

Rates of NASH progression in a real world setting

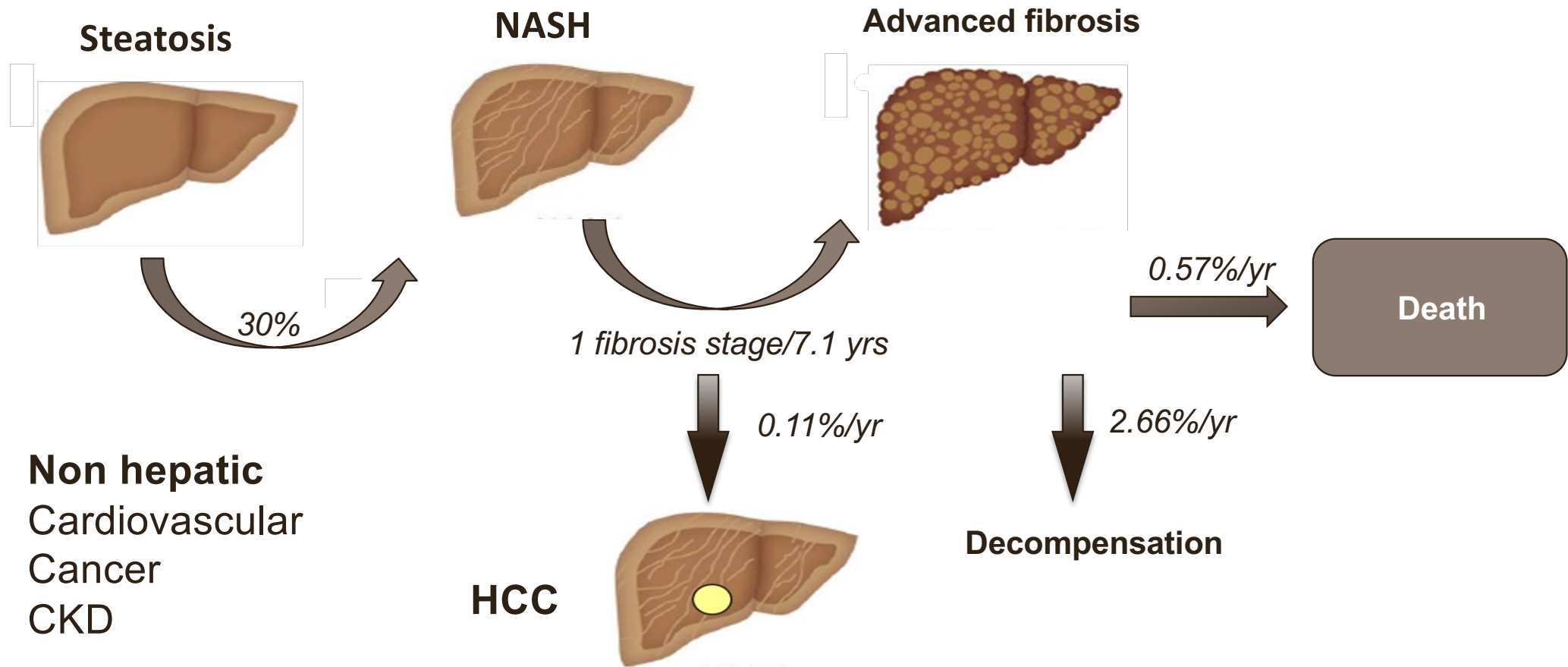
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Disclosures

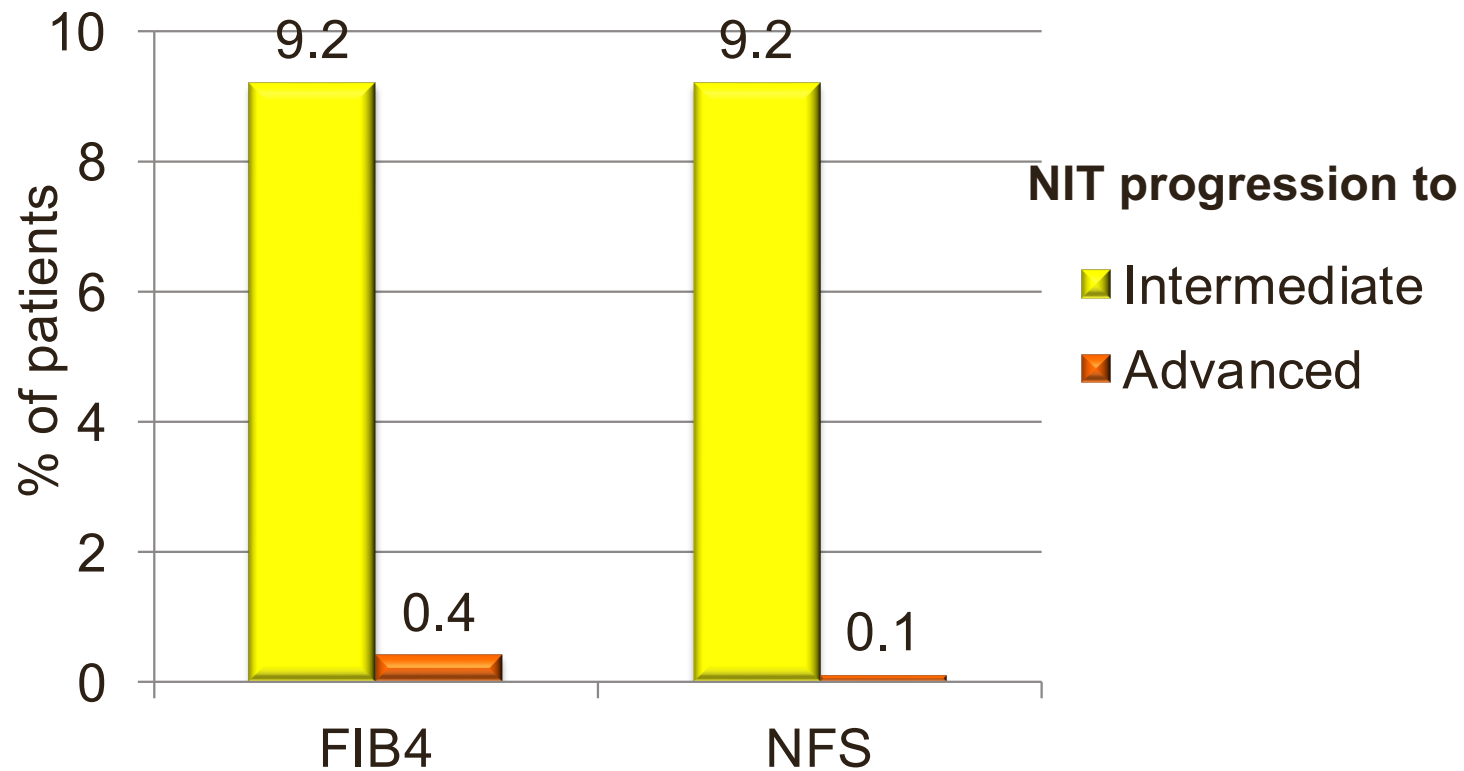
- BMS
- Gilead
- Intercept
- Novonordisk
- Novartis
- Pfizer
- TheraTechnologies

