

La maladie du foie gras
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SwissMilk
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Vous avez dit foie gras?



LE GROS, LÀ, DOIT TROP MANGER; ÇA M'ÉTONNERAIT QUE SON FOIE SOIT EN BON ÉTAT.

IL N'EST PAS GROS ET SON FOIE EST EN EXCELLENT ÉTAT!

Uderzo et Goscinny. Le bouclier Arverne. Dargaud 1968

De nos jours

Identification :

Echographie

CT, IRM

Approches quantitatives :

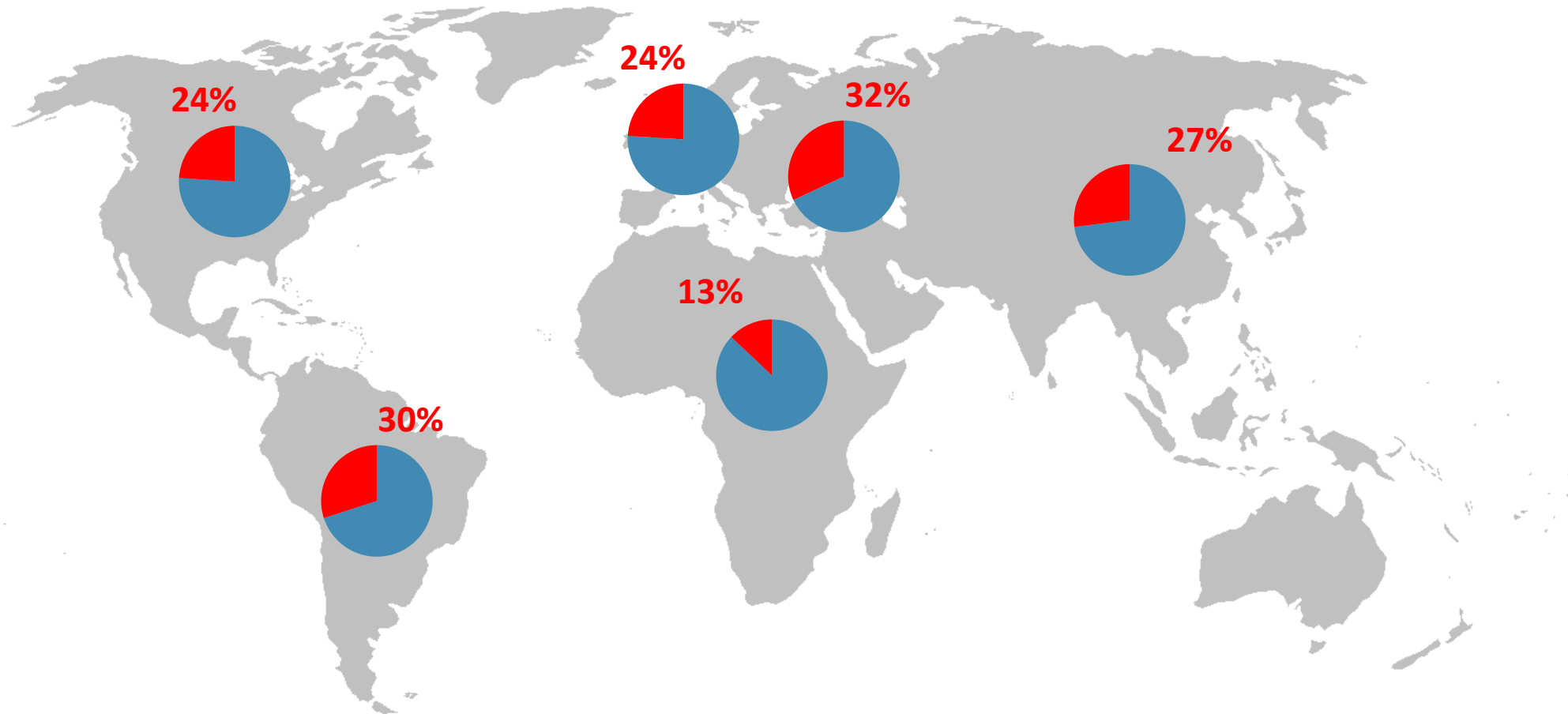
MRI-PDFF

CAP

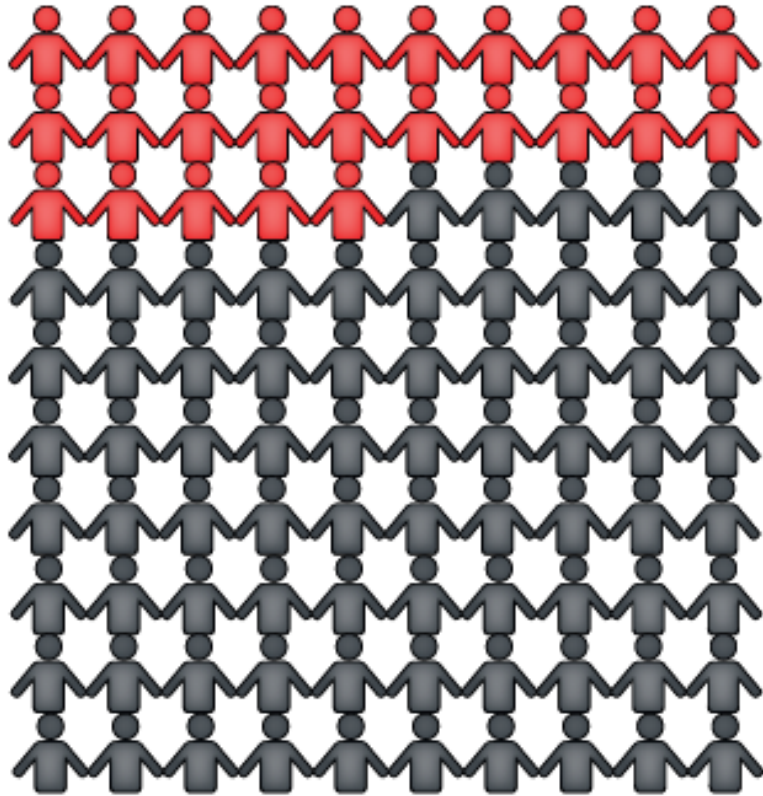
Histology

Globalité du problème

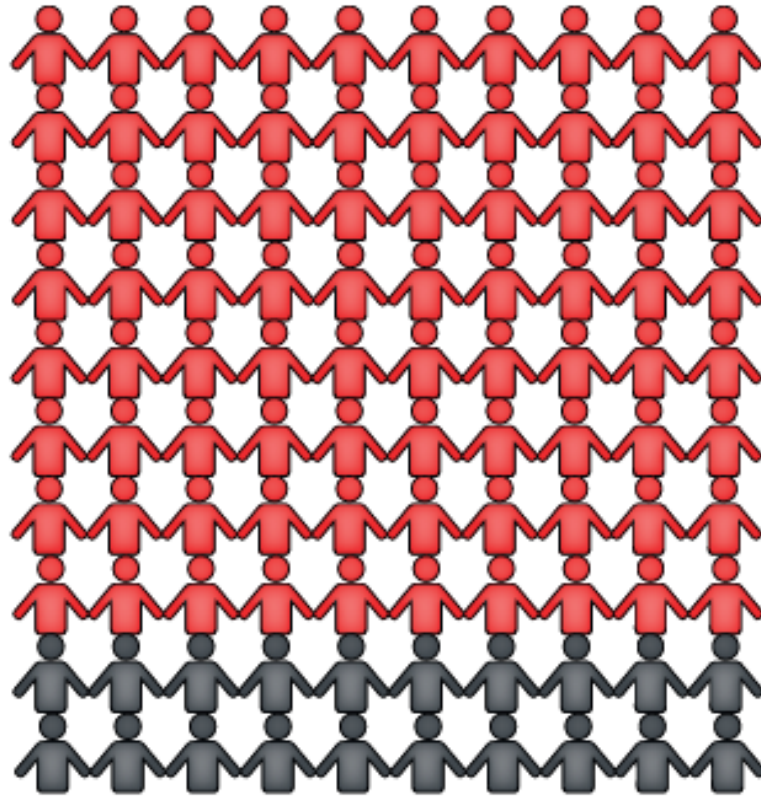
25% of the world population has fatty liver



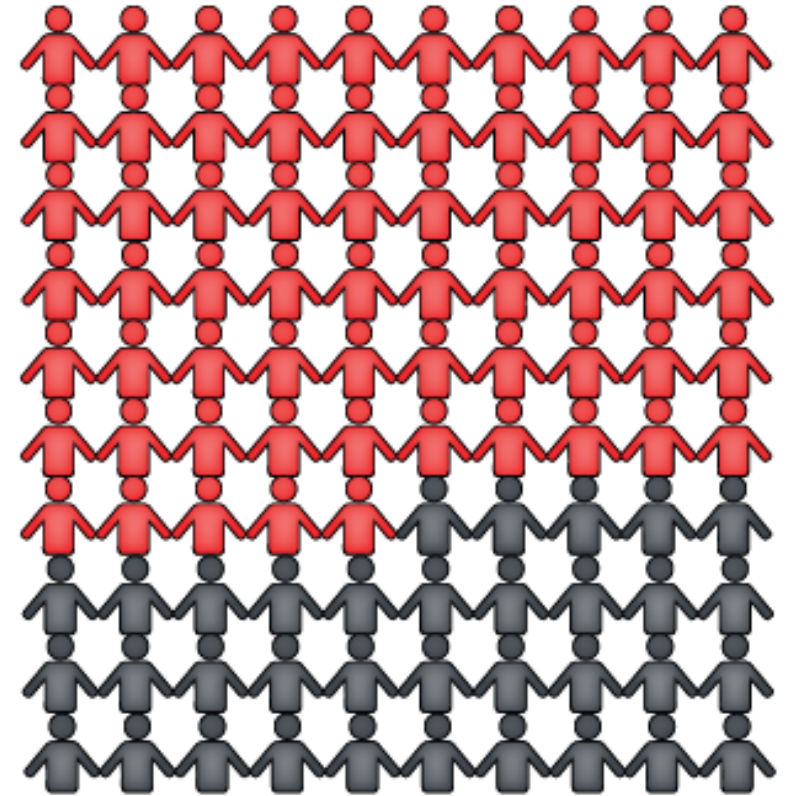
Fatty Liver in different populations



Community (25% NAFLD)



