



# Hypobetalipoproteinemia and the risk of HCC in the general population



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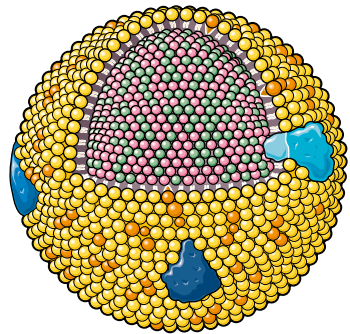


**PARIS  
MASH  
MEETING**

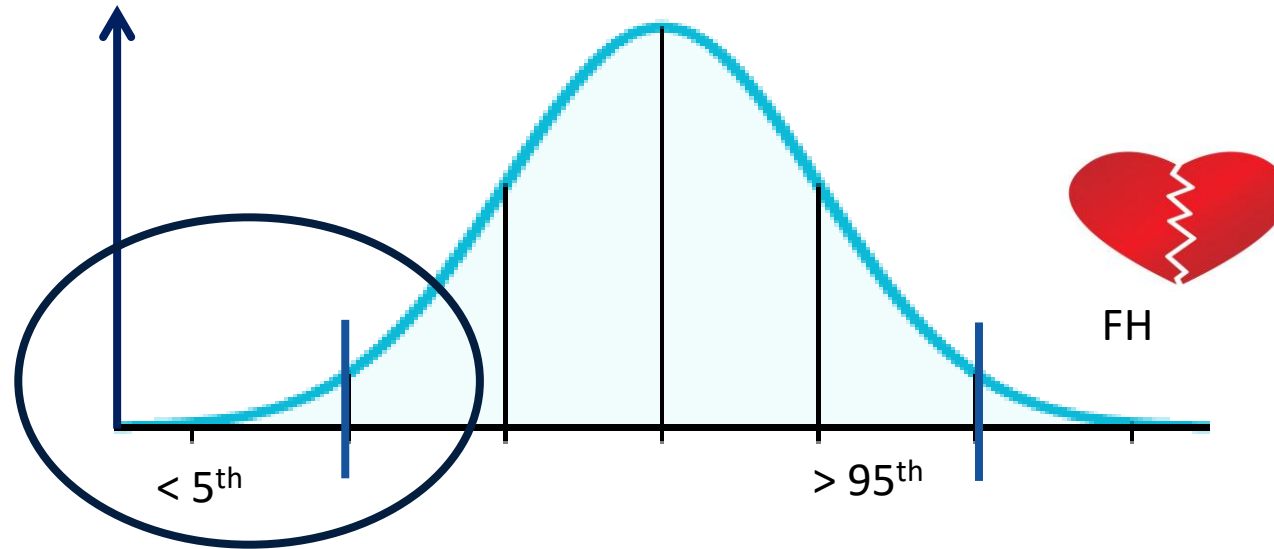
# Disclosures

<i>Company NameAS</i>	<i>Honoraria/ Expenses</i>	<i>Consulting/ Advisory Board</i>	<i>Funded Research</i>	<i>Royalties/ Patent</i>	<i>Stock Options</i>	<i>Ownership/ Equity Position</i>	<i>Employee</i>	<i>Other (please specify)</i>
AMGEN	X	X						
ASTRA-ZENECA	X	X						
GILEAD	X							
Eli-LILLY	X	X						
MSD		X						
NOVARTIS	X	X						
NOVO-NORDISK	X							
REGENERON	X		X					
SANOFI	X							
ULTRAGENYX	X	X						

# Hypobetalipoproteinemia : definition



LDL-C  
(ApoB)

