Foie gras : où en est-on en 2019 ? Quel rôle pour le médecin de famille ?

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Journées Romandes d'Hépatologie

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Hôpitaux Universitaires Genève

HÉPATOLOGIE GASTRO-ENTÉROLOGIE GENÈVE

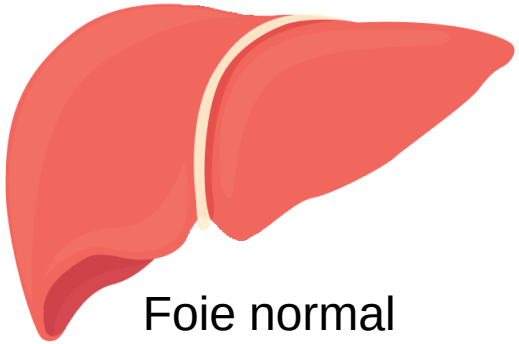
UNIVERSITÉ DE GENÈVE

FACULTÉ DE MÉDECINE

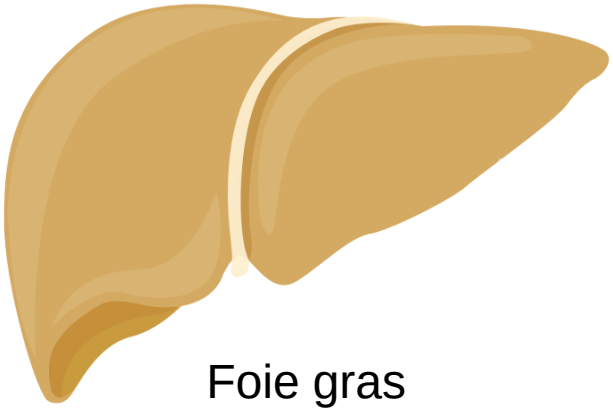
Le foie gras non-alcoolique (NAFLD)

Définition:
Stéatose dans > 5% des hépatocytes

Exclusion:
Hépatite virale B, C, Alcool, Hémochromatose, Auto-immune…



Foie normal



Foie gras

Facteurs liés à la progression

- Résistance à l'insuline
- Surpoids
- Syndrome métabolique
- Facteurs ethniques
- Facteurs génétiques
- Sexe
- Alimentation
- …

EASL, *J Hepatology*, 2016

La NAFLD, un diagnostic d'exclusion?

- **Définition**: "steatosis in >5% of hepatocytes according to histological analysis or by a proton density fat fraction >5.6% assessed by proton magnetic resonance spectroscopy"

- **"Non-alcoolique"**: Consommation OH de < 20g/j pour les femmes, < 30g/j pour les hommes

- **Exclusion** raisonnable d'autres causes d'hépatopathies: OH, HCV, HBV, médicamenteux (ex: méthotrexate), hémochromatose et d'autres causes plus rares selon l'anamnèse et les facteurs de risque

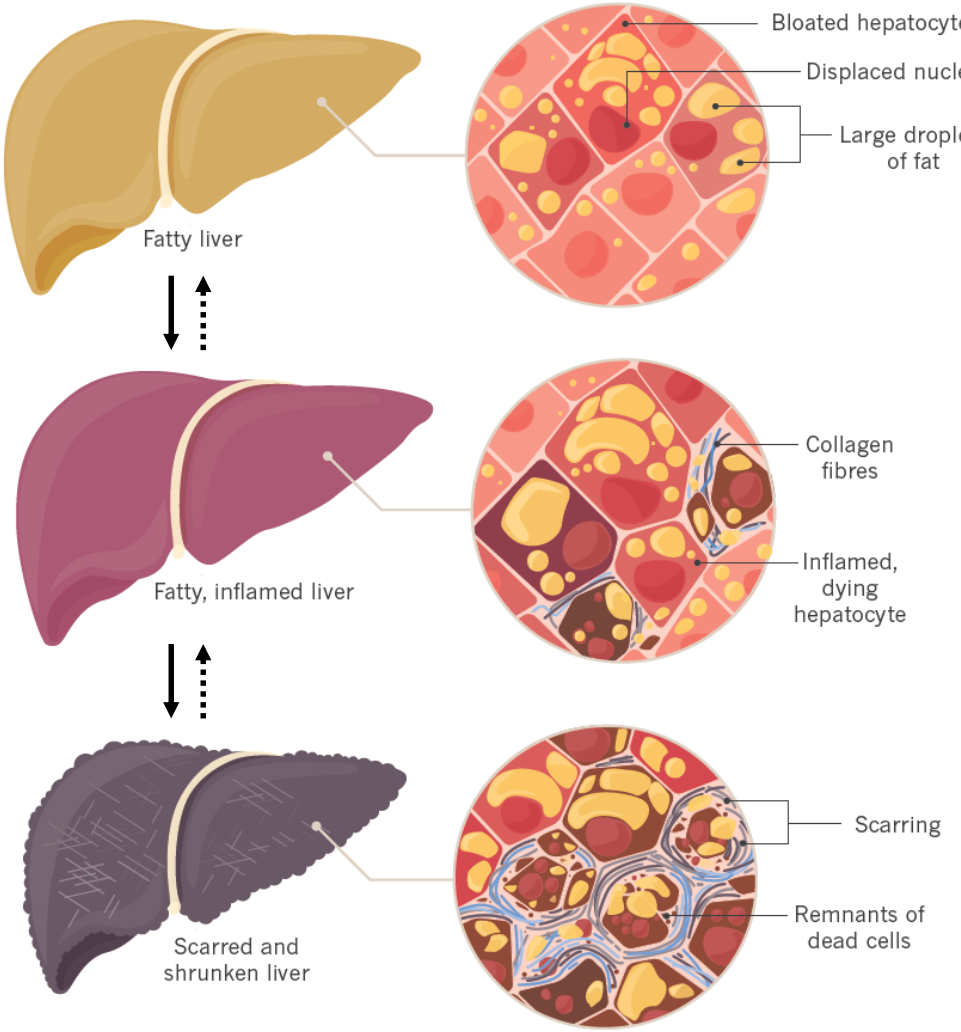
- Nouveau nom? "Metabolic liver disease "?

Le foie gras non-alcoolique et sa progression

Foie gras «simple»

Stéatohépatite (**NASH**) et **fibrose**

Cirrhose



Adapté de Drew, *Nature* 2017

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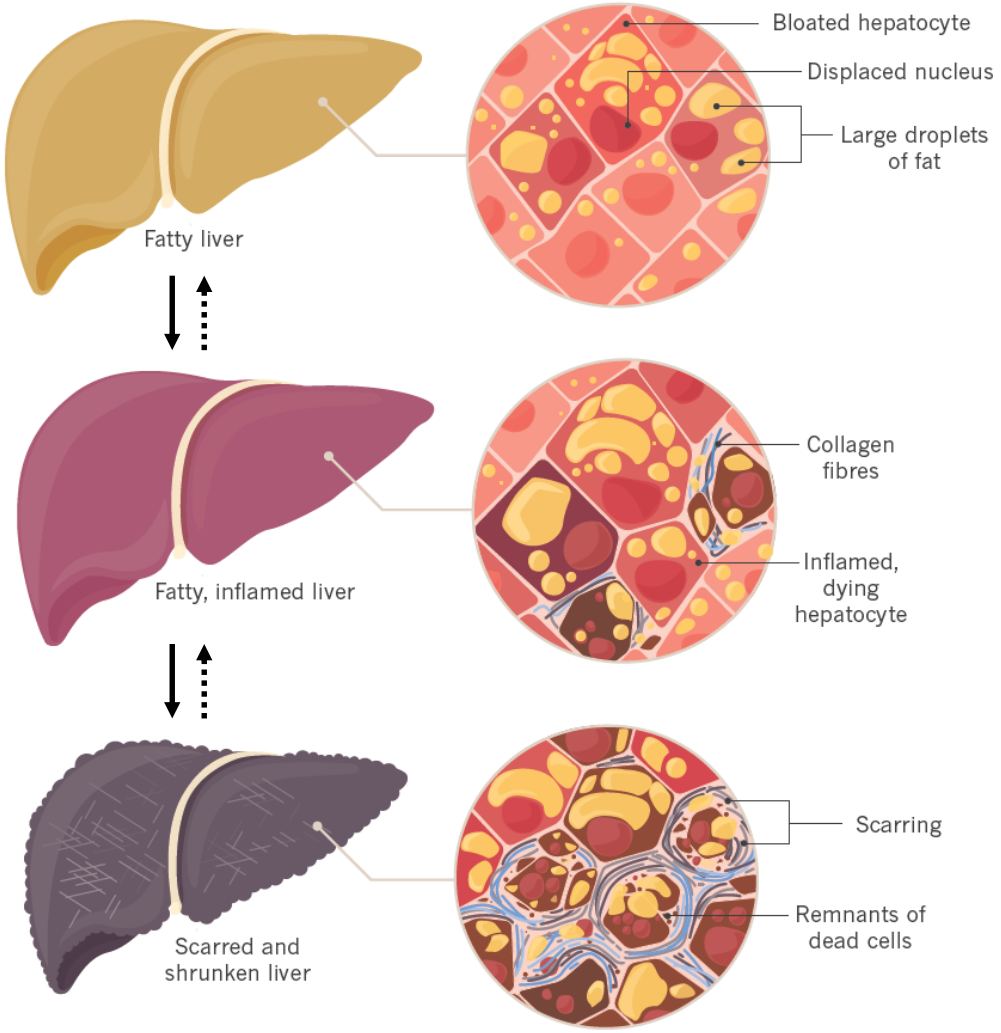

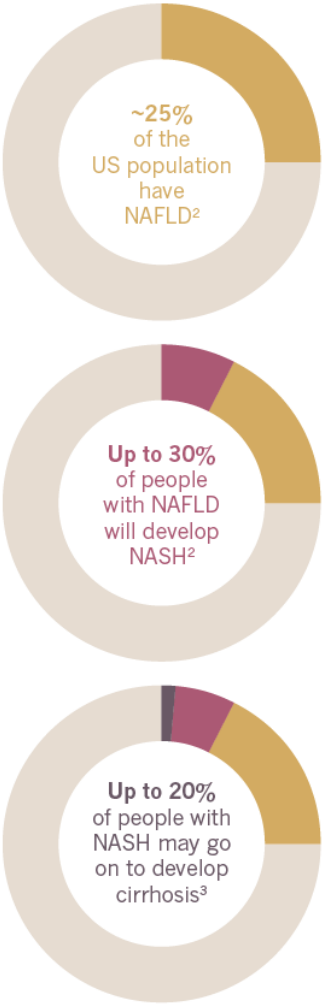

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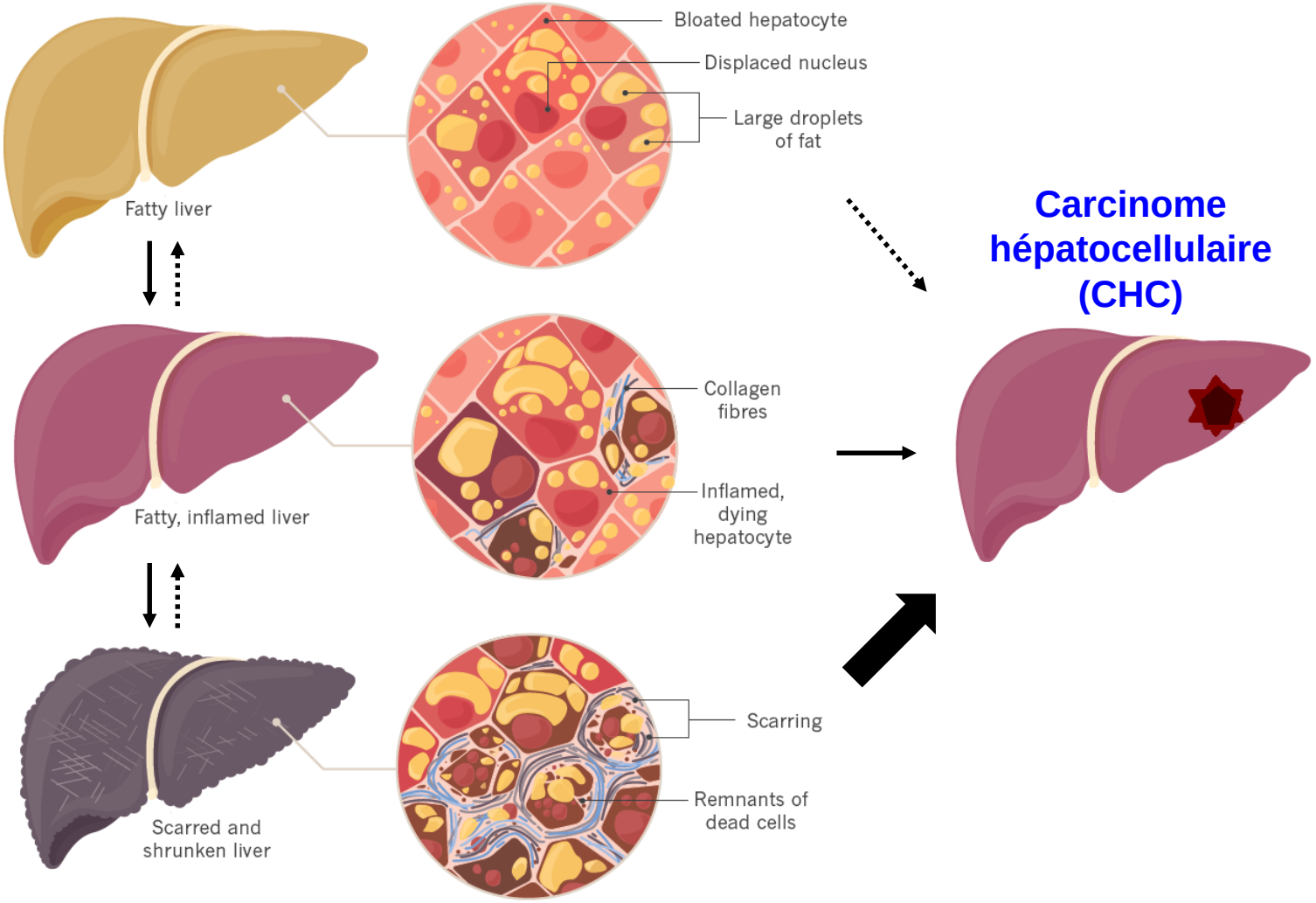
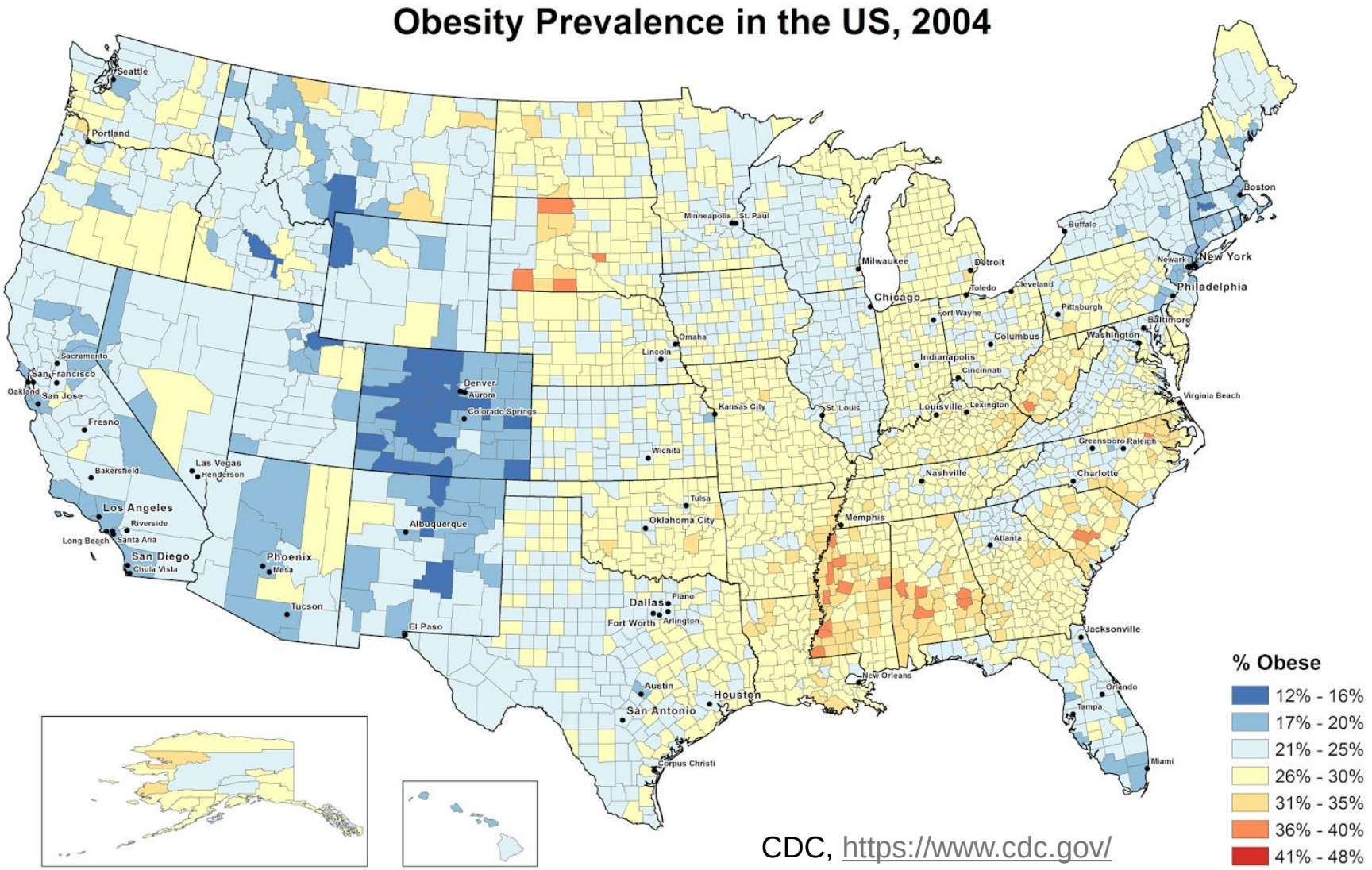


