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Poids de la Stéatopathie Métabolique en Population
Générale,

Lawrence Serfaty

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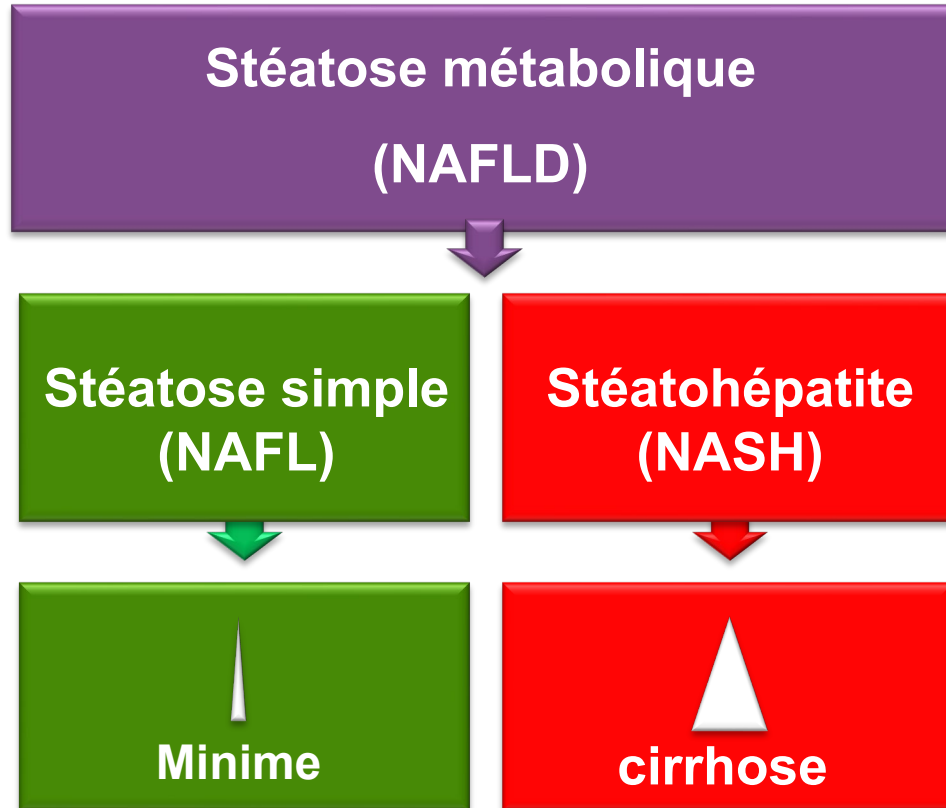
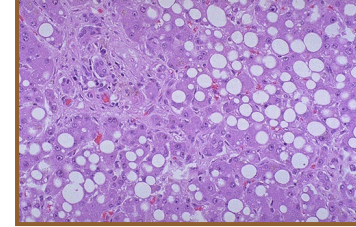
8ème journée scientifique des cohortes Constances et Gazel, 11 Juin 2024, Paris

Le poids de la stéatopathie métabolique en population générale

Lawrence Serfaty

*Hôpitaux Universitaire de Strasbourg
UMR_S 938
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Définitions



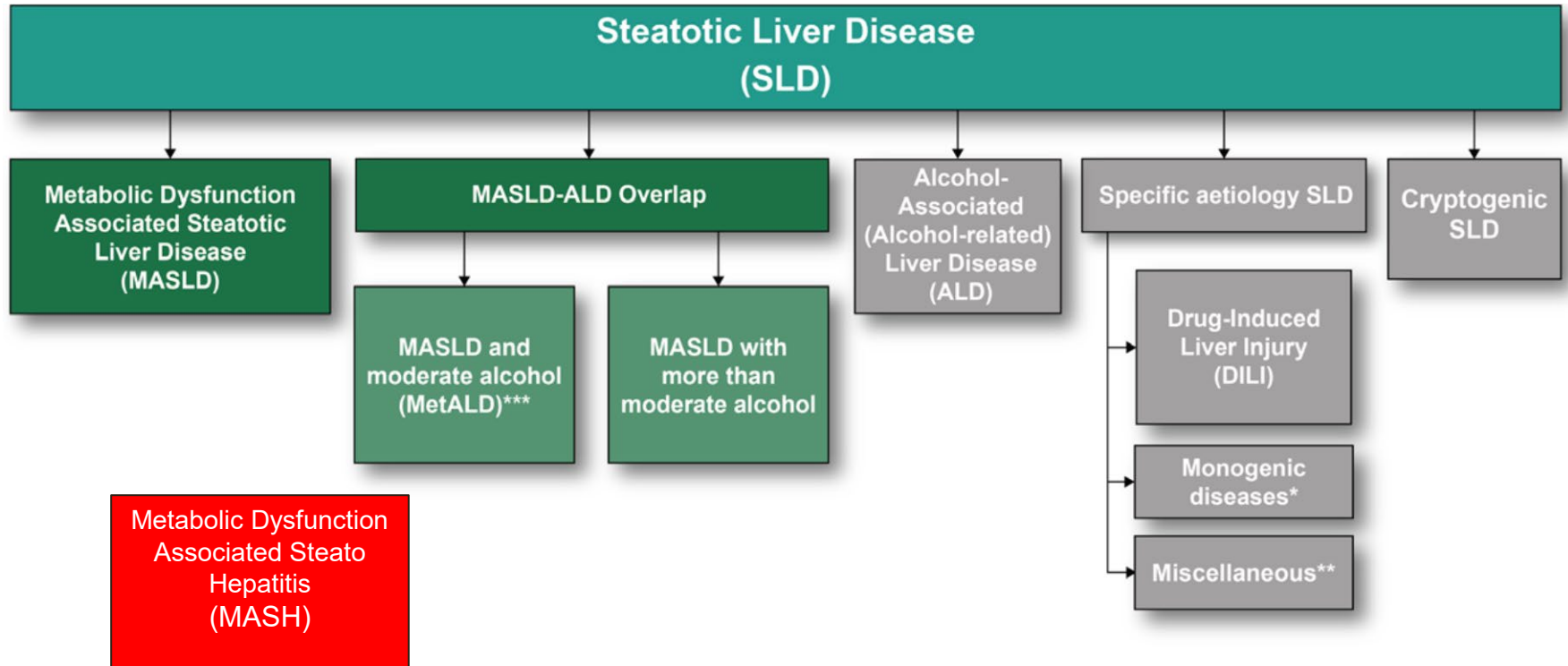
Accumulation de graisse dans le foie, d'origine métabolique, (obésité, diabète, insulino-résistance).
(OH < 30g/j H et < 20g/j F, HBV/HCV-)

Présence ou non de lésions nécrotico-inflammatoires (ballonisation hépatocytaire ++)