Obesity (80% NAFLD)



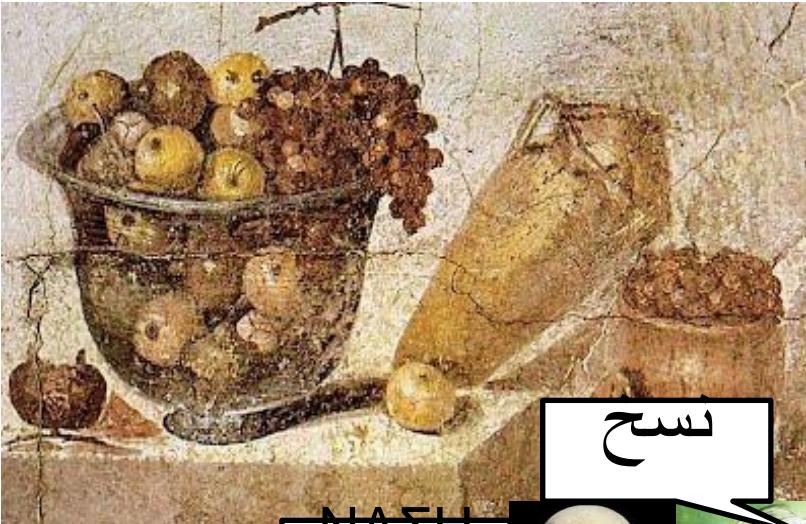
Type 2 diabetes (65% NAFLD)

Pathophysiologie

Fatty Liver from an evolutionary point of view



Fatty Liver from an evolutionary point of view

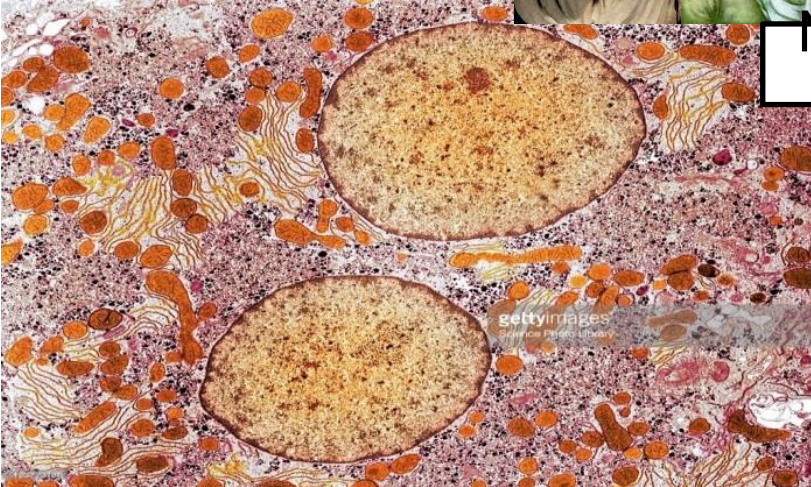


نسخ

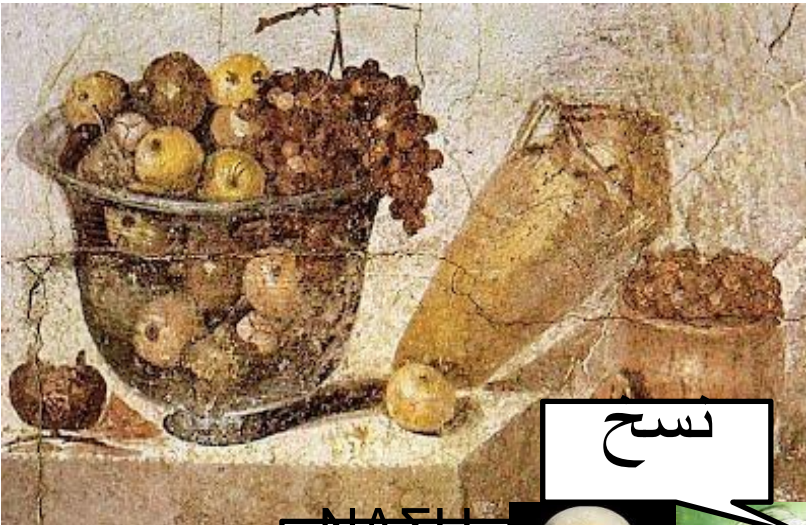
ΝΑΣΗ
?



ΝΑΣΗ
?



Fatty Liver from an evolutionary point of view



نسخ

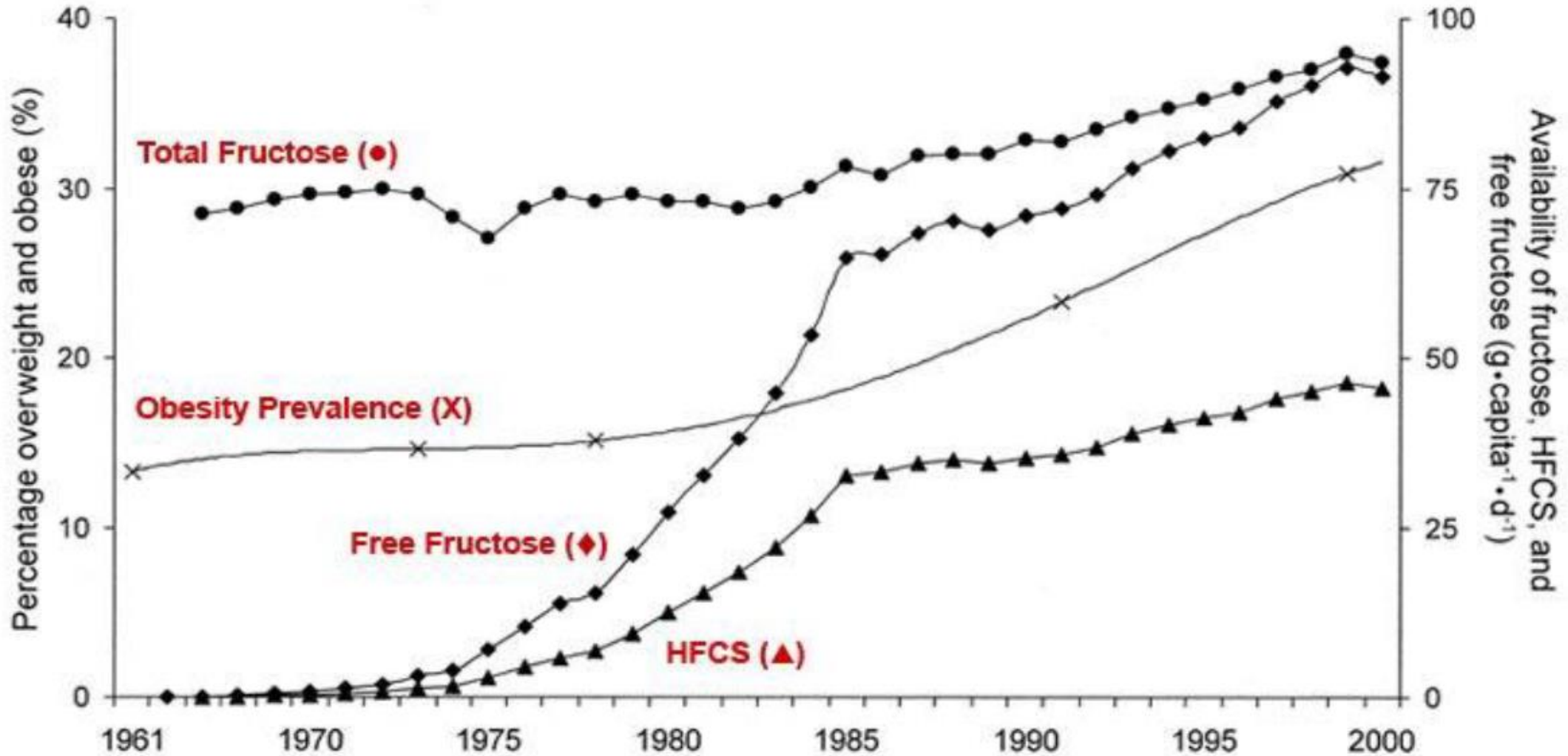
ΝΑΣΗ ?

ΝΑΣΗ ?



Fatty Liver from an evolutionary point of view

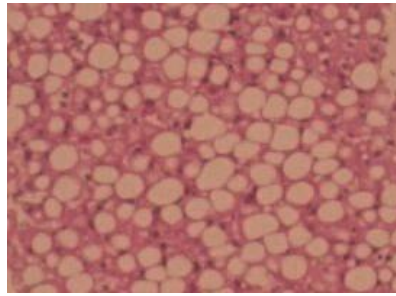
Non-alcoholic steatohepatitis (NASH), Ludwig et al. 1980



Définitions- nomenclature

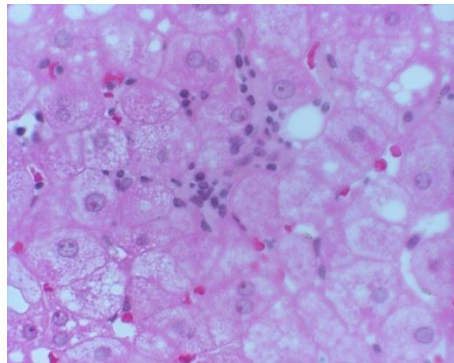
Le débat 'M ou N'