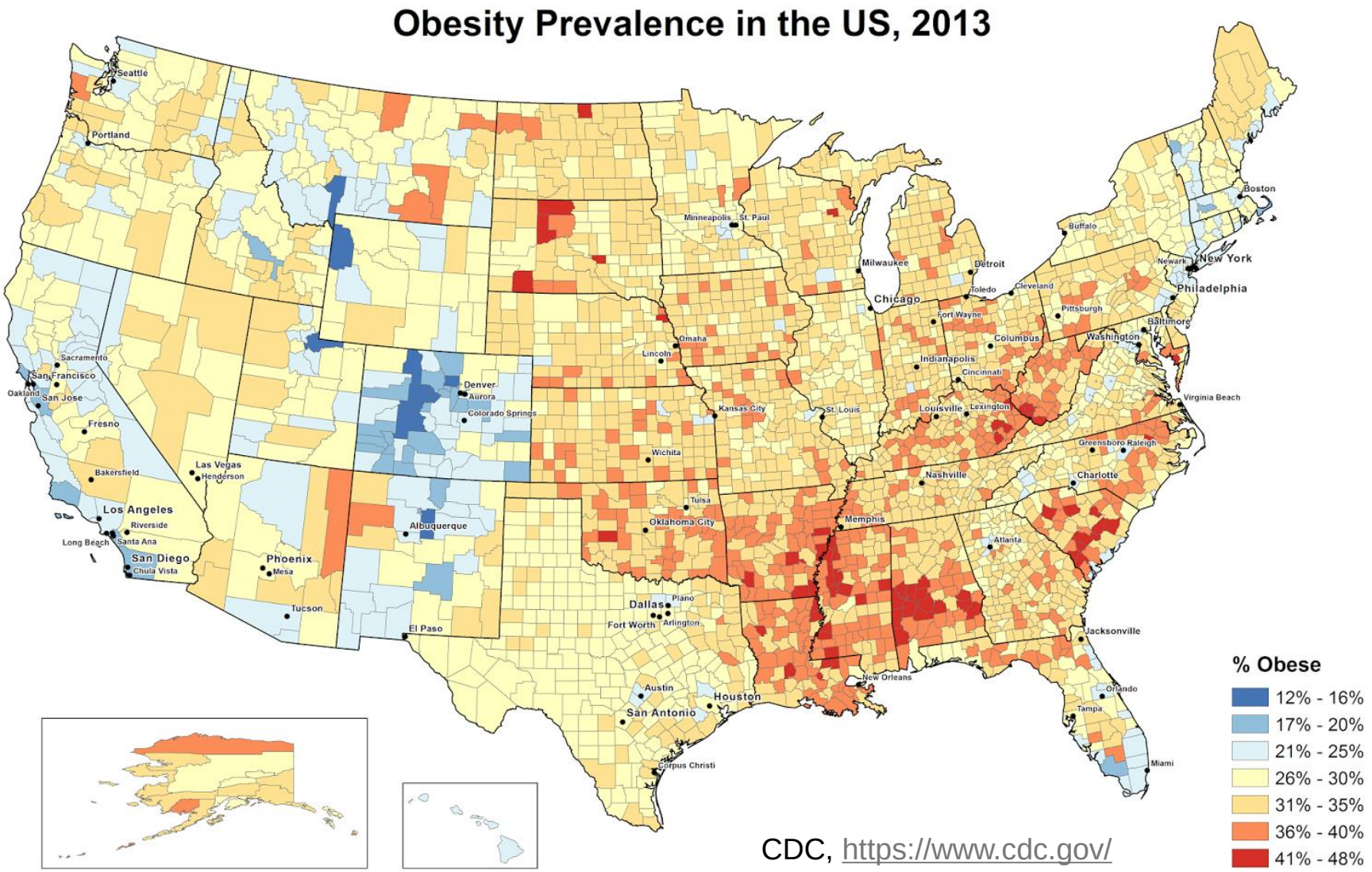
Adapté de Drew, *Nature* 2017

L’épidémie de l’obésité aux USA



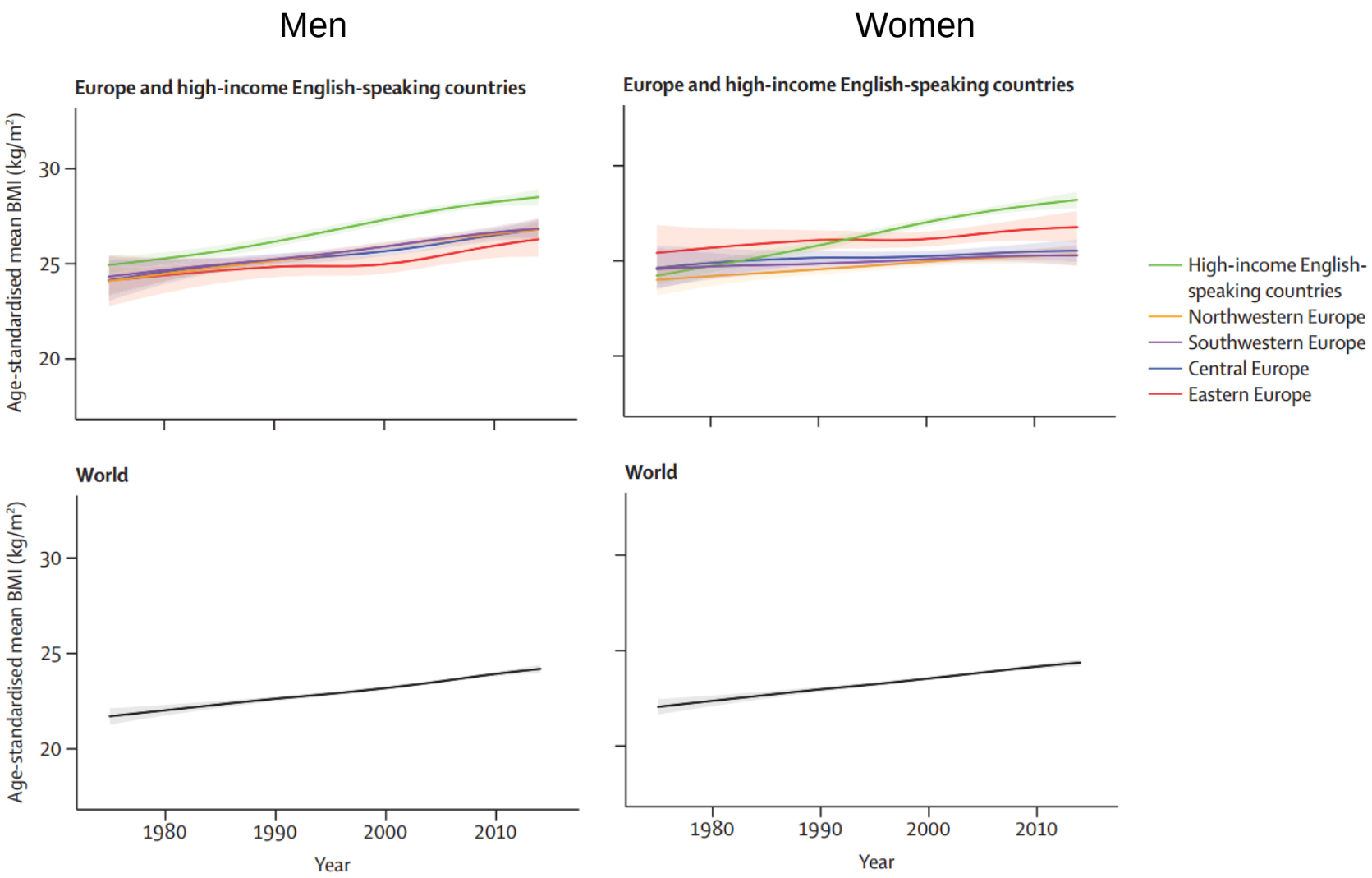
CDC, https://www.cdc.gov/

L’épidémie de l’obésité aux USA



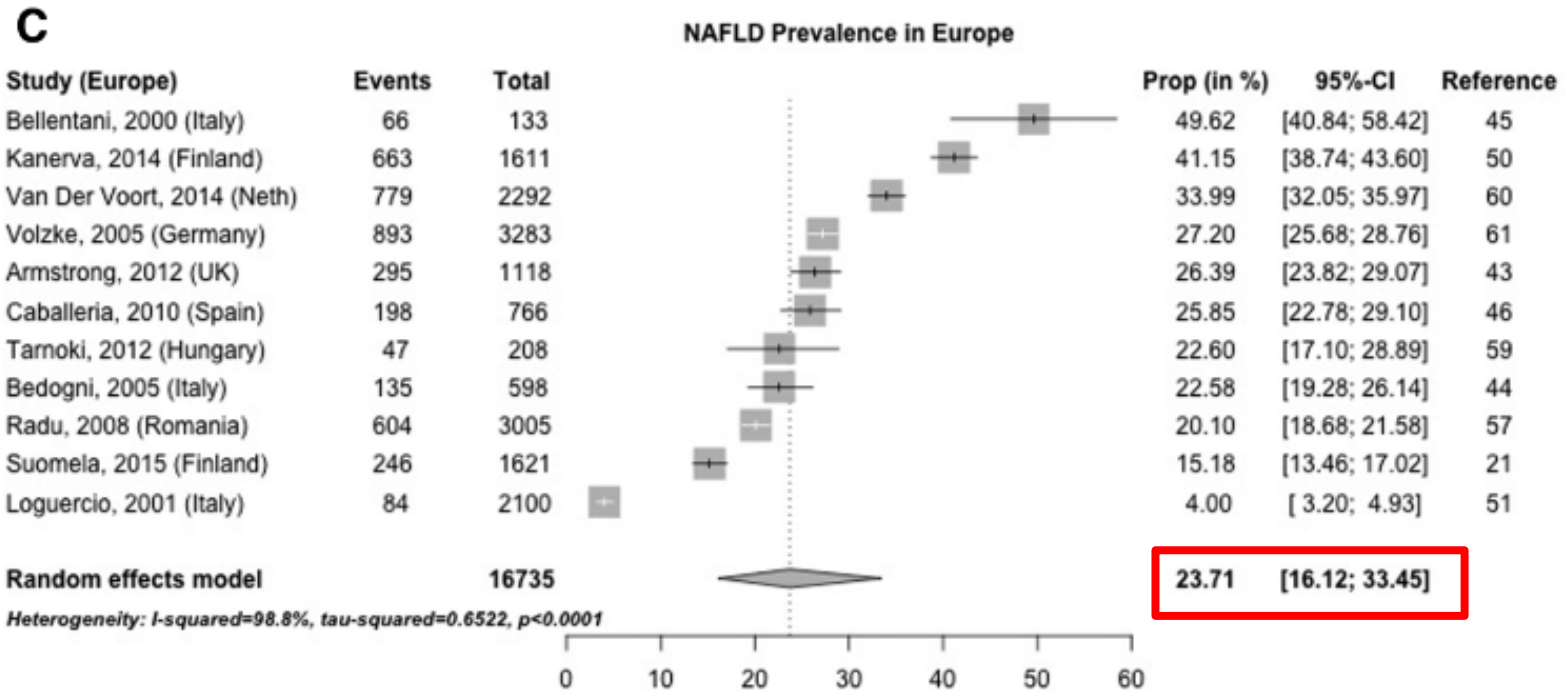
CDC, https://www.cdc.gov/

Augmentation de l'IMC mondial



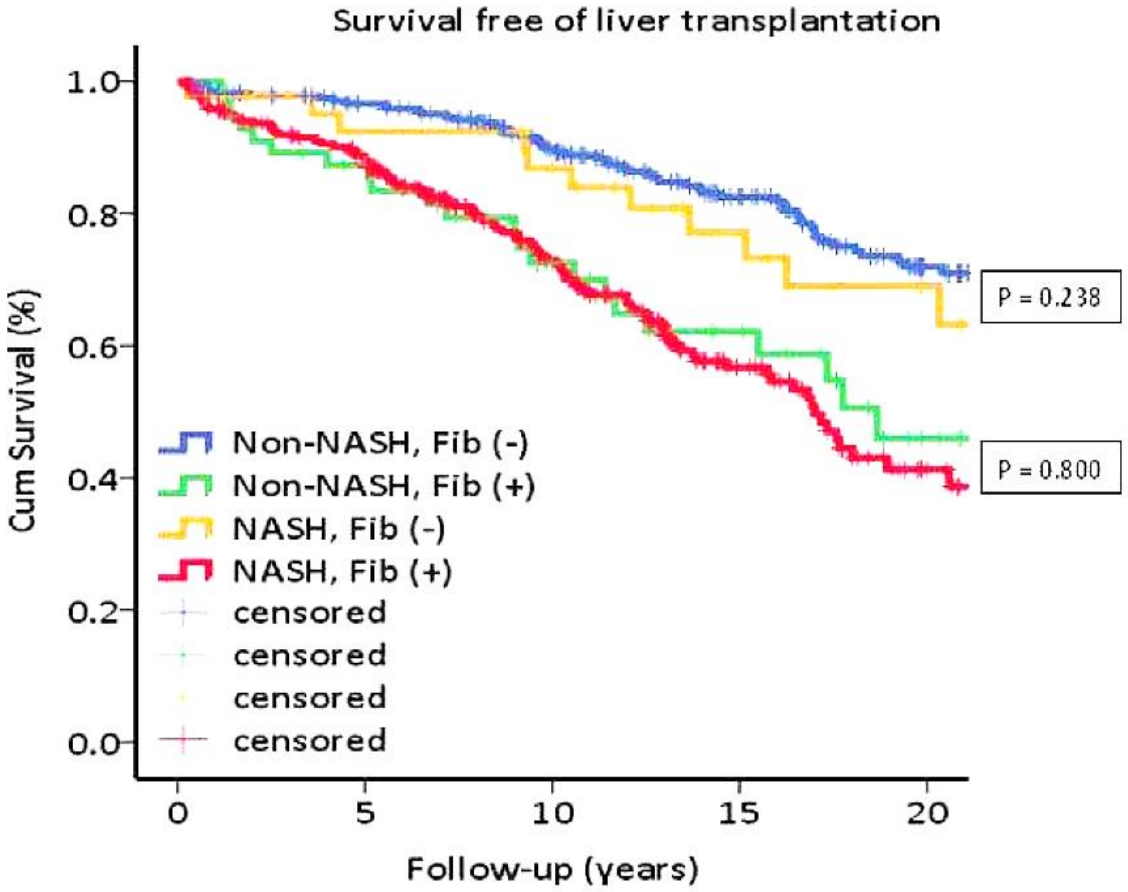
NCD-RisC, *Lancet* 2016

Prévalence élevée de la NAFLD en Europe



Younossi et al. *Hepatology* 2016

La fibrose hépatique est associée à la survie à long terme

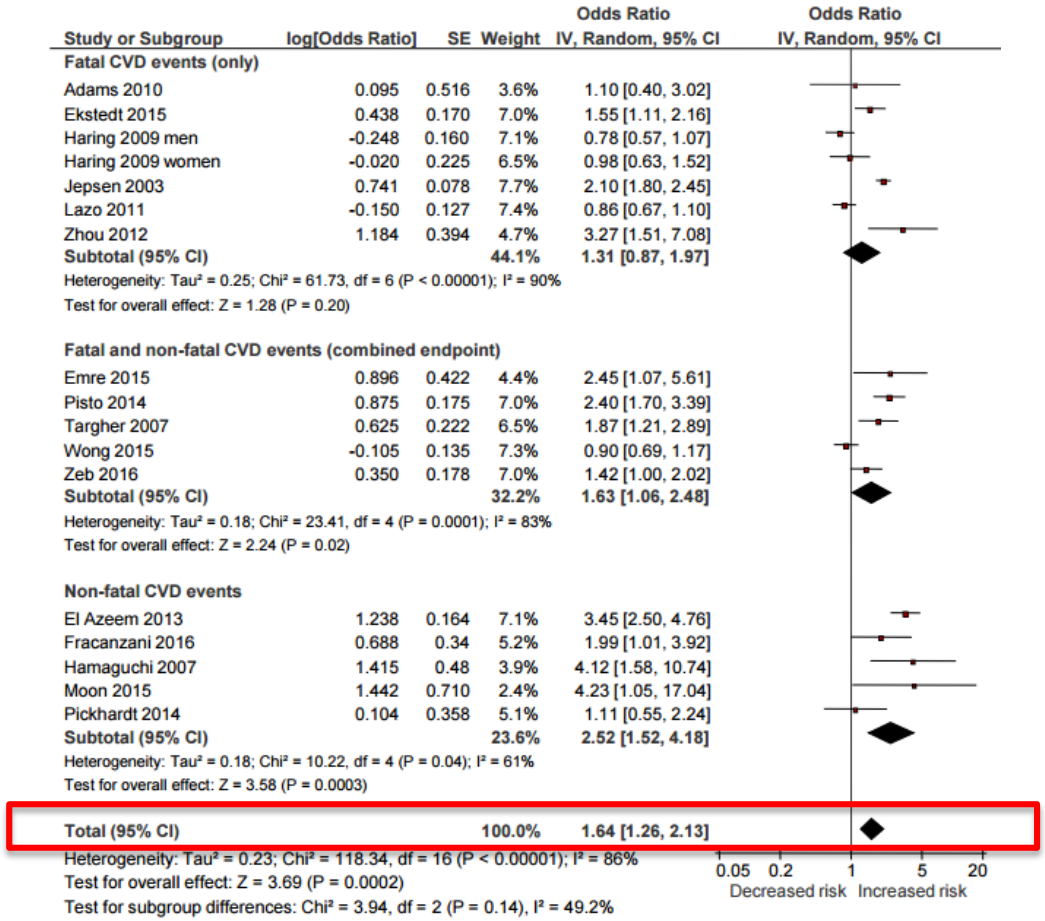


Cause de mortalité: cardiovasculaire 38%, cancer 19%, cirrhose 8%, CHC 1%

Prédicteurs indépendants: fibrose, diabète, tabac, absence statine

Angulo et al, *Gastro*, 2015

Augmentation des évènements cardiovasculaire



16 observational studies with 34,043 adult individuals and 2,600 CVD outcomes (>70% CVD deaths) over a median period of 6.9 years

Targher et al, *J Hep*, 2016

Le foie gras est sous-évalué par les médecins de premier recours US

Table 2. Proportions of patients meeting process measures

	N (%)[a]
All patients	251
Review of primary care records	
Elevation of transaminases	99 (39.4)
Consideration of NAFLD/NASH	54 (21.5)
Referral to GI/hepatology	26 (10.4)
Recommendation for lifestyle modification	37 (14.7)
Receipt of any NAFLD care	99 (39.4)

Seul facteur associé à prise en charge NAFLD: magnitude élévation ALAT