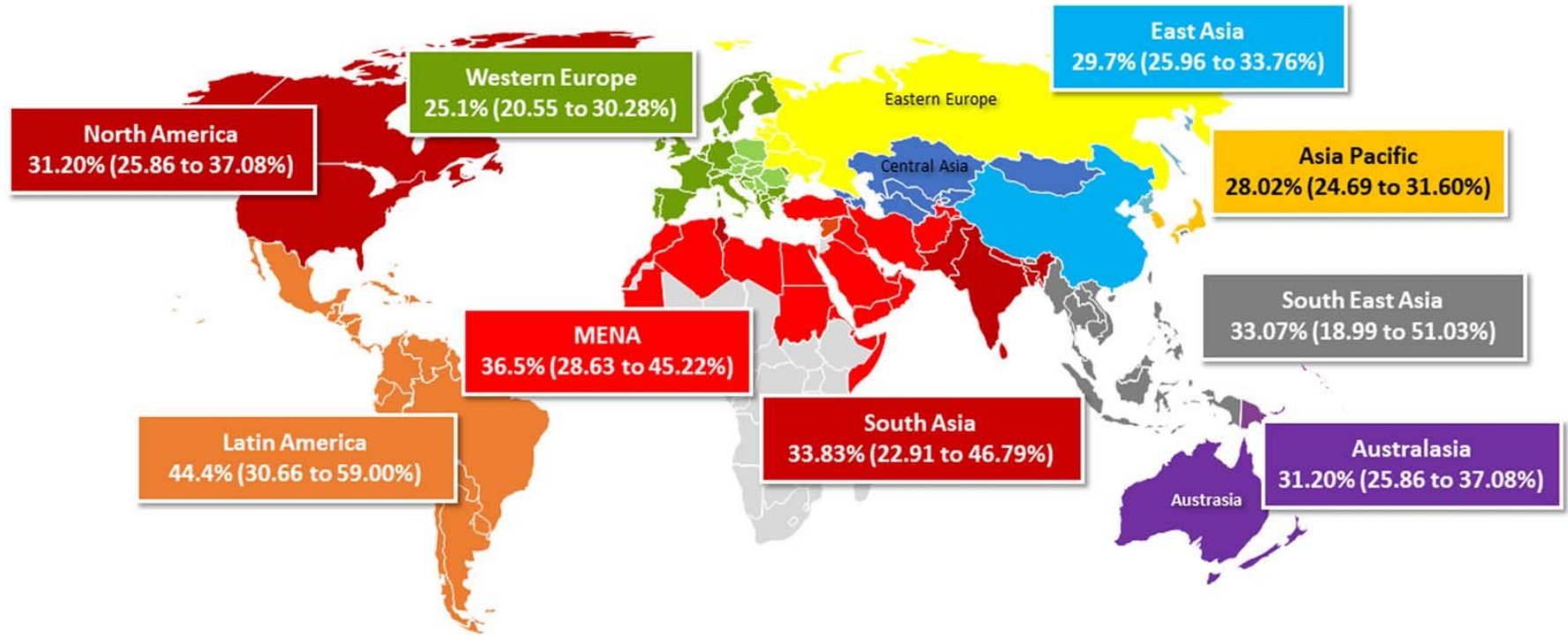
Risque de fibrose

Une nouvelle définition

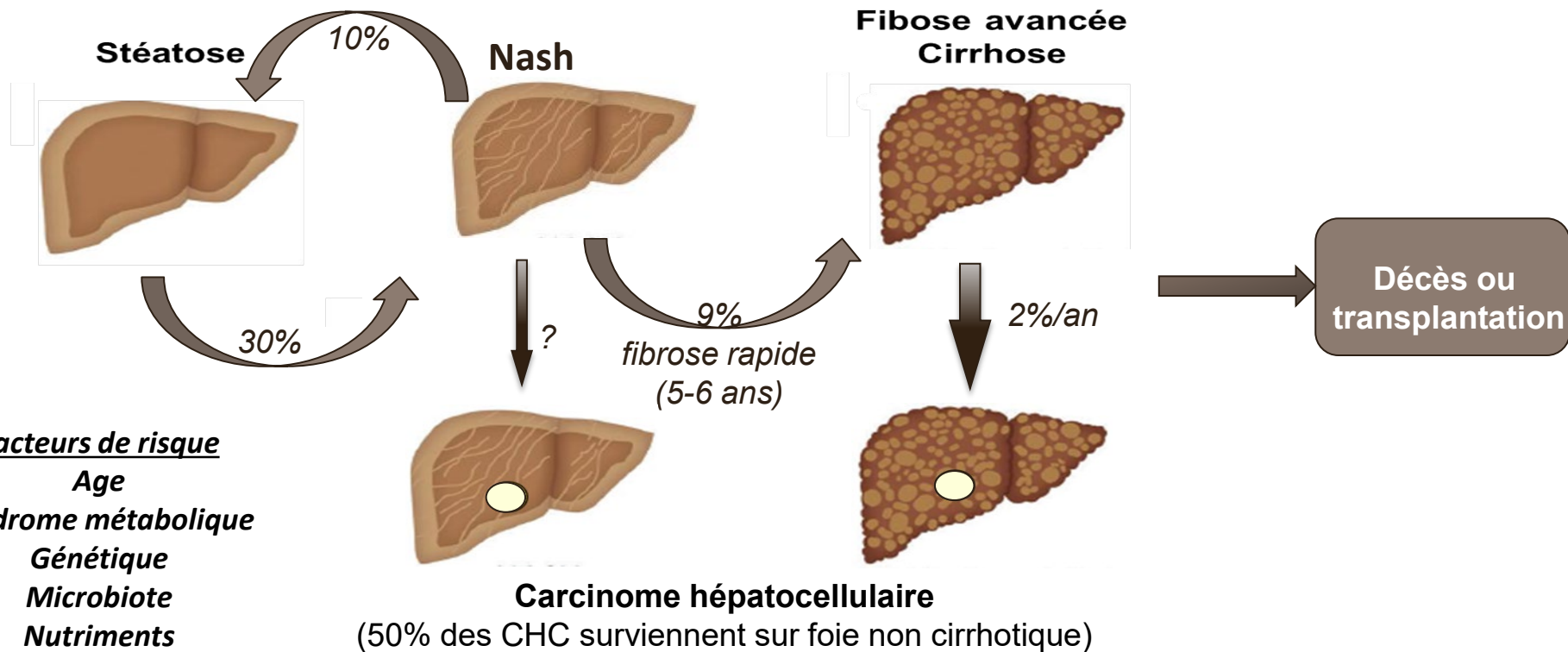
La MASLD (ou stéatopathie métabolique)



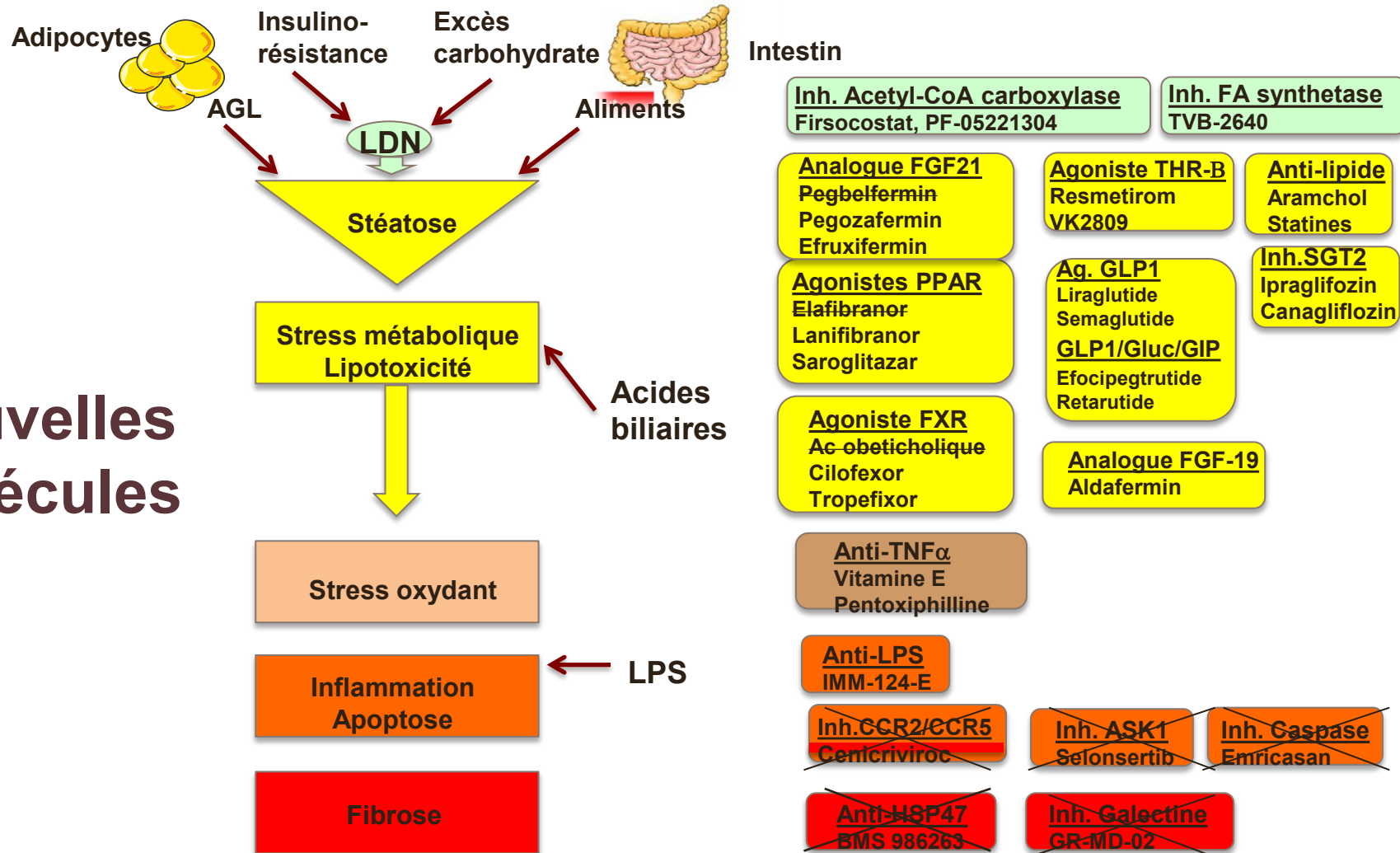
Prévalence de la stéatopathie métabolique dans le monde



