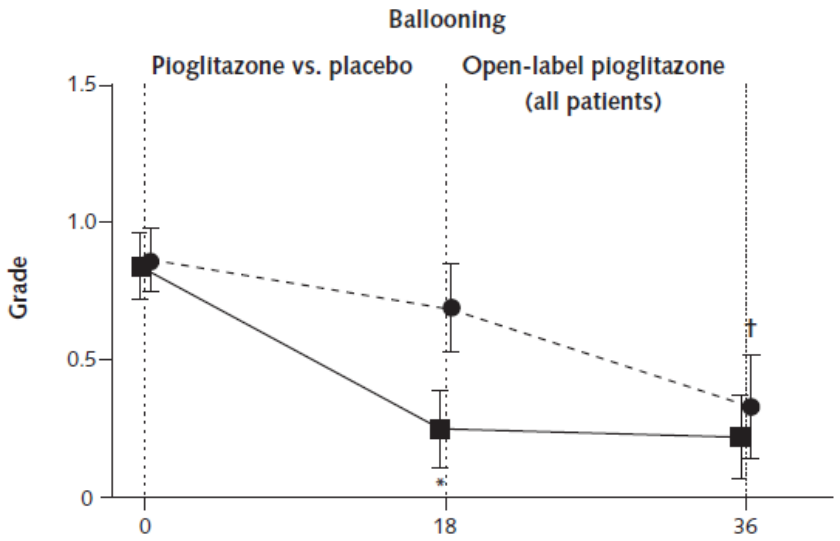


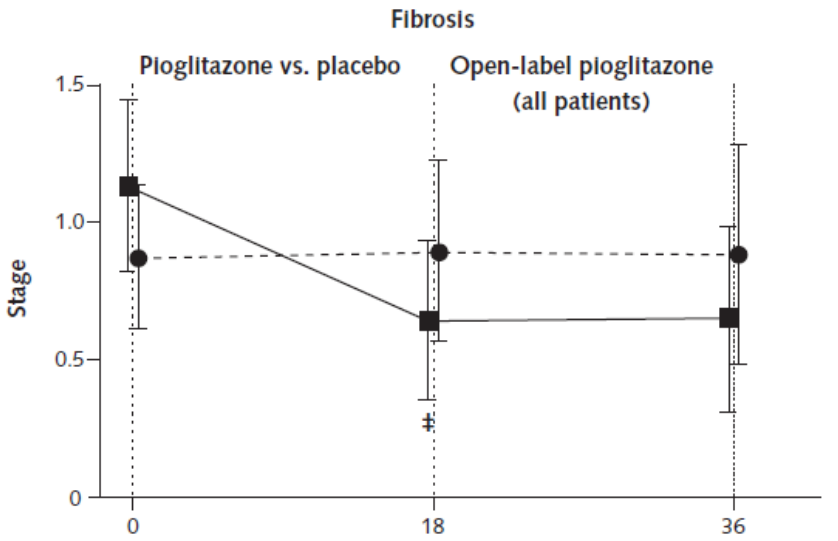
Cusi, Ann Intern Med 2016