MAIS: cohorte US (Vétérans), résultats à répliquer en Europe / Suisse

Blais et al, *Am J Gastro*, 2015

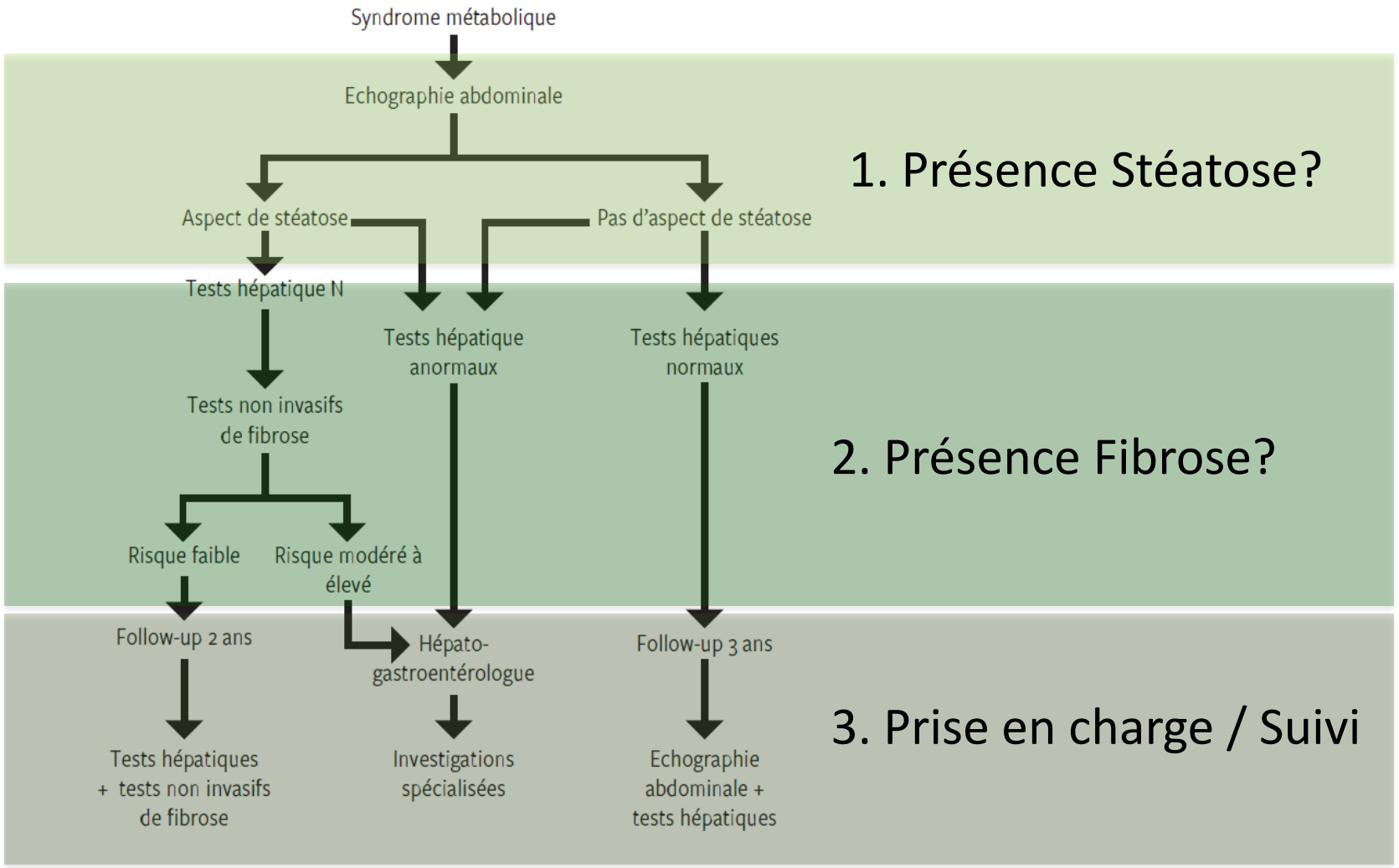
Recommandations dans la prise en charge de la NAFLD

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)

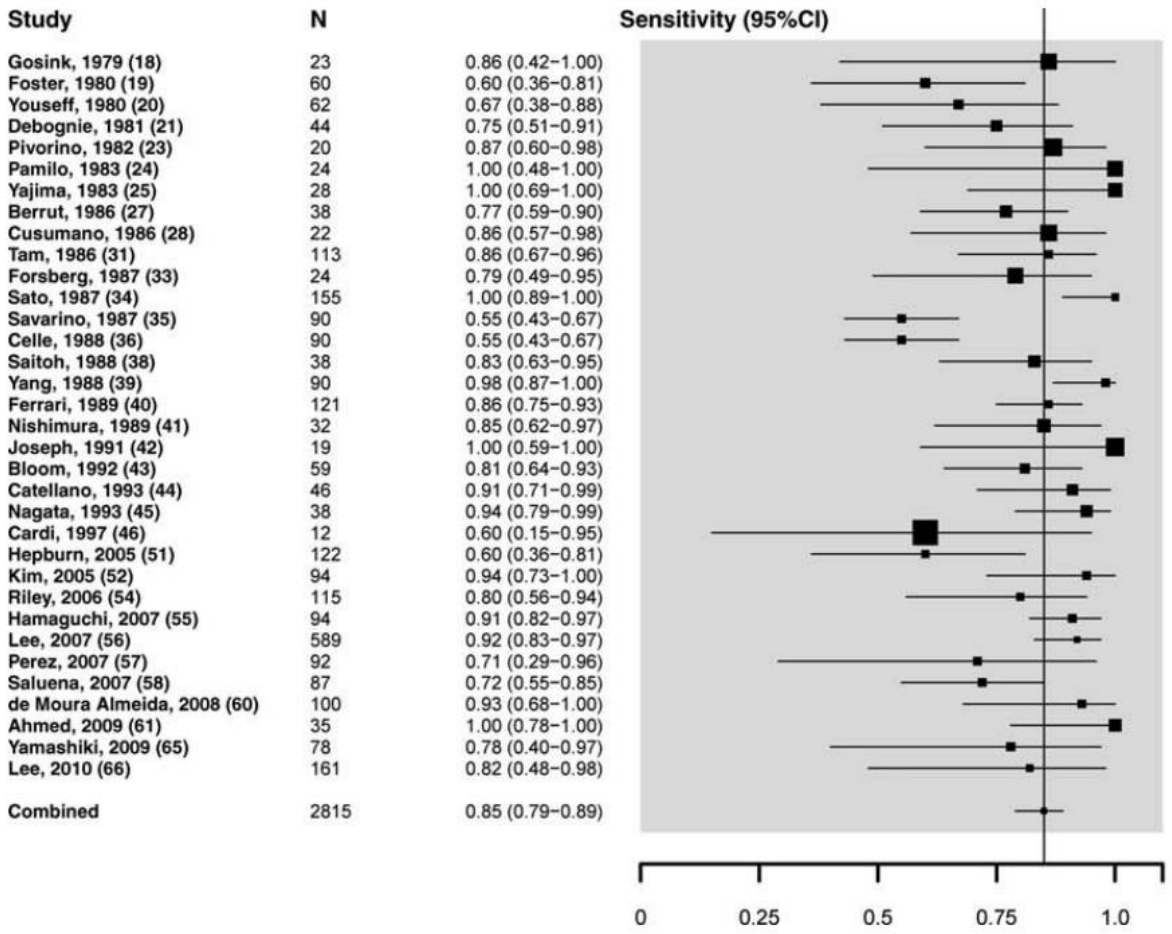
EASL, EASD, EASO, J Hep 2016

Proposition d'algorithme décisionnel devant un syndrome métabolique



Spahr, Goossens, Rev Med Suisse 2016, adapté de EASL, EASD, EASO, *J Hep* 2016

Dépistage de la stéatose hépatique – performance de l'échographie



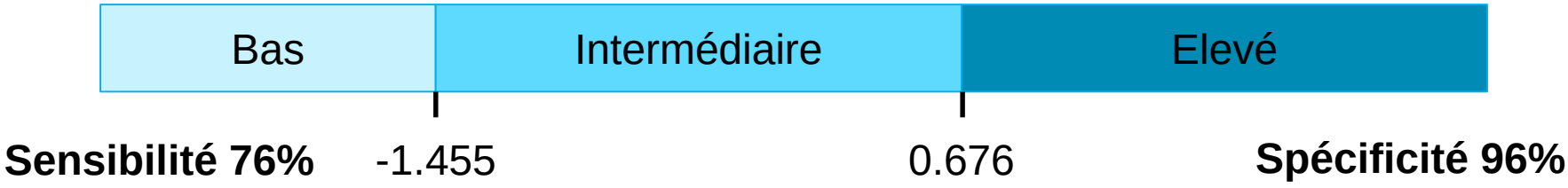
Pooled sensitivity (vs histology gold standard): 85% (80-89%)

Hernaez et al, Hepatology, 2011

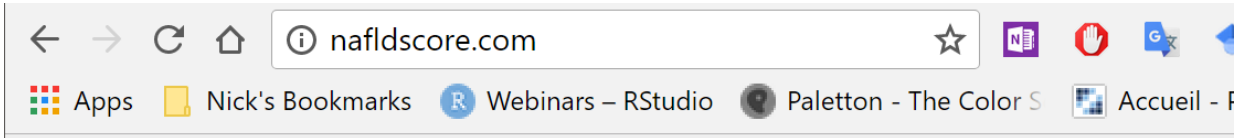
Evaluation non-invasive de la fibrose

Marqueur sérique: NAFLD fibrosis score

- Age, IMC, diabète, ASAT, ALAT, plaquettes, **albumine**
- http://nafldscore.com/
- Associé à la mortalité (Kim et al, *Hepatology* 2013)
- Surtout intéressant aux 2 extrêmes
- Classifie en 3 groupes lié au risque de fibrose (gold-standard biopsie)



Angulo et al, *Hepatology* 2007



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)

BMI (kg/m^2)

IGF/diabetes ☐

AST

ALT

Platelets ($x10^9/l$)

Albumin (g/l)

calculate score

BMI: body mass index
IGF: impaired fasting glucose

NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
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Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