Progression of NAFLD according to liver biopsy



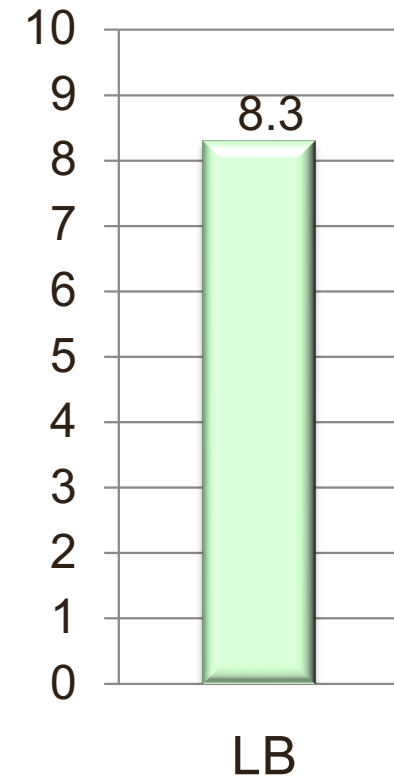
Progression of fibrosis in a population-based study

58,927 Korean adults with NAFLD (US) and low fibrosis score, median follow-up 4.8 yrs



Chang Y et al, Hepatology 2019

131 F0 NAFLD patients with paired LB
F3/F4 progressors, FU 5.9 yrs



Singh S et al. Clin Gastroenterol Hepatol 2015

Risk factors of fibrosis progression

Subgroup	Type of drinkers			P for trend	P for interaction
	Nondrinkers	Light drinkers	Moderate drinkers		
Age					0.075
<50 years (n = 54,646)	reference	0.91 (0.83-1.00)	1.20 (1.09-1.32)	<0.001	
≥50 years (n = 4,281)	reference	1.12 (0.96-1.31)	1.32 (1.11-1.56)	0.067	
Sex					0.987
Woman (n = 10,582)	reference	1.06 (0.89-1.26)	1.32 (0.92-1.90)	0.942	
Man (n = 48,345)	reference	1.06 (0.97-1.17)	1.29 (1.17-1.41)	<0.001	
BMI					0.514
<25 kg/m ² (n = 23,324)	reference	1.07 (0.95-1.21)	1.35 (1.19-1.53)	<0.001	
≥25 kg/m ² (n = 35,600)	reference	1.06 (0.95-1.18)	1.25 (1.12-1.39)	0.001	
Current smoker					0.756
No (n= 3 7,954)	reference	1.04 (0.94-1.14)	1.28 (1.15-1.42)	<0.001	
Yes (n = 18,948)	reference	1.12 (0.94-1.32)	1.35 (1.15-1.58)	<0.001	
Diabetes					0.440
No (n = 56,344)	reference	1.07 (0.98-1.16)	1.30 (1.19-1.42)	<0.001	
Yes (n = 2,583)	reference	1.03 (0.77-1.39)	1.08 (0.81-1.45)	0.953	

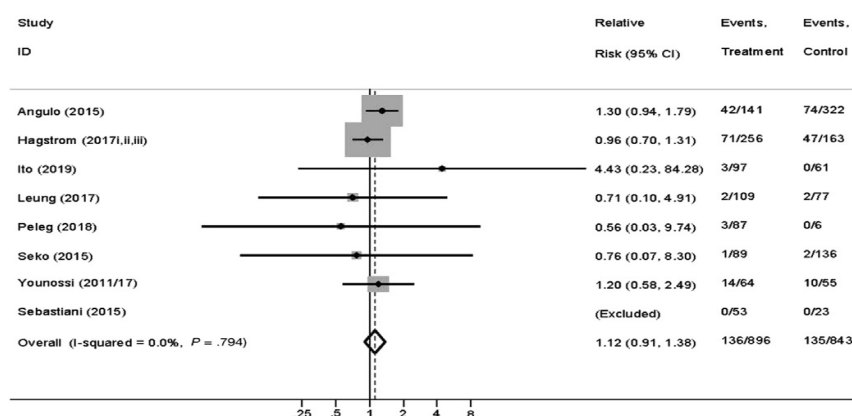
NAFLD and mortality in population-based studies