Short and long-term histological improvement

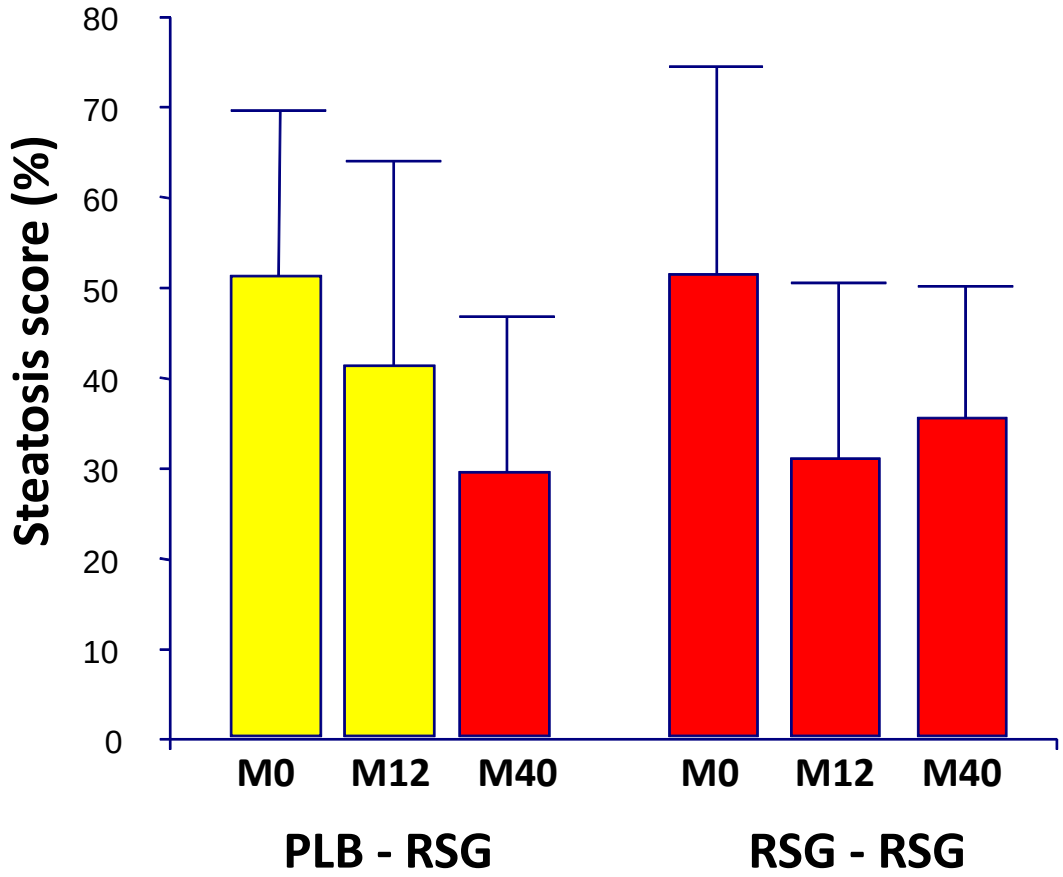








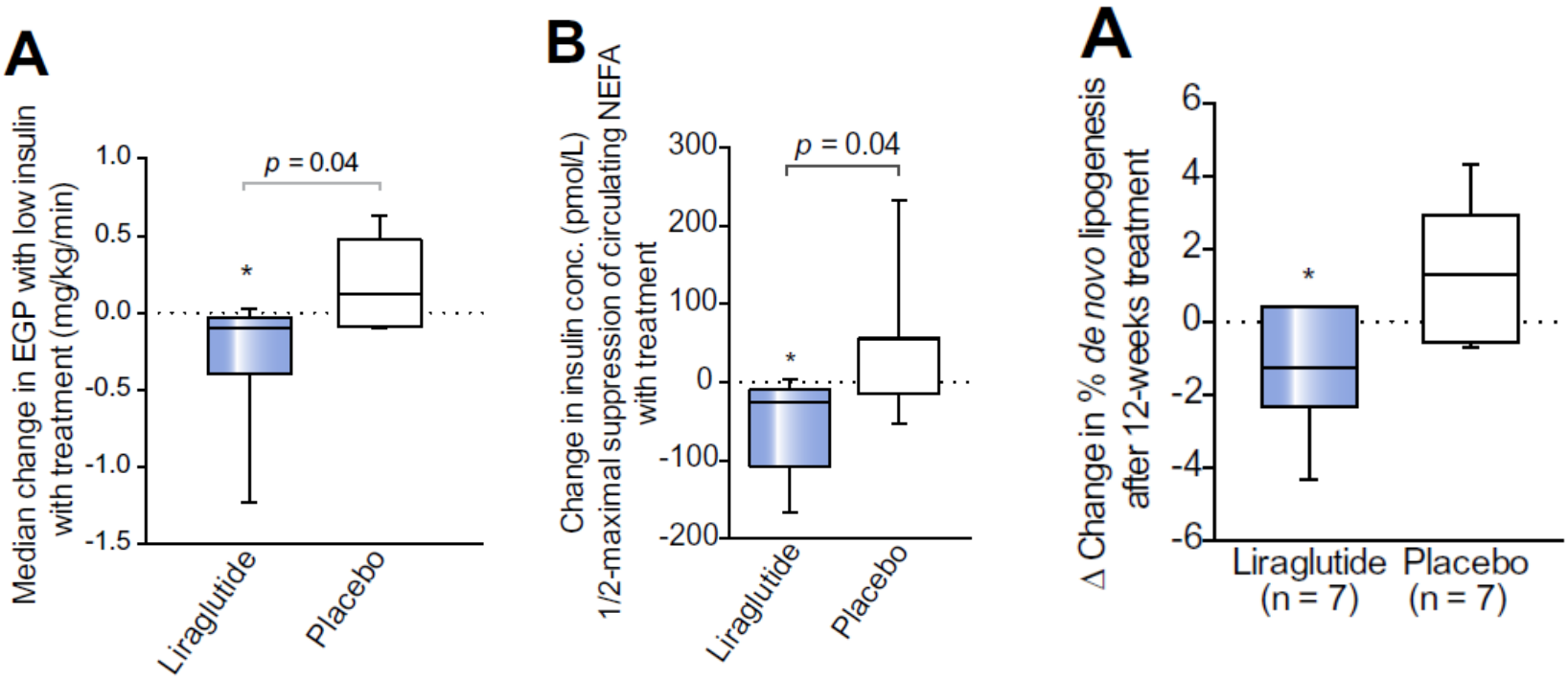