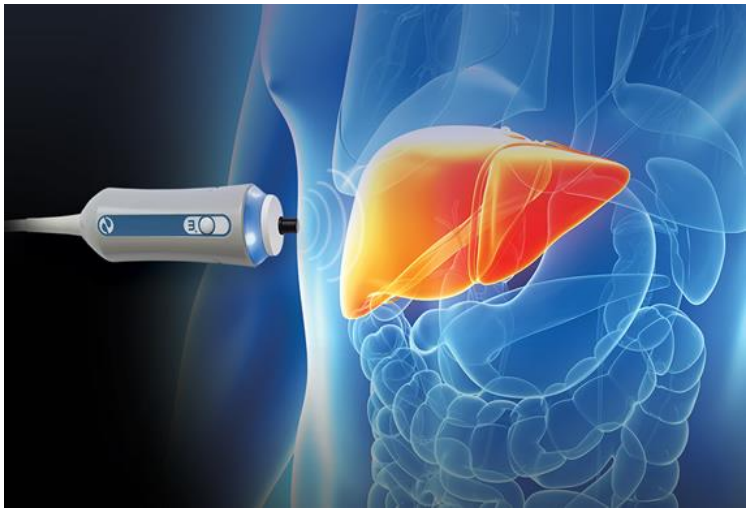
Age (years)	68
BMI (kg/m^2)	28.4
IGF/diabetes	☑
AST	54
ALT	76
Platelets (x10^9/l)	200
Albumin (g/l)	43
Score	-0.094

< -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)

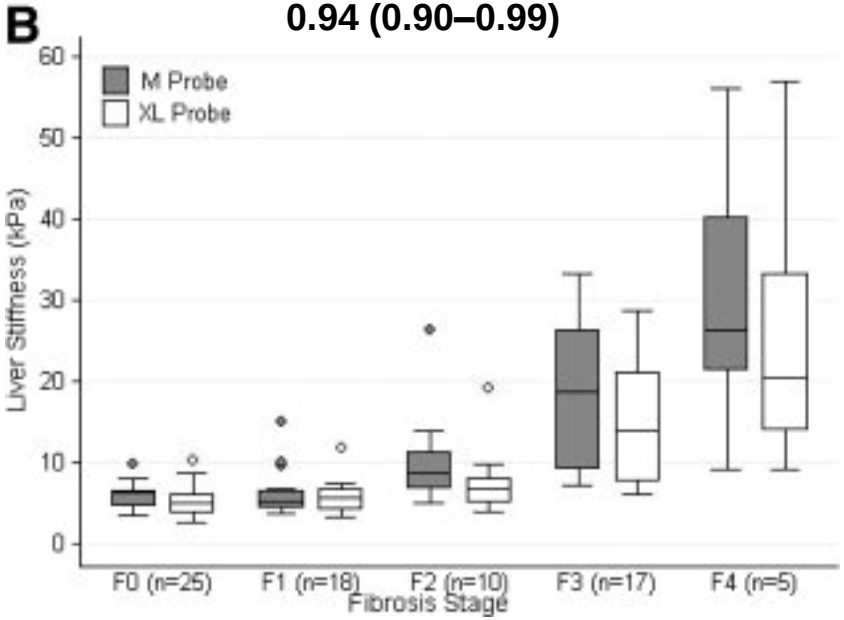
BMI: body mass index
IGF: impaired fasting glucose

Evaluation non-invasive de la fibrose par elastométrie hépatique

Fibroscan ®



Meta-analysis: pooled AUROC for adv fibrosis in NAFLD = 0.94 (0.90–0.99)



Myers et al. *Hepatology* 2011
Musso et al, Ann Med, 2011

Prise en charge - général

Dépistage et prise en charge syndrome métabolique

- En particulier résistance à l'insuline et diabète
- Identification et prise en charge **facteurs risque CV** (cause mortalité # 1 !!)

Mesures hygiéno-diététiques

- Perte de 7-10% du poids corporel (Lazo et al *Diab Care* 2010)
- Exercise physique (Thoma et al *J Hep* 2012)
- Limiter consommation alcool

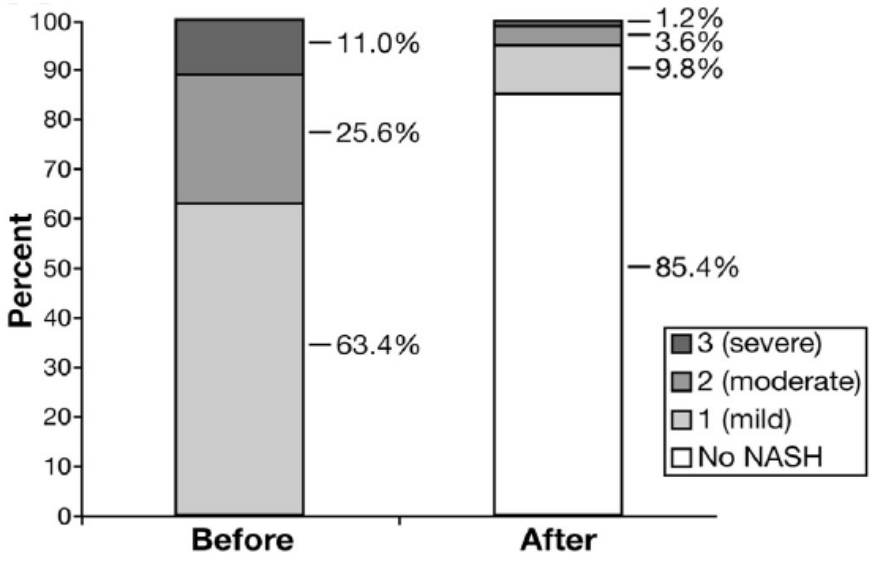
Prise en charge spécifique

- Indication traitement: Fibrose > NASH > stéatose
- Prise en charge hépatopathie (ex: dépistage CHC dans cirrhose)
- Place de la chirurgie bariatrique

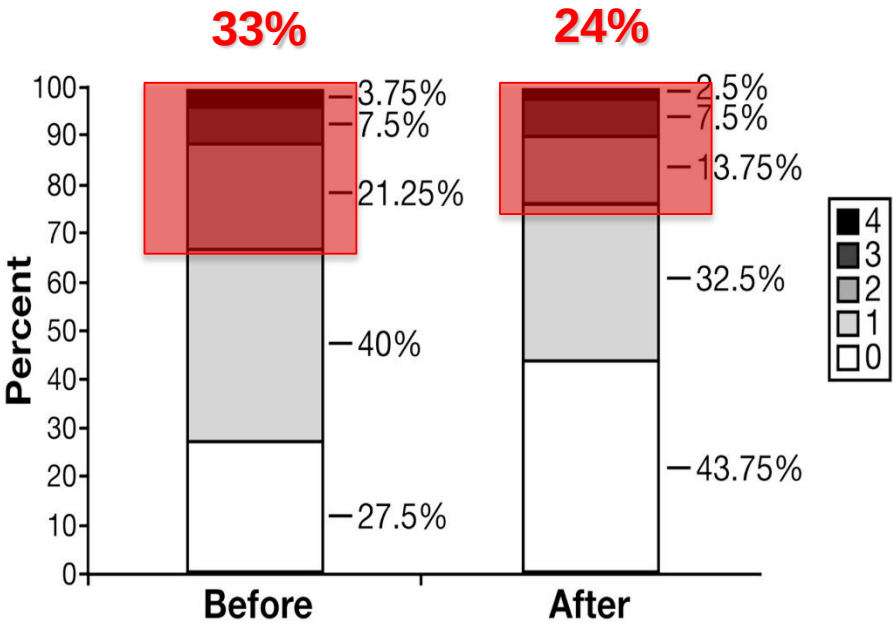
EASL, EASD, EASO, *J Hep* 2016

C’est une maladie réversible!

Résolution de la NASH



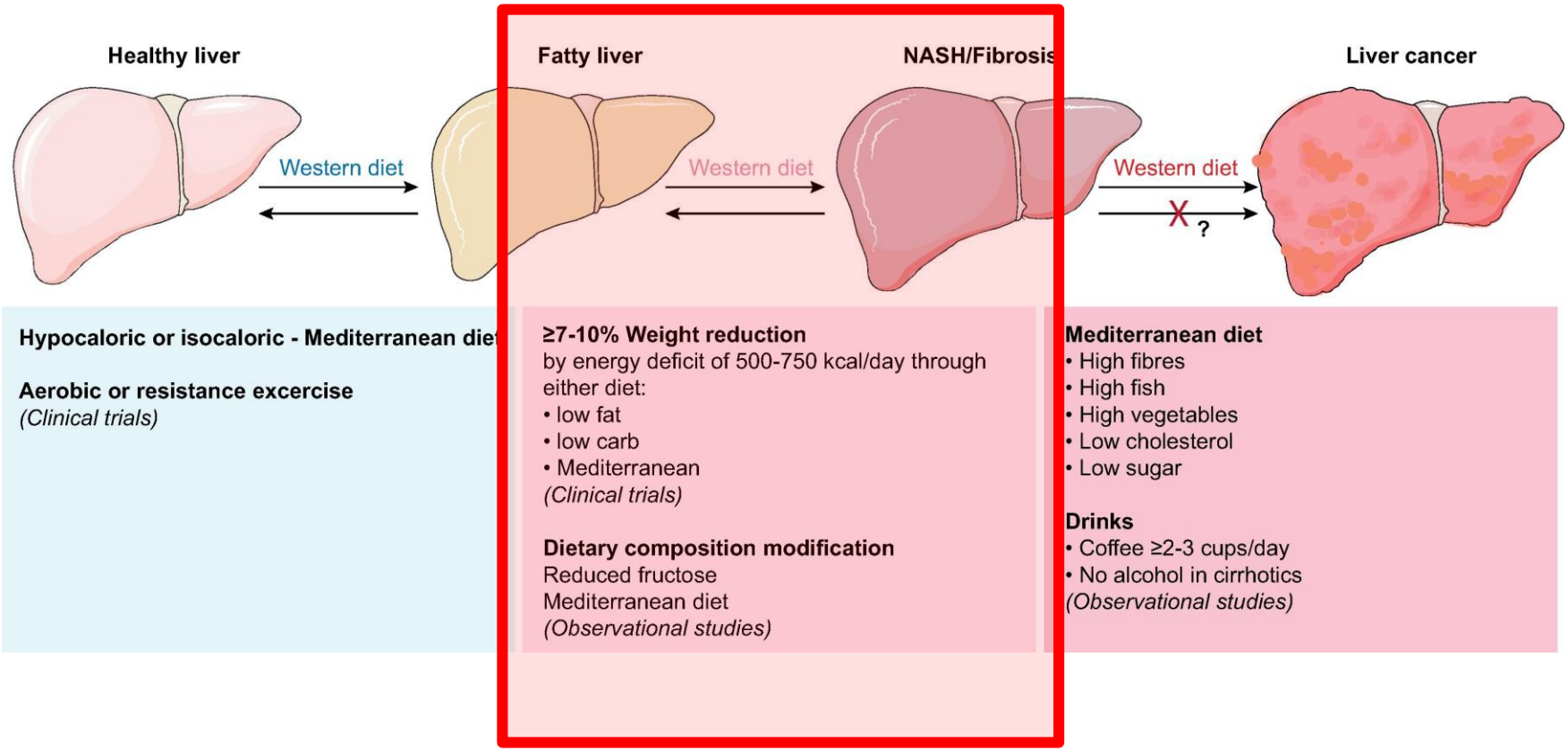
Amélioration de la fibrose



NASH : 1 an après chirurgie bariatrique (n=109)