Ref.	Study characteristics	Years of follow-up	NAFLD diagnosis	Study outcomes	Increased mortality
Calori <i>et al</i> ^[54] , 2011	Community based-cohort, <i>n</i> = 2074 (Cremona study)	15.0	FLI index	All-cause and cause- specific mortality	yes
Jepsen <i>et al</i> ^[56] , 2003	Population-based cohort, <i>n</i> = 1804 with hospital diagnosis of NAFLD (Danish national registry of patients)	16.0	US	All-cause and cause- specific mortality	yes
Lazo <i>et al</i> ^[59] , 2011	Population-based cohort, <i>n</i> = 11371 (NHANES-III)	14.5	US	All-cause and cause-specific mortality	no
Stepanova <i>et al</i> ^[60] , 2012	Population-based cohort, <i>n</i> = 11613 (NHANES-III)	14.2	US	All-cause and cause-specific mortality	no
Zhou <i>et al</i> ^[61] , 2012	Community-based cohort study, <i>n</i> = 3543 adult men and women	4.0	US	All-cause and CVD mortality	yes
Younossi <i>et al</i> ^[62] , 2013	Population-based cohort, <i>n</i> = 1448 with NAFLD (NHANES-III)	14.2	US	All-cause and cause- specific mortality	yes
Haring <i>et al</i> ^[63] , 2009	Population-based cohort, <i>n</i> = 4160 German subjects (Study of Health in Pomerania)	7.2	US and liver enzymes	All-cause and CVD mortality	yes
Kim <i>et al</i> ^[64] , 2013	Population-based cohort, <i>n</i> = 1154 (NHANES-III)	14.5	US and advanced fibrosis score systems	All-cause and cause- specific mortality	no

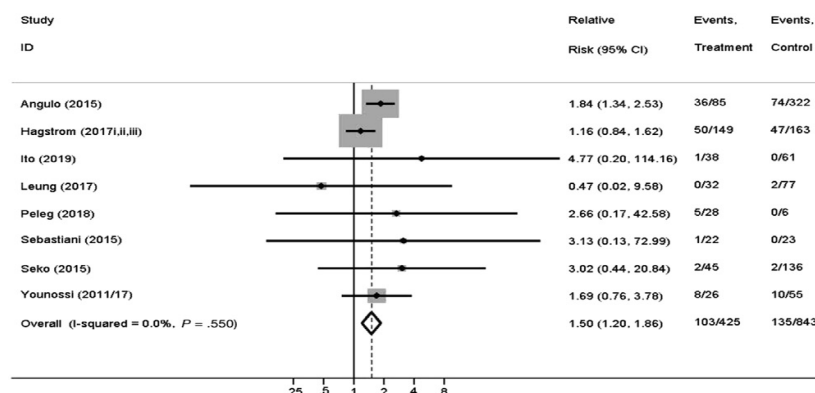
Ballestri S et al, WJG 2014
Rashmee P et al, WJG 2017

All cause mortality is related to fibrosis stage in biopsy-proven NAFLD patients: metaanalysis

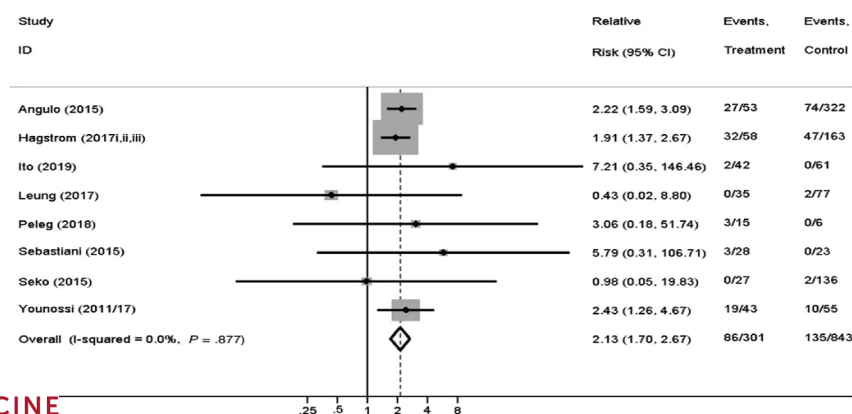
All cause mortality NAFLD stage 0 vs stage 1



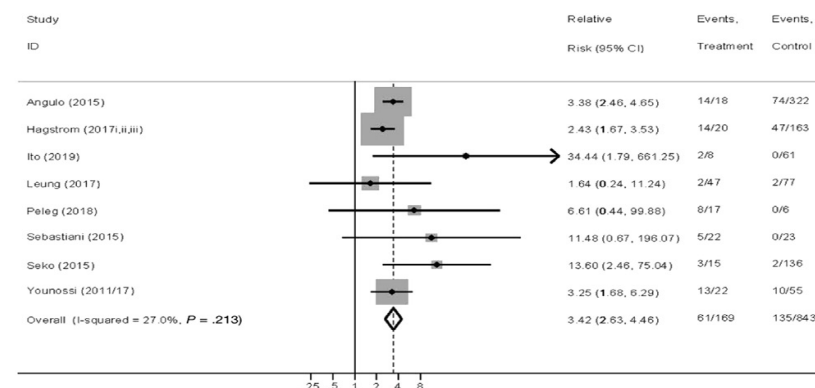
All cause mortality NAFLD stage 0 vs stage 2



All cause mortality NAFLD stage 0 vs stage 3



All cause mortality NAFLD stage 0 vs stage 4



Fibrosis markers are predictive of mortality in NAFLD population-based studies

11,154 participants (NHANES), 34% NAFLD (US)