Definition of NASH



Stéatose

Consommation
d'alcool



+ Inflammation

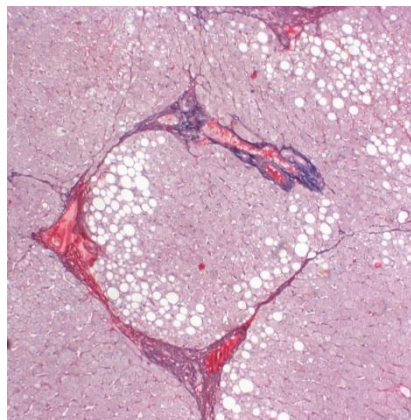
20 g/jour ♀

30 g/jour ♂

+ Ballooning

Dionysios Study

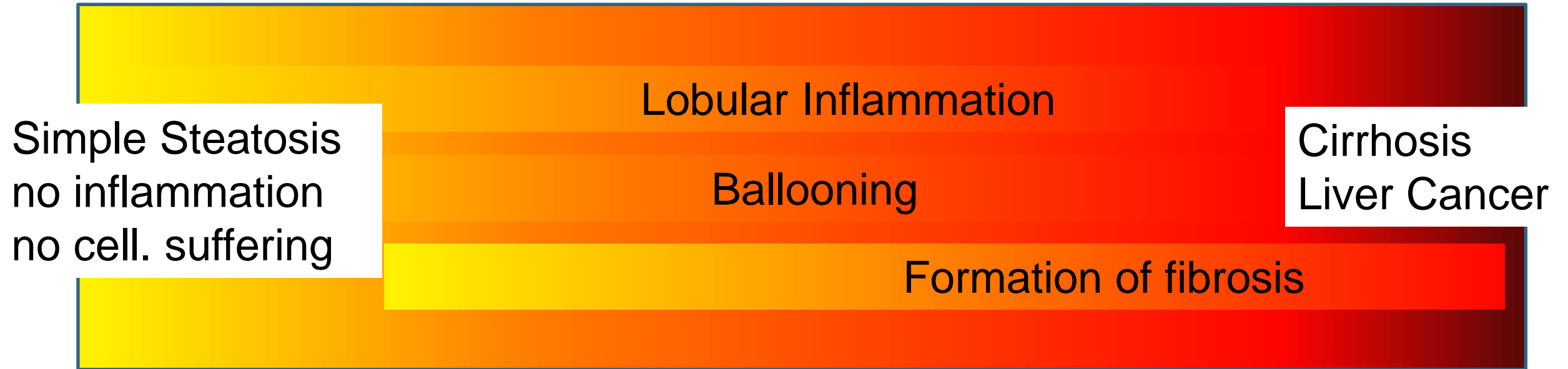
Gut 1997;41:845-50



+ Fibrosis

Cirrhosis

NASH is in a NAFLD continuum



Les risques du foie gras

Causes of death of NAFLD patients

Analyse retrospective de 619 patients avec un foie gras diagnostiqué
Entre 1975 et 2005 (Etats-Unis, Europe, Thaïlande)

Outcome	Number
Death or OLT	<i>n</i> = 193
Cardiovascular disease	74 (38.3%)
Non-liver cancer	36 (18.7%)
Cirrhosis complications	15 (7.8%)
HCC	2 (1%)
Liver transplantation	1 (0.5%)
Infections	15 (7.8%)
Others	35 (18.1%)

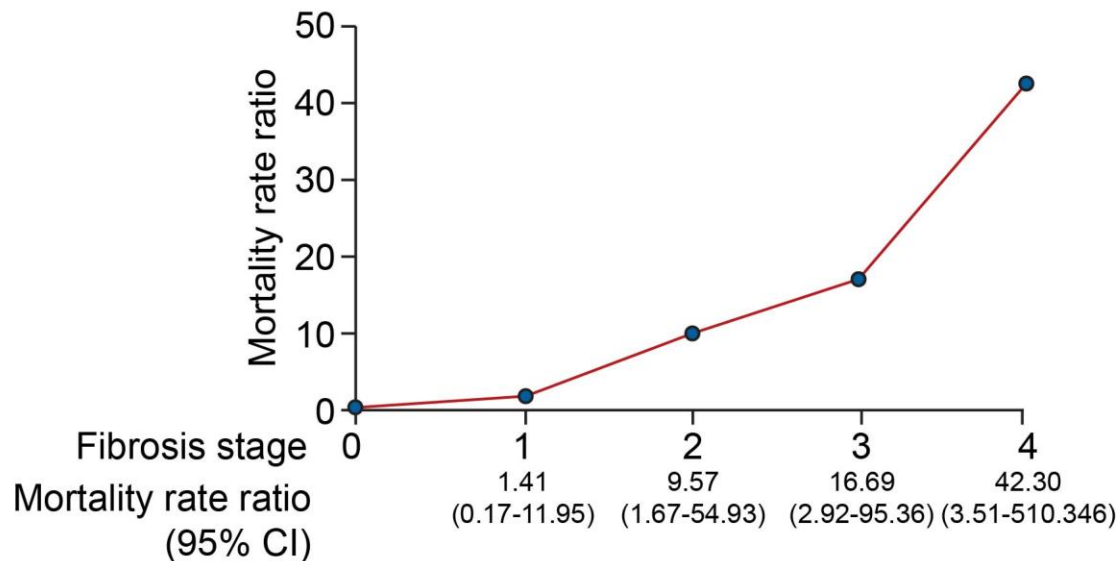
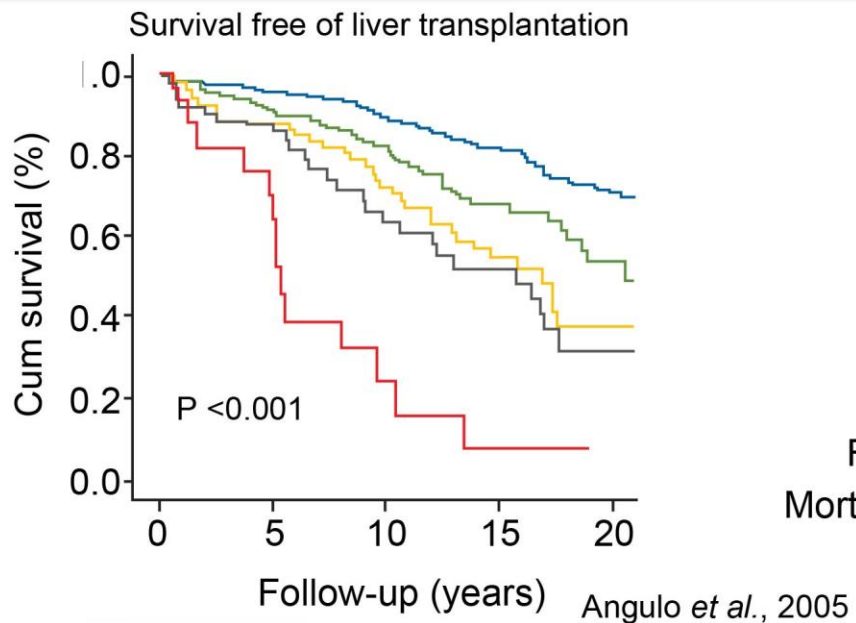
Fatty Liver and Cancer

Analyse rétrospective de 25,947 Coréens suivi pendant 7.5 ans en moyenne

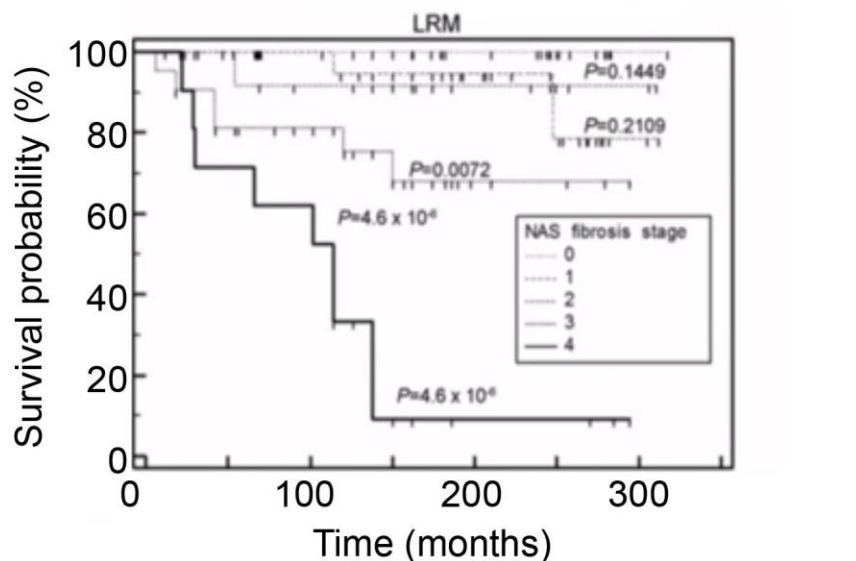
	Number of cancers	Cancer incidence rate per 100,000 person-years				<i>P</i> -values
		All	NAFLD	No NAFLD	IRR	
All cancers	1,083	657.7	782.9	592.8	1.32	<0.001
Colon/Rectum	76	46.2	69.4	34.1	2.04	0.002
HCC	14	8.5	23.1	0.9	25.09	0.002
Breast	91	119.7	181.6	102.5	1.77	0.01

Qui est à risque ?

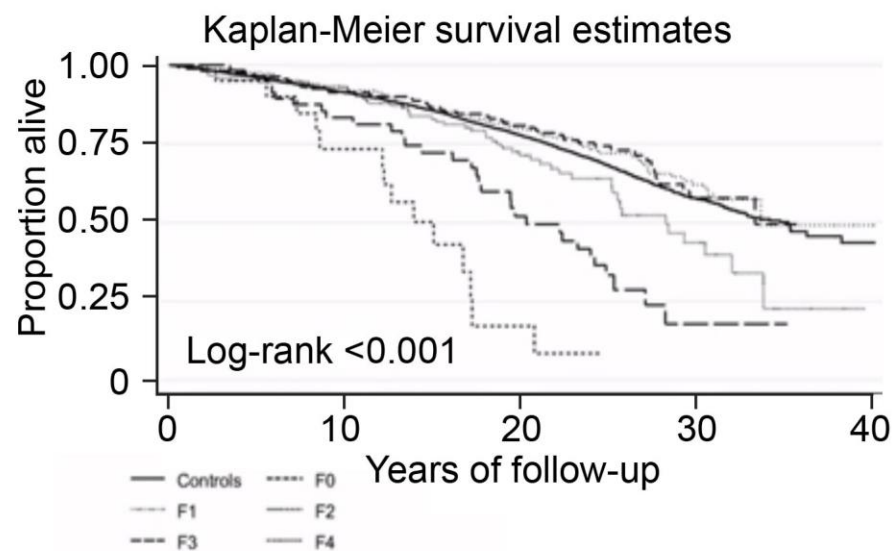
Fibrosis dictates prognosis



Dulai *et al.*, 2017



Younossi *et al.*, 2017



Hagström *et al.*, 2017

Qui référer ?