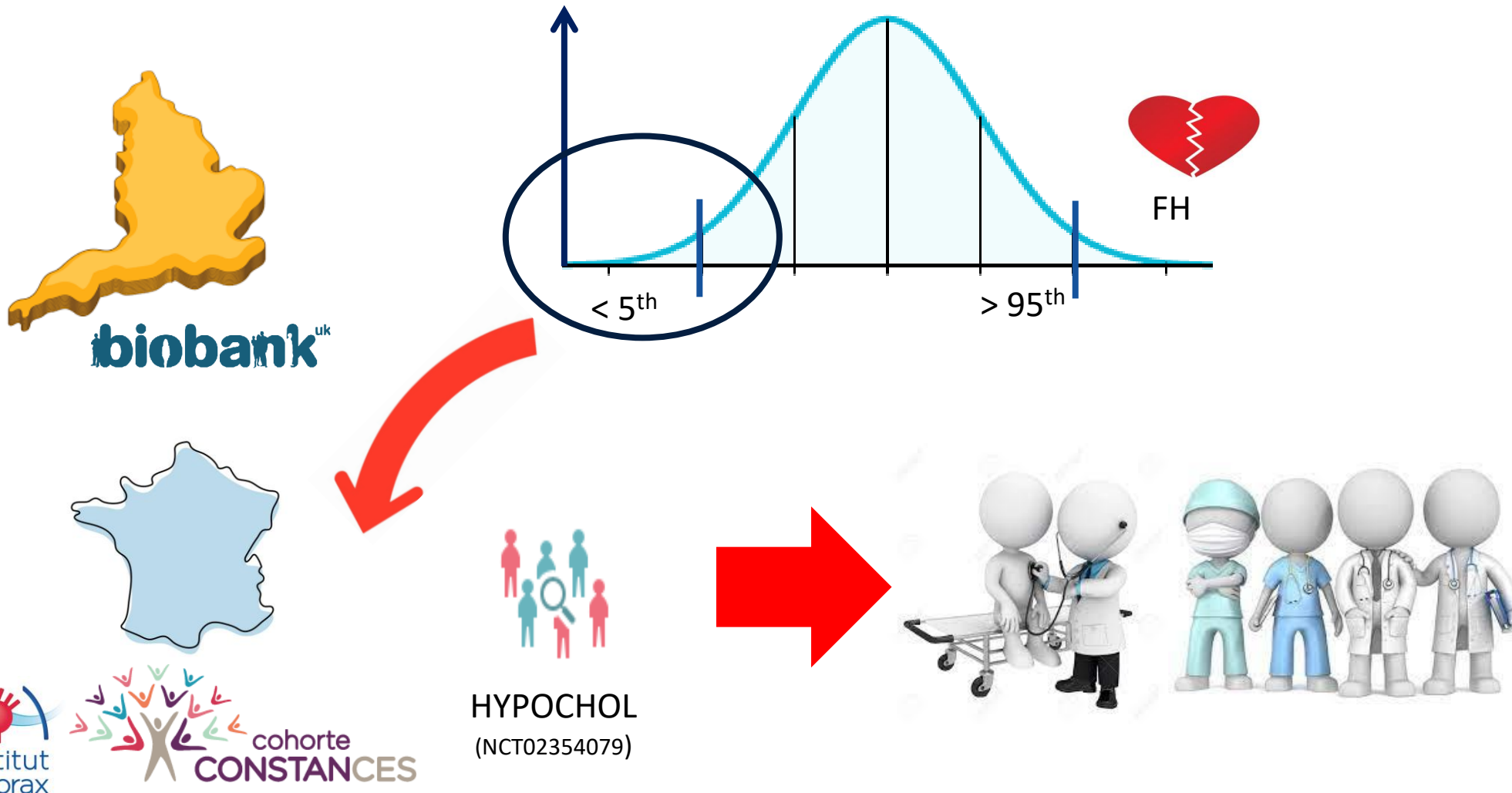


**LDL cholesterol (LDL-C) and/or apoB  $< 5^{\text{th}}$  percentile adjusted for age and sex**

# Our Global Scientific Strategy

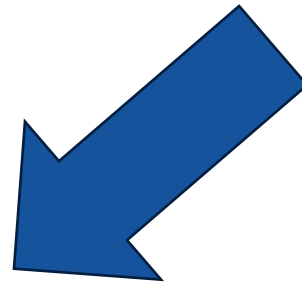
## Assessing the safety of very low LDL-C levels

### Cohorts with extreme LDL-C values



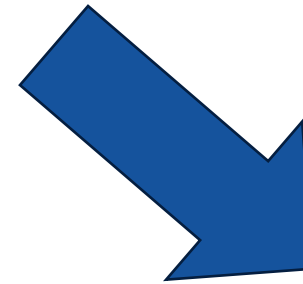
# Pathophysiology of hypobetalipoproteinemia

Two main mechanism of action



**Alteration of the assembly and secretion  
of apoB-containing lipoproteins  
(FHBL SD)**

**MTTP**  
**SAR1B**  
**APOB (LOF)**



**Increased catabolism  
of apoB-containing lipoproteins  
(FHBL EC)**

**ANGPTL3**  
**PCSK9 (LOF)**

# ABETALIPOPROTEINEMIA vs HYPOBETALIPOPROTEINEMIA

Onset at a pediatric age

Rare disease  
(autosomal recessive)

Symptoms

Specialized therapeutic care

Defect of lipoprotein secretion  
(*MTTP, SAR-1B, APOB*)