Histoire naturelle de la stéatopathie métabolique



Nouvelles molécules



NASHCO

Flow-chart

**119,150 subjects
on 01/01/2018**



486 excluded for withdrawal of consent

118,664 with consent



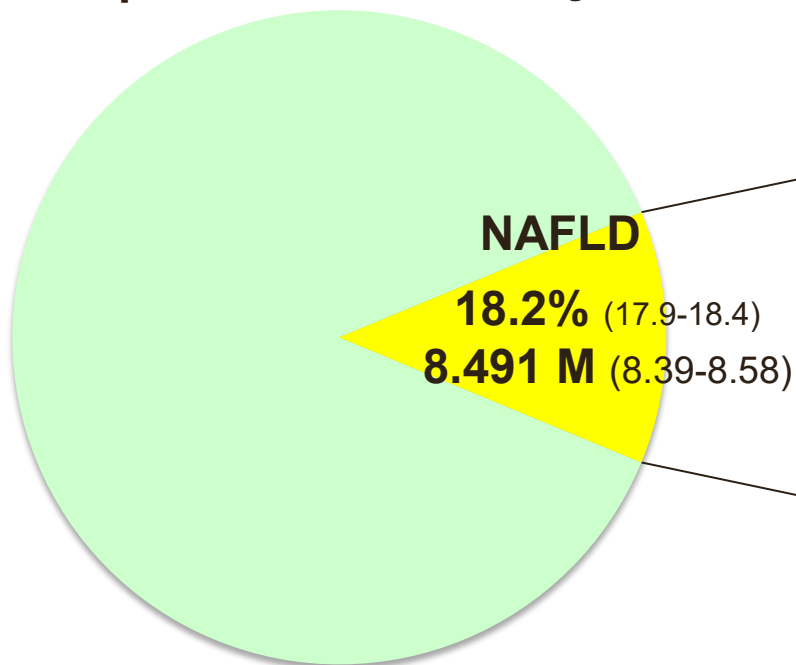
16,320 excluded

- **1108 HBV**
- **560 HCV**
- **3034 other liver diseases**
- **11618 excessive alcohol consumption**

**102,344 included in
final analysis**

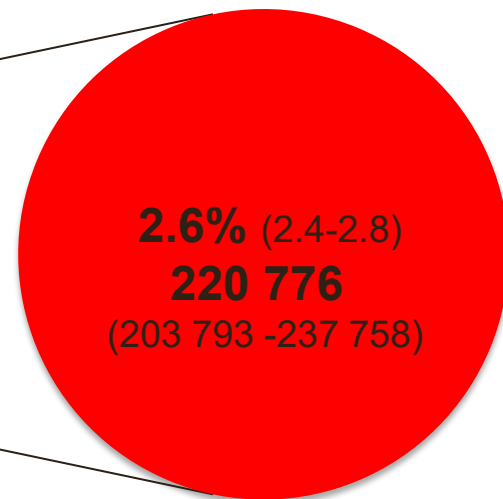
Prévalences de la NAFLD et de la fibrose avancée chez le sujet adulte en France