	APRI*		FIB-4*	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Mortality from all causes				
Low score	Reference		Reference	
Intermediate score	1.32 (0.78-2.23)	0.294	1.46 (1.16-1.82)	0.002
High score	1.85 (1.02-3.37)	0.044	1.66 (0.98-2.82)	0.060
CVD				
Low score	Reference		Reference	
Intermediate score	0.97 (0.40-2.34)	0.937	1.75 (1.26-2.43)	0.001
High score	2.53 (1.33-4.83)	0.006	2.68 (1.44-4.99)	0.003
Liver disease				
Low score	Reference		Reference	
Intermediate score	6.08 (0.77-48.21)	0.086	0.68 (0.11-4.05)	0.667
High score	3.01 (0.20-45.62)	0.420	1.32 (0.12-14.80)	0.821
Malignancy				
Low score	Reference		Reference	
Intermediate score	2.33 (0.91-5.96)	0.076	0.89 (0.49-1.63)	0.705
High score	2.31 (0.35-15.10)	0.374	0.96 (0.19-4.82)	0.962
Diabetes				
Low score	Reference		Reference	
Intermediate score	0.41 (0.12-1.46)	0.166	0.98 (0.57-1.68)	0.945
High score	29.36 (10.05-85.74)	<0.001	2.89 (0.33-25.35)	0.330

Questions

- The risk of clinical outcomes and death in real life NAFLD subjects according to the large CONSTANCES cohort.
- The incidence rates of outcomes in real life vs liver-biopsed NAFLD patients according to the stage of fibrosis :

CONSTANCES vs NASH CRN

n=137,206

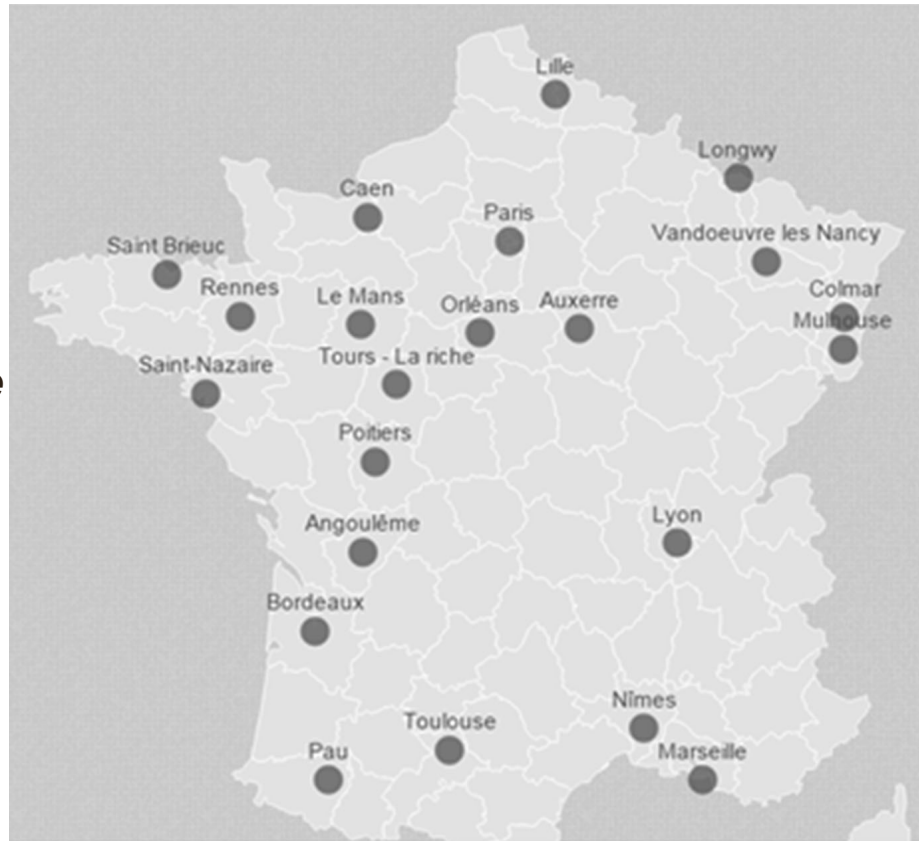
n=1773

The Constances cohort

CONSTANCES was designed as a sample representative for age, gender and socioeconomic status of French adult population aged 18-69. Restricted to salaried workers (85% of French population, 50 M people). More than 200,000 subjects were included since 2012