**Onset in adulthood**

**« Common disease »**  
**Autosomal co-dominant**

**Asymptomatic**

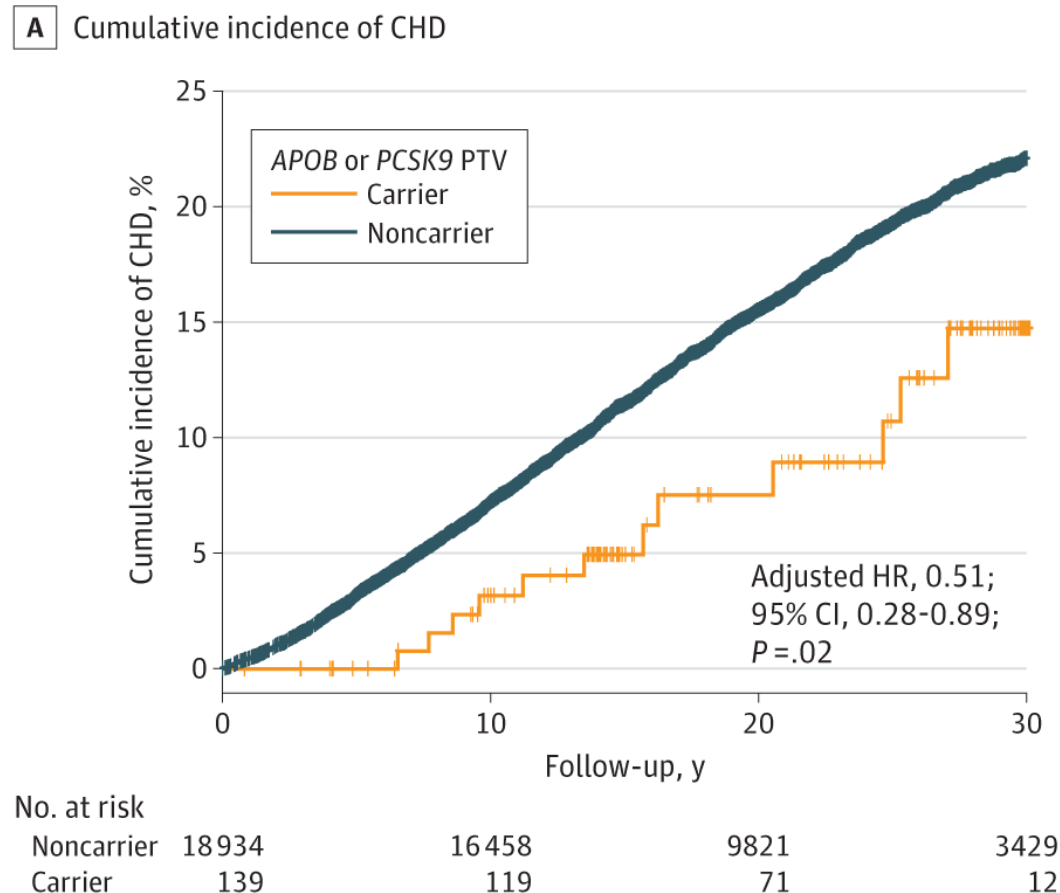
No specific therapeutic

Defect of lipoprotein secretion (*APOB*)  
or increased lipoprotein catabolism  
(*PCSK9, ANGPTL3*)

# FHBL and ASCVD protection



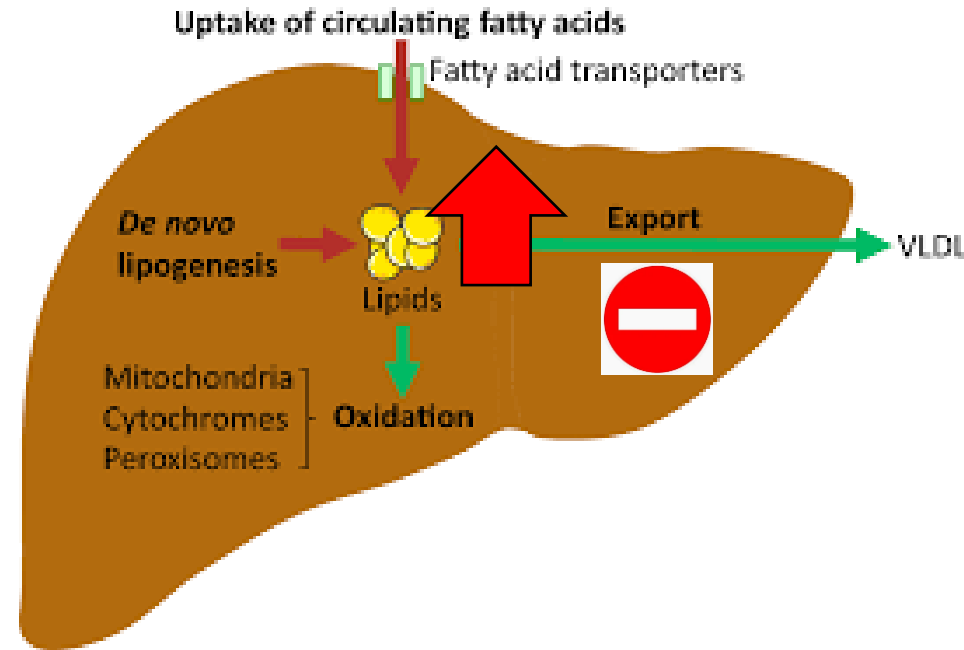
From: **Association of Rare Protein-Truncating DNA Variants in APOB or PCSK9 With Low-density Lipoprotein Cholesterol Level and Risk of Coronary Heart Disease**





# Hepatic consequences of FHBL

The lack of VLDL secretion in FHBL-SD is associated with an increased risk of hepatic steatosis

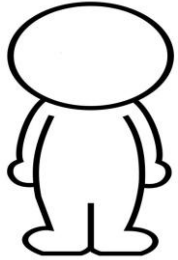


Long-term consequences?