Reduction in liver fat



Ratziu, Hepatology 2010

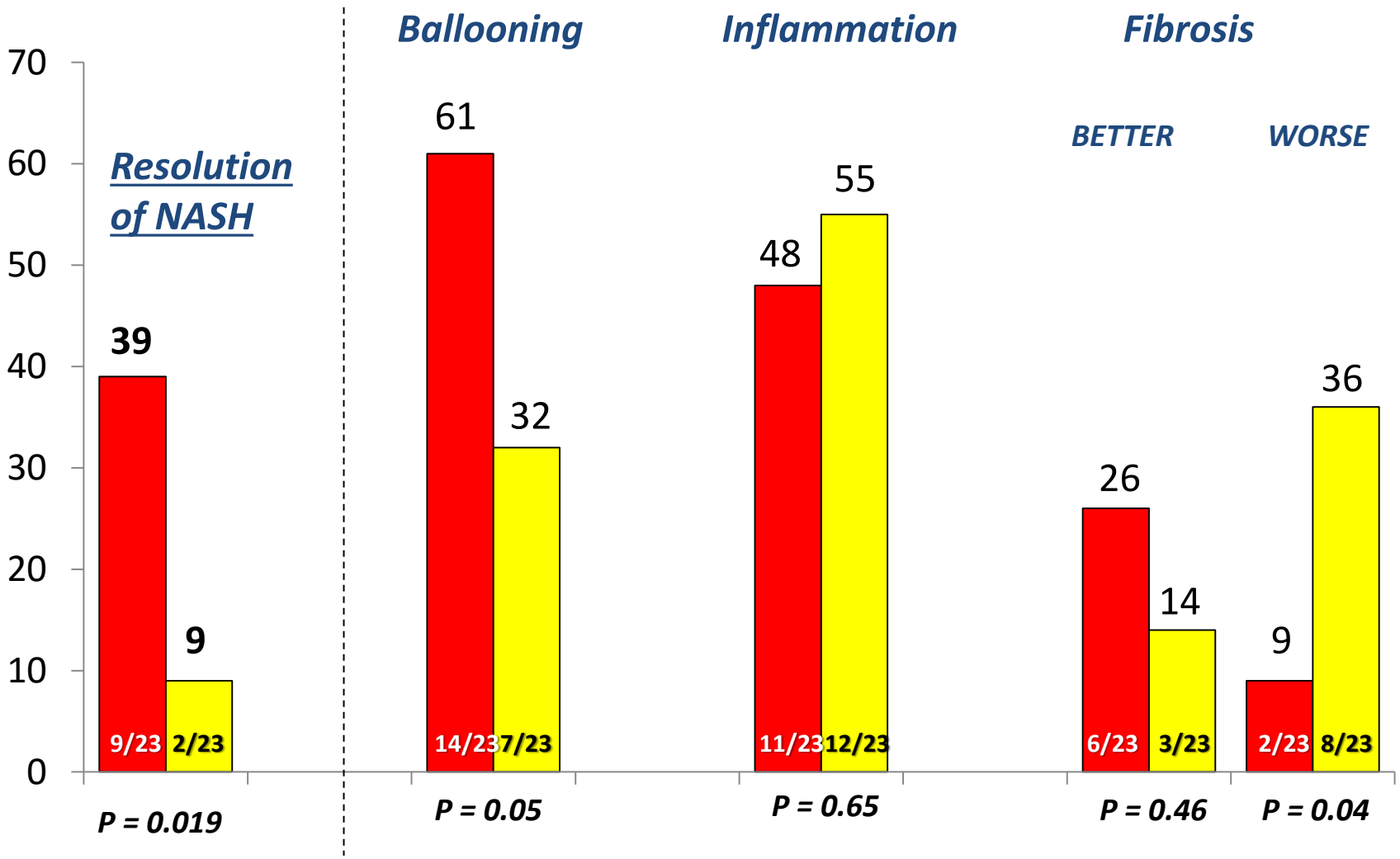
Liraglutide decreases lipotoxicity in NASH

