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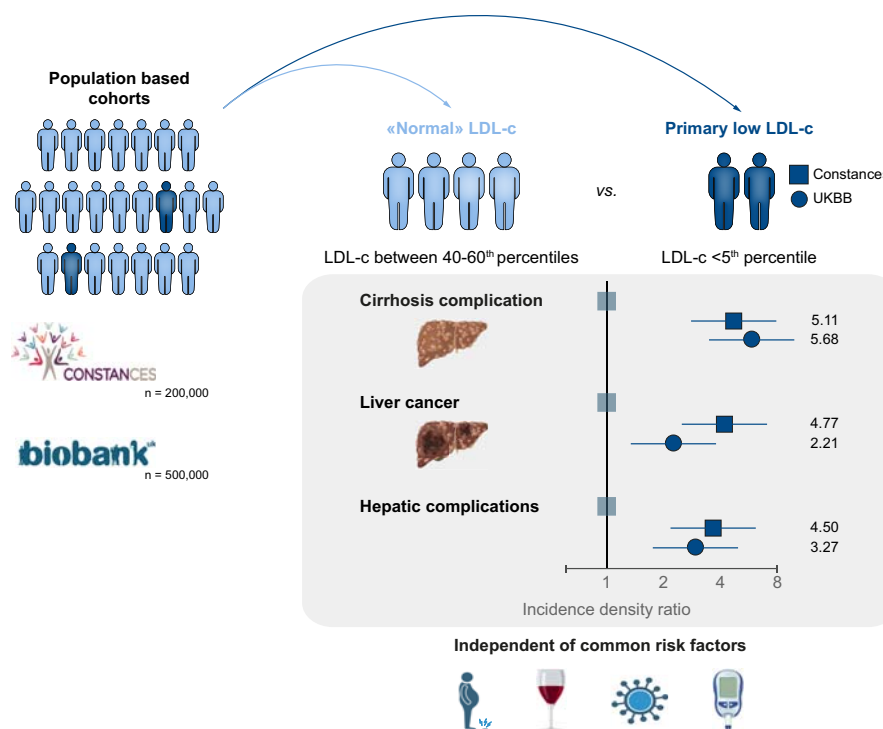
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Graphical abstract



Highlights

- Hypobetalipoproteinemia is defined by permanent, inherited low LDL-cholesterol levels.
- In two large population cohorts, hypobetalipoproteinemia increased the risk of cirrhosis complications and/or liver cancer.
- This risk was observed independently of classical risk factors for liver disease (obesity, alcohol, diabetes, viral hepatitis).
- Hypobetalipoproteinemia is a risk factor for liver disease complications that requires appropriate monitoring.

Impact and implications

Hypobetalipoproteinemia (HBL) is a lipid disorder characterized by permanent, inherited low levels (below the 5th percentile) of low-density lipoprotein-cholesterol. While HBL is associated with a lower risk of cardiovascular events, some studies suggest that it may be associated with a potential risk of hepatic steatosis and hepatic complications. Here, we studied the association between HBL and hepatic complications (defined as cirrhosis complications and/or primary liver cancer) in two populations of several hundred thousand people, both in France (CONSTANCES cohort) and the United Kingdom (UKBB). The results show that HBL is associated with a significant and independent excess risk of hepatic complications, including primary liver cancer. Thus, in people with HBL, the value of regular liver monitoring must be studied.

Primary hypocholesterolemia is associated with an increased risk of hepatic complications in the general population

Matthieu Wargny^{1,2}, Thomas Goronflot², Antoine Rimbert¹, Jérôme Boursier³, Sofiane Kab⁴, Joseph Henny⁴, Antoine Lainé¹, Christophe Leux⁵, Sarra Smati¹, Samy Hadjadj¹, Cédric Le May¹, Marcel Goldberg⁴, Marie Zins⁴, Bertrand Cariou^{1,*}

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Background & Aims: Beyond cardiovascular disease protection, the health consequences of very low concentrations of low-density lipoprotein-cholesterol (LDL-C) remain a matter of debate. In primary hypobetalipoproteinemia (HBL), liver steatosis and cirrhosis have occasionally been reported. Here, we aimed to investigate the association between HBL and the risk of hepatic complications (cirrhosis complications and/or primary liver cancer) in the general population.