# Assessing the liver safety of primary HBL

In FHBL population: HYPOCHOL cohort



**FHBL individuals**  
(N=104)

35.4 ± 16.4 yo

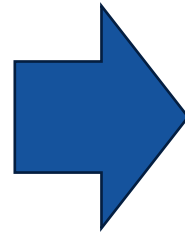
54.8% female

BMI: 23.8 kg/m<sup>2</sup>

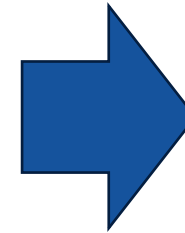
APOB variant : 28.8%

LDL-C: 47.7 ± 15.7 mg/dL

APOB: 48.7 ± 23.4 mg/dL



Fibroscan® exam

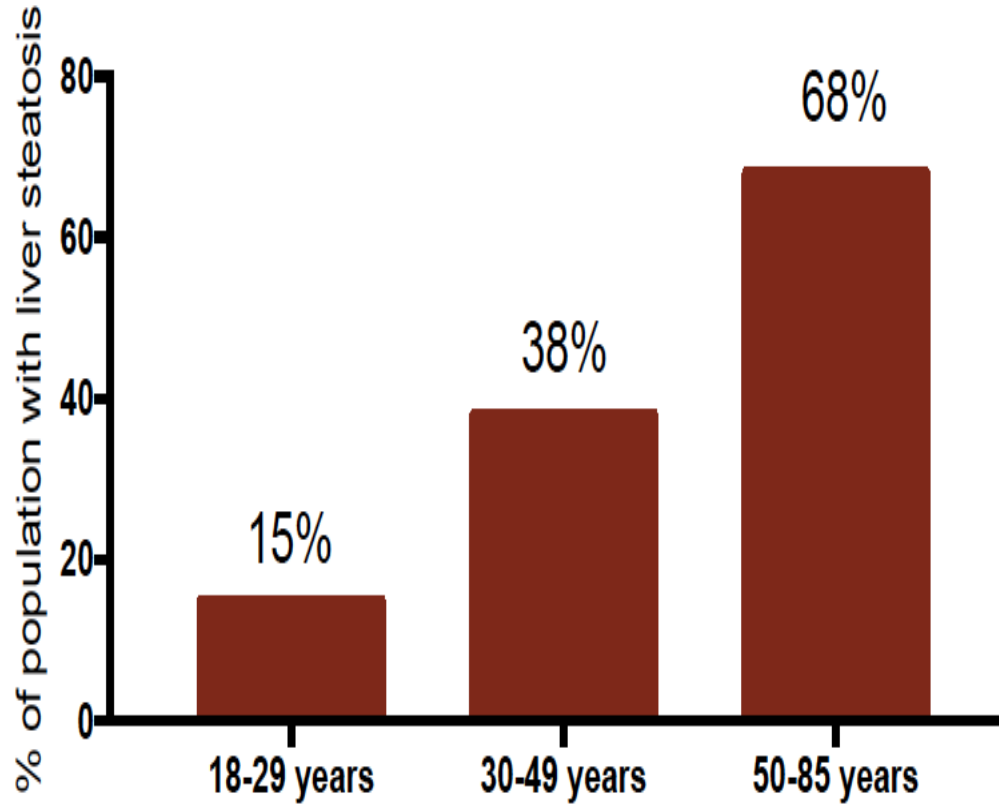


**Liver steatosis**  
CAP > 275 db/m

**Liver fibrosis**  
Liver steafness ≥ 8.0 kPa

**Advanced liver fibrosis**  
Liver steafness ≥ 12.0 kPa

# Prevalence of liver steatosis

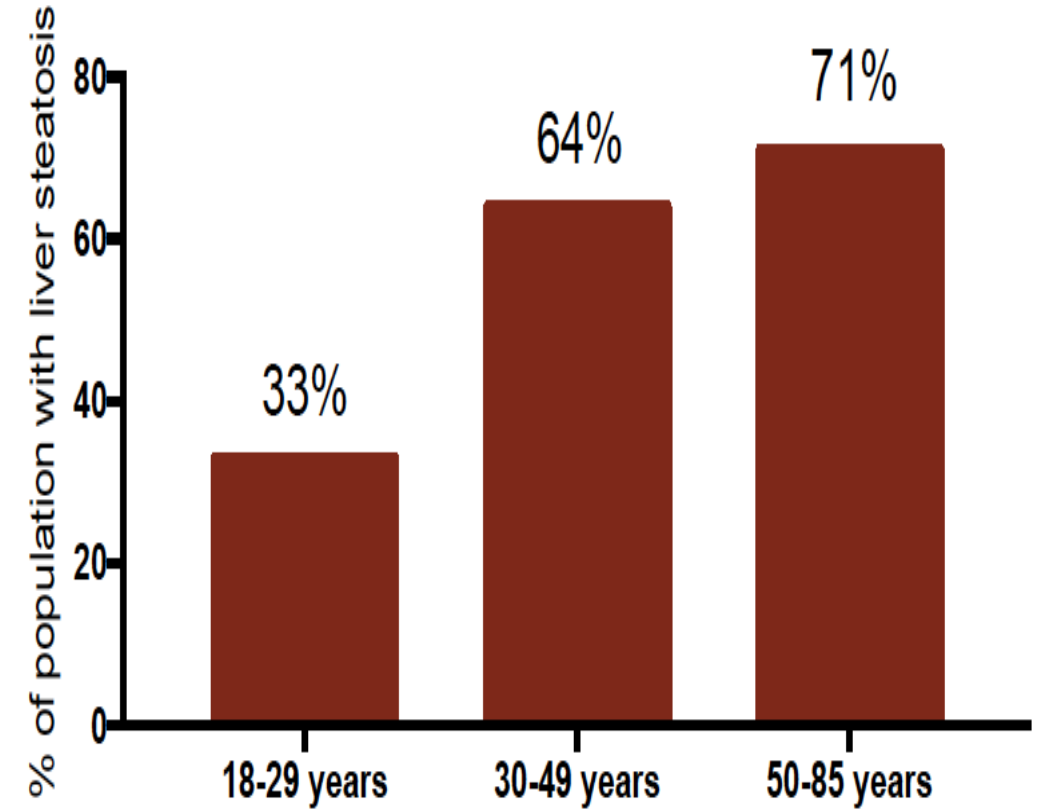


N (/all study population)

8/53

12/32

13/19



N (/patients with APOB pathogenic variant)