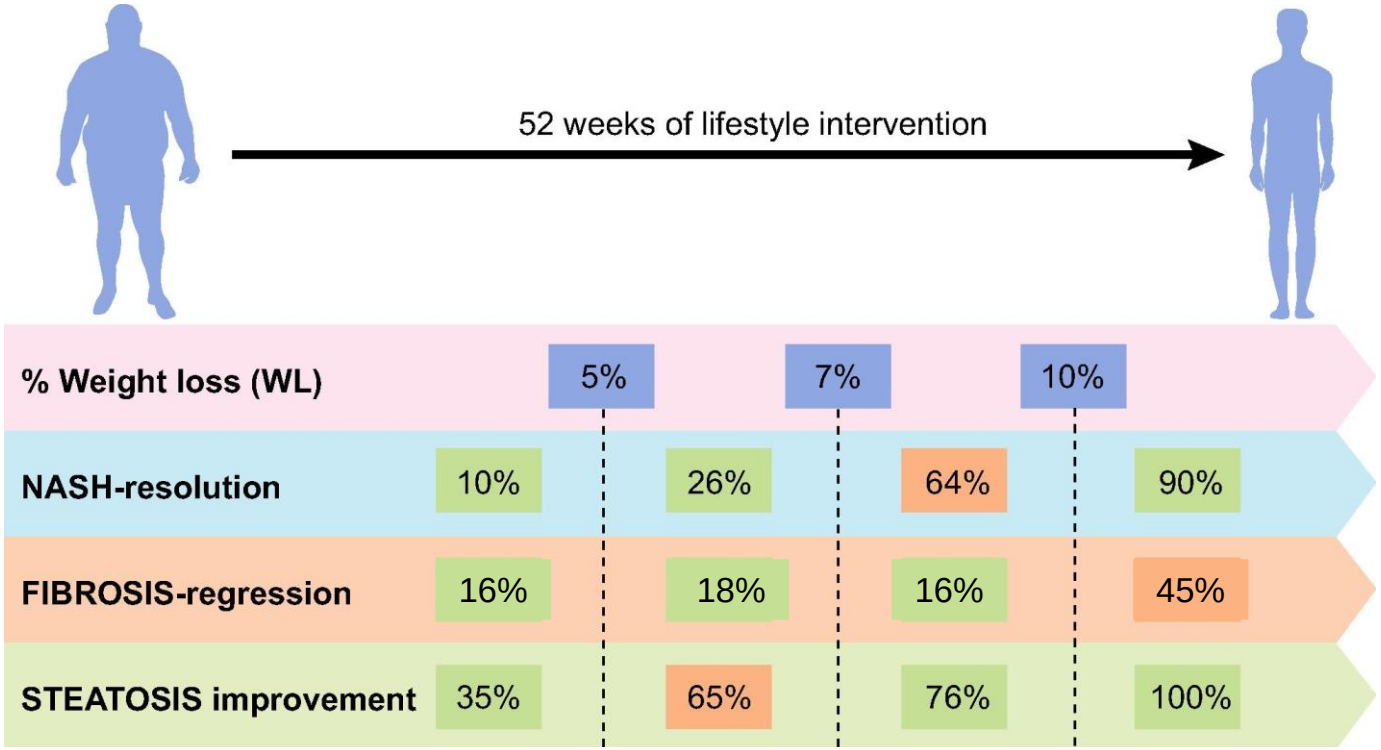
Lassailly et al, *Gastro* 2015

Strategies for lifestyle change in different stages of NAFLD



Romero-Gomez et al, *J Hep*, 2017

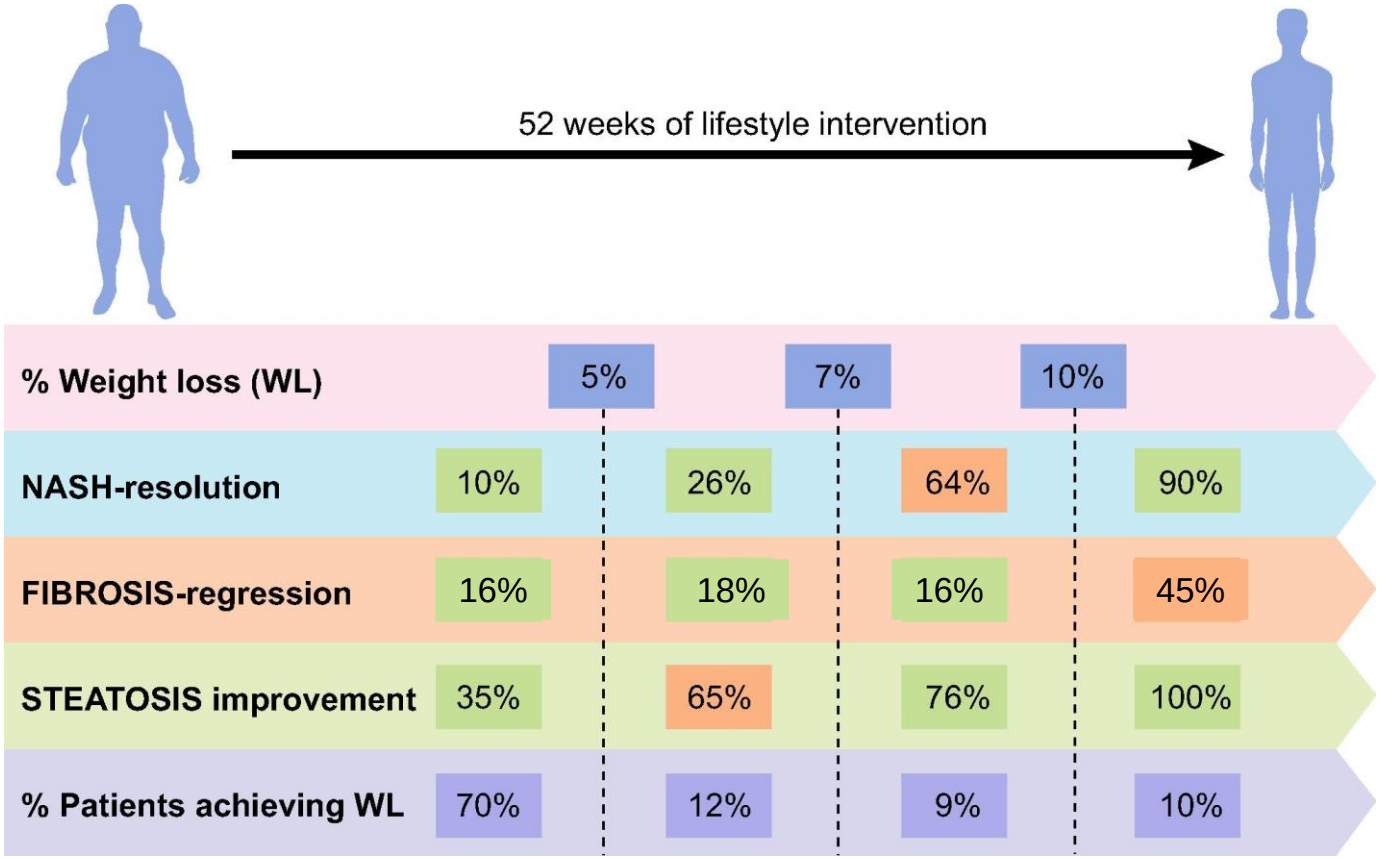
Lifestyle interventions



N=293 patients with biopsy-proven NASH.
52 weeks of lifestyle interventions (low-fat hypocaloric diet, walk 200 mins/week, behavioral sessions every week). 2nd liver biopsy at 52 weeks (n=261/293)

Vilar-Gomez et al, *Gastroenterology*, 2015
Romero-Gomez et al, *J Hep*, 2017

Lifestyle interventions



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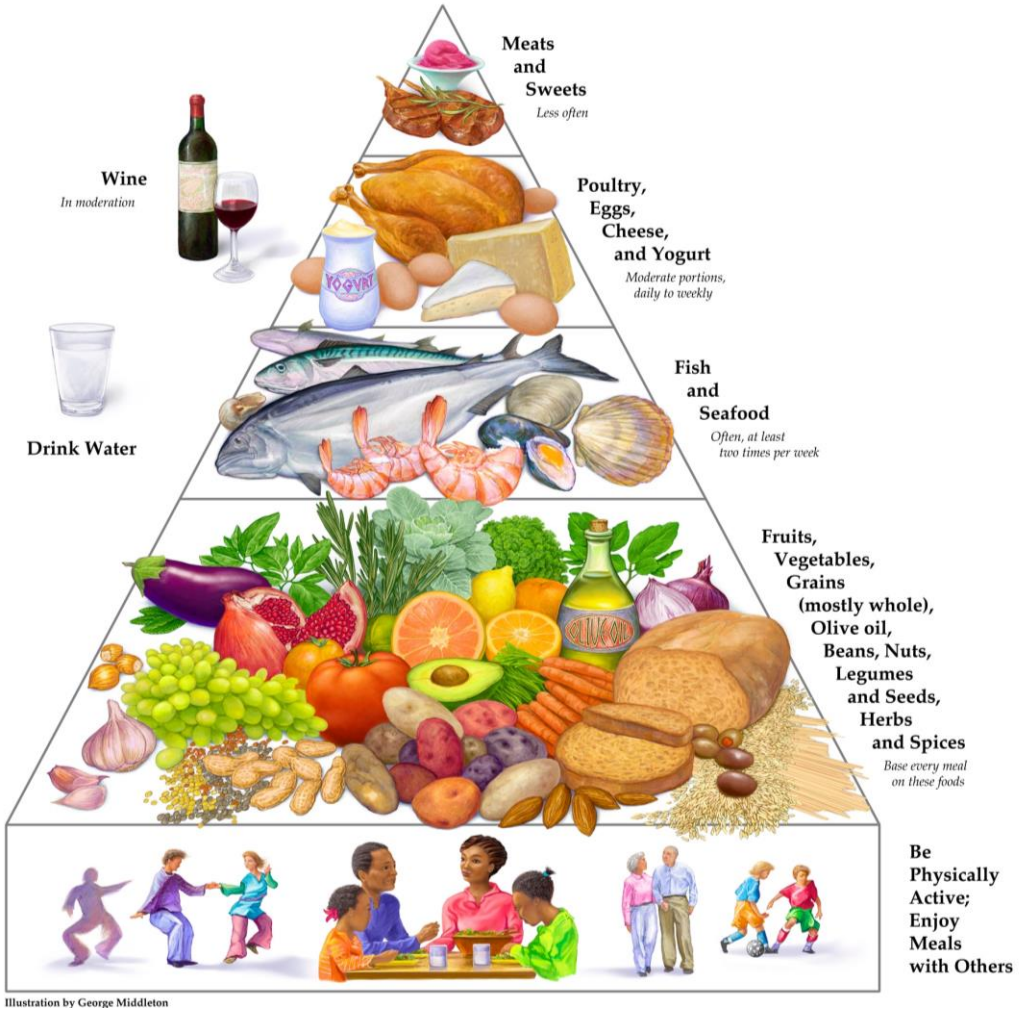
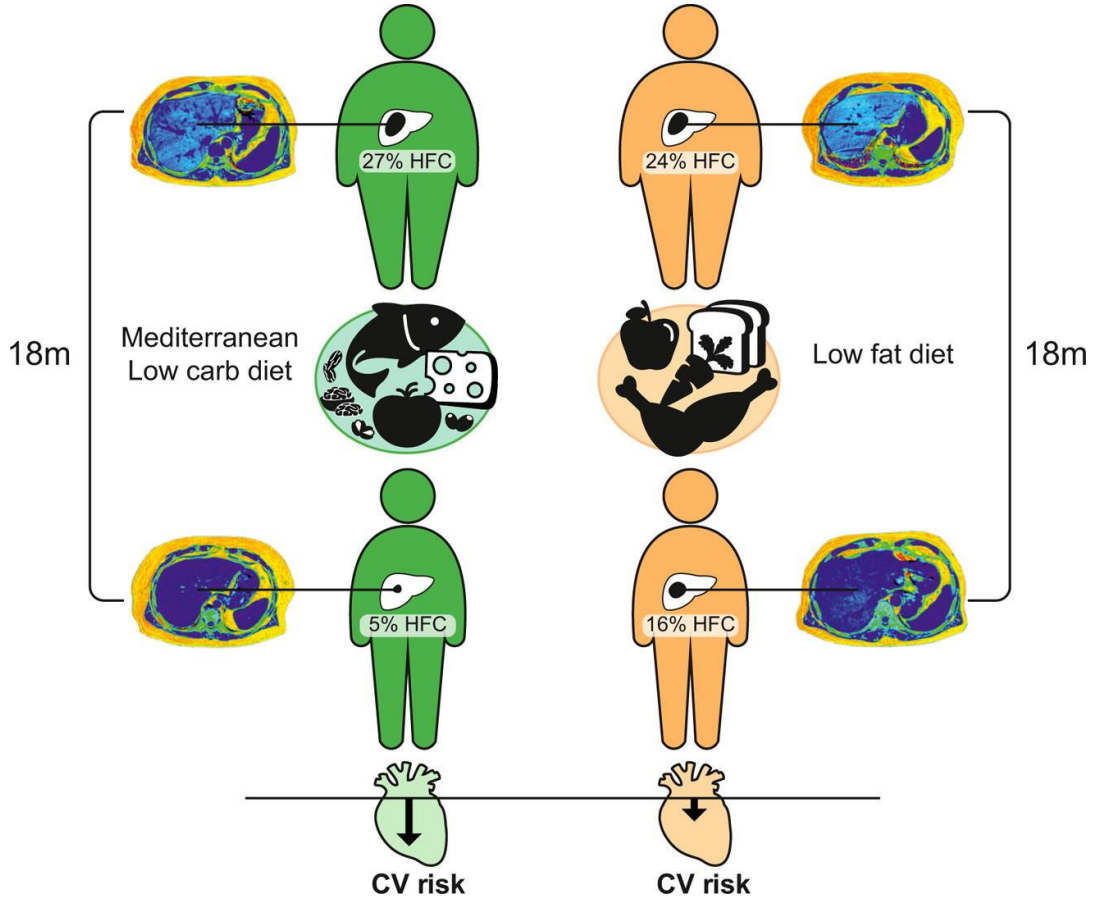
Vilar-Gomez et al, *Gastroenterology*, 2015
Romero-Gomez et al, *J Hep*, 2017

Mediterranean diet overview



From www.mayoclinic.org

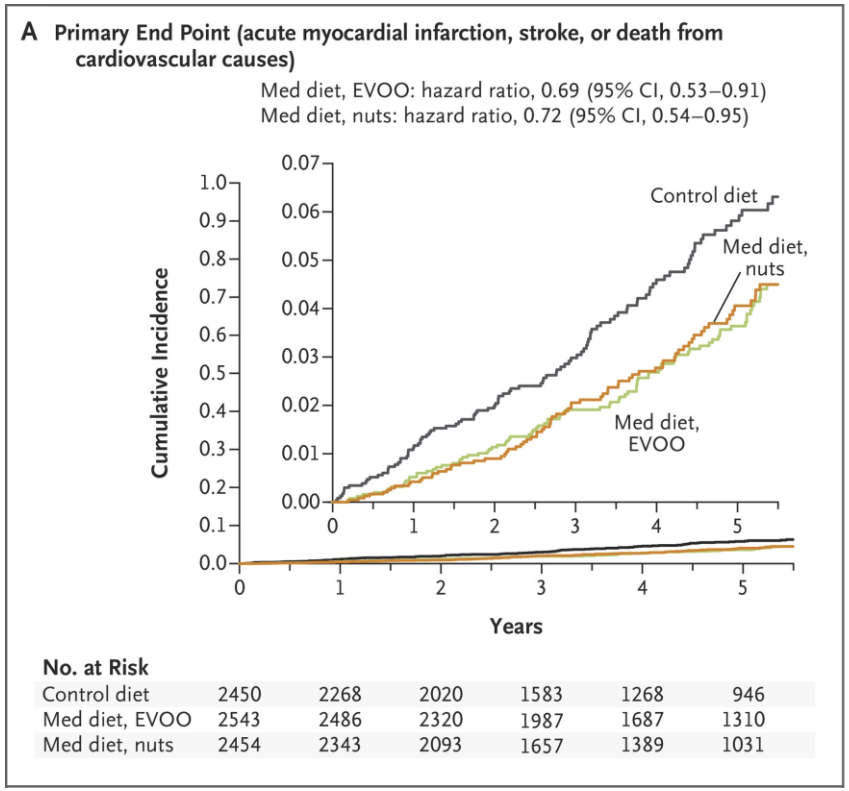
Beneficial effect of Mediterranean diet on hepatic fat content

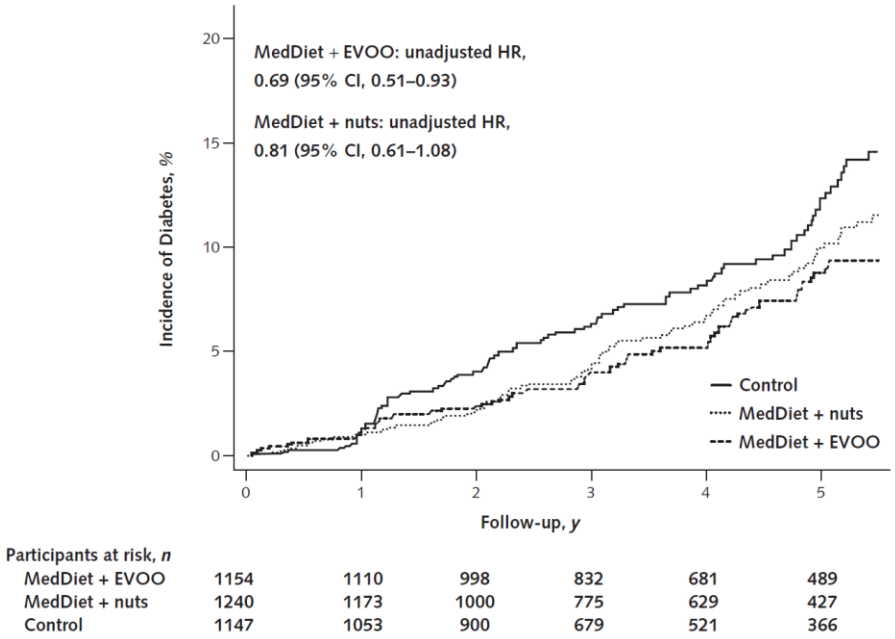


18-month trial in n=278 pts with abdominal obesity or dyslipidemia
Randomised to low fat or Med diet/low-carbohydrate +/- physical activity
Hepatic fat content (HFC) measured using MRI at baseline, 6 and 18 months.

Gepner et al, *J Hep*, 2019

Prevention of CV events and diabetes by the Mediterranean diet





N=7447 patients with T2D or ≥ 3 CV risk factors

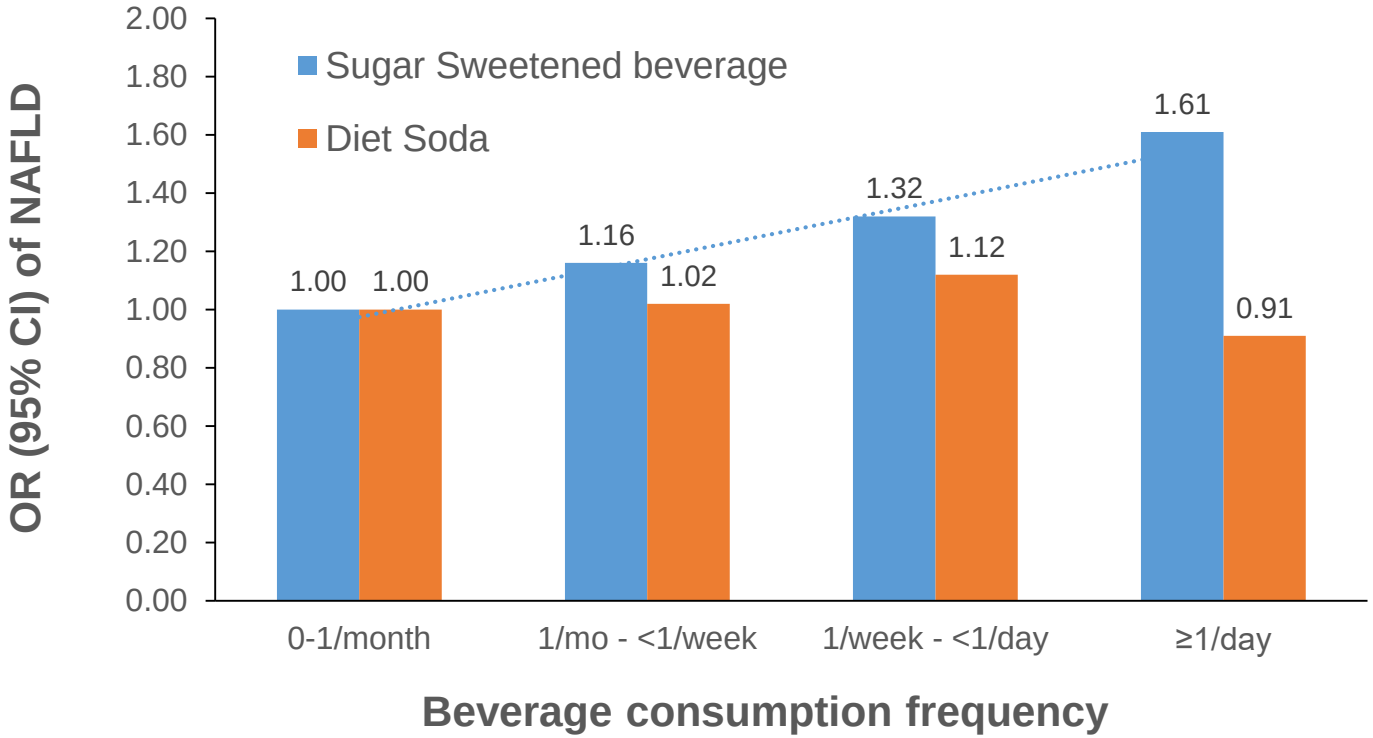
Multi-center RCT: Med diet + extra-virgin olive oil (EVOO), Med diet + nuts vs control diet (advice on a low-fat diet), no physical activity / weight loss intervention.