Methods: A cohort study was conducted in the French population-based cohort CONSTANCES. Participants with primary HBL (LDL-C <5th percentile for age and sex, [HBL]) were compared with those with normal LDL-C concentrations (40th-60th percentile, [Control]). Participants on lipid-lowering therapies were excluded. For hepatic complications, follow-up events were compared by calculating the incidence density ratio (IDR). The same analyses were replicated in the UK Biobank (UKBB) cohort.

Results: In the CONSTANCES and UKBB cohorts, 34,653 and 94,666 patients were analyzed, with median ages of 45 and 56 years, mean LDL-C concentrations (HBL vs. control) of 71 vs. 128 mg/dl and 86 vs. 142 mg/dl, and mean follow-up durations of 5.0 and 11.5 years, respectively. The HBL group presented a higher incidence of hepatic complications than the control group: 0.32/ vs. 0.07/1,000 person-years (IDR = 4.50, 95% CI 1.91-10.6) in CONSTANCES, and 0.69/ vs. 0.21/1,000 person-years (IDR = 3.27, 95% CI 2.63-4.06) in the UKBB. This risk proved to be independent of classic risk factors for liver disease (obesity, alcohol consumption, diabetes, viral hepatitis), including in a 5-year landmark analysis excluding early events. Sensitivity analyses based on apolipoprotein-B levels (instead of LDL-C levels) or genetically defined HBL showed similar results.

Conclusions: HBL is associated with a markedly increased risk of hepatic complications. HBL must be considered as a substantial independent risk factor for liver diseases which justifies specific prevention and screening.

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Introduction

Primary hypobetalipoproteinemia (HBL) is a lipid disorder characterized by inherently and permanently low levels (below the 5th percentile) of low-density lipoprotein-cholesterol (LDL-C) and apolipoprotein B (apoB).^{1,2} Primary HBL diagnosis requires elimination of all secondary causes associated with low LDL-C such as hyperthyroidism, severe malnutrition including strict vegan diet, critical illness, active cancers and lipid-lowering therapies.³ Primary monogenic HBL are referred to as familial hypobetalipoproteinemia (FHBL) disorders and are intricately related to lipoprotein metabolism. A simplified nomenclature has recently been proposed based on mechanisms that explain low plasma lipids.^{4,5} Class I FHBL disorders are due to defects in lipoprotein secretion (FHBL-SD) whereas Class II FHBL disorders relate to enhanced lipoprotein catabolism (FHBL-EC).

Most frequently, monogenic FHBL in adults results from mono-allelic *APOB* protein-truncating variants (*i.e.* FHBL-SD2).^{4,5} The liver is a key organ in the metabolism of lipoproteins since it regulates the balance between the production of very low-density lipoprotein (VLDL) and the catabolism of LDL. ApoB is the main protein component of VLDL and is required for its assembly and secretion by the liver. As such, the impairment of hepatic VLDL secretion in FHBL-SD2 could contribute to fat accumulation in the liver and consequently lead to potentially harmful hepatic consequences.⁶ This would appear to mean an increased risk of steatotic liver disease and cryptogenic cirrhosis in individuals with FHBL, especially in those with short-truncated apoB isoforms.⁷⁻¹⁰ We recently showed that the risk of liver steatosis and liver injury was more pronounced in patients with a monogenic origin to their HBL, compared with those with a polygenic origin.¹¹ Apart from

Keywords: Hypobetalipoproteinemia; low-density lipoprotein; cirrhosis; liver cancer; population-based cohorts; administrative health records.

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these small case series of genetic FHBL disorders, we lack large-scale epidemiological data on the relationship between primary low LDL-C levels and liver disease. This question is of major clinical interest because primary HBL is highly prevalent² and often undiagnosed in adulthood and could therefore have potentially deleterious consequences for the liver in many people.

The aim of the present study was to determine the potential deleterious effects of primary HBL, defined by spontaneously low LDL-C (<5th percentile for age and sex), on liver health in the general population. For this purpose, we first used the nationwide French CONSTANCES cohort, then the UK Biobank (UKBB) as a replication cohort, to assess the association between primary HBL and hepatic complications, defined as cirrhosis complications and/or primary liver cancer.