Population adulte française



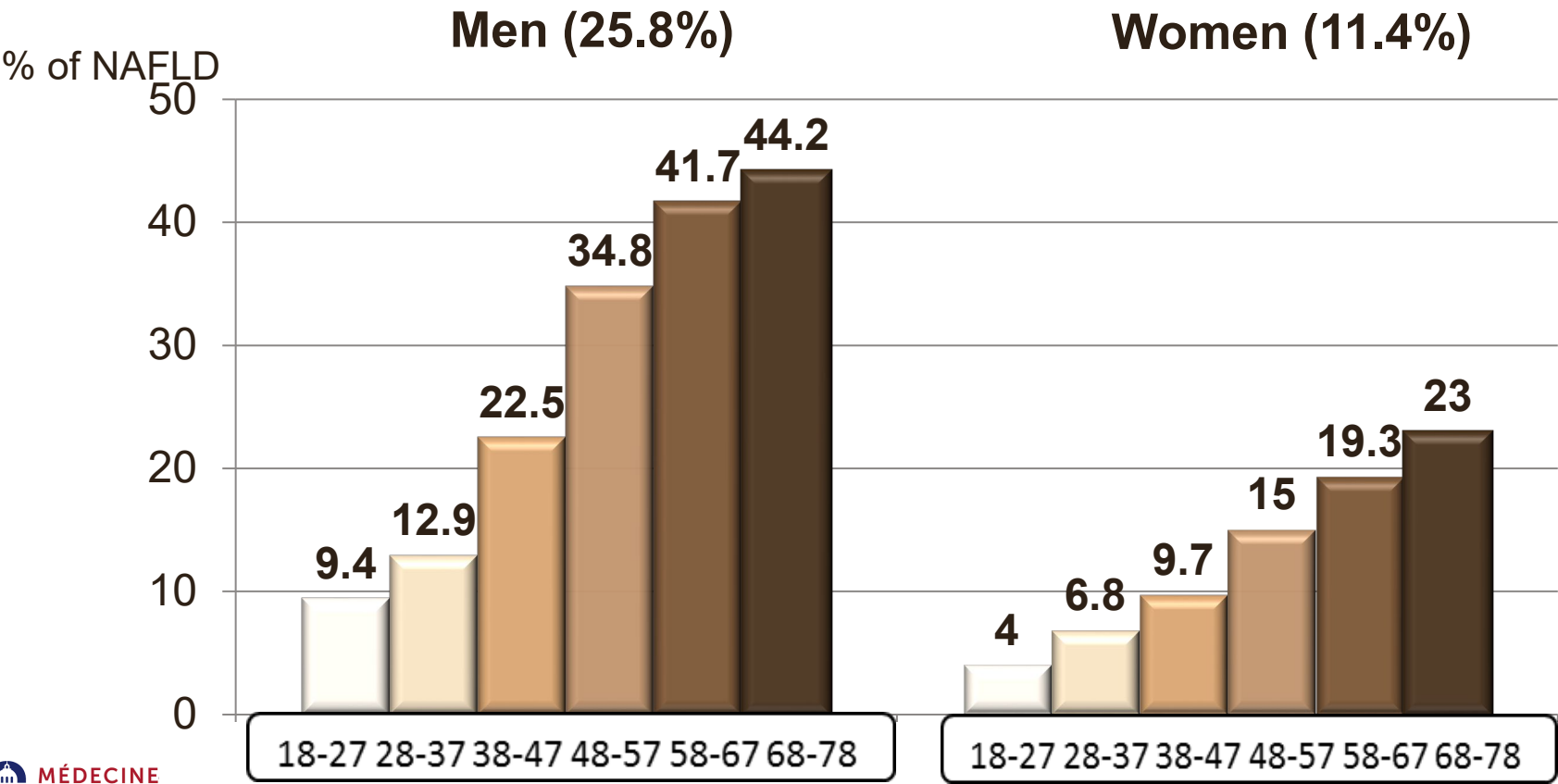
Fatty Liver Index > 60

NAFLD avec fibrose avancée

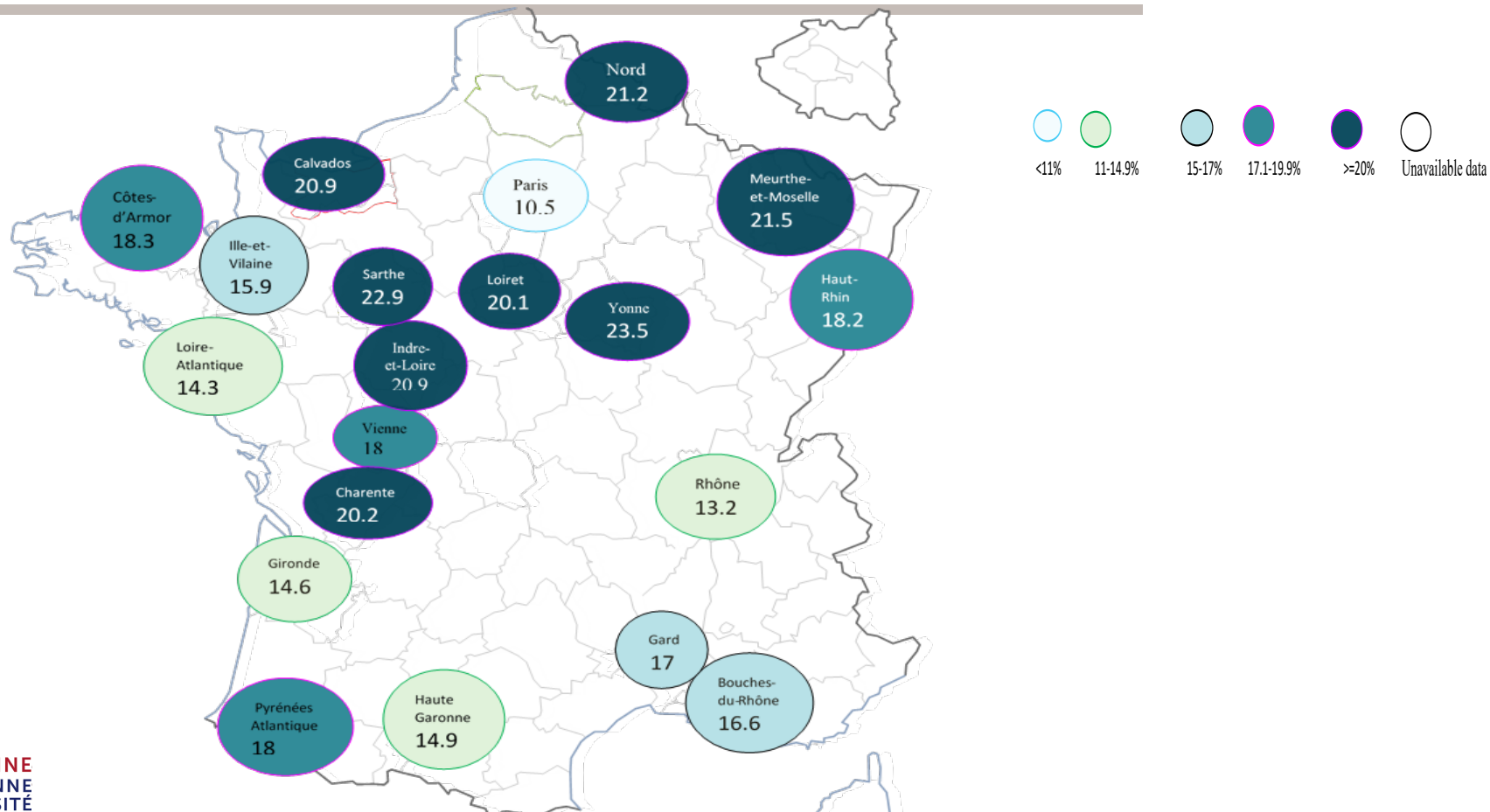


Forns Index > 6.9

Prévalence de la NAFLD en fonction de l'âge et du sexe

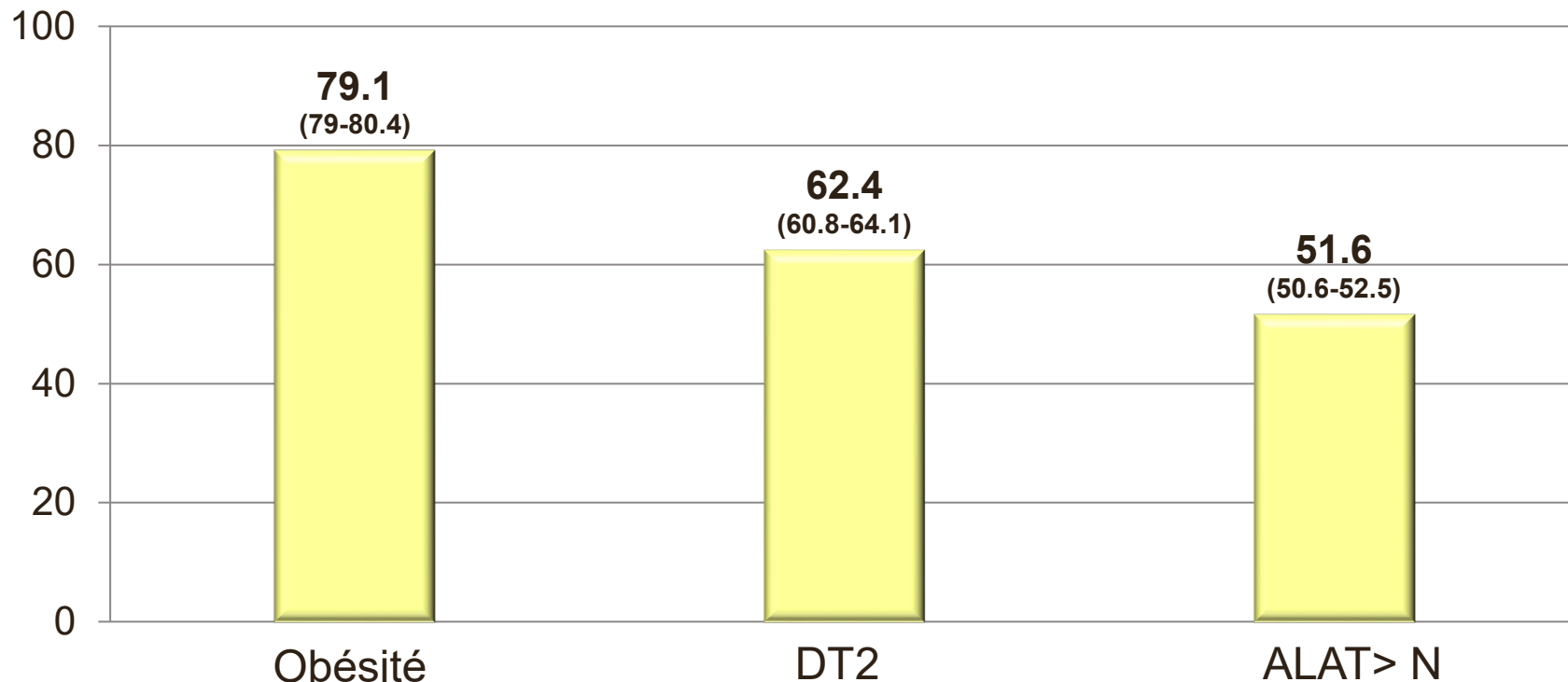


Distribution régionale de la NAFLD



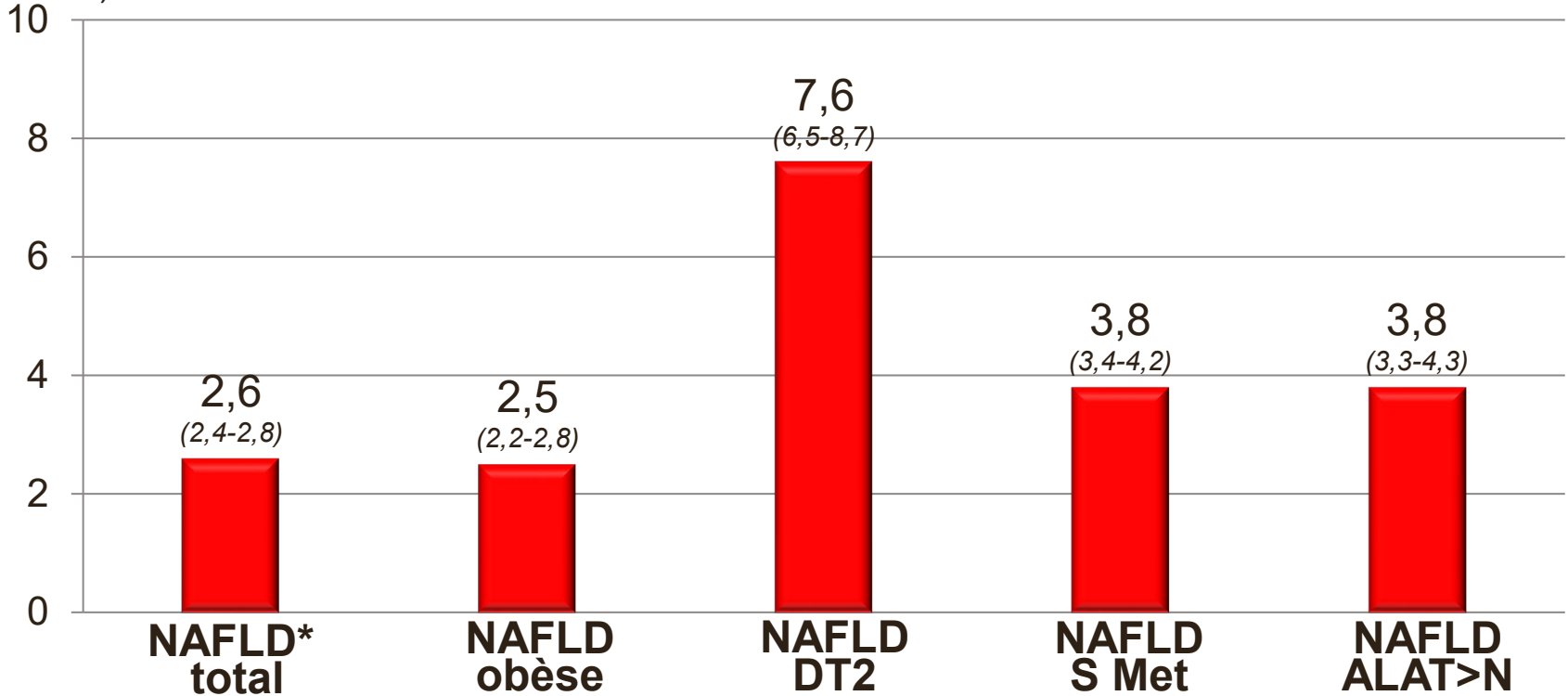
Prévalence de la NAFLD dans les groupes à risque