Estruch et al, *NEJM*, 2013 [retracted]

Estruch et al, *NEJM*, 2018

Salas-Salvadó et al, Ann Int Med, 2014

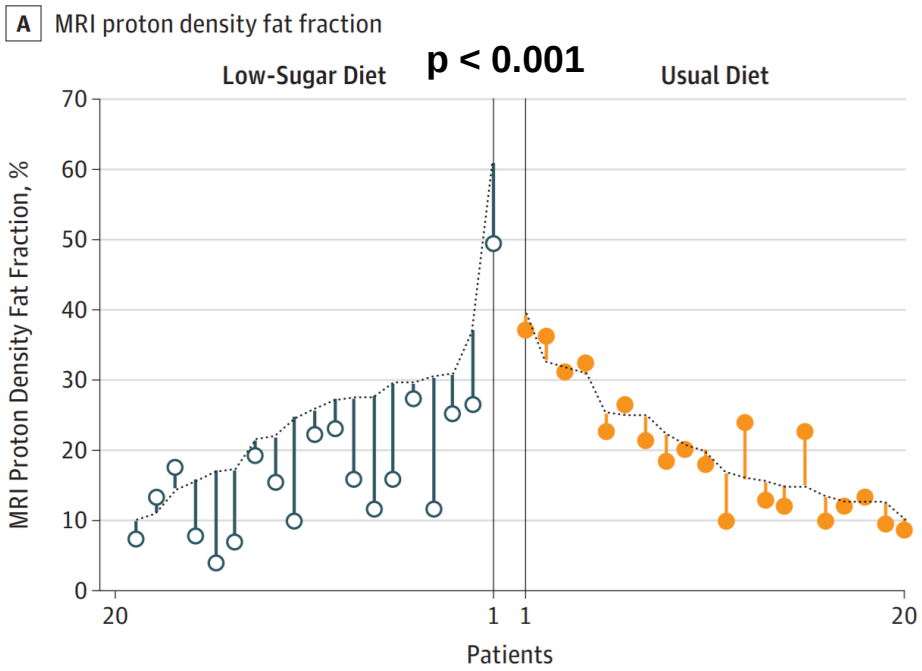
Association between sugar-sweetened beverages and NAFLD

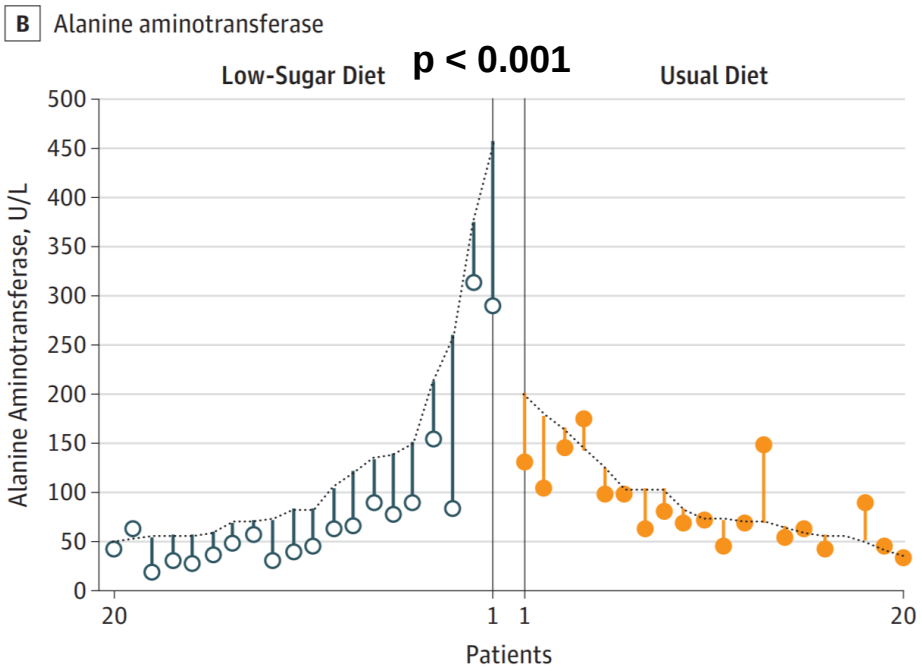


N=2566, Framingham Offspring and Third Generation cohorts
Fatty liver disease measured using liver attenuation on CT
Adjusted for age, sex, energy intake, alcohol intake, dietary intake, smoking, and cohort.

Ma et al, *J Hep*, 2015

Low free sugar diet leads to reduced steatosis in adolescent boys with NAFLD

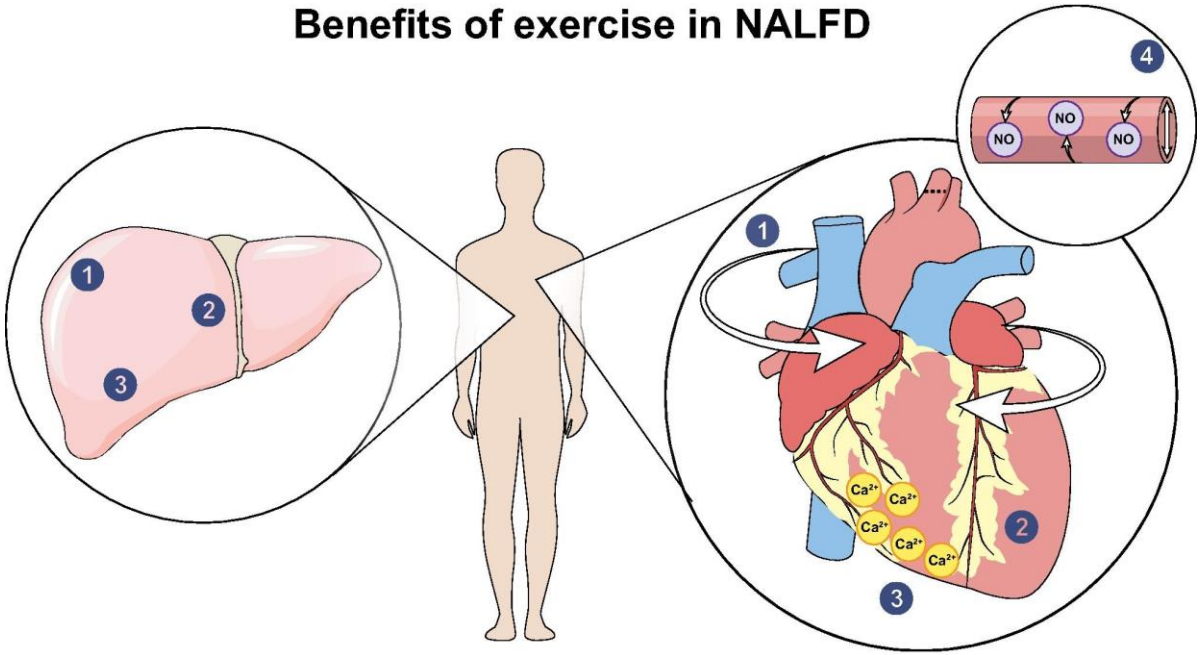




N=40 adolescent boys aged 11-16 years old with NAFLD (MRI-PDFF > 10% and ALT ≥ 45)
RCT: Restricted free sugar <3% daily calories for 8 weeks vs control (regular diet)
MRI-proton-density fat fraction measurement

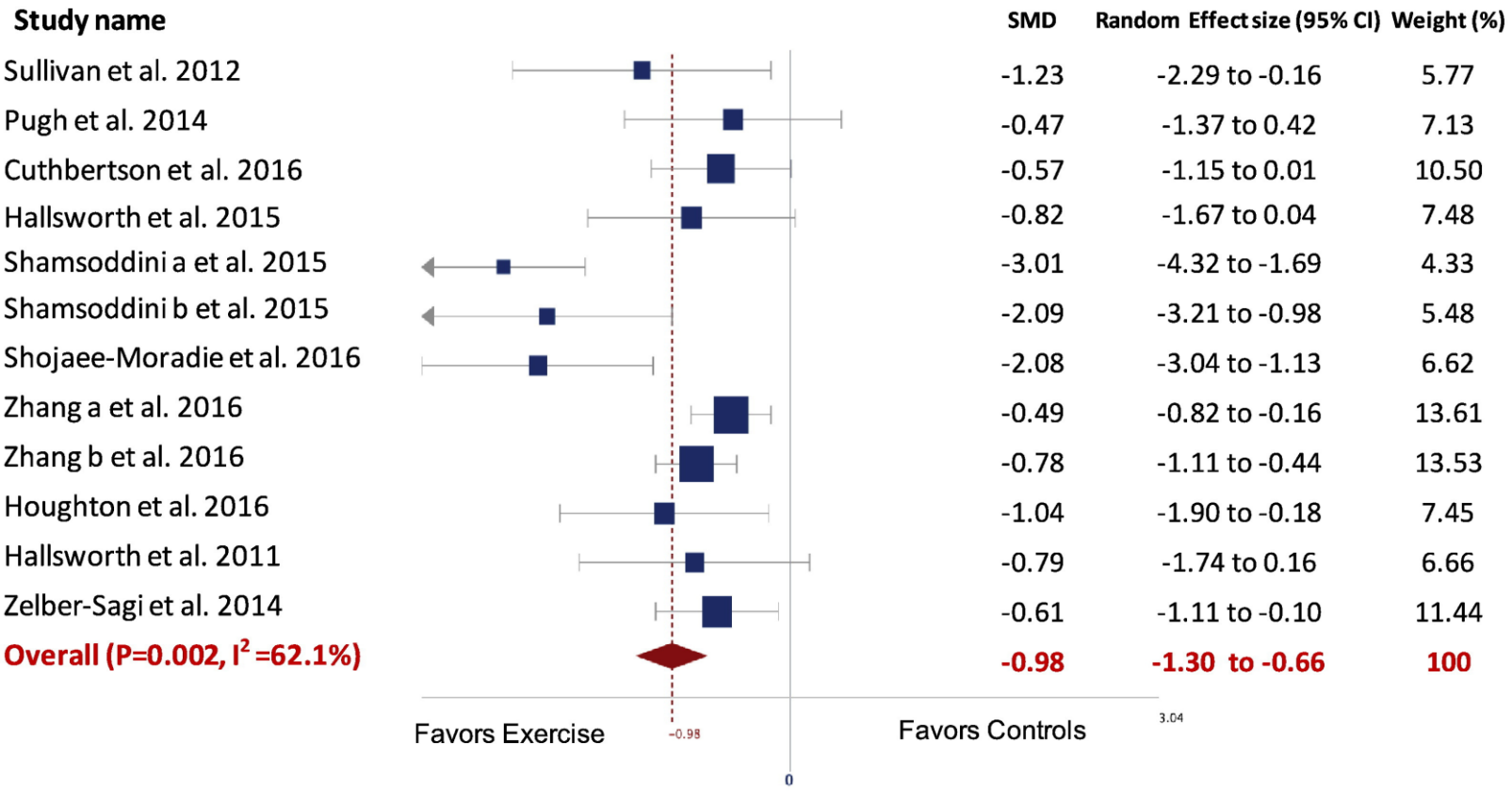
Schwimmer et al, *JAMA*, 2019

Benefits of exercise in NAFLD



Romero-Gomez et al, *J Hep*, 2017

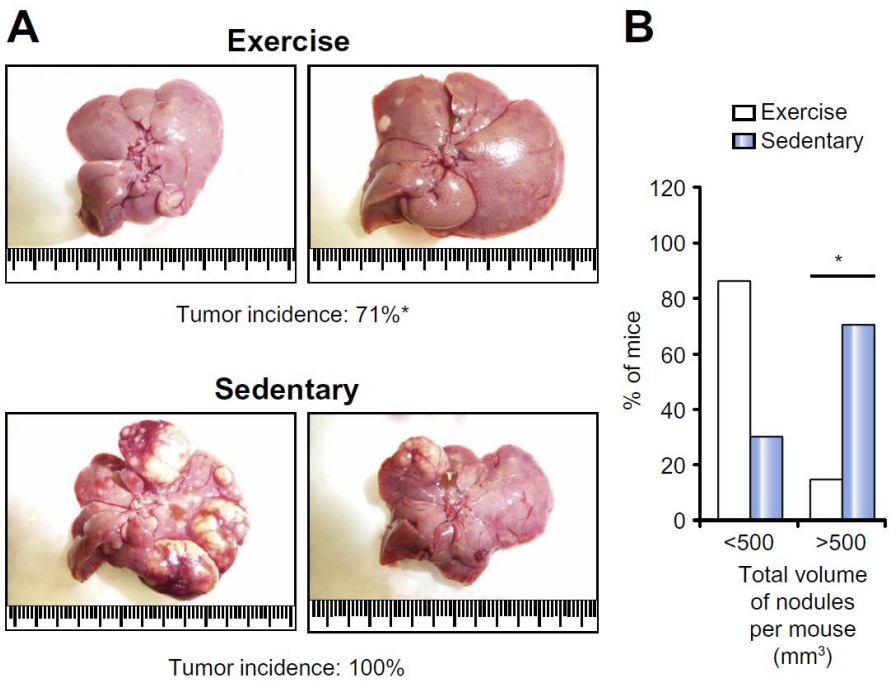
Impact of exercise on intrahepatic lipid – Meta-Analysis



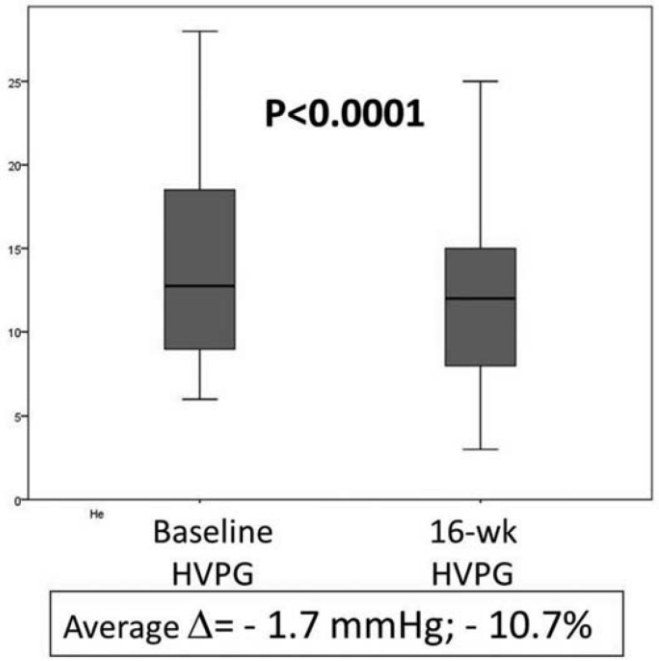
d. Effect of exercise alone (left) vs. control (right) on IHTG