4/12

7/11

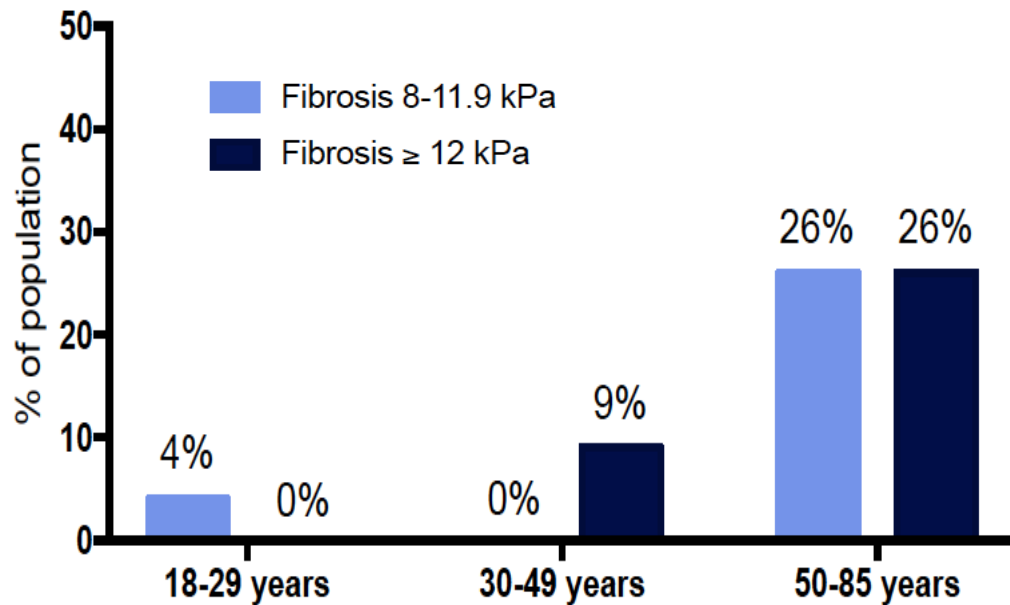
5/7

# Factors associated with the presence of steatosis

Steatosis (33/104)	Logistic regression - univariate		Logistic regression - multivariate (without selection)		Logistic regression - Multivariate (selection)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age (+ 1 SD (16.4 ans))	2.67 (1.70; 4.44)	<0.0001	1.32 [0.68; 2.54]	0.40	-	-
Sex (women/men)	0.33 [0.14; 0.77]	0.011	0.69 [0.21; 2.33]	0.54	-	-
<b>BMI (+1 SD (5.2 kg/m<sup>2</sup>))</b>	<b>4.54 [2.54; 9.34]</b>	<b>&lt;0.0001</b>	<b>3.68 [1.90; 8.06]</b>	<b>0.0003</b>	<b>4.71 [2.63; 9.65]</b>	<b>&lt;0.0001</b>
Excessive alcohol intake (yes/no)	7.00 [0.86; 145]	0.098	7.86 [0.36; 289]	0.20	-	-
Diabetes (yes/no)	6.60 [2.15; 23.0]	0.0015	1.56 [0.22; 9.92]	0.64	-	-
Plasma TG (+1 SD (41 mg/dL))	1.86 [1.20; 3.19]	0.012	1.37 [0.74; 2.96]	0.34	-	-
<b>Genetic variant APOB (yes/no)</b>	<b>3.83 [1.57; 9.59]</b>	<b>0.0034</b>	<b>5.56 [1.64; 21.5]</b>	<b>0.0078</b>	<b>5.26 [1.81; 16.6]</b>	<b>0.0030</b>

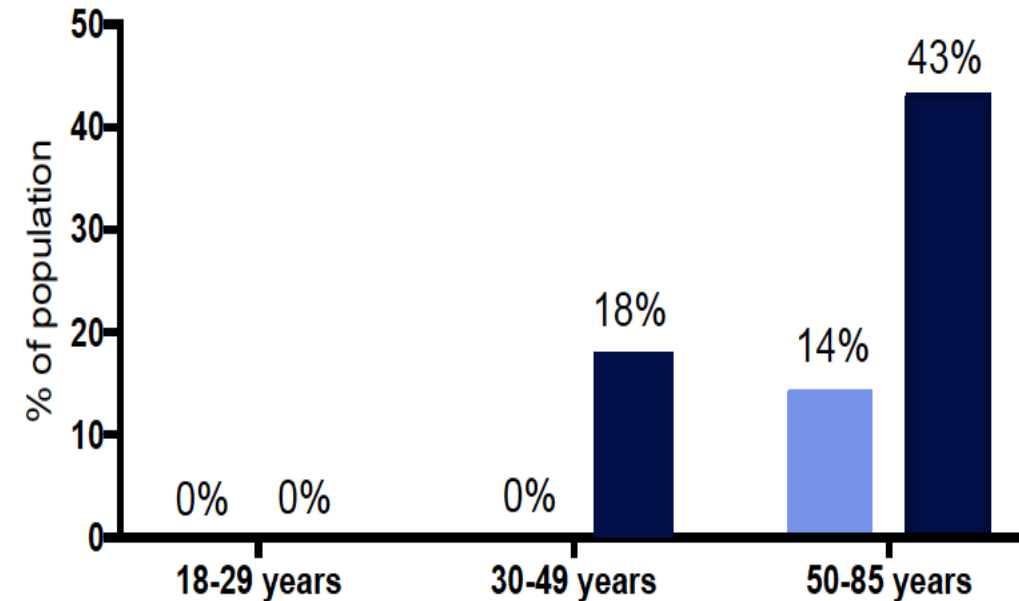
# Prevalence of liver fibrosis

Significant liver fibrosis in 15 patients, 14% of the study population



N (/all study population)

Age Group	Fibrosis 8-11.9 kPa (N)	Fibrosis ≥ 12 kPa (N)
18-29 years	2/53	0/53
30-49 years	0/32	3/32
50-85 years	5/19	5/19



N (/patients with APOB pathogenic variant)