% (95%CI)



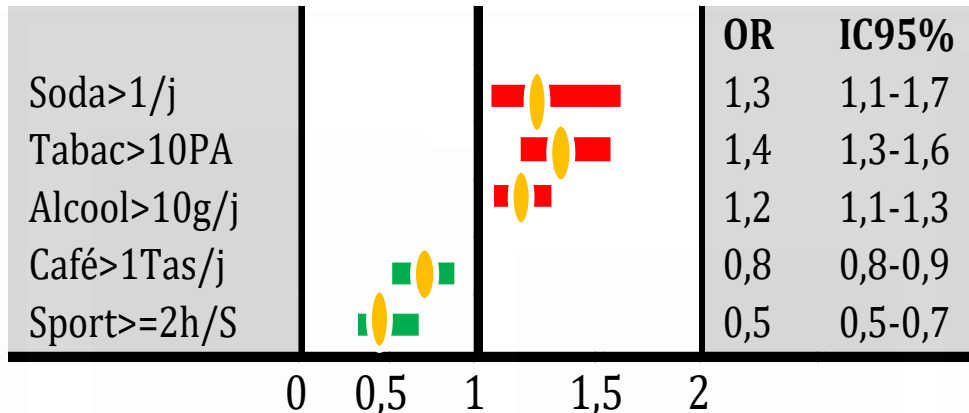
Prévalence de la fibrose avancée (Forns>6,9) chez les sujets NAFLD (n=16273)

% (IC95%)

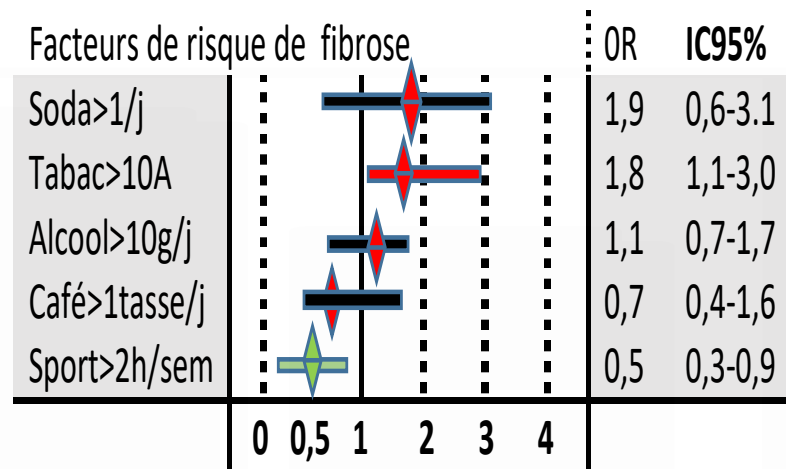


NAFLD, fibrose et mode de vie

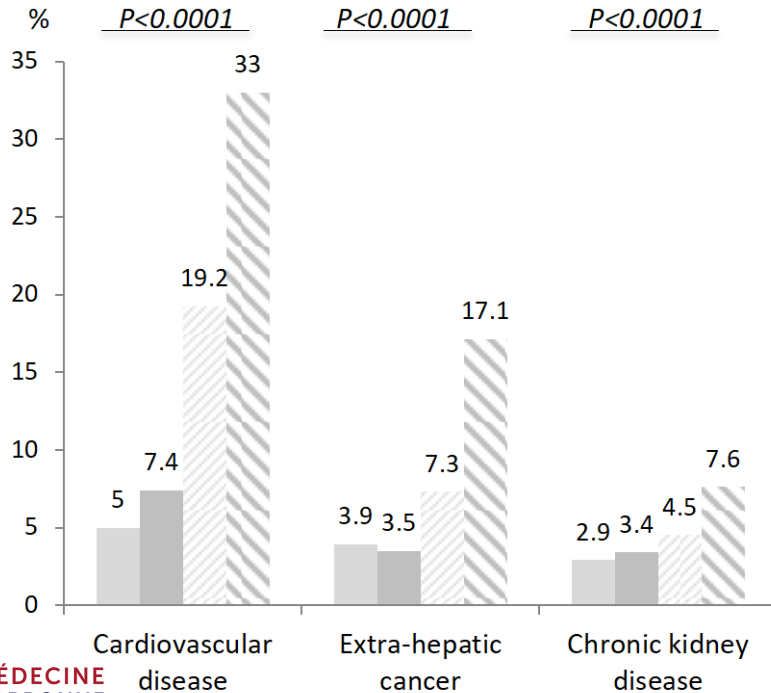
Facteurs de risque de Nafld



Facteurs de risque de fibrose avancée chez les Nafld



La prévalence des comorbidités augmente avec le stade de fibrose



	Cardiovascular disease		Extra-hepatic cancer		Chronic kidney disease	
Class	OR (95% CI)	p Value*	OR (95% CI)	p Value*	OR (95% CI)	p Value*
No NAFLD	Reference	-	Reference	-	Reference	-
Indeterminate status of NAFLD	1.16 (1.06-1.27)	0.001	1.10 (0.99-1.21)	ns	1.06 (0.94-1.20)	ns
NAFLD with mild fibrosis	0.93 (0.81-1.06)	ns	1.13 (0.97-1.31)	ns	1.03 (0.87-1.22)	ns
NAFLD with intermediate fibrosis	1.36 (1.21-1.53)	<0.0001	1.24 (1.08-1.41)	0.001	1.18 (1.01-1.39)	0.03
NAFLD with advanced fibrosis	3.07 (2.36-3.98)	<0.0001	1.64 (1.15-2.29)	0.004	2.09 (1.42-2.98)	<0.0001

*Adjusted on age, gender, overweight/obesity, diabetes, high blood pressure, hypercholesterolemia, and smoking. OR : odds ratio, CI : confidence interval.

- Non NAFLD (n=62440)
- NAFLD with mild fibrosis (n=8278)
- ▨ NAFLD with intermediate fibrosis (n=7498)
- ▨ NAFLD with advanced fibrosis (n=427)

Type de cancers associés de façon indépendante au stade de fibrose chez les sujet NAFLD

	Overall NAFLD		NAFLD with mild fibrosis		NAFLD with intermediate fibrosis		NAFLD with advanced fibrosis	
	OR (CI 95%)	P value*	OR (CI 95%)	P value*	OR (CI 95%)	P value*	OR (CI 95%)	P value*
<u>Extra hepatic cancer in men</u>	1.24 (1.06-1.44)	0.007	1.21(0.93-1.57)	ns	1.28 (1.04-1.58)	0.02	1.77 (1.19-2.59)	0.004
Prostate	1.38 (1.07-1.79)	0.01	1.60 (1.13-2.28)	0.008	1.91 (1.18-3.10)	0.008	2.13 (1.19-3.80)	0.01
Lung	2.61 (0.83-8.28)	ns	1.49 (0.15-14.54)	ns	3.52 (0.73-17.10)	ns	3.30 (0.98-3.77)	ns
Colon	1.16 (1.12-1.19)	<0.0001	1.03 (0.36-2.97)	ns	1.46 (0.71-3.04)	ns	2.19 (1.07-6.54)	0.01
Thyroid	1.16 (0.48-2.80)	ns	0.81 (0.40-1.86)	ns	1.24 (0.40-3.87)	ns	1.98 (0.23-17.07)	ns
<u>Extra hepatic cancer in women</u>	1.27 (1.06-1.51)	0.008	1.13 (0.98-1.29)	ns	1.30 (1.03-1.63)	0.02	1.47 (1.16-1.84)	0.001
Ovarian	0.90 (0.70-1.34)	ns	0.45 (0.15-1.37)	ns	1.78 (0.50-6.37)	ns	2.87 (0.78-10.60)	ns
Uterus	0.99 (0.61-1.62)	ns	0.91 (0.64-1.36)	ns	0.61 (0.31-1.20)	ns	0.99 (0.51-1.91)	ns
Breast	1.09 (1.08-1.09)	<0.0001	1.08 (0.88-1.32)	ns	1.03 (0.73-1.44)	ns	1.49 (1.08-2.04)	0.01
Colon	1.44 (0.84-2.49)	ns	1.25 (0.47-3.35)	ns	1.07 (0.73-4.30)	ns	1.15 (1.12-1.18)	<0.0001
Lung	1.12 (1.06-1.17)	<0.0001	0.87 (0.49-1.03)	ns	1.05 (0.88-1.77)	ns	1.15 (0.86-2.99)	ns
Thyroid	1.55 (0.91-2.66)	ns	1.01 (0.43-2.36)	ns	1.23 (0.76-2.02)	ns	1.97 (0.96-4.06)	ns