N=14 NASH patients from the LEAN trial



Armstrong, J Hepatol 2016

Histological improvement in the LEAN trial



Armstrong &Newsome, Lancet 2015

Babies born/day	**15**	**45**

One year follow-up

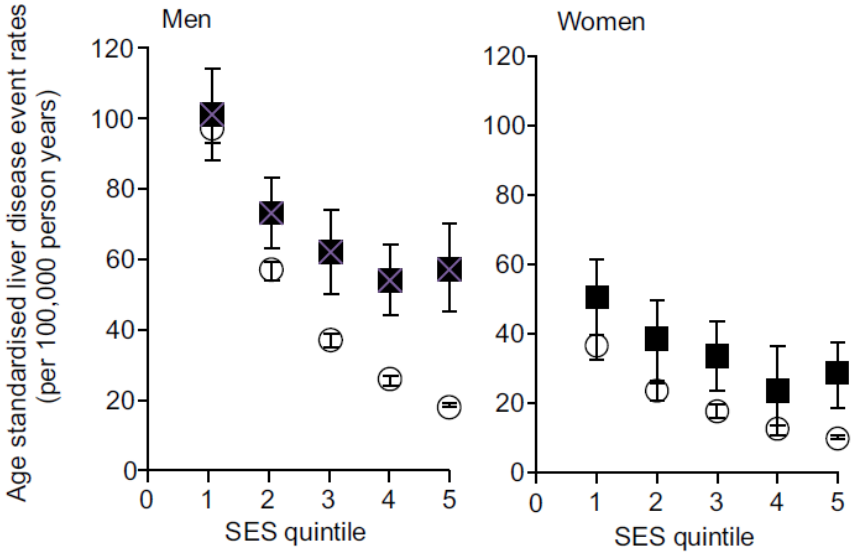
Record # days with >60% boys

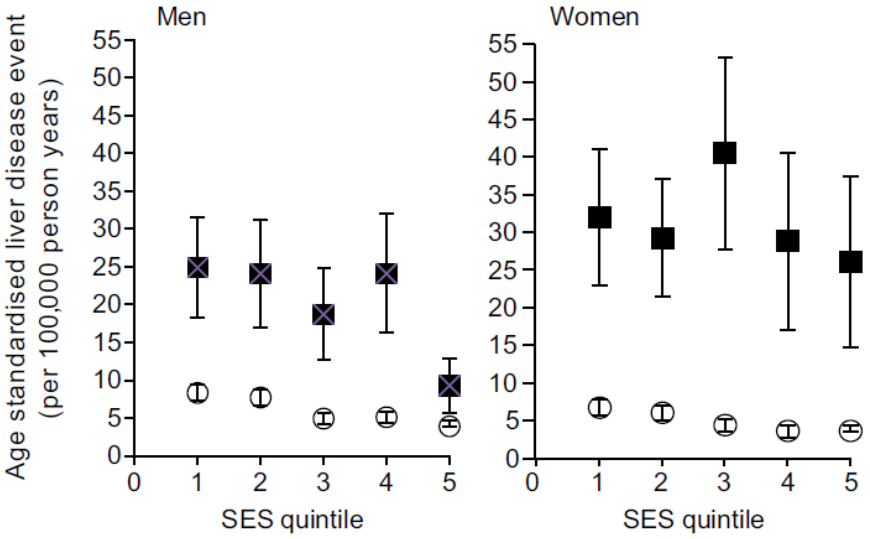
Higher in large hospital ?

Higher in smaller hospital ?