Age Group	Fibrosis 8-11.9 kPa (N)	Fibrosis ≥ 12 kPa (N)
18-29 years	0/12	0/12
30-49 years	0/11	2/11
50-85 years	1/7	3/7

# And in the general population ?



# HYPOBETA.fr study: goal

Assessing the risk of liver disease-related events in patients with HBL

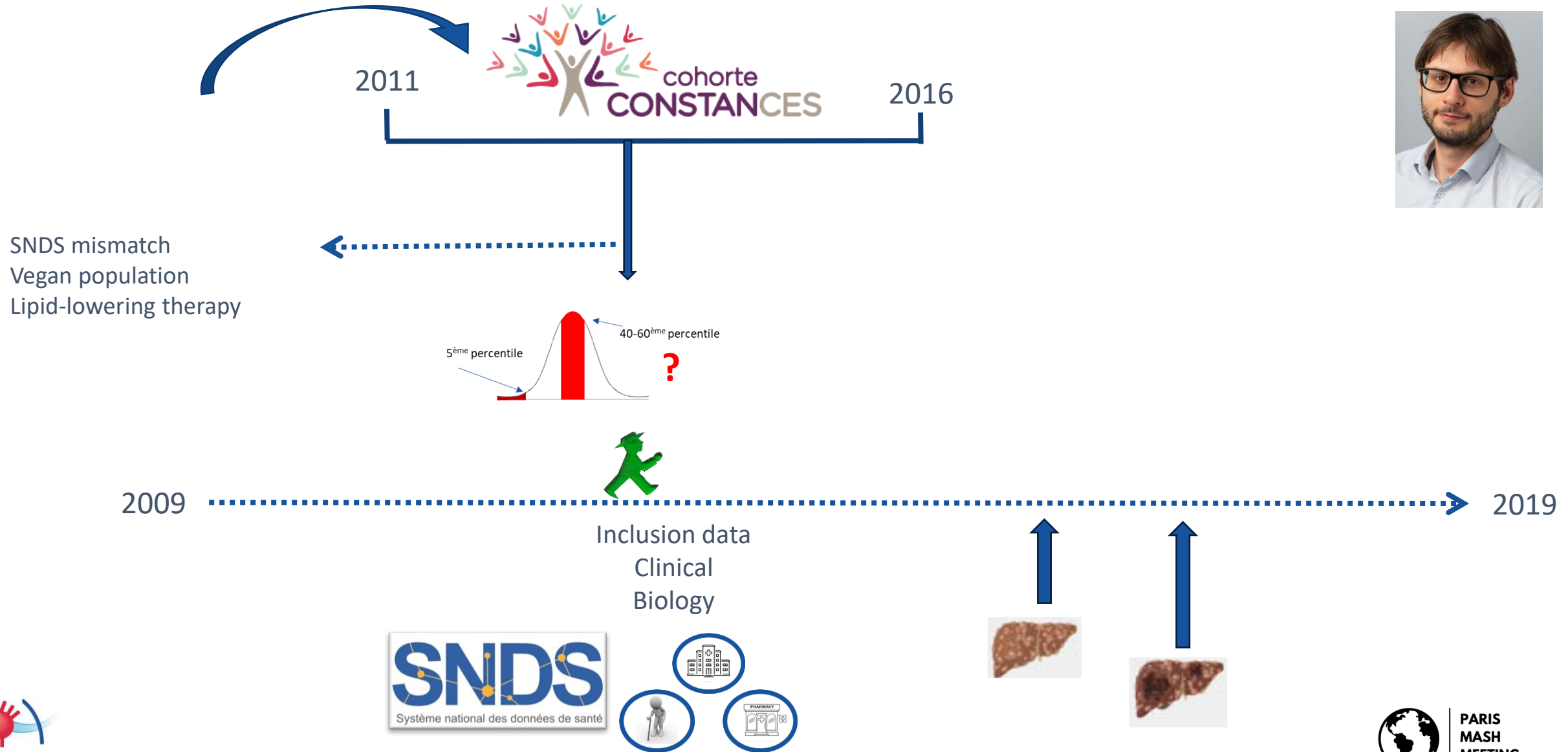
In particular: cirrhosis and primary liver cancer

## ➤ Challenges and needs

- ✓ Weak expected signals
- ✓ “General population”
- ✓ Large sample size
- ✓ Long follow-up



# METHODS





# Assessing the liver safety of primary HBL



N = 169,093

N = 138,591

LDL-C < 5<sup>th</sup>  
71 mg/dL  
45 yo  
N=6,939

**HBL**

40 < LDL-C < 60<sup>th</sup>  
128 mg/dL  
45 yo  
N=27,714

**CTRL**

Follow-up: 5,0 ± 1,9 yr

## In General Population

Exclusion of patients with LLTs  
or secondary causes of HBL

Selection on LDL-C categorized  
by sex and 5-year age ranges

Identification of liver complications:  
MASLD, cirrhosis complication,  
primary liver cancer