*Adjusted on age, gender, overweight/obesity, diabetes, high blood pressure, hypercholesterolemia, and smoking. Reference group is non NAFLD (FLI<30)

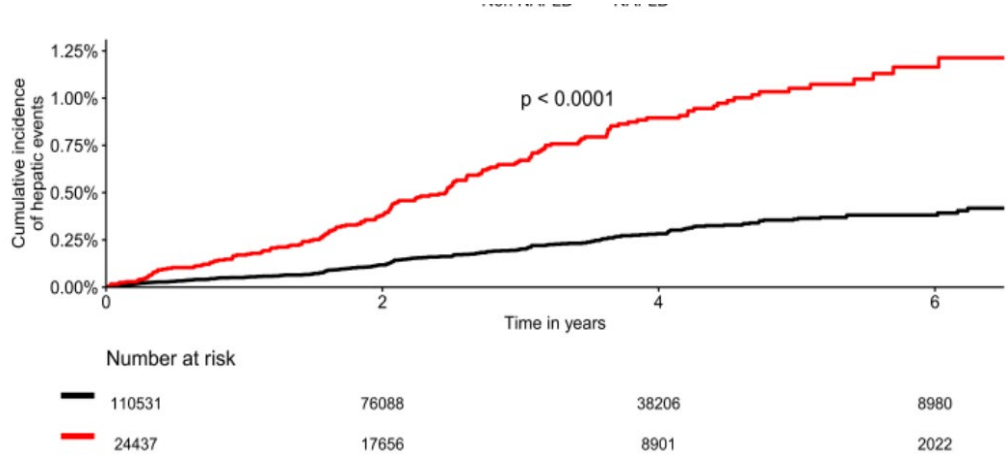
Evènements cliniques chez les sujets NAFLD (CIM-10)

Median follow-up=3.62 yrs

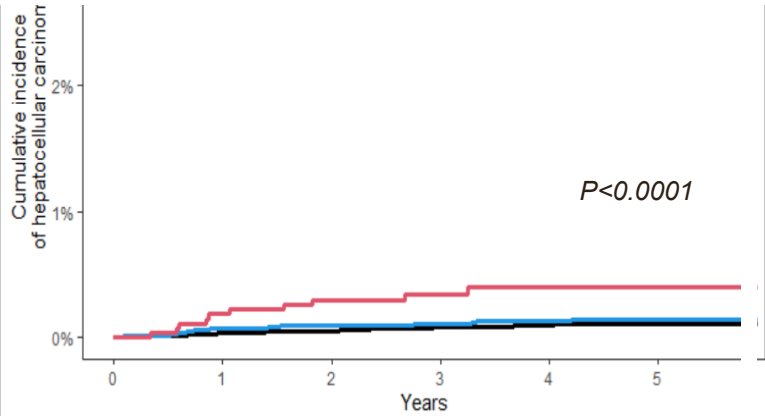
	NAFLD subjects n=25753
Hepatic event	682
HCC	122
Liver transplantation	18
Cardiovascular event	2050
Chronic kidney disease	471
Extra hepatic malignancy	1954
Death	685