Suspicion de stéatose avec fibrose

Dépistage FIB-4, élastographie

Contexte

Diabète de type 2

Obésité

Hypertension artérielle

Hyperlipidémie

Syndrome d'apnées du sommeil

Approche – Prise en charge

Lifestyles and Fatty Liver



Weight
Sport



Diet
Beverages



Screens
Sleep



Weight loss



52 weeks of lifestyle intervention



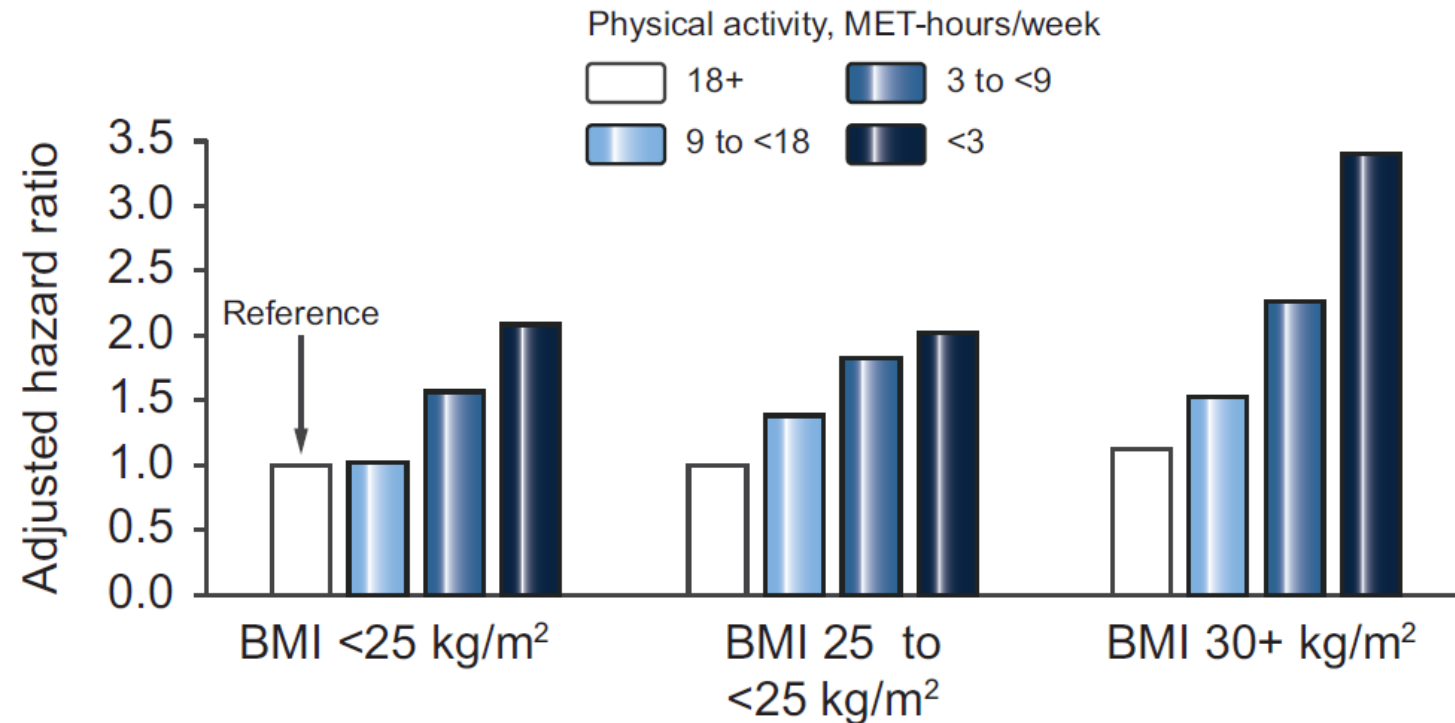
293 patients with NASH

52 weeks intervention
(diet and 'lifestyle sessions')

Biopsies

Physical activity and Liver mortality

Liver-related mortality risk in U.S. men and women
without established liver disease at baseline (1986-2012)

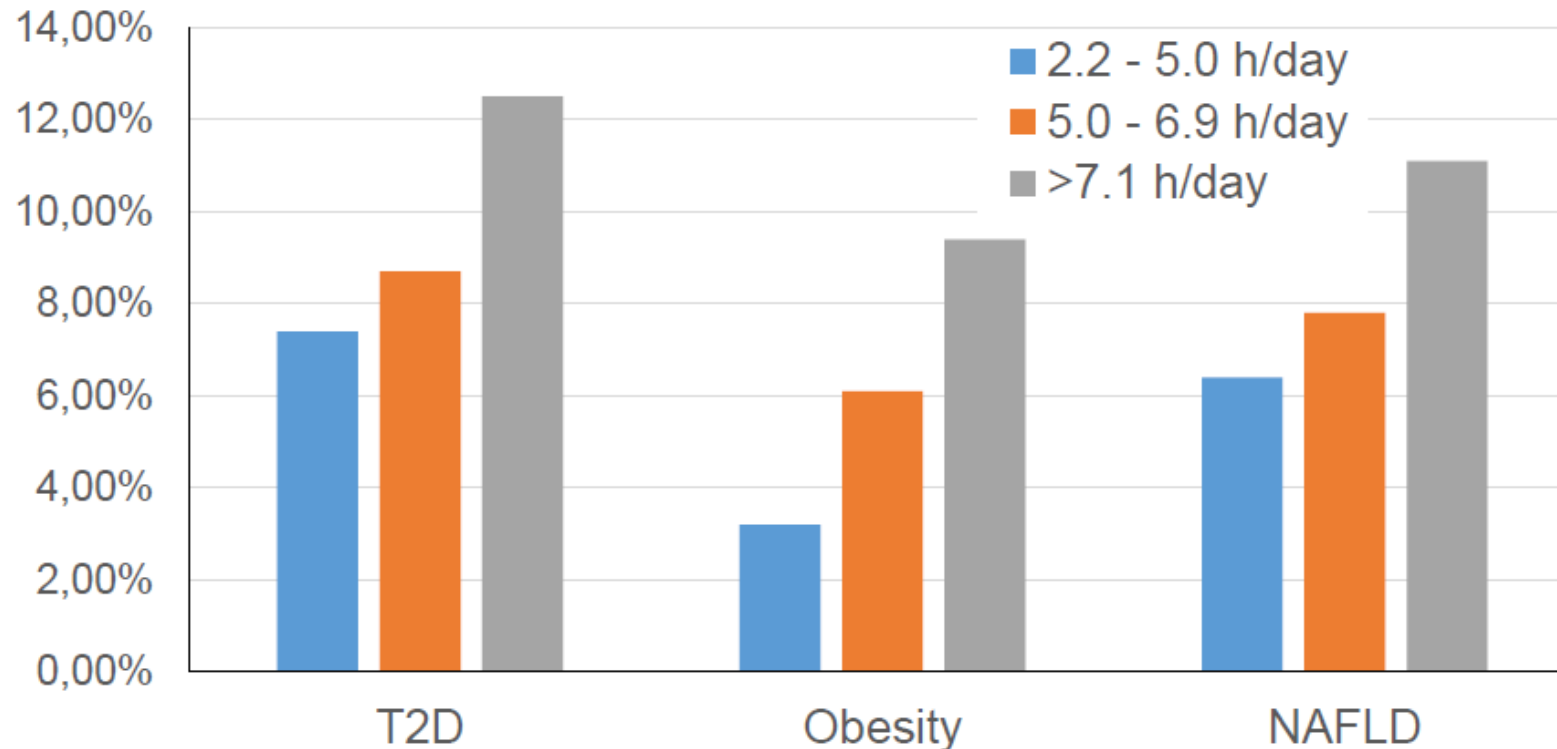


N = 125,864
adults

- Higher physical activity levels predicted significantly lower risk of liver-related mortality, across all levels of body mass index (BMI)
- Average-pace walking for >3 hours per week could have prevented 25% of liver-related deaths

Sedentarity and Fatty Liver

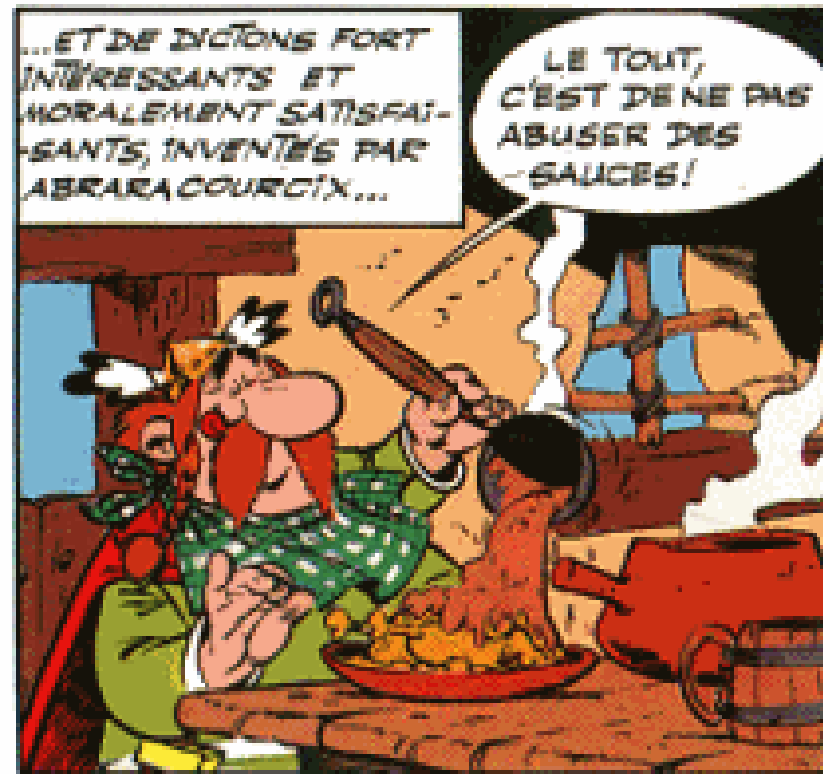
Prevalence of NAFLD, T2DM and obesity according to the tertiles of sitting time (hours/day)