**biobank**<sup>uk</sup>

N 502,413

N = 378,856

LDL-C < 5<sup>th</sup>  
86 mg/dL  
56 yo  
N=18,914

**HBL**

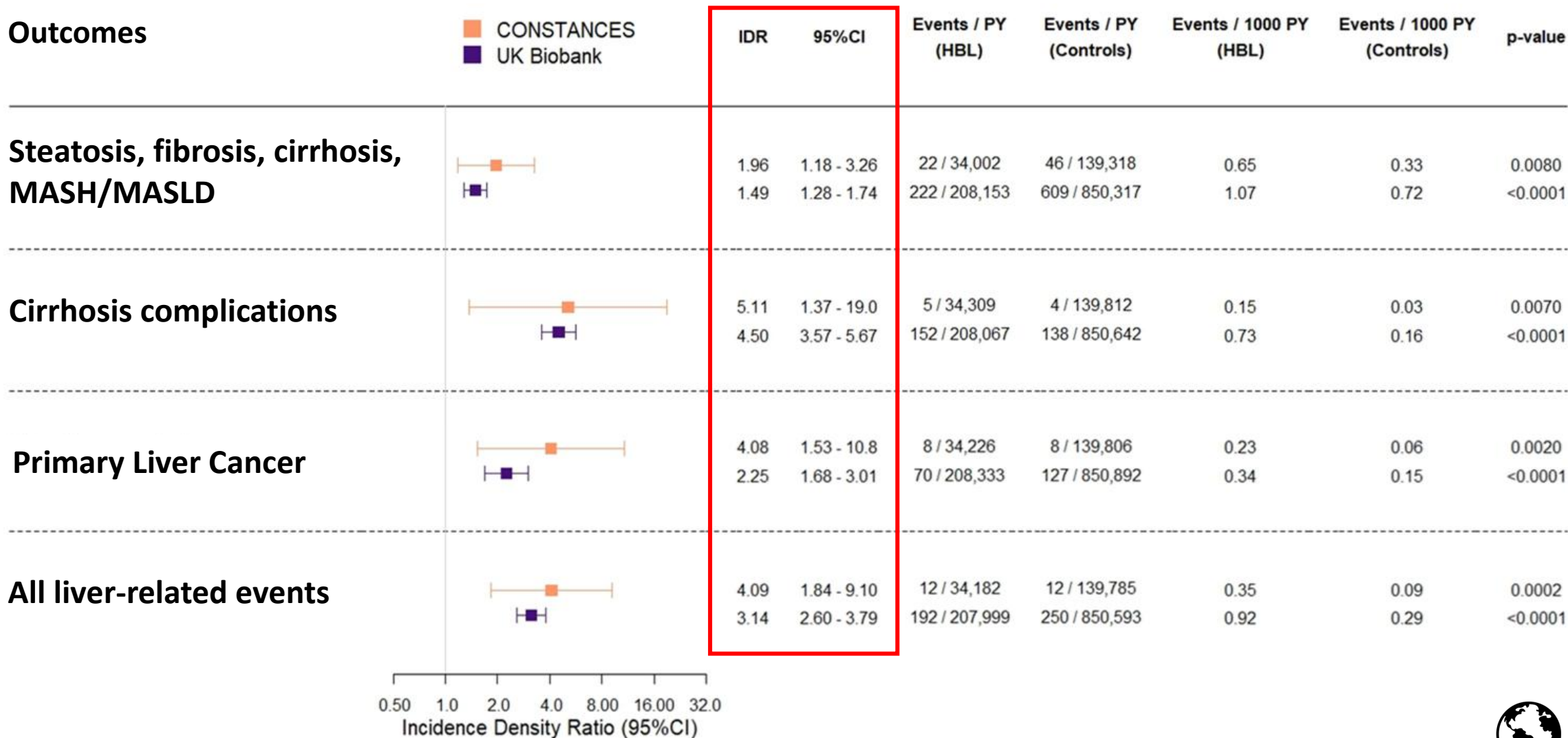
40 < LDL-C < 60<sup>th</sup>  
142 mg/dL  
56 yo  
N=75,752