Patients and methods

The reporting of this work followed the RECORD recommendations ([Supplementary data](#) – RECORD checklist).

Population-based cohort description

CONSTANCES ("*CONSultANTS des Centres d'Examens de Santé*" or Consultants of Health Screening Center (HSC)) is a population-based general-purpose cohort designed as a randomly selected sample of French adults aged 18–73 years on study inception. The design of the cohort has been previously detailed elsewhere.^{15,16} Briefly, CONSTANCES includes more than 219,000 volunteers throughout metropolitan France from February 2012 to December 2019. Participants were covered by the national general health insurance scheme or partner health insurance companies (~85% of the French population) using a random sampling scheme stratified by place of residence, age, sex, occupation and socioeconomic status. Eligible individuals were invited by mail to participate in the study. On inclusion, the selected participants were invited to complete questionnaires and to visit an HSC for a comprehensive health examination and undergo a fasting blood sampling. Follow-up included a yearly self-administered questionnaire and a periodic visit to an HSC. Complementary follow-up data were collected from the French National Healthcare Data System (SNDS).¹⁴ The CONSTANCES cohort obtained authorization from the French National Commission for Information Technology and Liberties (CNIL) and the institutional review board of the National Institute for Medical Research (Inserm). All participants gave written consent for the use of their data for scientific research. The HYPOBETA.fr study project was approved by the CONSTANCES scientific committee on 8 January 2021.

UKBB study population

The UKBB study, previously described in detail,¹⁵ is a population-based prospective cohort conducted in the United Kingdom in which >500,000 individuals aged 40–69 years were included from 2006 to 2010. The study was approved by the Northwest Multi-Centre Research Ethics Committee for the United Kingdom, from the National Information Governance Board for Health and Social Care for England and Wales, and by the Community Health Index Advisory Group for Scotland.^{16,17} Eligible participants were invited by email to visit an

assessment center where they gave their consent to join the study. Participants then completed a touchscreen questionnaire before undergoing a series of measurements and finally provided blood and urine samples. Because eligible participants were initially identified using the National Health Service (NHS) registry, all hospitalization data of the included participants were available for follow-up. The present research has been conducted using the UKBB resource under the application number 49823. The records of 77 individuals (last update February 22, 2022) who withdrew from the UKBB were removed from the analyses.

Inclusion and exclusion criteria

All participants in the CONSTANCES cohort included before December 31, 2019 were screened for the HYPOBETA.fr study. The following exclusion criteria were applied: no baseline medical data, matching failure with the SNDS database, inconsistency with SNDS data regarding vital status on inclusion, participant declared as vegan according to baseline self-questionnaire on food habits (never/almost never consumption of meat, poultry and fish) or missing data, lipid-lowering therapy (LLT) declared at baseline, LDL-C not calculable according to the Friedewald formula (missing total cholesterol, high-density lipoprotein-cholesterol [HDL-C] or triglycerides [TG], and/or TG >350 mg/dl). Participants with ≥1 delivery of LLT identified in the SNDS in the past 2 years before baseline were also excluded.

Finally, for the main analysis, only participants with LDL-C <5th (HBL) or between the 40th and 60th percentile (controls) according to sex and age (5-year ranges) were conserved.

The same eligibility criteria were adapted to the available data in the UKBB.

Data collection and baseline parameters

Two sources of data were used: (i) baseline clinical and biological data collected from the CONSTANCES or UKBB cohorts; and (ii) data on healthcare consumption: French SNDS for CONSTANCES, drug delivery, declaration of long-term chronic diseases (eligible for full reimbursement on a list defined by decree after expertise from the French National Authority for Health) and diagnoses associated with hospitalization coded using ICD-10th, from January 1, 2009 to December 31, 2019; British NHS for the UKBB, using ICD-9th or -10th, from December 12, 1980 to February 2, 2021. At baseline in both cohorts, the participants were interviewed and examined by a physician who measured weight, height and waist size and completed the medical questionnaire. The participant also completed different self-questionnaires (including lifestyle with the AUDIT [Alcohol Use Disorders Identification Test] score in CONSTANCES and a food questionnaire).¹⁸ A fasting blood sample was drawn with routine biological analyses including lipid profile (total cholesterol, TG, HDL-C, and LDL-C calculated using the Friedewald formula), fasting plasma glucose, hemoglobin, white cell and platelet counts and alanine aminotransferase (ALT), and, in the UKBB only, the fibrosis-4 index (FIB-4) with 1.30 and 2.67 thresholds to determinate low, intermediate and high risk of advanced liver fibrosis, respectively.¹⁹ A complete description of data collection has been provided elsewhere for CONSTANCES^{12,13} and the UKBB.¹⁵