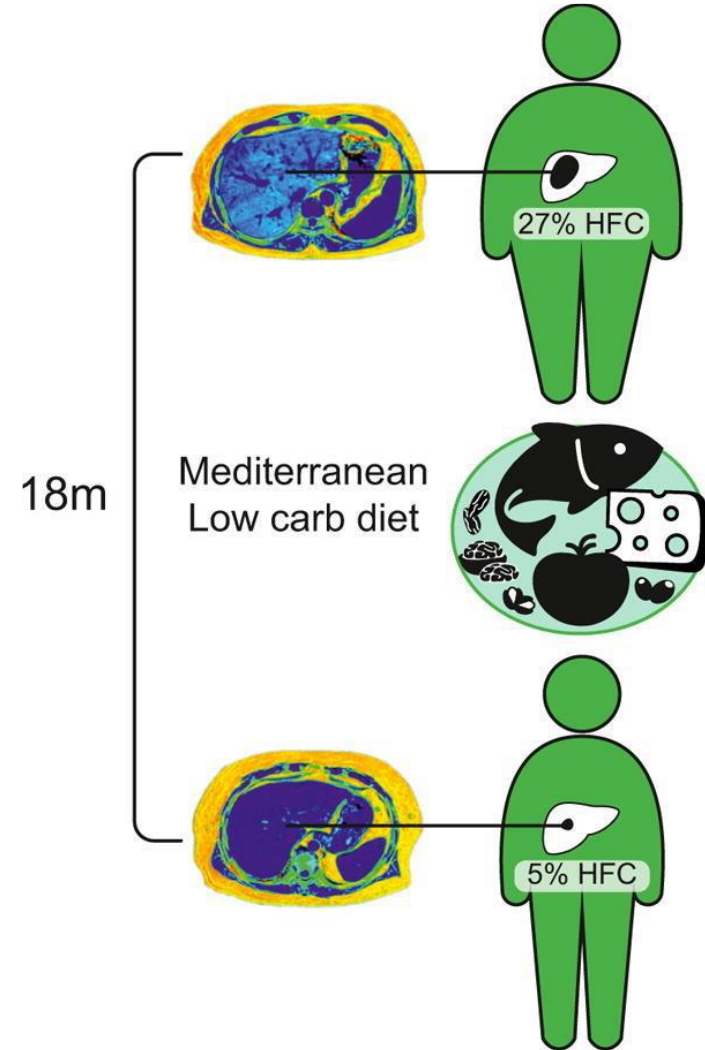
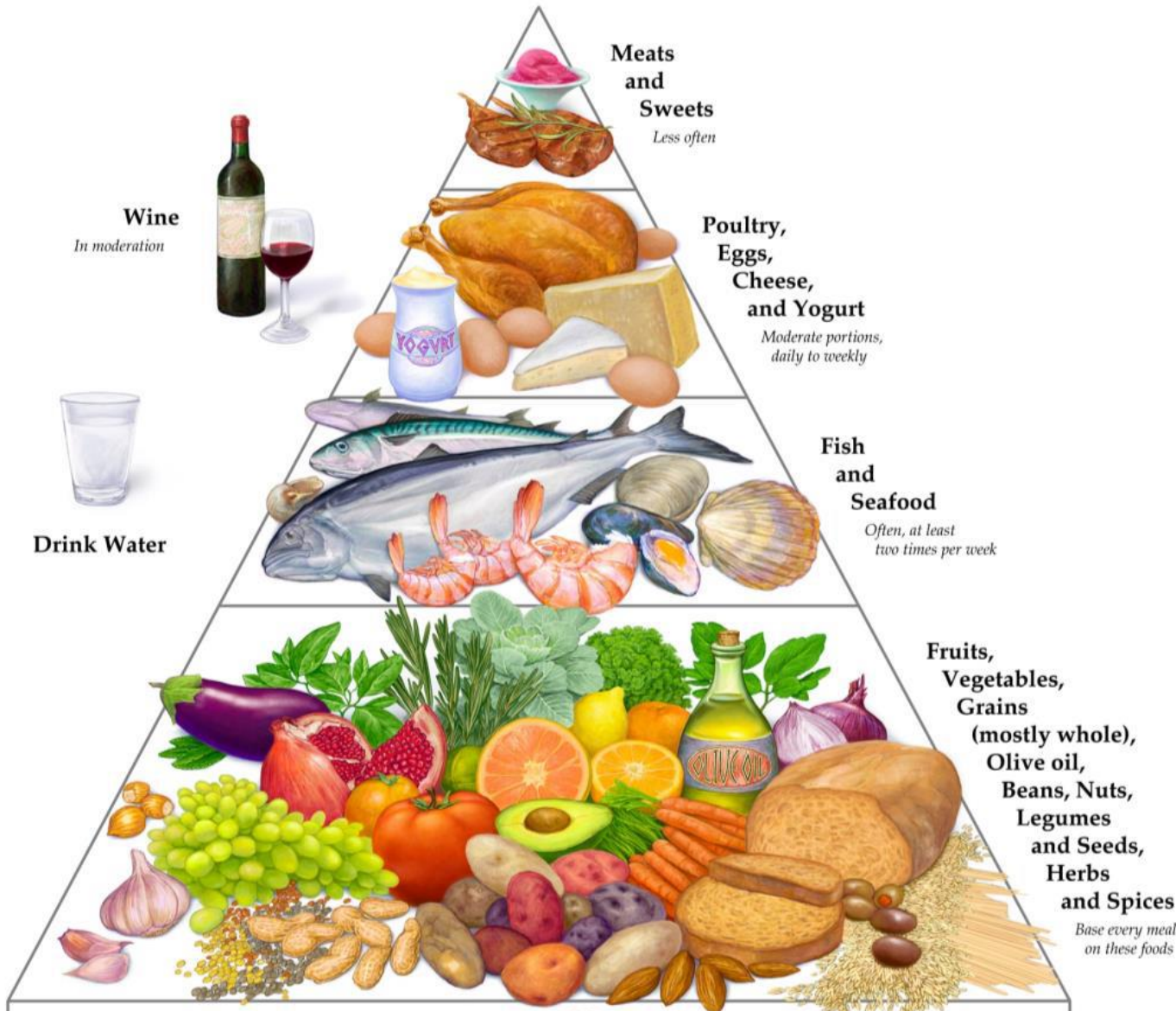
Cross-sectional study in 2054 male participants in China

NAFLD diagnosed after exclusion of other liver disease and fatty liver index > 60

Which Diet ?