Complications hépatiques

Liver events

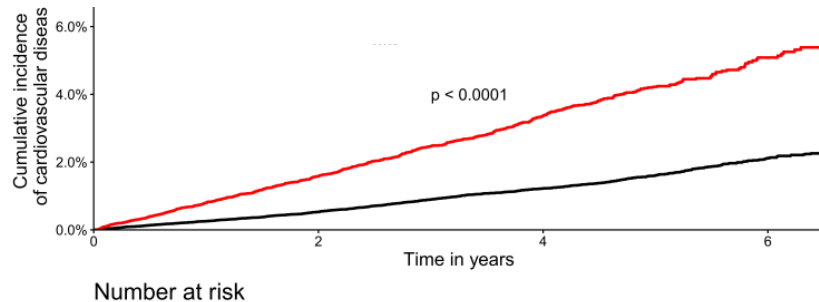


Hepatocellular carcinoma

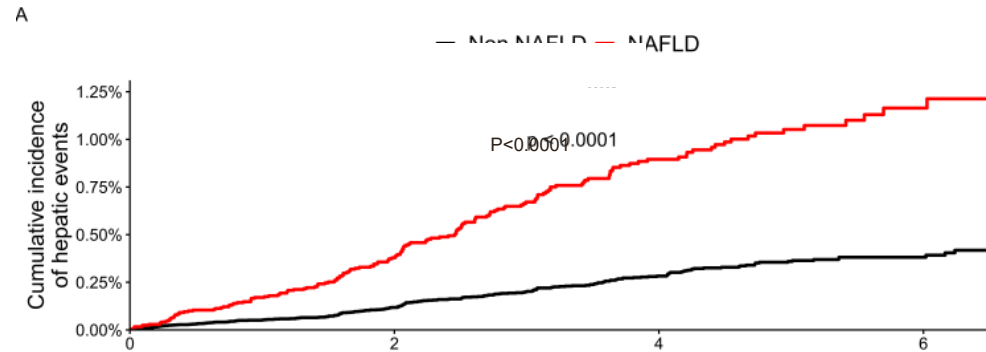


Complications extra-hépatiques

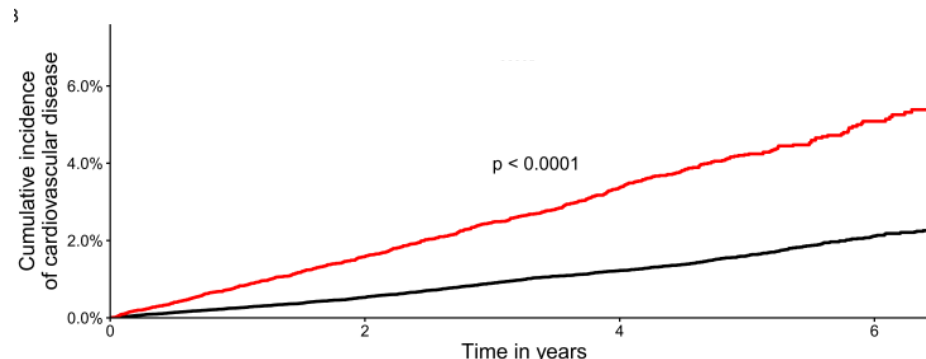
Cardiovascular disease



Extra-hepatic cancer

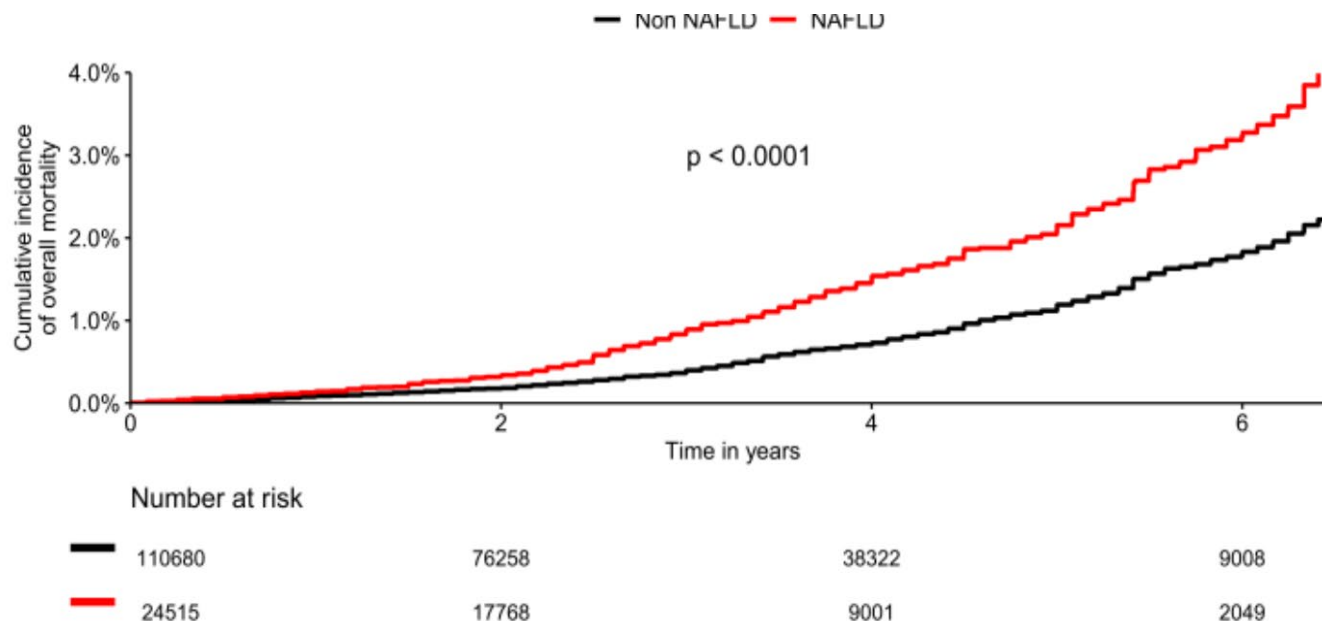


Chronic kidney disease



Mortalité globale

All cause death



Taux d'incidence, risque d'événement clinique et de mortalité globale

La NAFLD est un facteur de risque indépendant

	Incidence rate per 1000 person-yr		Hazard ratio (95%CI)*	
	NAFLD (FLI ≥60)	Non-NAFLD (FLI<60)	NAFLD vs non NAFLD	
	<i>n</i> =25,753	<i>n</i> = 111,453	HR (95%CI)	<i>P</i>
Hepatic events	4.51	1.59	2.63 (1.96-2.87)	<0.001
Cardiovascular diseases	45.67	13.30	2.33 (1.20-2.78)	<0.001
Extra-hepatic malignancies	15.34	10.55	1.09 (0.90-1.23)	<i>NS</i>
Chronic kidney disease	5.39	1.65	1.89 (1.48-2.40)	<0.001
Death	4.91	2.38	1.43 (1.25-1.65)	<0.001

*Adjusted in age, sex, geographic origin, level of education, diabetes, metabolic syndrome, alcohol consumption, smoking, soda intake, coffee intake, and sports practice, cholesterol and ALT

Taux d'incidence, risque d'événement clinique et de mortalité globale

Le stade fibrose est un facteur de risque indépendant

	Incidence rate per 1000 person-yr			Hazard Ratio (95%CI)*			
	NAFLD and advanced fibrosis	NAFLD and intermediate fibrosis	NAFLD and mild fibrosis	Advanced fibrosis vs No/mild fibrosis		Intermediate fibrosis vs no/mild fibrosis	
	<i>n</i> =535	<i>n</i> =10638	<i>n</i> =13297	HR (95%CI)	<i>P</i>	HR(95%CI)	<i>P</i>
Hepatic events	71.91	4.17	3.46	8.61 (5.04-14.7)	<0.001	1.11 (0.77-1.61)	<i>NS</i>
Cardiovascular diseases	85.1	66.86	15.30	2.38 (1.92-3.08)	0.012	1.01 (0.83-1.24)	<i>NS</i>
Extra-hepatic malignancies	37.88	22.23	9.27	1.88 (1.16-3.06)	0.011	1.19 (0.92-1.55)	<i>NS</i>
Chronic kidney disease	28.51	6.81	3.33	2.80 (1.66-4.71)	<0.001	1.01 (0.73-1.33)	<i>NS</i>
Death	22.28	5.76	3.56	2.97 (1.94-4.56)	<0.001	1.06 (0.82-1.38)	<i>NS</i>

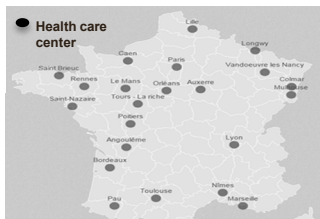
*Adjusted in sex, geographic origin, level of education, diabetes, metabolic syndrome, waist circumference, alcohol consumption, smoking, soda intake, coffee intake, and sports practice, TGs and ALT

Le poids de la NAFLD dans les populations d'intérêt

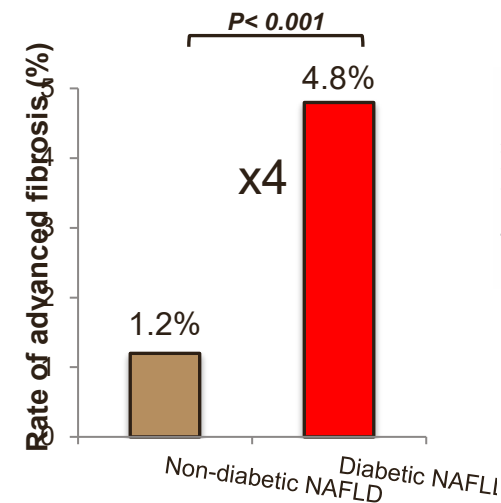
- le diabétique de type 2**
- le sujet mince**

Study population

CONSTANCES



Diabetic NAFLD have higher rate of advanced fibrosis (*Forns Index* > 6.9)



159,203 subjects with no excessive alcohol, no known chronic liver disease

7189 subjects with type 2 diabetes

152,014 non-diabetic subjects

Fatty Liver Index ≤ 60

4392 diabetic subjects with NAFLD

2797 diabetic subjects w/o NAFLD

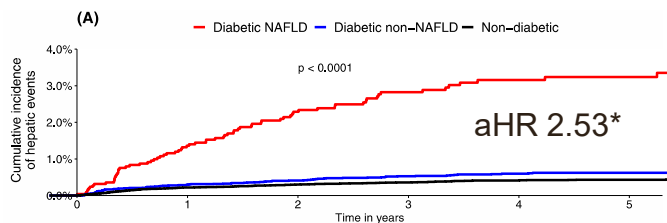
Fatty Liver Index ≤ 60

23,106 subjects with NAFLD

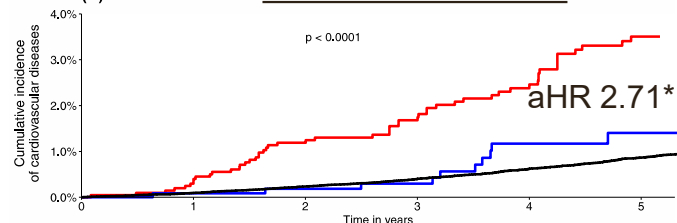
128,908 subjects w/o NAFLD

NAFLD is associated with more hepatic events, cardiovascular disease and overall mortality in diabetic subjects

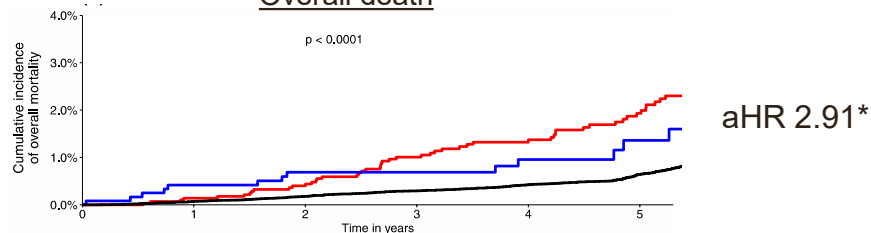
Hepatic events



Cardiovascular disease



Overall death

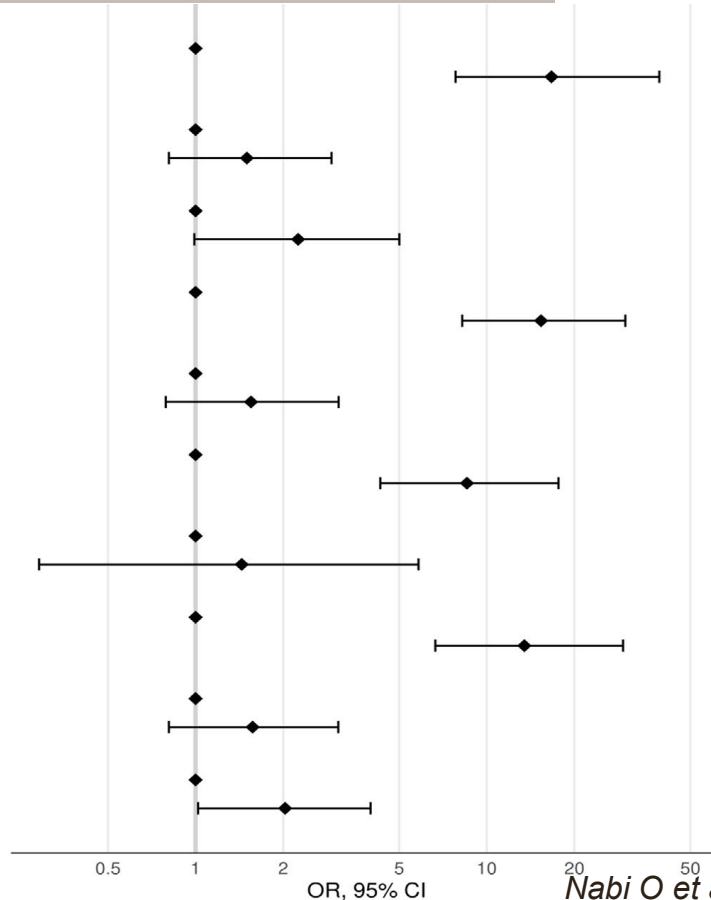


*NAFLD vs non NAFLD with T2D

Nabi O et al. Liver Int 2022

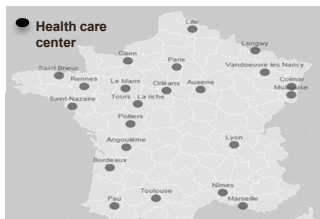
Le stade de fibrose est corrélé à la sévérité du diabète