Outcomes

Two types of outcomes of interest were assessed: hepatic diseases at baseline and hepatic complications during follow-up. For baseline, we considered data both from the CONSTANCES cohort and the SNDS (or the UKBB and the British NHS, respectively). This could involve two different sources: (1) diseases declared in the baseline questionnaires of CONSTANCES or (2) diseases identified as a long-term disease in the SNDS (ICD-10th classification: for example: “K74”, liver fibrosis or cirrhosis) as the main diagnosis associated with a hospital stay (ICD-10th also), or the delivery of a drug specific for a disease (ATC code, for example, any starting with “A10” for drugs used in diabetes). Details of the codes used to define each condition are provided in the [supplementary information](#).

For participant follow-up events, the same approach was applied using only SNDS data. For a specific condition, patients were excluded from the analysis if the condition was already known at baseline.

Statistical analyses

First, we proposed the comparison of participant history at baseline with the two groups defined according to their baseline LDL-C level below 5th percentile (age, sex) [HBL] or between the 40th-60th percentiles [control]. Categorical data are presented with population size (%) and compared using a prevalence ratio (95% CI) for hepatic diseases (steatosis, fibrosis, and cirrhosis) and hepatic complications (cirrhosis complications and primary liver cancer). Quantitative data are presented as mean (\pm SD) or median [25th-75th percentile] according to their distribution assessed from the histogram. The groups were compared using the mean difference with the 95% CI of the estimation of the mean.

Secondly, we proposed a comparison of hepatic complications during follow-up. Categorical data are presented with the number of events and the total of patient-year (PY) follow-up, then converted to the number of events per 1,000 PY. These incidence densities were compared using an incidence density ratio (IDR), with the associated 95% CI. In the UKBB, this approach was completed by a time-to-event analysis using Cox models based on proportional hazard hypothesis (tested using Schoenfeld residuals), comparing HBL vs. control group for the risk of liver cancer. The adjustment parameters were chosen according to background knowledge: age, sex, diabetes, known alcohol consumption and history of viral hepatitis B or C. Multivariable models were not applied in the CONSTANCES population owing to the small number of events.

Four sensitivity analyses were performed, replicating the study of the main outcomes (hepatic complications and their composite elements) in other settings: (i) replication in the population free of classic risk factors for liver disease at baseline, excluding individuals with obesity, excessive alcohol consumption, diabetes mellitus, and viral hepatitis; (ii) landmark analyses excluding patients with hepatic complications discovered in the 5 years following baseline; (iii) replication by replacing LDL-C level stratification (<5th percentile) with baseline apoB level stratification (<5th percentile also); (iv) replication by replacing LDL-C level stratification (<5th percentile) with genetically confirmed FHBL (*i.e.* pathogenic or likely pathogenic *APOB* truncating variants according to the American

College of Medical Genetics and Genomics classification). Due to data limitation, the last three analyses were performed only in the UKBB population.

All analyses of CONSTANCES were performed on the “Secured Remote Access Center” (CASD, Malakoff, France) servers, using R software²⁰. A two-tailed *p* value <0.05 was deemed statistically significant. All analyses of the UKBB were performed using R studio server interface provided by the Bioinformatics Core Facility of Nantes: BiRD. Access to data was limited in time on an annual renewal basis. No imputation was performed and no correction was applied for multiple testing.

Results

Characteristics of the study populations in the CONSTANCES cohort

At the time of analysis, data were available for 205,051 participants in the CONSTANCES cohort including 169,093 with complete baseline data and available matching with the SNDS database for follow-up. After exclusion of patients under LLT and those on a vegan diet, 138,591 patients were analyzable for this study (detailed flowchart in [Fig. 1](#)).