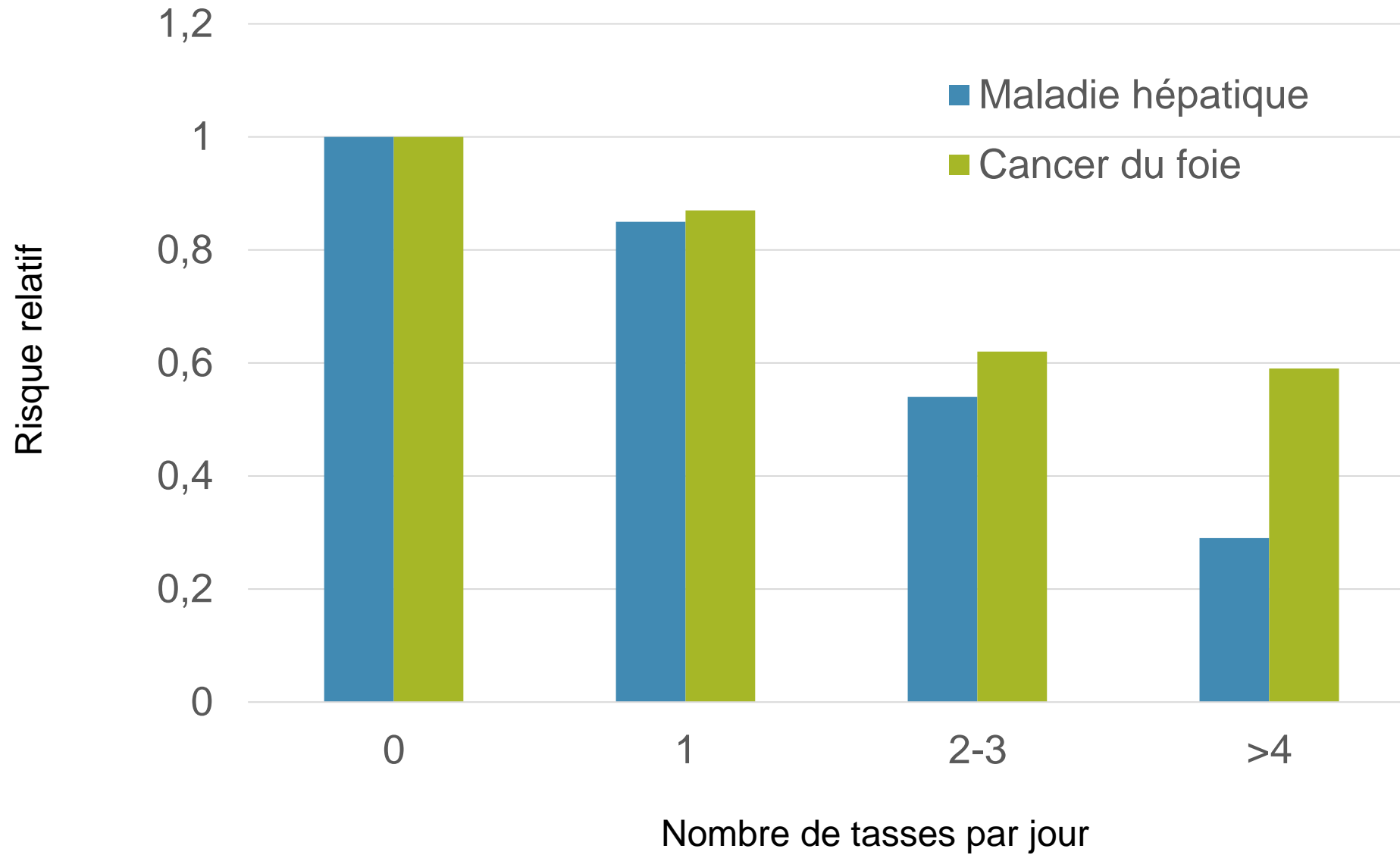
Mediterranean Diet



Sugar Content in sodas

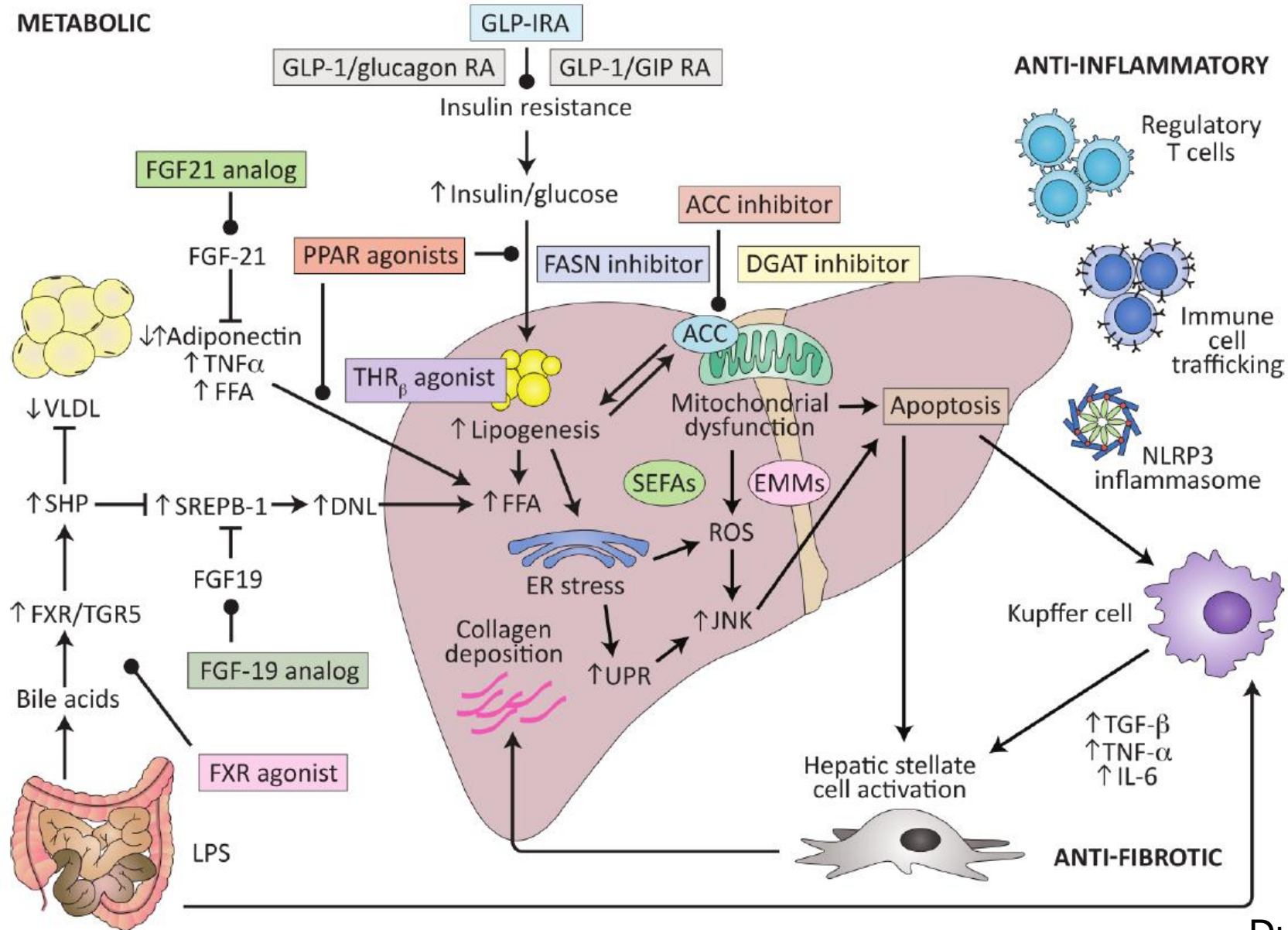


Le café

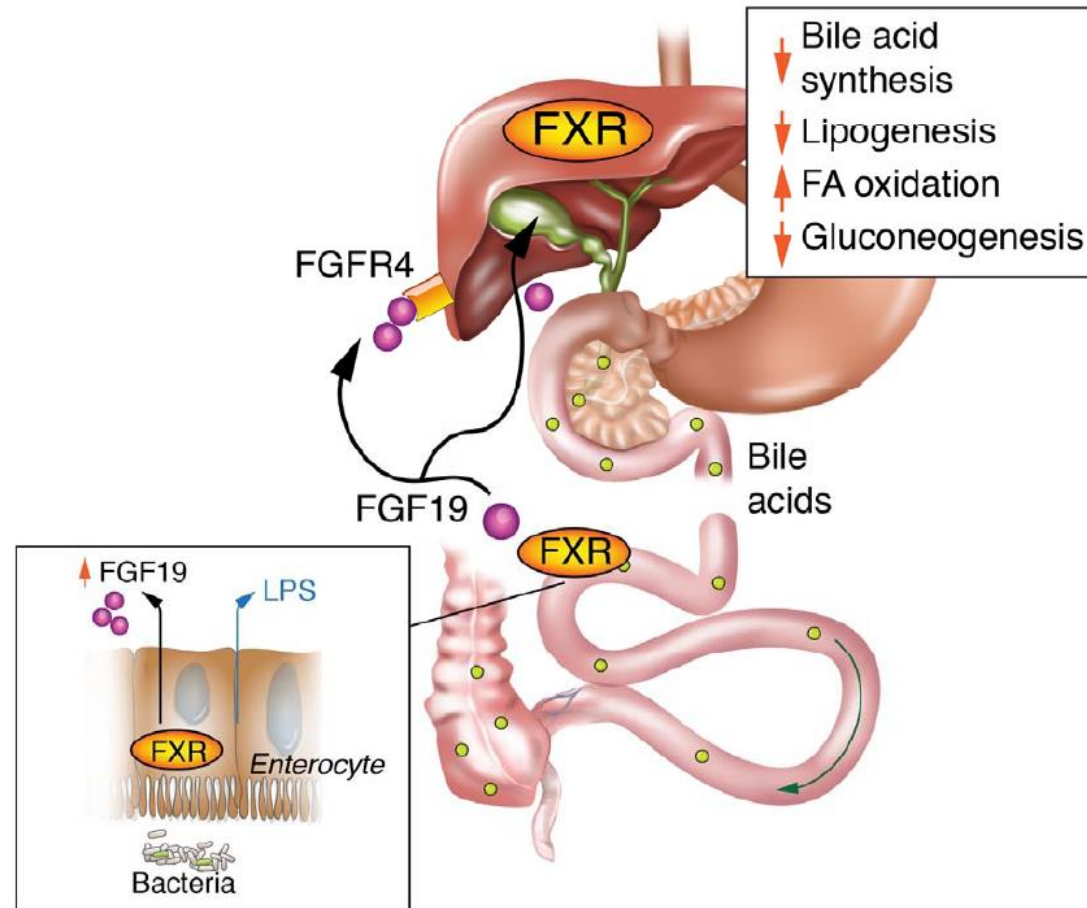


Médicaments

Les cibles thérapeutiques



FXR – FGF19 – FXR Axis



FXR – FGF19 – FXR Axis

FXR agonists<	Phase	Resolution NASH	Improvement fibrosis	
Obeticholic acid	3*	n.s.	✓	Younossi, Lancet 2019
		Dose/duration	MRI-PDFF responder rate (%) with relative liver fat change from baseline >30%	
Obeticholic acid	3*	25 mg/W 72	26%	Younossi Lancet 2019
Tropifexor	2	200 ug/W 12	69%	Sanyal AASLD 2020
Cilofexor	2	100 mg/W 12	31%	Patel Hepatology 2020
Vonafexor	2	100 mg/W 12	50%	Harrison AASLD 2021
EDP-305	2	2.5 mg/W 12	45%	Ratziu J Hepatol 2021
MET409	2	80 mg/W 12	93%	Harrison J Hepatol 2021
* Interim Analysis				

REGENERATE second interim analysis

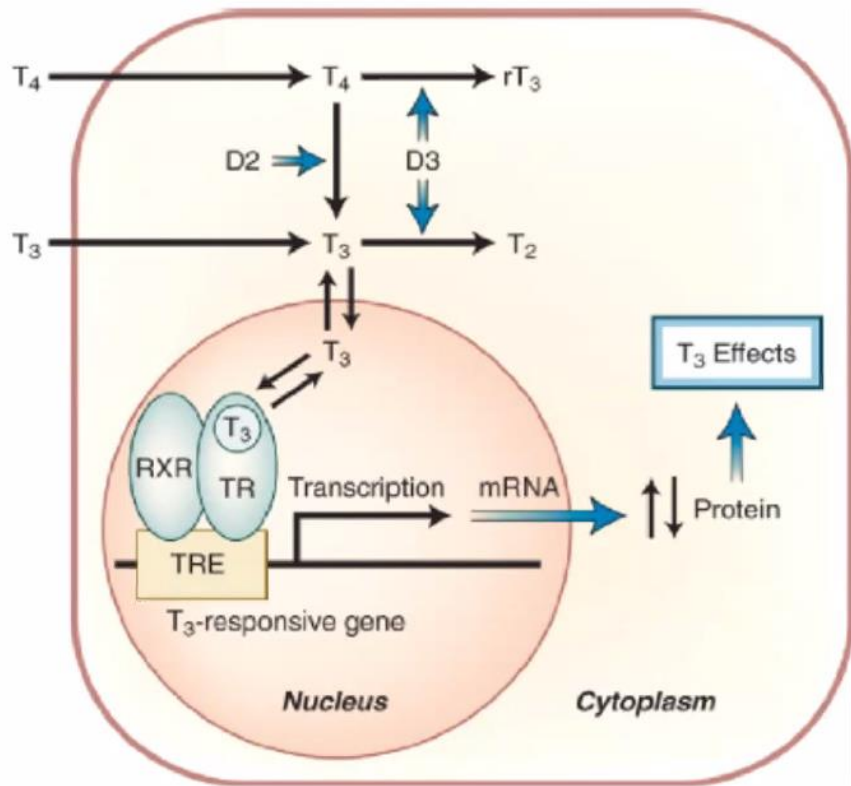
ITT population of 931 subjects with biopsy proven NASH F2-F3