Katsagoni et al, Metabolism, 2018

Other beneficial effects of exercise and diet in advanced disease



Reduced HCC in a PTEN-deficient model

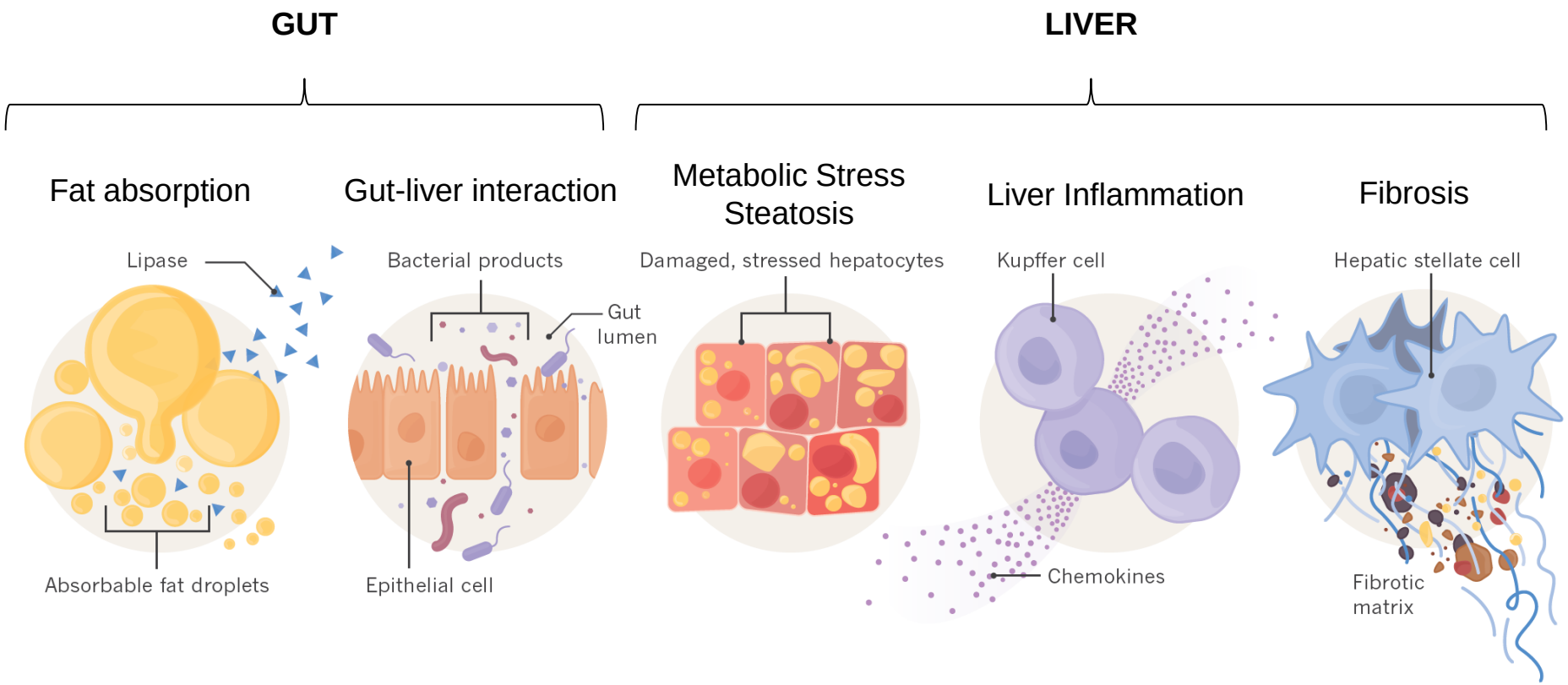


16 weeks of diet and moderate exercise reduced portal pressure in overweight/obese pts with cirrhosis and portal HTN

Piguet et al, *J Hep*, 2015

Berzigotti et al, *Hepatology*, 2017

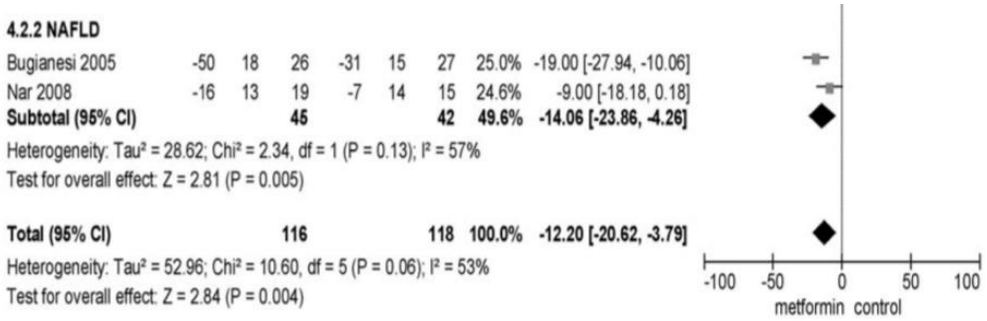
Strategies for pharmacological management of NAFLD



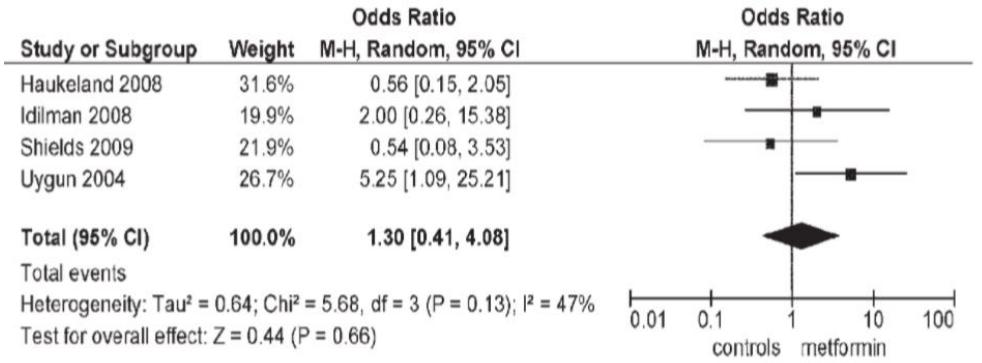
Adapted from Drew, Nature, 2017

No clear role for metformin

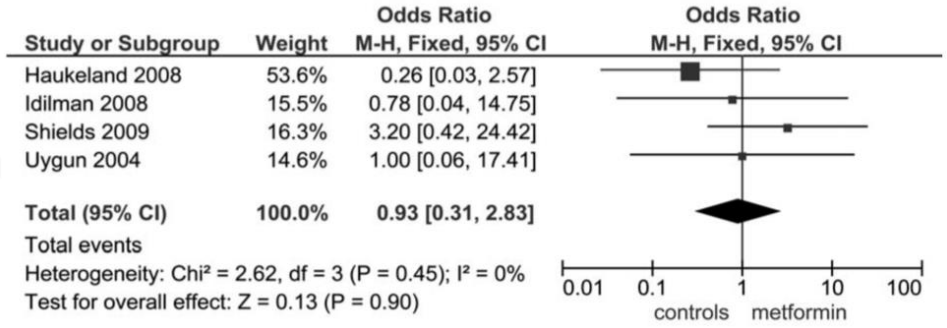
AST/ALT



Steatosis

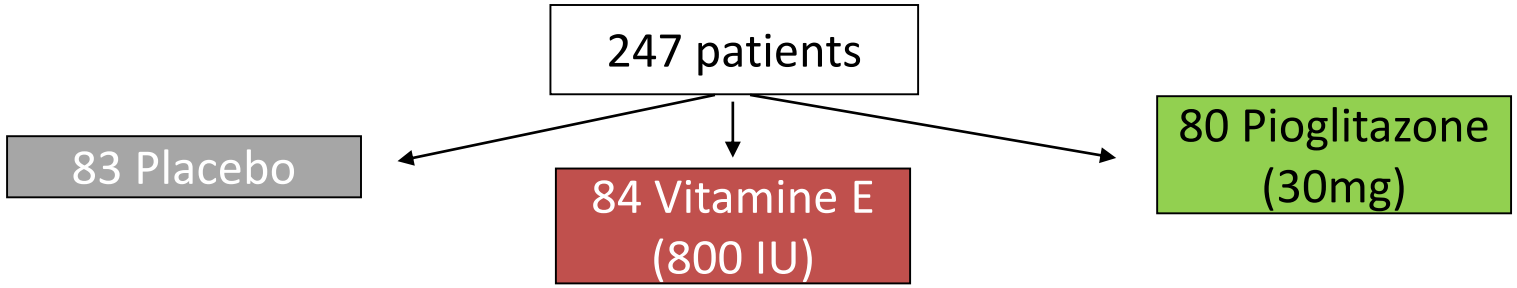


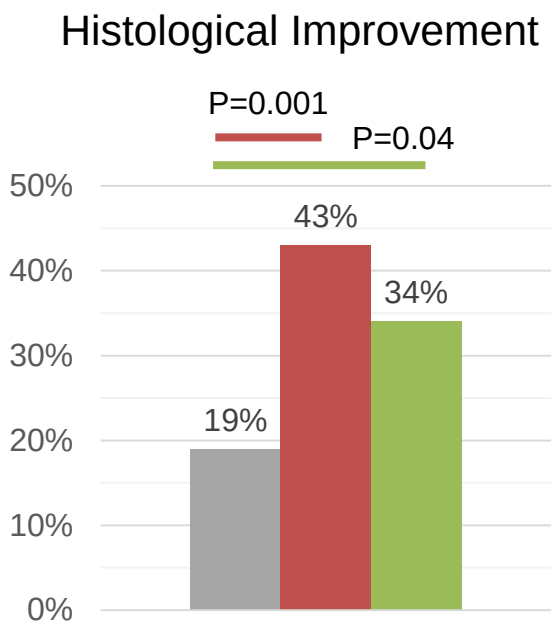
Fibrosis resolution

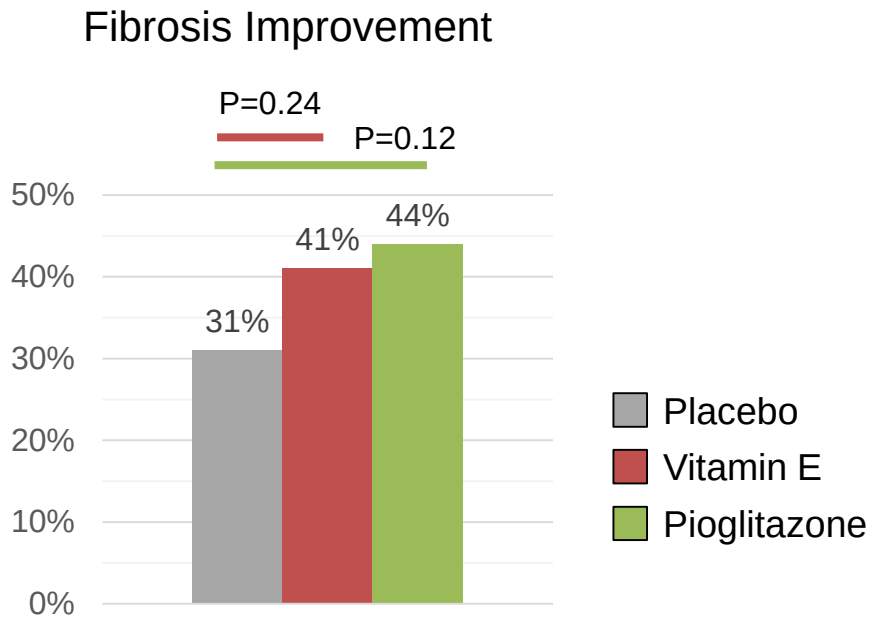


Musso, Hepatology, 2010

Pioglitazone and Vitamine E in non-diabetic patients with NASH (22 months)

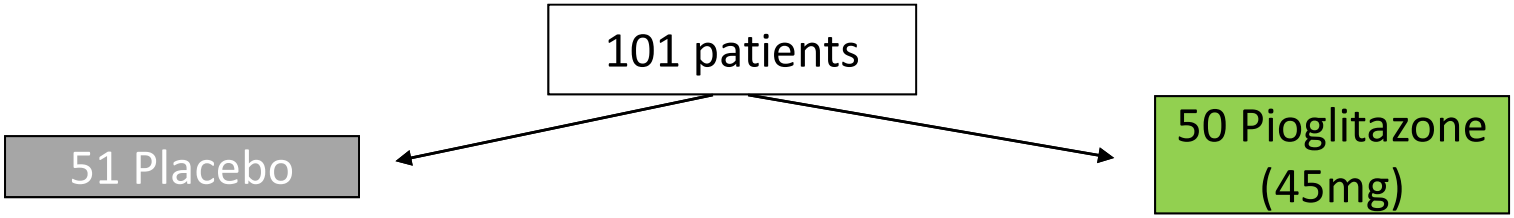




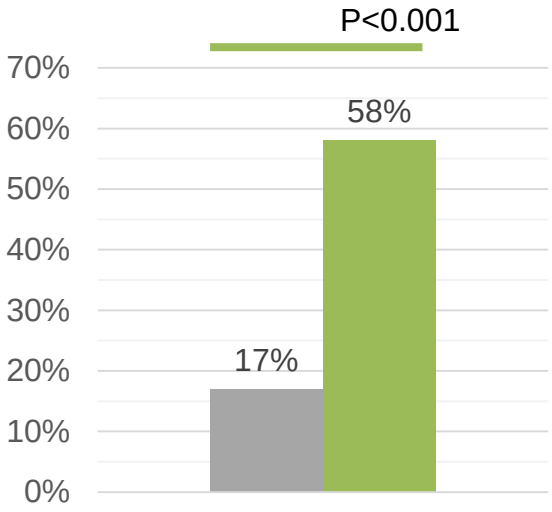


Sanyal, *NEJM*, 2010

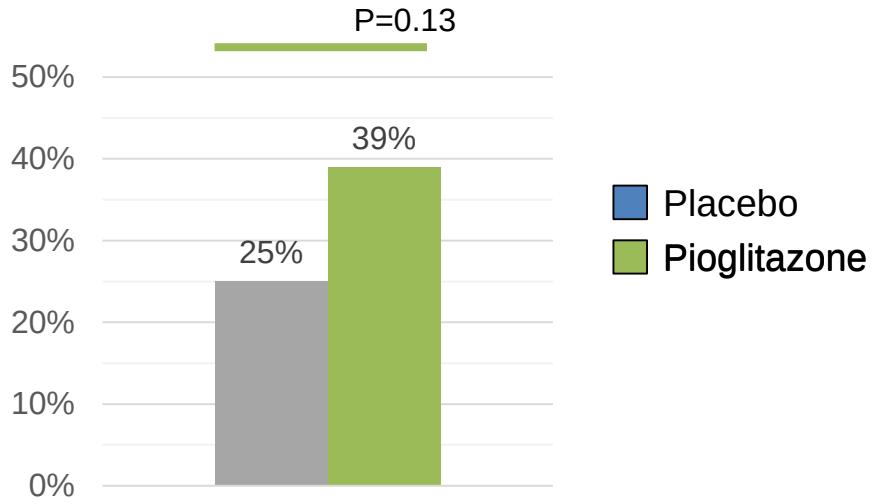
Pioglitazone in patients with (pre-) diabetes and NASH (18 months)



Improvement NAS ≥ 2 with no worsening fibrosis



Fibrosis ≥ 1 Improvement



Cusi, *Ann Int Med*, 2016

Pioglitazone and Vitamin E in patients with NASH

EASL:

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**)