In a first approach, we established LDL-C reference values in order to select our study populations and define LDL-C percentiles for sex and age (by 5-year ranges) (see [Table S1](#)). As illustrated in [Fig. S1](#), LDL-C increases with age, especially in women from the age of 50 onwards, which is probably linked to the onset of menopause.

[Table 1](#) shows the characteristics of individuals with HBL compared with the control population. Median age of the population was 45 years and 54.5% were women. Mean LDL-C concentration was 71 (\pm 15) mg/dl in the HBL group compared to 128 (\pm 16) mg/dl in the control group. Plasma TG concentration was lower (77 (\pm 45) vs. 92 (\pm 44) mg/dl) while HDL-C was higher (63 (\pm 19) vs. 59 (\pm 14) mg/dl) in the HBL group compared to the control group. Furthermore, the HBL group had lower BMI, waist circumference and blood pressure but more frequent diabetes than those in the control group. Regarding alcohol consumption, the mean AUDIT score was within the normal range, although it was higher in the HBL group (mean difference between groups = 0.45, 95% CI 0.35-0.56).

Primary hypobetalipoproteinemia and baseline hepatic diseases in CONSTANCES cohort

When looking at the liver enzymes available in the CONSTANCES cohort, there was no significant difference in ALT concentrations between the HBL and control groups ([Table 1](#)). On the other hand, the mean gamma-glutamyltransferase value was modestly but significantly lower in the HBL group, with a slight difference between the two groups when looking at the proportion of individuals with gamma-glutamyltransferase values above normal (7.7% vs. 8.8% in HBL vs. control group, respectively).

At baseline, it is worth noting that individuals with HBL presented more frequently with a known liver disease than those in the control group ([Table 2](#)). For example, individuals with HBL had a two-fold higher prevalence of hepatic disease – as defined by the ICD-10 classification as the combination of