Reassessment of the baseline and Month 18 liver biopsies using a consensus reading methodology

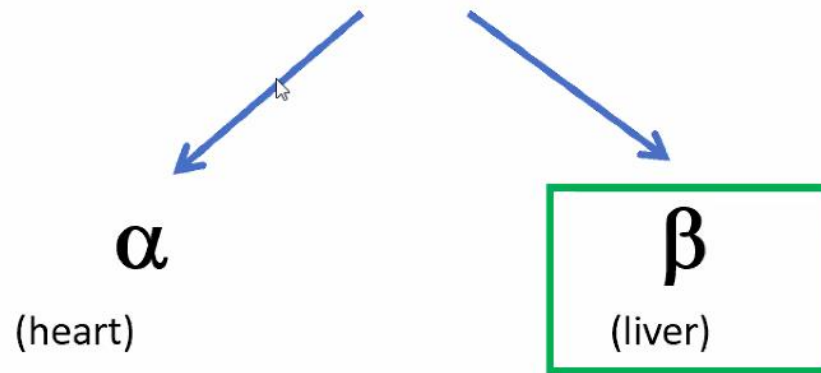
	Placebo N=311	OCA 10 mg N=312	OCA 25 mg N=308
At least one stage of fibrosis improvement with no worsening of NASH	9.6%	14.1%	22.4% P<0.0001
Resolution of NASHo without worsening of fibrosis	3.5%	6.1%	6.5% NS

Safety evaluated in 2477 subjects, median exposure 42 months
pruritus 24%, 33% and 55%

Thyroid Hormone Receptors



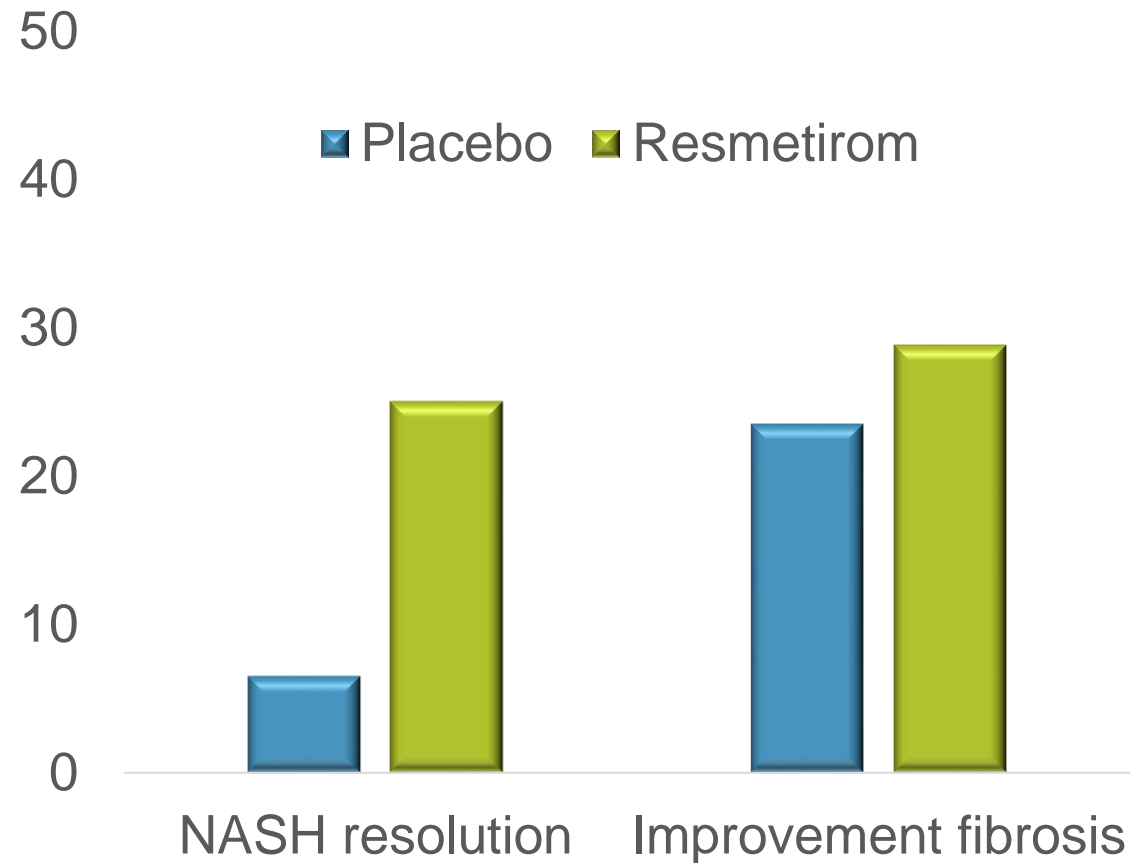
THYROID HORMONE RECEPTOR



- ~~Increases FFA release from adipose tissue~~
- ~~Increases de novo lipogenesis~~
- ~~Cardiac effects~~
- ~~Bone effects~~

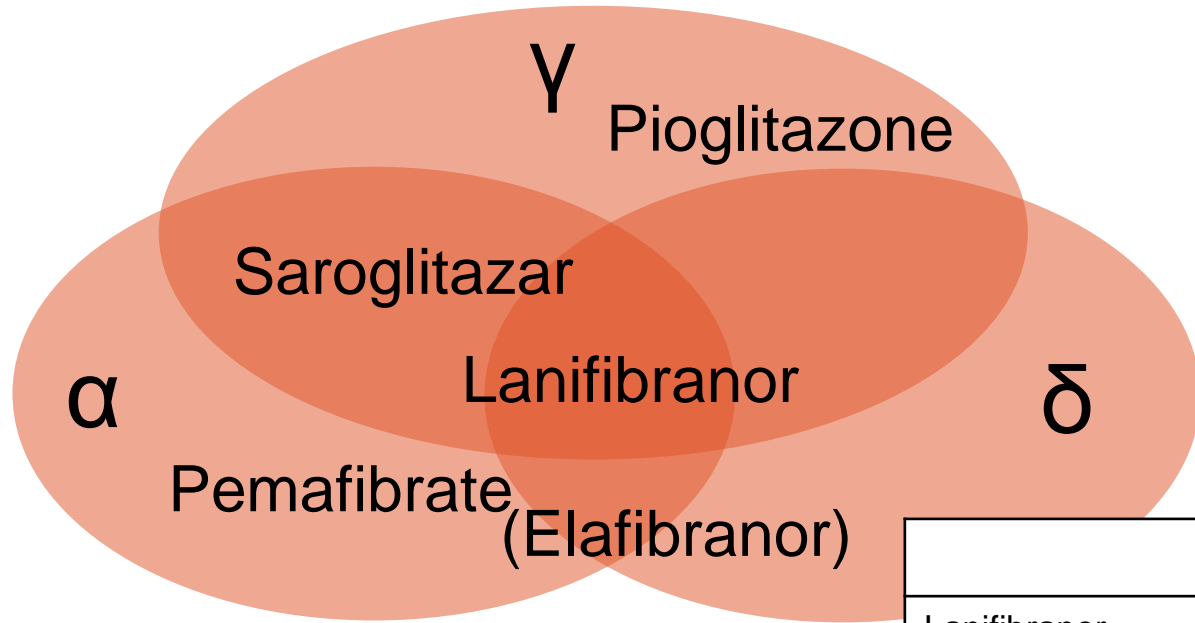
- Reduces lipogenesis
- Reduces LDLc and TG
- Increases mitochondrial biogenesis
- Increases beta-oxidation, lipophagy
- Increases autophagy
- Antifibrotic effects