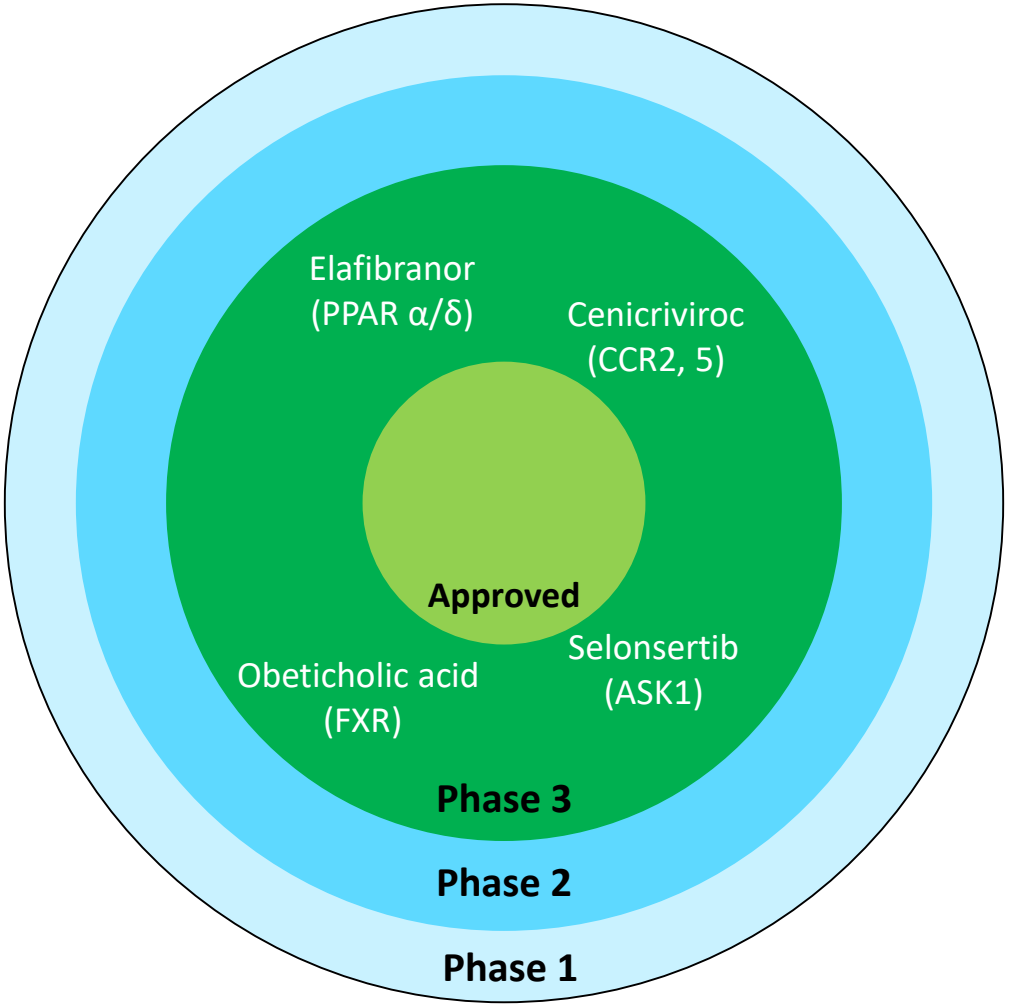
no general recommendation for vitamin E or pioglitazone

- concerns about cardiovascular risk for glitazones
- concerns about increased risk for malignancies with vitamin E
- No clear effect on fibrosis

Upcoming therapies in NAFLD

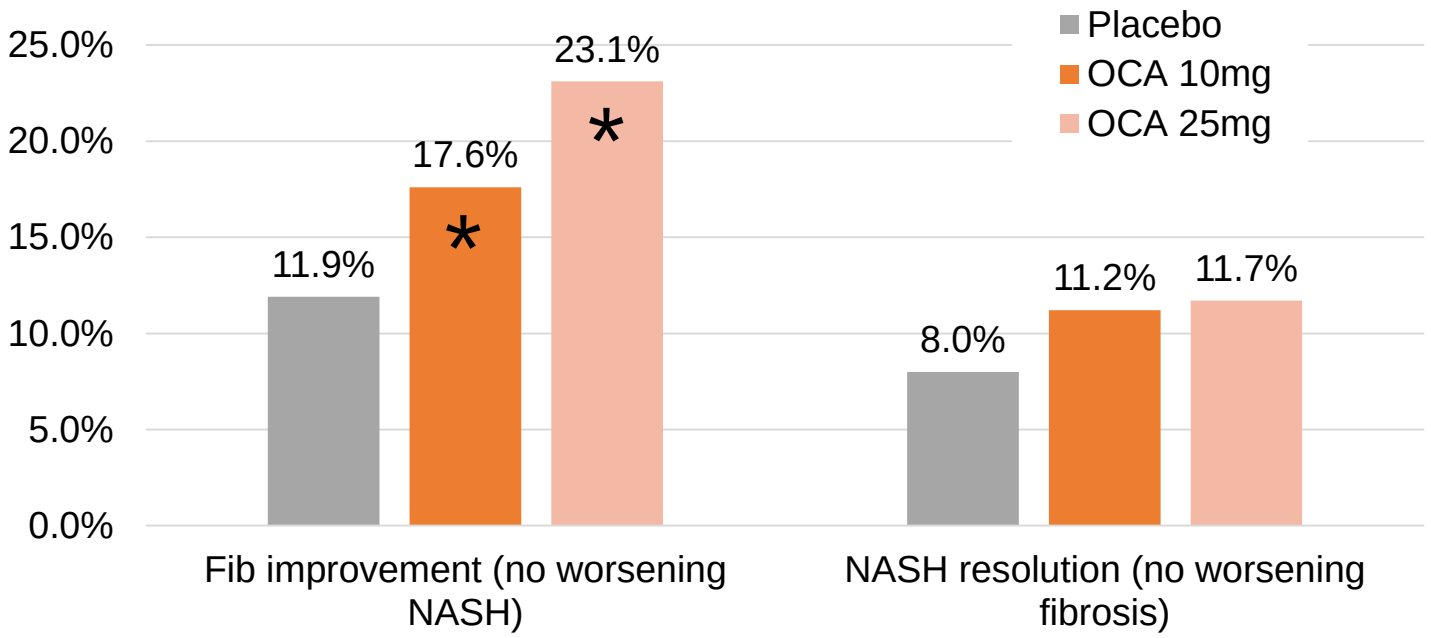
Drew, Nature, 2017

Management – Ongoing phase 3 clinical trials in NASH



Positive results from REGENERATE: A phase 3 international, randomized, placebo-controlled study of obeticholic acid treatment for NASH

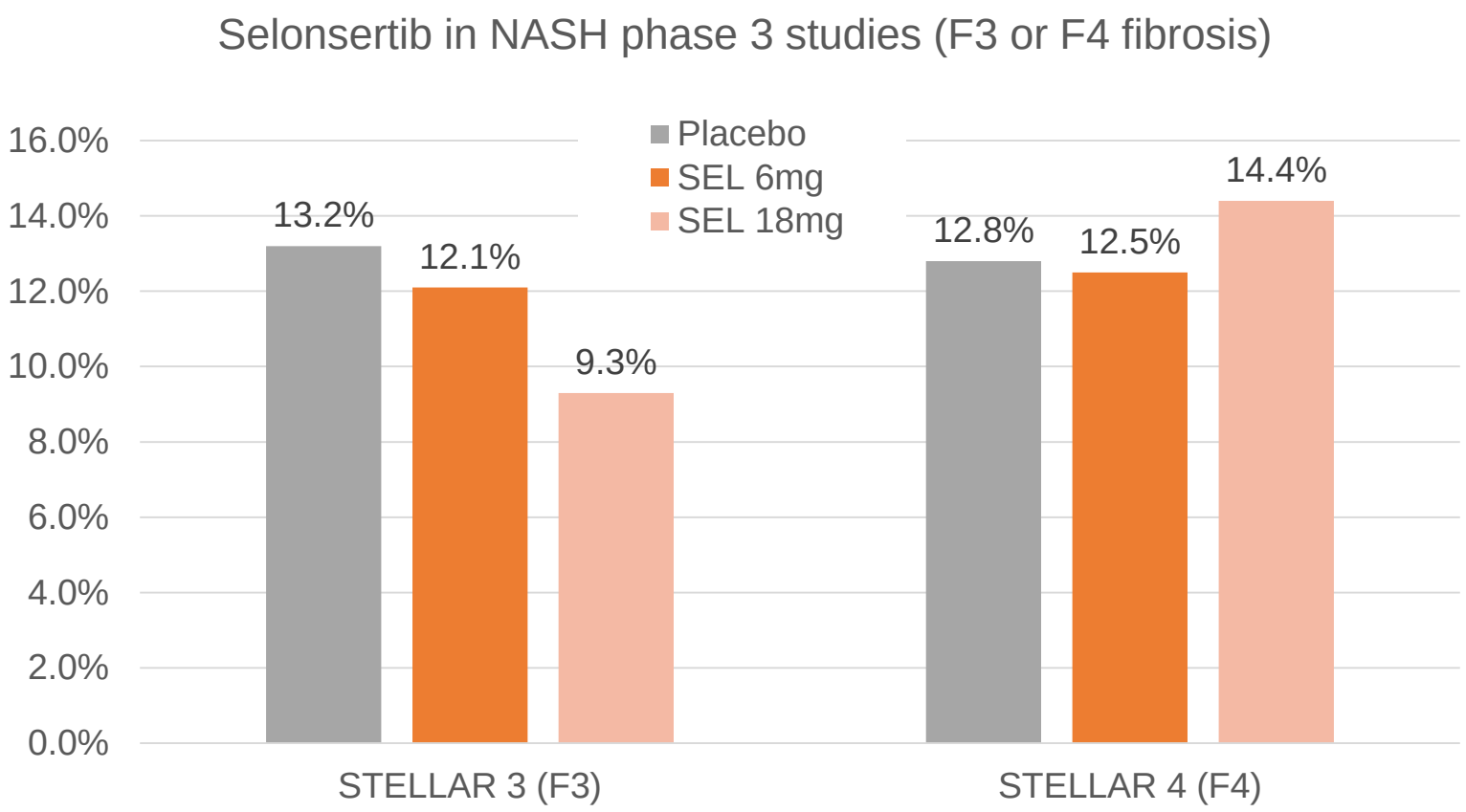
REGENERATE phase 3 study (OCA in stage 2-3 NASH – month 18 interim analysis)



* $p < 0.05$ compared to placebo

INTERCEPT press release Feb 19th 2019
Oral presentation EASL ILC 2019, April 2019

Phase 3 trials of selonsertib in NASH with advanced fibrosis (STELLAR-3 and -4) did not meet week 48 primary endpoint

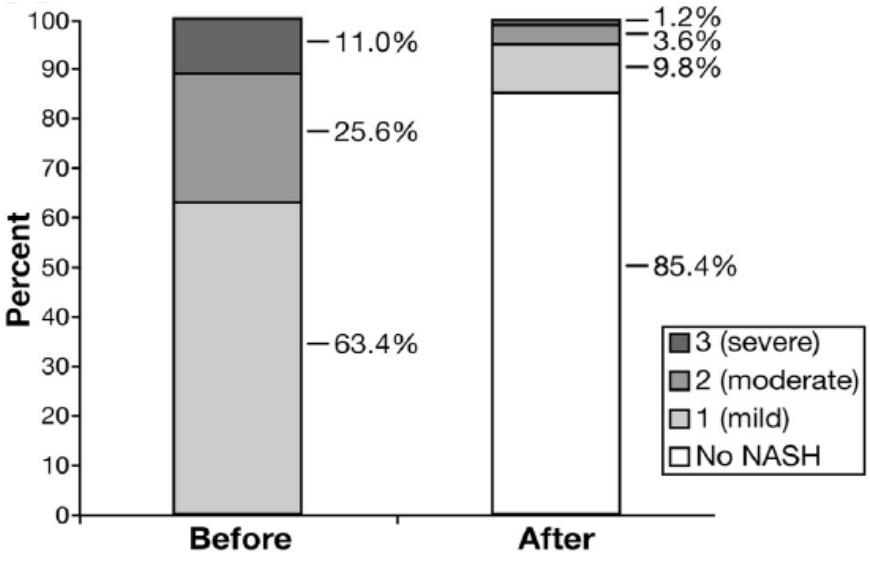


Fibrosis improvement without worsening of NASH

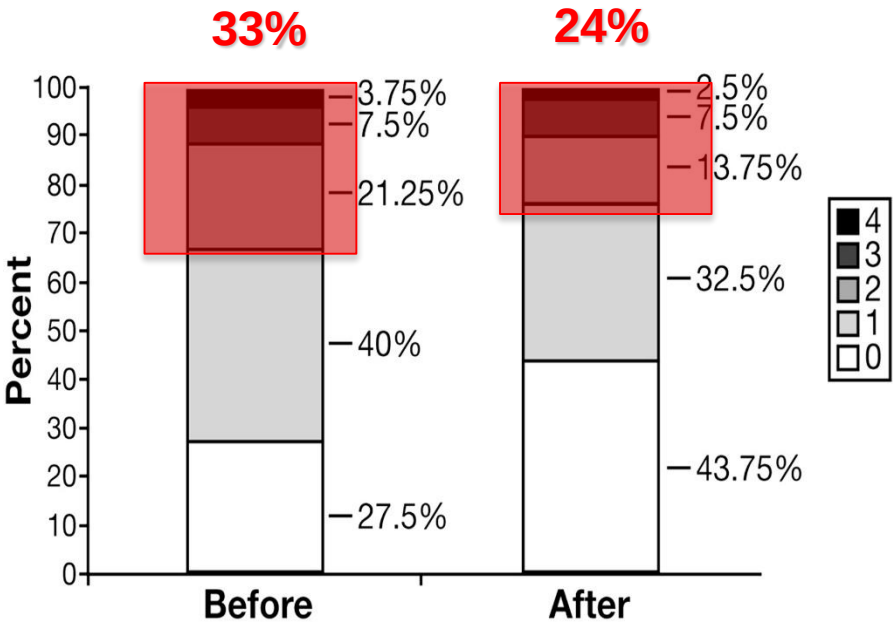
GILEAD press release Feb 11th 2019 and April 25th 2019

Rappel: Penser à la chirurgie bariatrique!

Résolution de la NASH



Amélioration de la fibrose



NASH : 1 an après chirurgie bariatrique (n=109)

Lassailly et al, *Gastro* 2015

Penser au dépistage du CHC!

Table 3. Recommendations for HCC surveillance: Categories of adult patients in whom surveillance is recommended.

- Cirrhotic patients, Child-Pugh stage A and B (**evidence low; recommendation strong**)
- Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation (**evidence low; recommendation strong**)
- Non-cirrhotic HBV patients at intermediate or high risk of HCC* (according to PAGE-B† classes for Caucasian subjects, respectively 10–17 and ≥18 score points) (**evidence low; recommendation weak**)
- Non-cirrhotic F3 patients, regardless of aetiology may be considered for surveillance based on an individual risk assessment (**evidence low; recommendation weak**)

Le dépistage par échographie hépatique 2x/an est préconisé chez les patients cirrhotiques (+/- les patients F3)

Conclusions

- Le foie gras est une pathologie en pleine **expansion** épidémiologique.
- Un **dépistage** de la NAFLD, en particulier la fibrose avancée, est recommandée chez les patients avec syndrome métabolique.
- Le rôle du **médecin de premier recours** est fondamental pour l'identification des patients à haut risque d'évolution, le suivi et la prise en charge thérapeutique.
- Rôle des mesures hygiéno-diététiques: perte de 7-10% du poids et activité physique.
- Pas de traitement encore approuvé. De **nouvelles molécules** sont en phase de développement.
- Ne pas oublier: dépistage du CHC si cirrhose et penser à la chirurgie bariatrique si indication.

Hôpitaux Universitaires Genève

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Merci de votre attention !