22 health centers
in 19 departments

Health questionnaire
Clinical
Biological



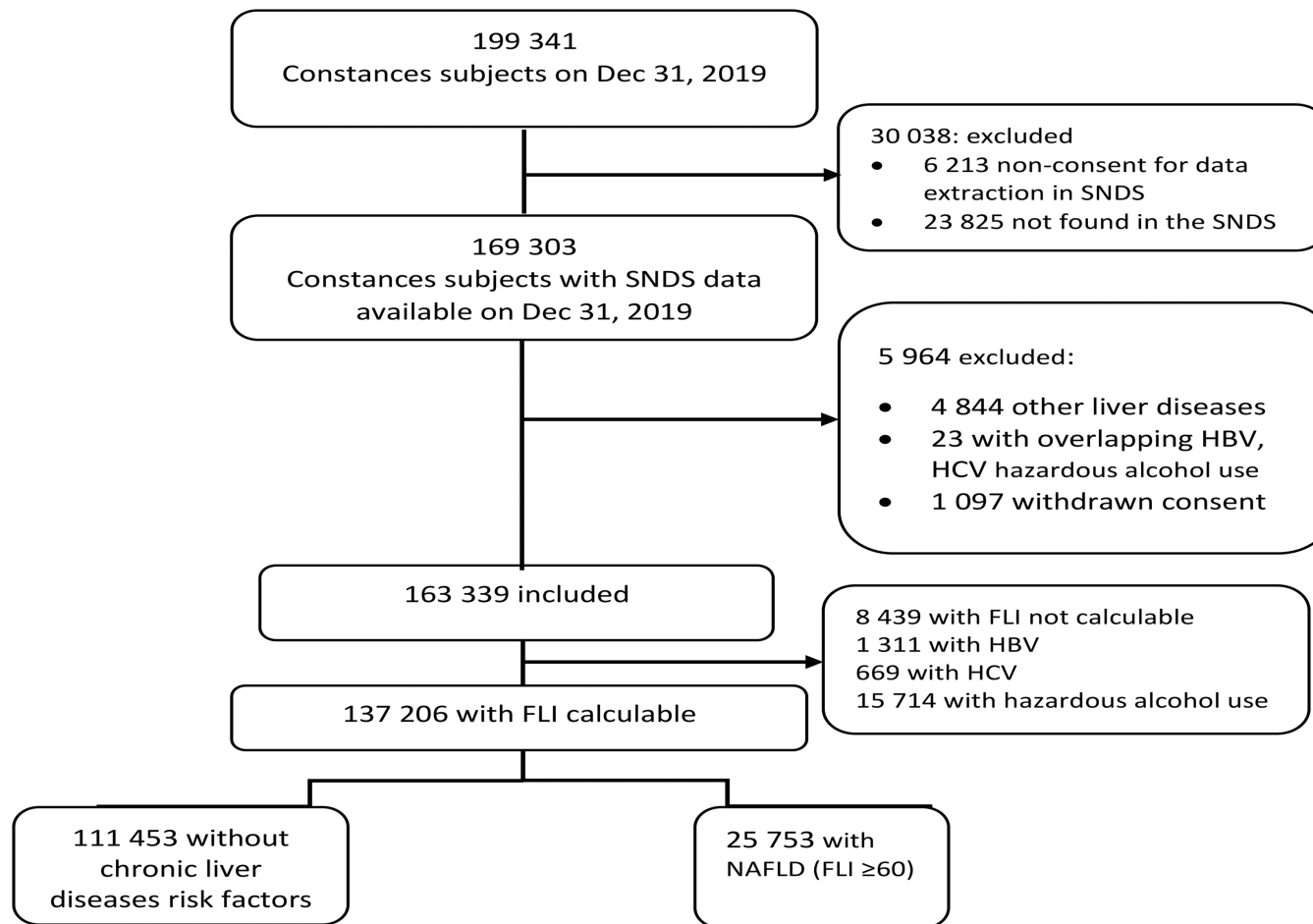
Follow-up

Linkage
with
SNDS

SNDS
Système national des données de santé



Flow Chart



General characteristics of NAFLD subjects

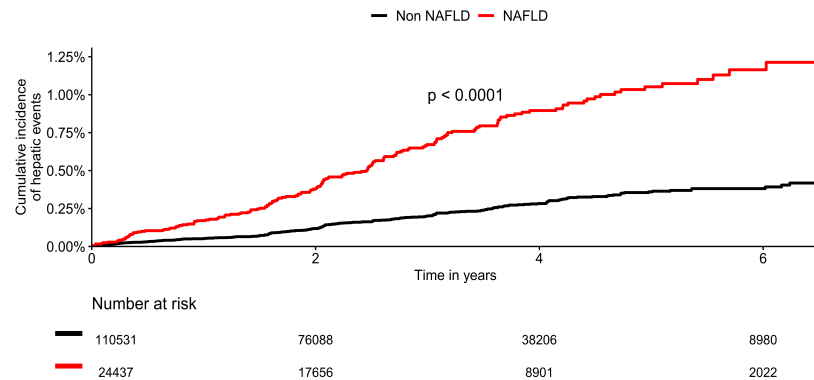
	Overall sample N = 137 206	Non-NAFLD (FLI <60) N = 111 453	NAFLD (FLI ≥60) N = 25 753
Age (years), mean [SD]	46.8 [13.3]	45.6 [13.2]	52.4 [11.8]
Male sex, n (%)	62 223 (45.4)	46 895 (41.4)	15 328 (66.9)
Obesity (BMI ≥30 kg/m ²), n (%)	16 628 (12.1)	3341 (3.0)	13 287 (58.0)
HBP, n (%)	14 485 (10.6)	8370 (7.6)	6115 (27.3)
Waist circumference (cm), mean [SD]	84.7 [12.9]	80.8 [9.5]	103.9 [9.5]
Diabetes, n (%)	6419 (5.3)	2473 (2.2)	3946 (15.6)
Hypercholesterolemia, n (%)	10 094 (11.5)	5991 (5.4)	4103 (18.5)
ALT > N, n (%)	15 410 (11.3)	7404 (6.5)	8006 (35.0)
GGT > N, n (%)	13 790 (10.1)	6232 (5.5)	7558 (33.0)

Outcomes: ICD-10, median FU 3.62 yrs

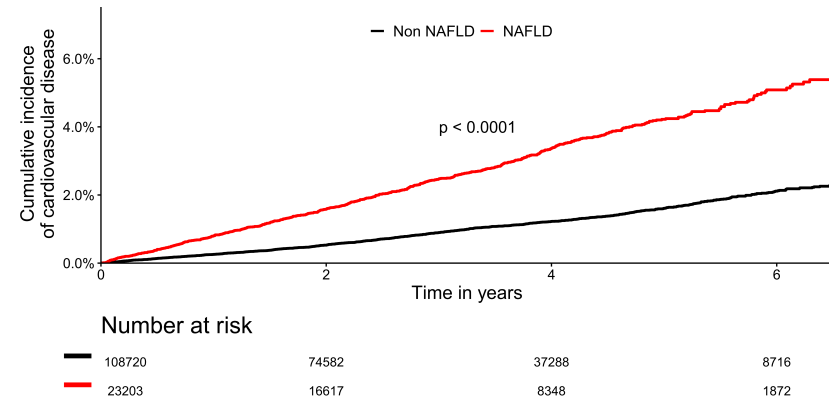
	NAFLD subjects n=25753
Hepatic event	682
HCC	122
Liver transplantation	18
Cardiovascular event	2050
Chronic kidney disease	471
Extra hepatic malignancy	1954
Death	1166