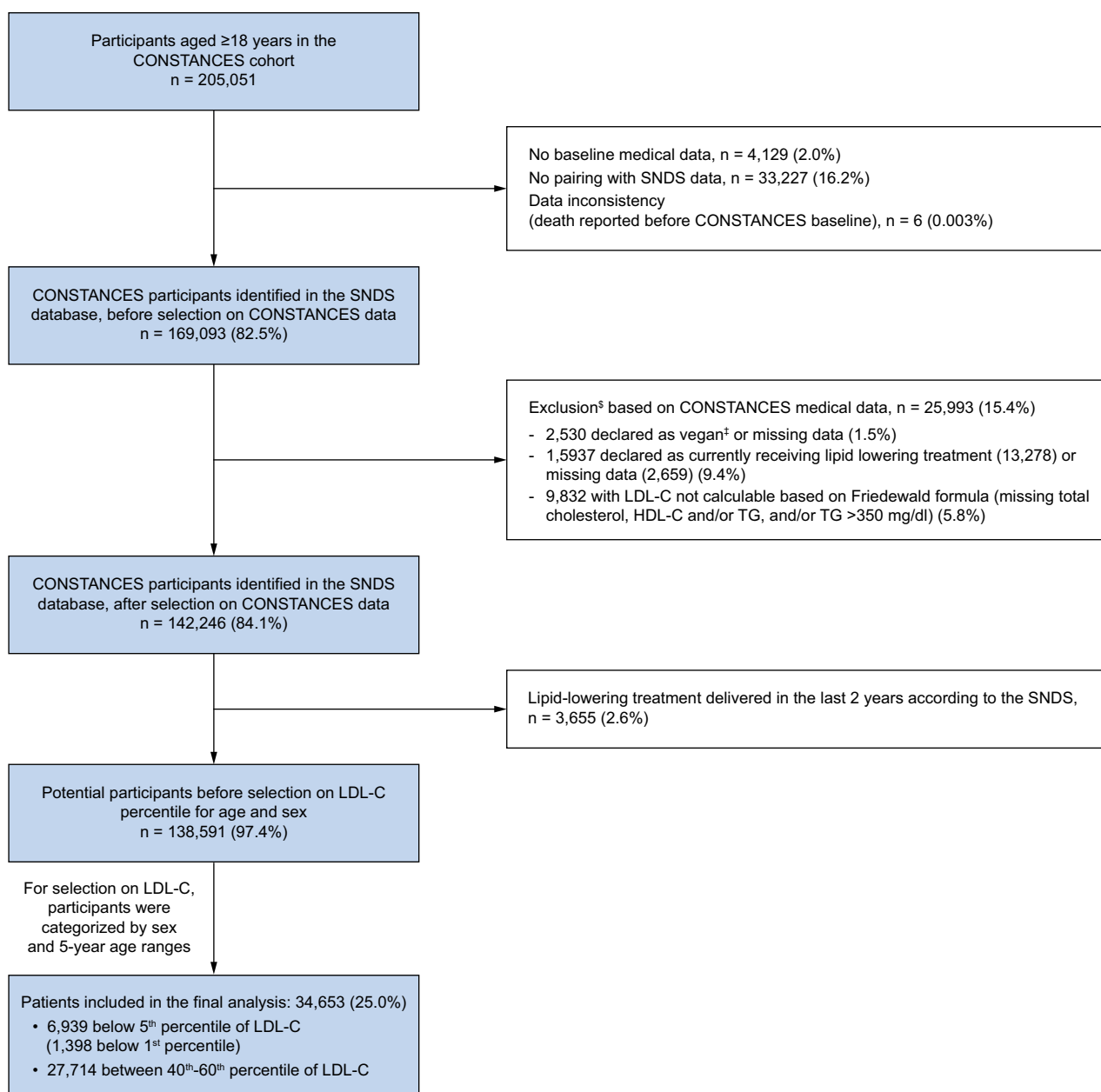


Fig. 1. Flowchart of the HYPOBETA.fr population. [§]The participants could be excluded for >1 of the detailed reasons. Therefore, the sum might be higher than the total number of excluded patients. [‡]Defined as the declaration of never/almost never consumption of meat, poultry and fish, including participants who partially answered for these three food items. HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SNDS, French National Healthcare System; TG, triglycerides.

liver steatosis, fibrosis, uncomplicated cirrhosis, metabolic dysfunction-associated steatotic liver disease (MASLD) and/or metabolic dysfunction-associated steatohepatitis (MASH) – than the controls (0.59% vs. 0.29%, $p = 0.0002$). When focusing on hepatic complications defined by cirrhosis complications and/or primary liver cancer, the effect was even more marked with a prevalence ratio of 7.32 in the HBL group compared with the control group (0.16% vs. 0.02%, $p < 0.0001$). In addition, there was a more frequent history of viral hepatitis (hepatitis B and/or C virus infection) in the HBL group (2.16% vs. 1.08%, $p < 0.0001$).

Primary hypobetalipoproteinemia and incidence of hepatic complications during follow-up in the CONSTANCES cohort

As a next step, we compared the incidence of liver-related events in the two study populations during a mean follow-up of 5.0 (± 1.9) years. As shown in Fig. 2, the HBL group was characterized by a more frequent occurrence of liver steatosis and/or fibrosis (IDR 1.96, 95% CI 1.18-3.26) compared to the control group. Concerning the incidence of hepatic complications, the IDR rose to as high as 4.09 (95% CI 1.84-9.10).

Association of hypocholesterolemia with hepatic complications

Table 1. Characteristics of the HYPOBETA.fr population (n = 34,653), according to baseline LDL-C levels (<5th vs. 40-60th percentiles).