Gender	Female		
	Male	16.7 (7.8–39.1)	$p < 0.001$
Obesity	No		
	Yes	1.5 (0.8–2.9)	$p = 0.20$
HBP	No		
	Yes	2.2 (1.0–5.0)	$p < 0.05$
Elevated ALT	No		
	Yes	15.4 (8.2–29.9)	$p < 0.001$
Hyperglycemia	No		
	Yes	1.6 (0.8–3.1)	$p = 0.21$
Insulin requirement	No		
	Yes	8.6 (4.3–17.6)	$p < 0.001$
Oral antidiabetic	No		
	Yes	1.4 (0.3–5.8)	$p = 0.63$
Previous diabetes complications	No		
	Yes	13.5 (6.7–29.4)	$p < 0.001$
Tobacco	No		
	Yes	1.6 (0.8–3.1)	$p = 0.18$
Alcohol	No		
	Yes	2.0 (1.0–4.0)	$p = 0.041$

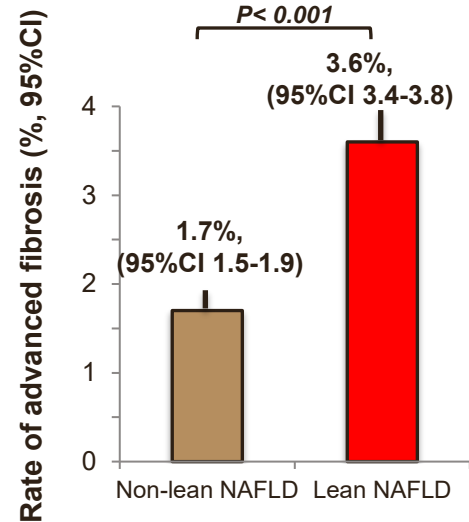


LEAN

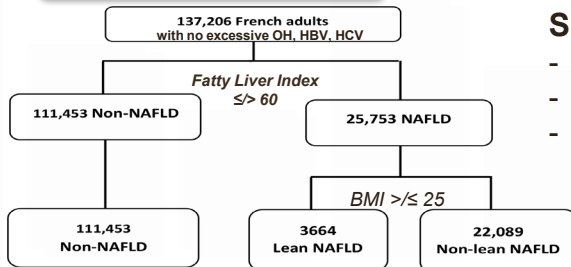
CONSTANCES



Lean NAFLD have higher rate of advanced fibrosis (*Forns Index* > 6.9)



Study population

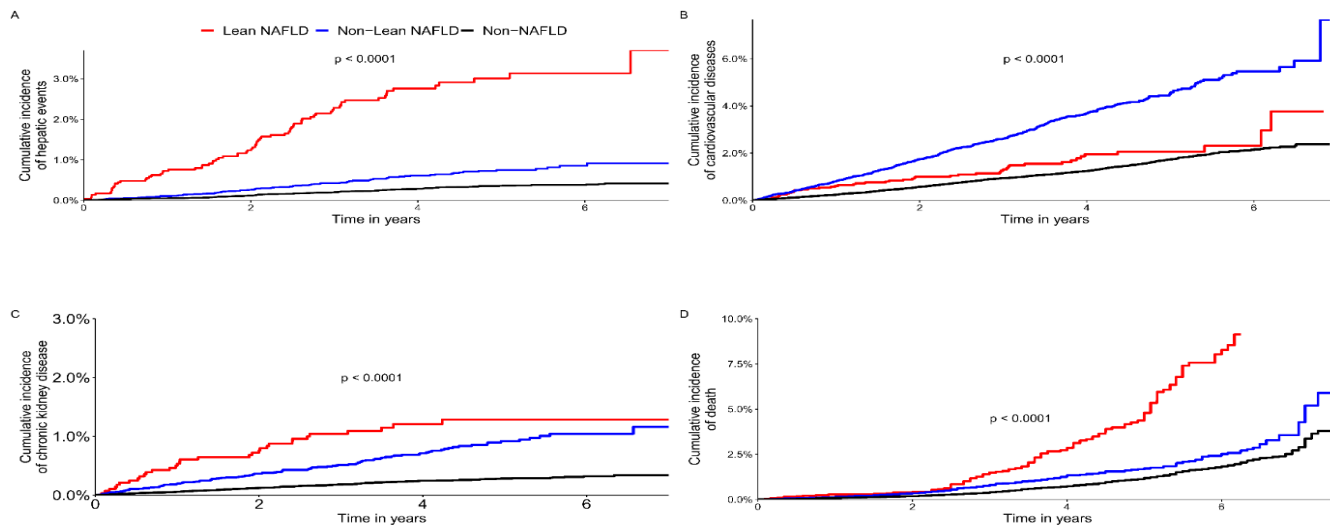


Prevalence: 16.3% Overweight 41%/Obese 42.7%

Specific risk factors of NAFLD in lean:

- Young age
- Female sex
- Asian ethnicity

Lean NAFLD have poorer outcomes



Conclusions (1)

Les biomarqueurs de NAFLD et de fibrose appliqués à une large cohorte représentative de la population générale adulte française sans consommation excessive d'alcool ou hépatites virales chroniques indiquent:

- La NAFLD atteint un sujet adulte sur six en France.
- La fibrose avancée est observée chez 2.6% des sujets NAFLD, et quatre fois plus chez les sujets diabétiques de type 2.
- L'âge, le sexe, les anomalies métaboliques et le mode de vie sont les principaux facteurs de risque de NAFLD et de fibrose.
- La NAFLD et surtout la fibrose, sont associées à un surrisque de complications hépatiques, cardio-vasculaires et à une surmortalité, indépendamment des FDR habituels.

Conclusions (2)

- CONSTANCES permet de générer des données vraie vie pour l'évaluation de la NAFLD en France.
- En termes de politique de santé, ces données peuvent être utilisées pour estimer le fardeau sanitaire et économique de la NAFLD et définir les populations cibles pour le dépistage.
- Ces données pourraient également permettre d'optimiser les stratégies pour la conception des essais thérapeutiques: populations cibles, taille et durée des essais.

Articles NASH CO

- ✓ *Nabi O, et al. Prevalence and Risk Factors of Nonalcoholic Fatty Liver Disease and Advanced Fibrosis in General Population: the French Nationwide NASH-CO Study. **Gastroenterology** 2020;159: 791-793.*
- ✓ *Nabi O, et al. Comorbidities Are Associated with Fibrosis in NAFLD Subjects: A Nationwide Study (NASH-CO Study). **Dig Dis Sci** 2022; 67: 2584-2593.*
- ✓ *Nabi O, et al. The burden of NAFLD in type 2 diabetic subjects from the general population: A Nationwide population-based follow-up study (NASHCO). **Liver Int** 2022; 42: 595-606.*
- ✓ *Amadou C, et al. Association between birth weight, preterm birth, and nonalcoholic fatty liver disease in a community-based cohort. **Hepatology** 2022;76: 1438-1451.*
- ✓ *Nabi O, et al. Lean individuals with NAFLD have more severe liver disease and poorer clinical outcomes (NASH-CO Study). **Hepatology** 2023;78:272–283*
- ✓ *Nabi O, et al. The NAFLD Burden on Mortality and Morbidities in General Population: a Community-Based Longitudinal Study (NASH-CO study). **Liver Int** 2023*
- ✓ *Ossima AN, et al. Factors associated with high costs of patients with metabolic dysfunction-associated steatotic liver disease: an observational study using the French CONSTANCES cohort. **Clin Diabetes Endocrinol** 2024*