Clinical outcomes according to NAFLD

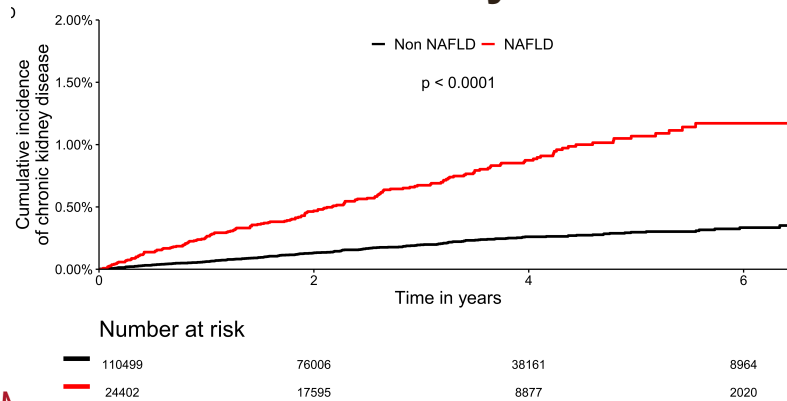
Hepatic events



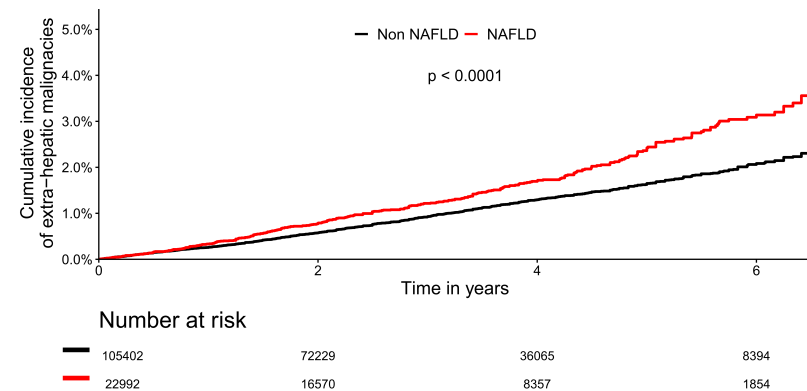
Cardiovascular event



Chronic kidney disease

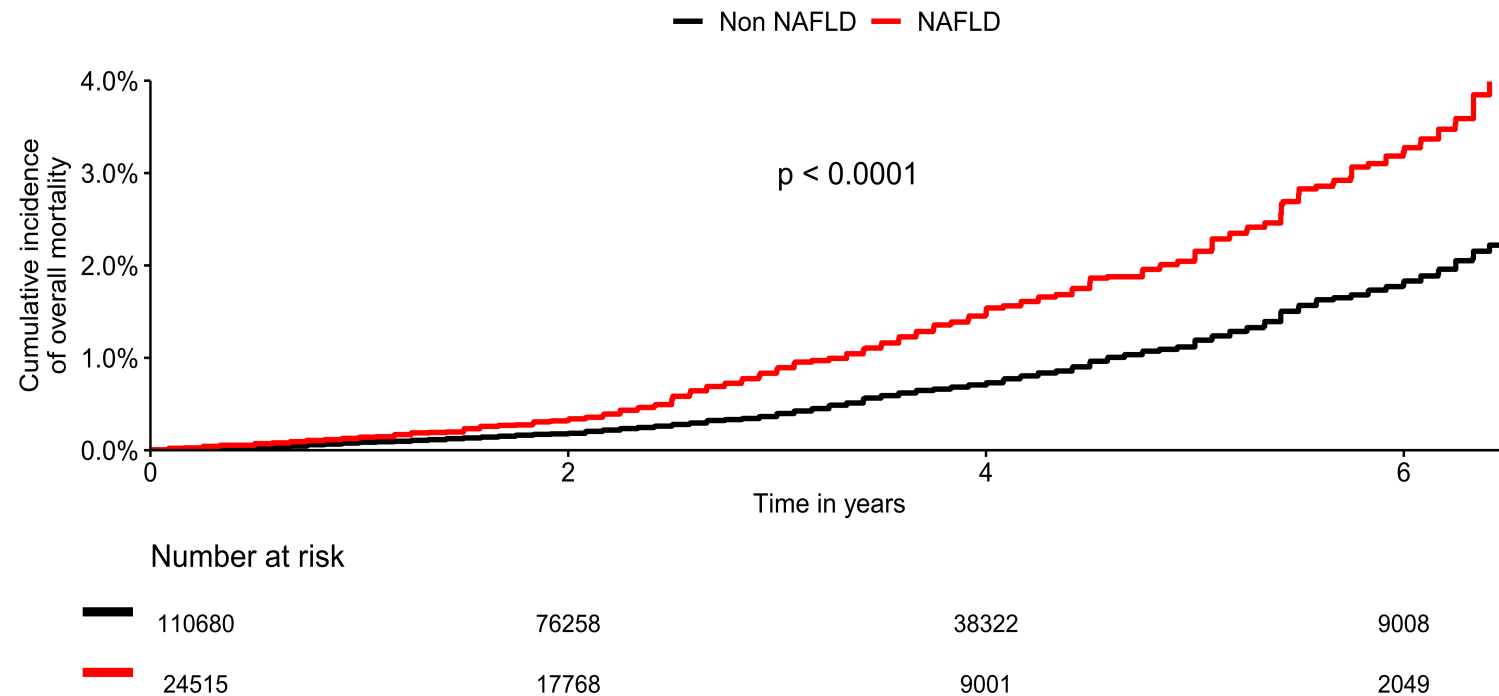


Extra-hepatic cancer



All cause death according to NALFD

All cause death



Incidence rate and risk of clinical outcomes

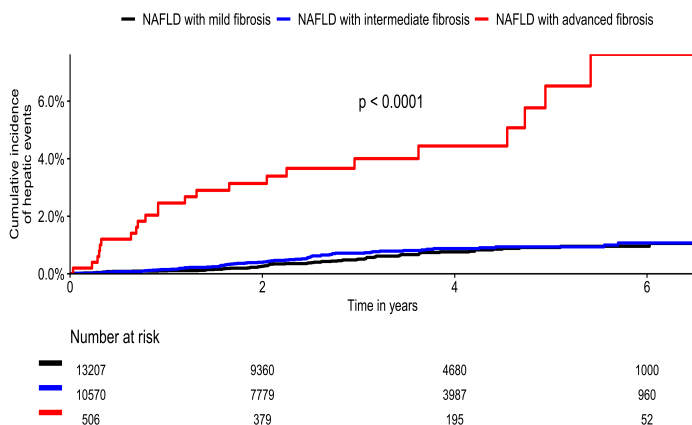
	Incidence rate per 1000 person-yr		Hazard ratio (95%CI)*	
	NAFLD (FLI ≥ 60)	Non-NAFLD (FLI < 60)	NAFLD vs non NAFLD	
	<i>n</i> =25,753	<i>n</i> = 111,453	HR (95%CI)	<i>P</i>
Hepatic events	4.51	1.59	2.63 (1.96-2.87)	<i><0.001</i>
Cardiovascular diseases	45.67	13.30	2.33 (1.20-2.78)	<i><0.001</i>
Extra-hepatic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

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

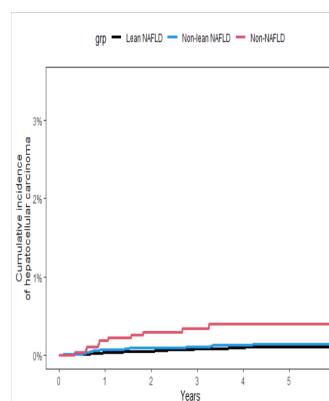
Clinical outcomes according to fibrosis in NAFLD subjects (Forns Index)

— NAFLD mild fibrosis — NAFLD with intermediate fibrosis — NAFLD with advanced fibrosis