Same for both ?

Socio-economic status and NAFLD





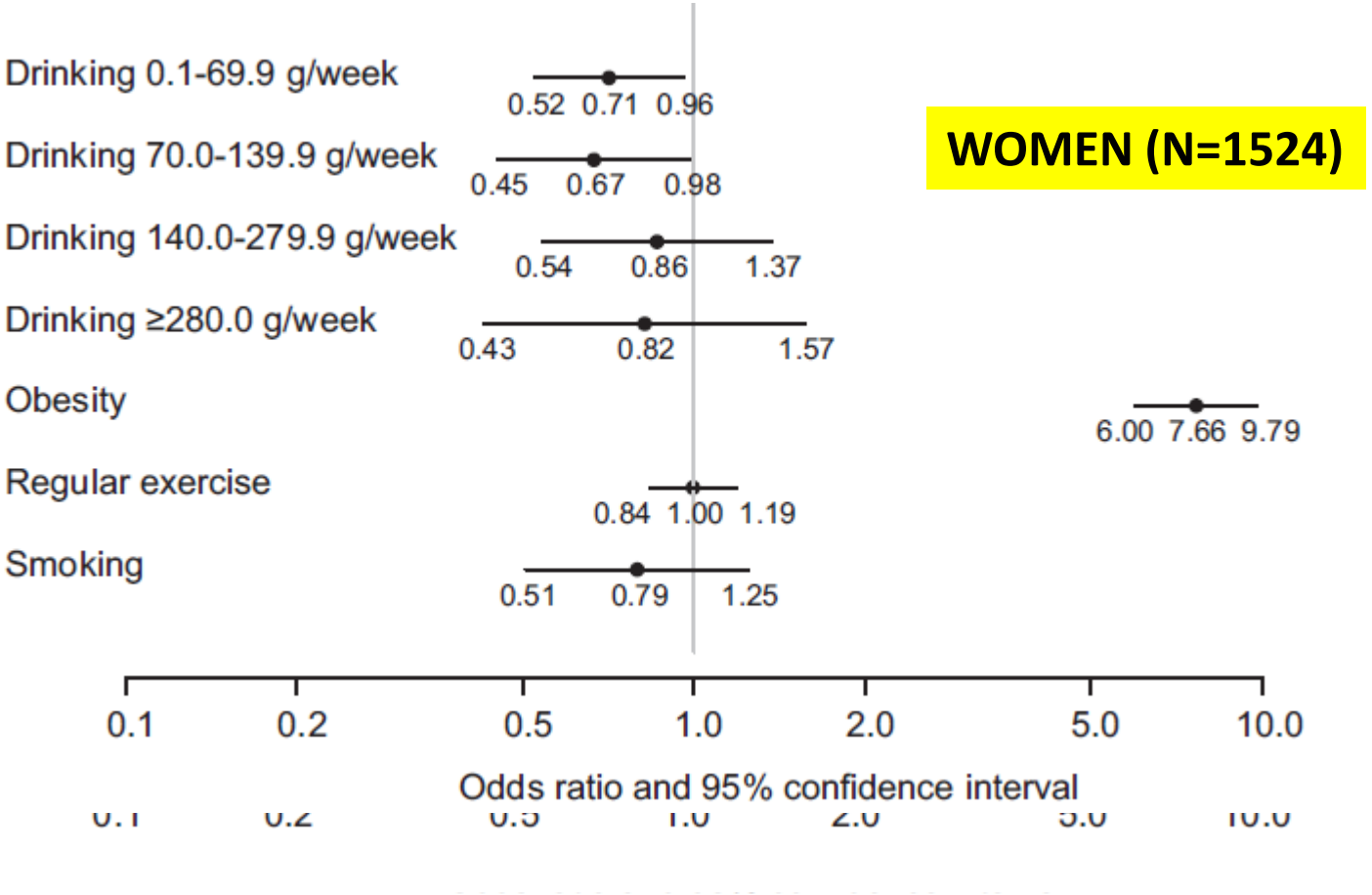
Wild, J Hepatol 2016

Socio-economic status and NAFLD

Nowadays, the only difference between poor and rich people ….

is money !

Association between alcohol consumption and fatty liver in Asians



WOMEN (N=1524)

After adjustment for obesity, smoking, exercise.

Moriya, J Hepatol 2015