Characteristics	Data availability	LDL-C 40-60 th percentile, n = 27,714	LDL-C <5 th percentile, n = 6,939	Difference*	p value
Age	100%	45.0 [35.5; 56.5]	45.0 [35.5; 56.5]	-0.1 (-0.5 to 0.2)	NR
Women	100%	15,109 (54.5%)	3,782 (54.5%)	1.00 (0.98-1.02)	NR
Clinical examination					
BMI (kg/m ²)	98.8%	24.7 (±4.3)	23.4 (±4.2)	-1.2 (-1.3 to -1.1)	<0.0001
BMI (categories)	98.8%				<0.0001
<18.5 kg/m ²		711 (2.6%)	393 (5.8%)		
18.5-24.9 kg/m ²		15,893 (58.0%)	4,561 (66.9%)		
25-29.9 kg/m ²		7,976 (29.1%)	1,380 (20.2%)		
≥30 kg/m ²		2,823 (10.3%)	484 (7.1%)		
Waist circ. (cm)	99.6%	83.8 (±12.2)	80.7 (±12.1)	-3.0 (-3.4 to -2.7)	<0.0001
Waist/Hip	99.5%	0.85 (±0.09)	0.83 (±0.09)	-0.01 (-0.02 to -0.01)	<0.0001
Diabetes	100%	453 (1.63%)	223 (3.21%)	1.97 (1.68-2.30)	<0.0001
Arterial hypertension	97.6%	9,178 (33.9%)	1,957 (29.2%)	0.86 (0.83-0.90)	<0.0001
Systolic BP (mmHg)	97.5%	128.1 (±15.7)	126.0 (±16.1)	-2.2 (-2.6 to -1.7)	<0.0001
Diastolic BP (mmHg)	97.5%	76.2 (±9.5)	74.8 (±9.5)	-1.4 (-1.7 to -1.2)	<0.0001
Smoking habits	95.9%				0.0009
0-Never		13,093 (49.2%)	3,163 (47.8%)		
1-Former		4,742 (17.8%)	1,309 (19.8%)		
2-Current		8,781 (33.0%)	2,140 (32.4%)		
Alcohol Intake	93.9%				0.060
≥1/week		16,187 (62.1%)	4,123 (63.6%)		
2-3/month		5,354 (20.5%)	1,261 (19.5%)		
1/month or less		3,464 (13.3%)	817 (12.6%)		
Never		1,062 (4.1%)	279 (4.3%)		
Alcohol consumption ≥5 units daily (women) or ≥6 (men)	89.5%	177 (0.71%)	81 (1.32%)	1.85 (1.42-2.40)	<0.0001
AUDIT score (quantities)	89.8%	5 [3; 7]	5 [4; 7]	0.45 (0.35 to 0.56)	<0.0001
AUDIT score (thresholds)	89.8%				<0.0001
<8		20,034 (80.4%)	4,736 (76.7%)		
8 to 12		3,777 (15.1%)	1,012 (16.4%)		
≥13		1,120 (4.5%)	426 (6.9%)		
Biology					
Total cholesterol (mg/dl)	100%	205.2 (±23.6)	149.6 (±24.4)	-55.6 (-56.3 to -55.0)	NR
HDL-C (mg/dl)	100%	59.2 (±14.3)	63.3 (±18.8)	4.1 (3.6 to 4.6)	<0.0001
Triglycerides (mg/dl)	100%	92.4 (±44.4)	76.8 (±45.3)	-15.6 (-16.7 to -14.4)	<0.0001
LDL-C (mg/dl)	100%	127.6 (±16.3)	71.0 (±15.0)	-56.6 (-57.0 to -56.2)	NR
FPG (mg/dl)	99.9%	94 (±12)	94 (±16)	0 (-1 to 0)	0.060
Plasma creatinine (μmol/L)	100%	73.8 (±13.5)	73.2 (±15.4)	-0.6 (-1.0 to -0.2)	0.005
eGFR (MDRD, ml/min)	100%	86.7 [77.4; 97.2]	87.8 [78.0; 98.7]	1.1 (0.7 to 1.5)	<0.0001
Hemoglobin (g/dl)	98.5%	14.2 [13.4; 15.1]	14.0 [13.1; 14.9]	-0.3 (-0.3 to -0.2)	<0.0001
White cell count (10 ⁶ /L)	99.8%	6,102 (±2,469)	5,997 (±1,866)	-105 (-157 to -52)	0.0001
Platelets (10 ⁹ /L)	99.7%	245 (±54)	235 (±58)	-10 (-11 to -8)	<0.0001
GGT (IU/L)	99.9%	20.0 [14.0; 30.0]	18.0 [13.0; 27.0]	-0.9 (-1.9 to 0.0)	<0.0001
GGT (>ULN)	99.9%	2,441 (8.8%)	536 (7.7%)	0.88 (0.80-0.96)	0.005
ALT (IU/L)	99.9%	21.0 [16.0; 29.0]	20.0 [15.0; 27.0]	-0.3 (-1.7 to 1.0)	<0.0001
ALT (>ULN)	99.9%	1,399 (5.1%)	343 (4.9%)	0.98 (0.87-1.10)	0.75

ALT, alanine aminotransferase; AUDIT, Alcohol Use Disorders Identification Test; BP, blood pressure; eGFR, estimated glomerular filtration; FPG, fasting plasma glucose; GGT, gamma-glutamyltransferase; NR, not relevant. ULN, upper limit normal.