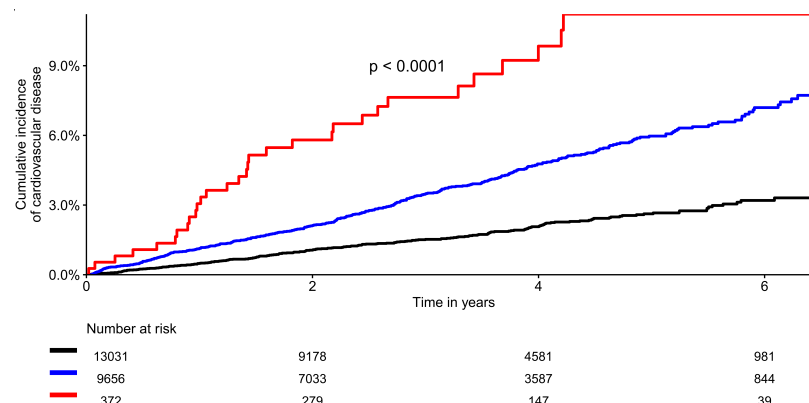
Hepatic events



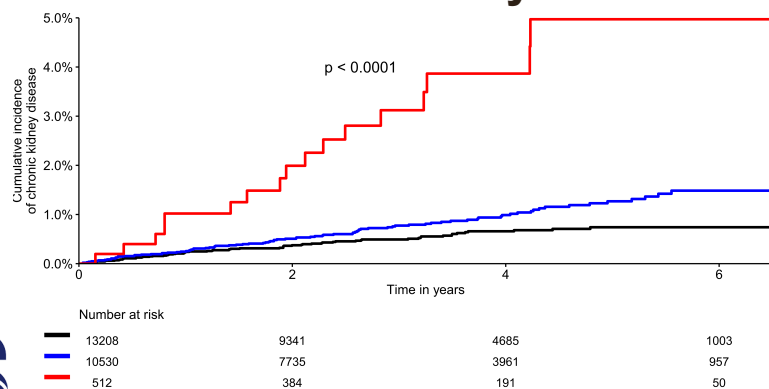
HCC



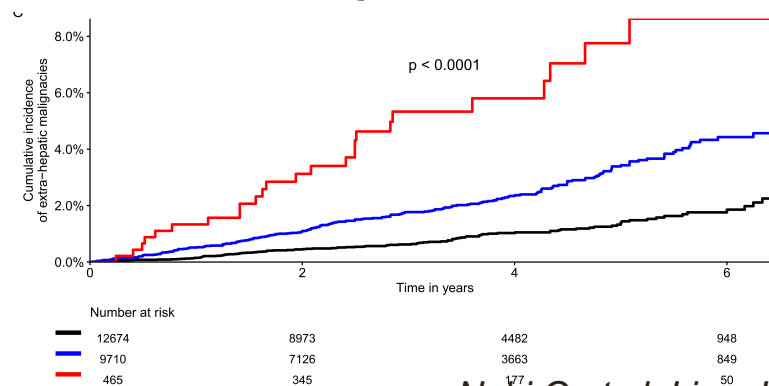
Cardiovascular events



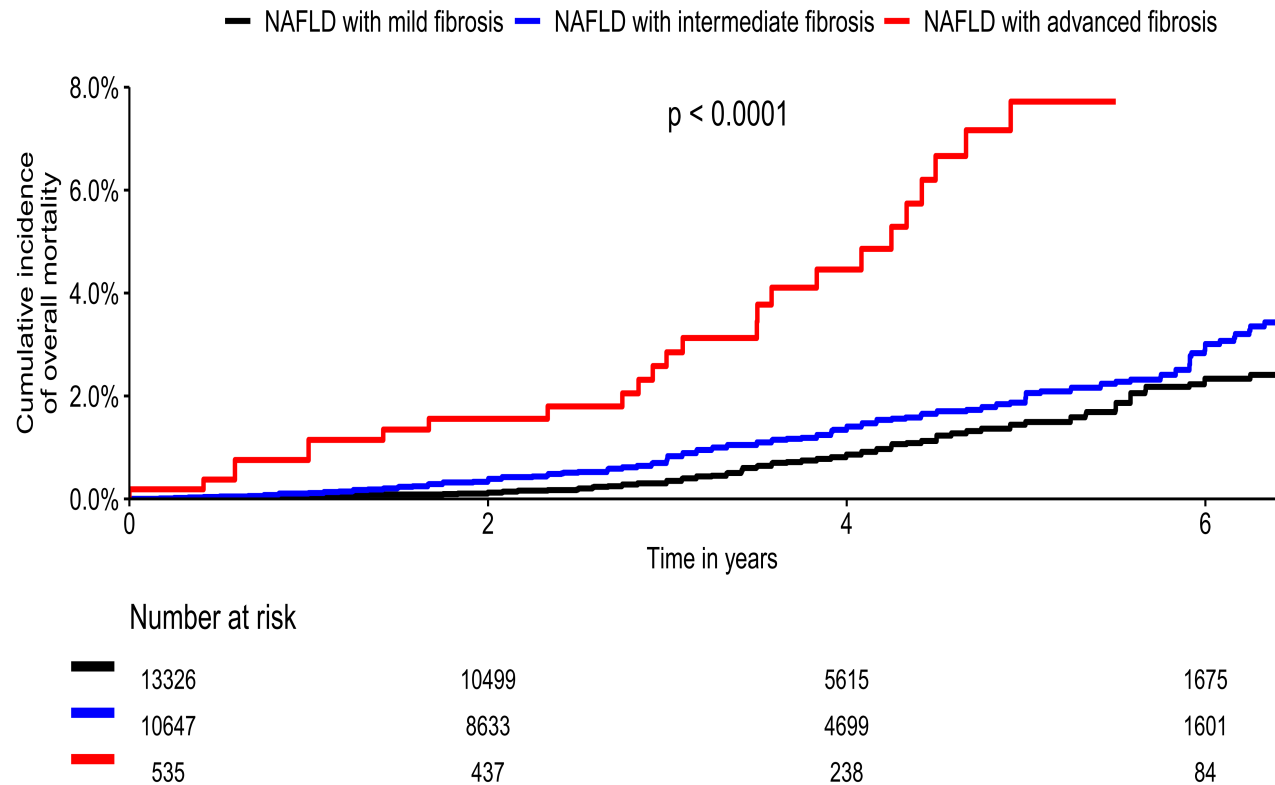
Chronic kidney disease



Extra-hepatic cancer



All cause death according to fibrosis in NAFLD subjects



Incidence rate and risk of clinical outcomes according to fibrosis in NAFLD subjects

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

Incidence rates (per 100 person-yr) according to fibrosis in NAFLD subjects

	Incidence rate per 100 person-yr		
	NAFLD and advanced fibrosis	NAFLD and intermediate fibrosis	NAFLD and mild fibrosis
	<i>n</i> =535	<i>n</i> =10638	<i>n</i> =13297
Hepatic events	7.2	0.4	0.3
Cardiovascular diseases	8.5	6.6	1.5
Extra-hepatic malignancies	3.8	2.2	0.9
Chronic kidney disease	2.8	0.7	0.3
Death	2.2	0.6	0.4

Clinical outcomes and death in biopsy proven NAFLD subjects

Variable	Total		Stage F4, Cirrhosis		Stage F3, Bridging Fibrosis		Stage F0 to F2, No, Mild, or Moderate Fibrosis	
	rate per 100 person-yr	no. of events/ no. at risk	rate per 100 person-yr	no. of events/ no. at risk	rate per 100 person-yr	no. of events/ no. at risk	rate per 100 person-yr	no. of events/ no. at risk
Death from any cause	0.57	47/1773	1.76	13/167	0.89	16/369	0.32	18/1237
Liver-related events								
Variceal bleeding	0.07	6/1757	0.70	5/163	0.06	1/362	0.00	0/1232
Ascites	0.24	19/1747	1.20	8/155	0.52	9/363	0.04	2/1229
Encephalopathy	0.37	30/1757	2.39	16/161	0.75	13/364	0.02	1/1232