Resmetirom agoniste du récepteur à la TSH



Harrison et al. Lancet 2019

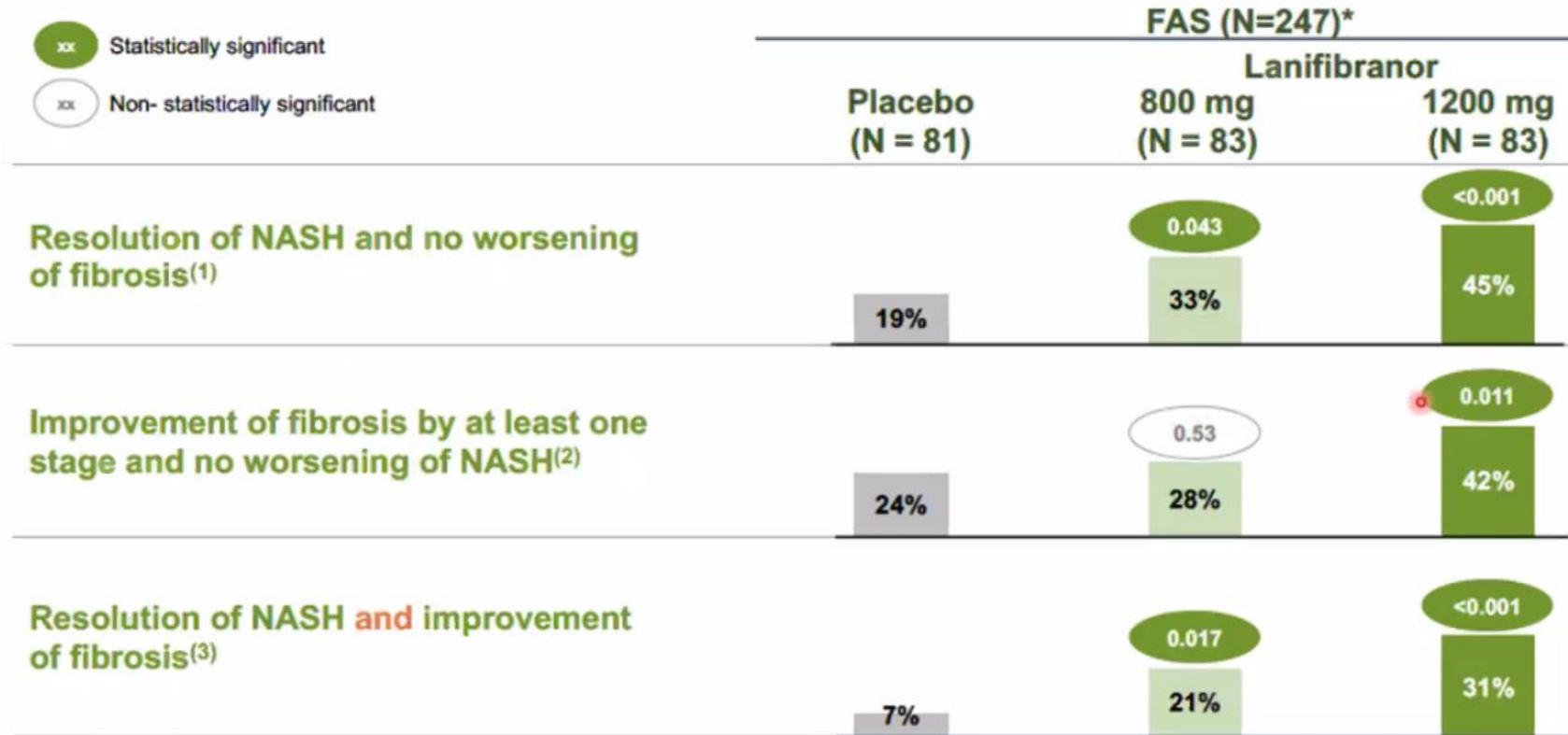
PPARs Agonists



	Phase	Resolution NASH	Improvement fibrosis
Lanifibranor	2→3	✓	✓
Saroglitazar	2→3	(✓)	(✓)
Pemaifibrate	2	No histo data	No histo data
Pioglitazone	2*	✓	n.s.
Pioglitazone	**	✓	✓

* PIVENS RCT in non-diabetics ** Meta-analysis in diabetics

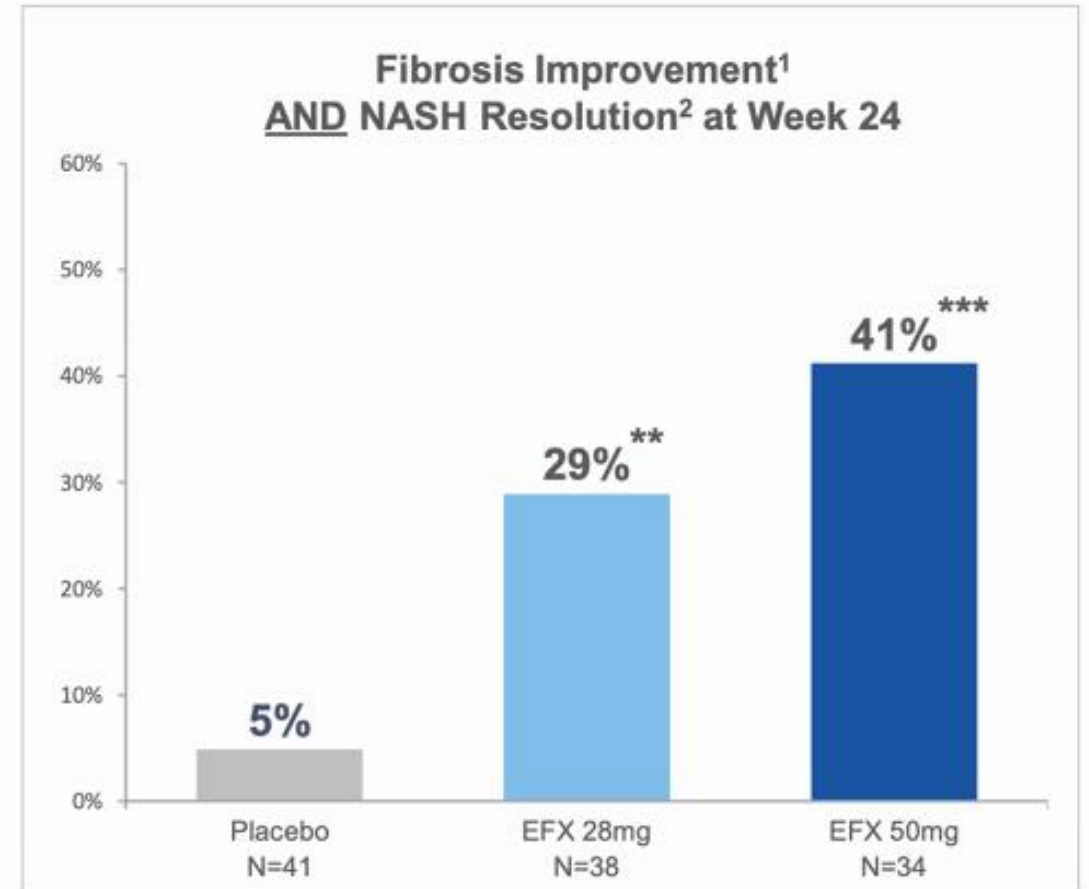
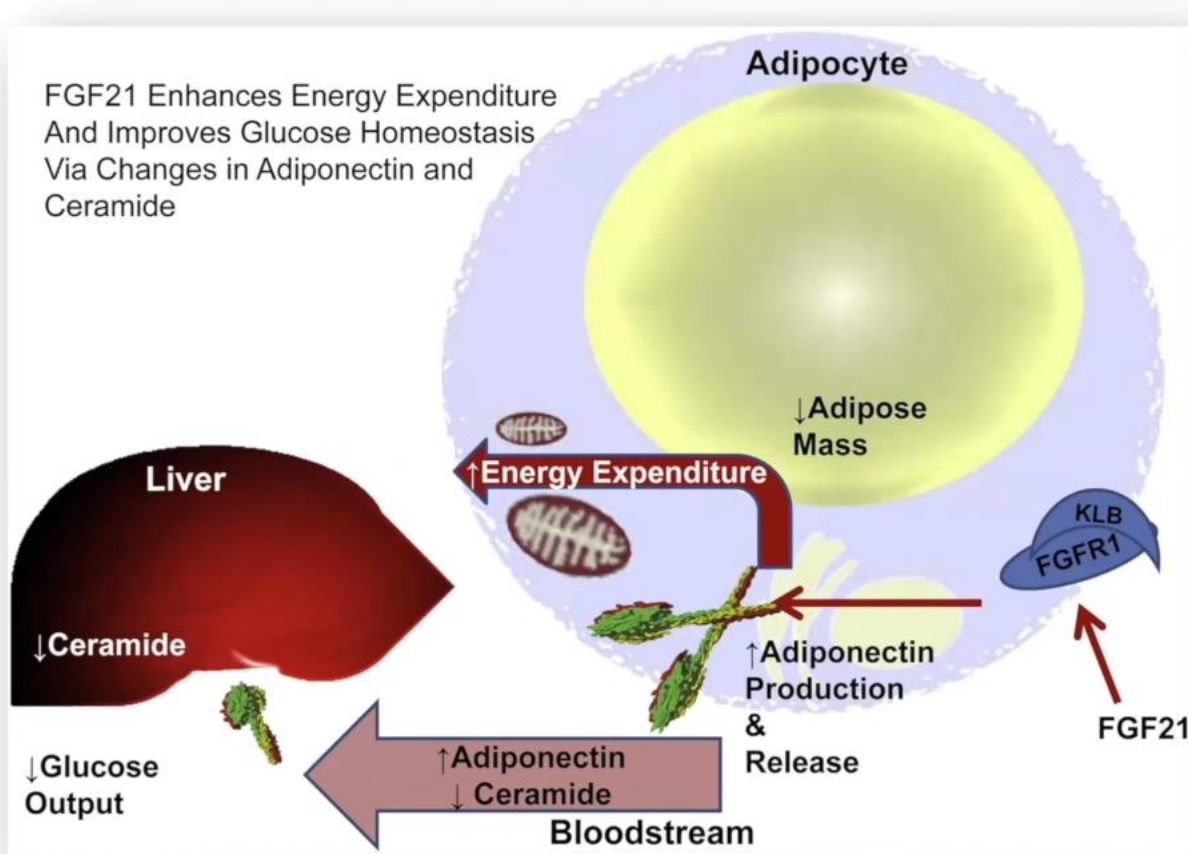
Lanifibranor



Les agonistes du GLP-1

GLP1 Agonists	Phase	Resolution NASH	Improvement fibrosis
Semaglutide	2→3	✓	n.s.
Liraglutide	2→3	✓	n.s.
Oral formulation			
Beyond GLP1 Agonists			
Tirzepatide ¹	2	Ongoing	Ongoing
Cotadutide ²	2	Ongoing	Ongoing
HM15211 ³	2	Ongoing	Ongoing
¹ Dual agonist GIP/GLP1 ² Dual agonist Glucagon/GLP1 ³ Triple agonist Glucagon/GIP/GLP1 triple agonist			

Analogue FGF21: Efruxifermine



¹ Improvement in liver fibrosis greater than or equal to one stage

² NAS score of 0 or 1 for lobular inflammation and a score of 0 for ballooning

** p<0.01, *** p<0.001, versus placebo (CMH)

<http://diabetes.diabetesjournals.org/content/58/1/250.long>

<https://www.nature.com/articles/s41467-017-02677-9.pdf>

[https://www.cell.com/cell-metabolism/fulltext/S1550-4131\(13\)00153-8](https://www.cell.com/cell-metabolism/fulltext/S1550-4131(13)00153-8)

Lifestyles or drug ?

	Lifestyles	Drug therapy
Availability	Yes	Soon?
Cost	Cheap	Not cheap!
Side effects	Little	Likely
Acceptance	Poor	Good
Efficacy	Good	To be proven