**CTRL**

Follow-up: 11,5 ± 1 yr



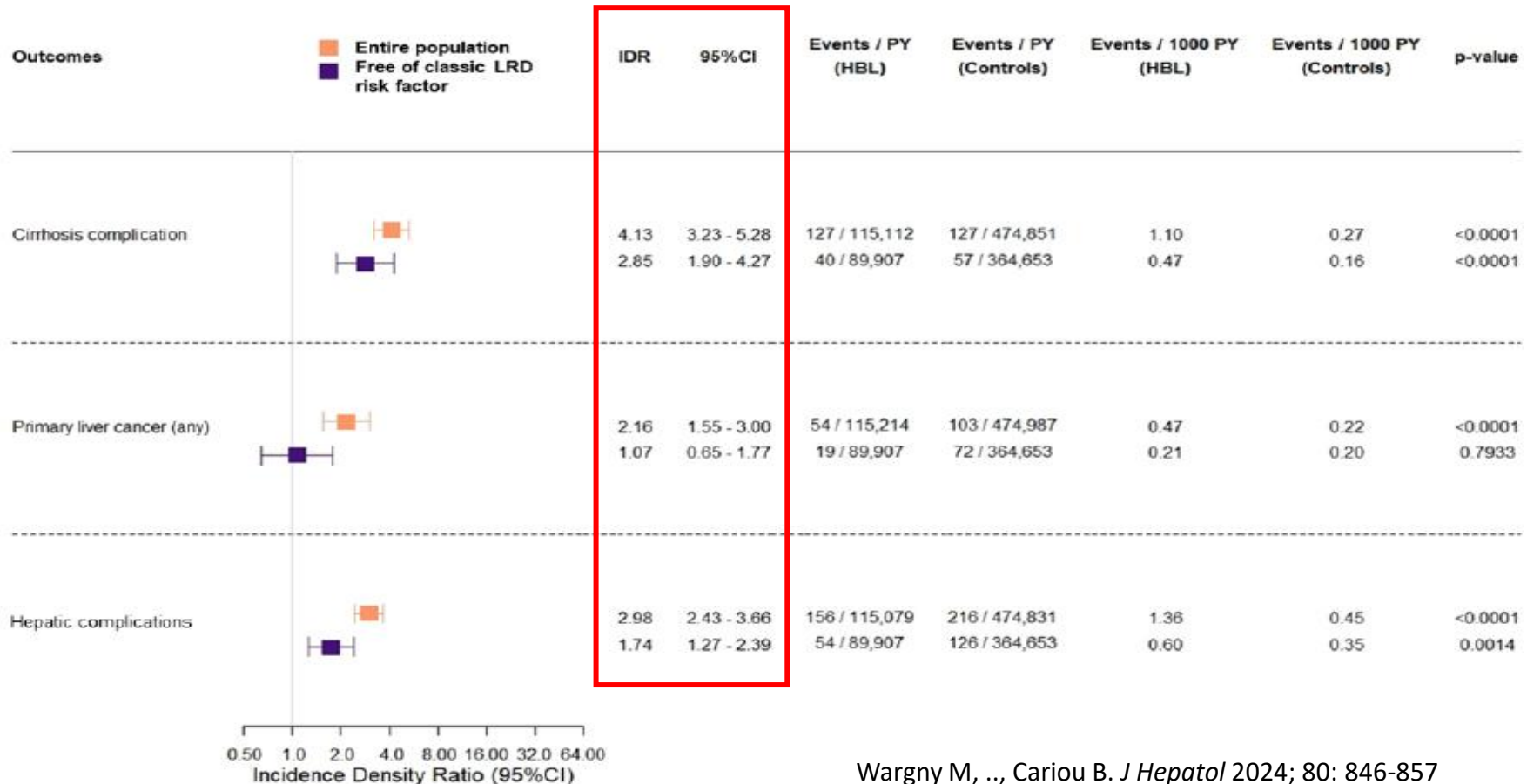
# RESULTS: liver-related events



# RESULTS: sensitivity analyses

## Five-year landmark analysis

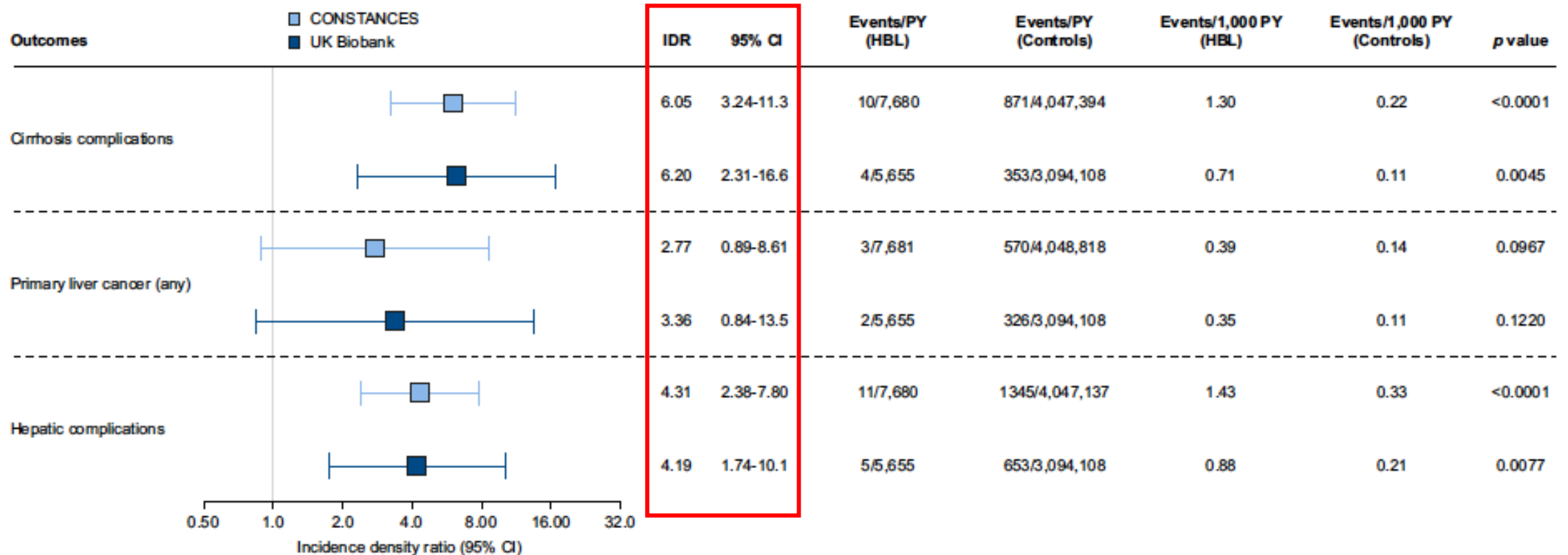
in **entire population** and restricted to **population free of classic liver-disease risk factors**  
(obesity, diabetes, alcohol consumption, viral hepatitis)



biobank<sup>uk</sup>

# RESULTS: sensitivity analyses

Analysis in **individuals with truncating variant in *APOB***  
in entire population and restricted to population free of classic liver-disease risk factors



# TAKE HOME MESSAGES

- Primary HBL (FHBL) is underdiagnosed in adulthood
- The phenotypic consequences depend on the mechanism of action of FHBL: SD vs EC
- Both FHBL SD and EC are associated with reduced ASCVD risk
- FHBL SD are associated with an increased risk of liver diseases, especially FHBL SD2 (*APOB* truncating variants)
- **A close monitoring of liver function is required in FHBL in adulthood**



# ACKNOWLEDGMENTS



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+




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