Any hepatic decompensation event†	0.46	37/1745	2.69	17/153	0.99	17/362	0.05	3/1230
Hepatocellular carcinoma	0.11	9/1761	0.14	1/165	0.34	6/364	0.04	2/1232
Cardiac and vascular events‡								
Cardiovascular disease	0.83	63/1667	0.81	5/144	0.93	15/340	0.80	43/1183
Cerebrovascular disease	0.40	32/1745	0.99	7/163	0.46	8/363	0.30	17/1219
Hypertension	7.76	202/695	14.49	18/45	12.17	49/122	6.50	135/528
Renal function								
eGFR <60 ml/min/1.73 m ²	2.53	185/1660	4.49	27/153	2.97	46/337	2.17	112/1170
Decrease in eGFR of >40%	1.21	97/1761	2.98	20/164	1.31	23/368	0.97	54/1229
Other new coexisting events								
Nonhepatic cancer	0.82	58/1582	1.00	6/141	1.03	15/313	0.73	37/1128

Sanyal A et al, NEJM 2021

Incidence rates (per 100 person-yr) according to fibrosis in NAFLD subjects

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Decrease in eGFR of >40%	1.21	97/1761	2.98	20/164	1.31	23/368	0.97	54/1229
Other new coexisting events								
Nonhepatic cancer	0.82	58/1582	1.00	6/141	1.03	15/313	0.73	37/1128

Conclusions

- In the real world CONSTANCES cohort, rates of liver complications, cardiovascular disease, chronic kidney disease and all-cause death are increased in NAFLD subjects, independent of usual risk factors.
- At constant baseline fibrosis grade, rates of clinical outcomes and death are similar between real world and liver-biopsed NAFLD patients.
- CONSTANCES may provide data that could be used to estimate clinical and economic burden of NAFLD in France and to define target populations for screening.