Categorical data are expressed as n (%). Quantitative data are expressed as mean (±SD) or median [25th; 75th percentiles], according to the distribution.

*The differences are expressed as prevalence ratio (95% CI) for categorical parameters, and mean difference (95% CI) for all quantitative parameters. p values are calculated using Fisher's exact test or Student's t test for unpaired series.

Replication of the results in the UK Biobank cohort

In order to verify our results obtained in CONSTANCES, we replicated the analyses in the UKBB cohort. We applied the same strategy to select the two study populations: primary HBL (LDL-C <5th percentile) and control (LDL-C 40-60th percentile) groups (flowchart detailed in Fig. S2). We identified 18,914 individuals in the HBL group (mean LDL-C 86 (±12) mg/dl) and 75,752 individuals in the control group (mean LDL-C 142 (±9) mg/dl). The UKBB population was older than the CONSTANCES population, with a median age of 56 years, while 57.1% were women. The baseline characteristics of the HBL and control groups in the UKBB are described in Table 3. The observed differences in the

metabolic phenotype of the HBL individuals were similar to those observed in CONSTANCES with lower BMI, lower blood pressure and greater prevalence of diabetes than in the control group. Plasma ALT was more frequently above normal in the HBL group, with a higher FIB-4 suggesting more frequent liver fibrosis in HBL (median 1.29 [1.02-1.67]) than in the control group (1.21 [0.96-1.52], p <0.0001).

At baseline, there was a higher prevalence of hepatic disease (prevalence ratio 3.36, 95% CI 2.70-4.19), primary liver cancer (prevalence ratio: 6.01, 95% CI 2.14-16.9) and hepatic complications (prevalence ratio: 7.83, 95% CI 4.84-12.7) in individuals with HBL compared to the control group (Table 2).

Table 2. Hepatic diseases at baseline for the HYPOBETA.fr (n = 34,653) and UKBB (n = 94,966) populations, according to baseline LDL-c levels (<5th percentile vs. 40-60th).

Hepatic diseases at baseline	Data availability	40 th <LDL-C≤60 th percentiles n = 27,714	LDL-C <5 th percentile n = 6,939	Prevalence ratio (95% CI)	p value
HYPOBETA.fr					
Viral hepatitis B and/or C	100%	298/27,714 (1.08%)	150/6,939 (2.16%)	2.01 (1.66-2.44)	<0.0001
Steatosis, fibrosis, cirrhosis (without complication), MASLD or MASH	100%	79/27,714 (0.29%)	41/6,939 (0.59%)	2.07 (1.42-3.02)	0.0002
Cirrhosis complication	100%	3/27,714 (0.01%)	8/6,939 (0.12%)	10.6 (2.83-40.1)	<0.0001
Liver cancer (excl. hepatitis)	98.7%	3/27,416 (0.01%)	4/6,789 (0.06%)	5.38 (1.21-24.0)	0.045
Liver cancer (any)	100%	3/27,714 (0.01%)	4/6,939 (0.06%)	5.33 (1.19-23.7)	0.047
Hepatic complications: cirrhosis complications and/or liver cancer	100%	6/27,714 (0.02%)	11/6,939 (0.16%)	7.32 (2.71-19.7)	<0.0001
UKBB					
Viral hepatitis B and/or C+	100%	46 (0.06%)	55 (0.29%)	4.78 (3.23-7.07)	<0.0001
Steatosis, fibrosis, cirrhosis (without complication), MASLD or MASH	100%	172 (0.23%)	145 (0.77%)	3.36 (2.70-4.19)	<0.0001
Cirrhosis complication	100%	19 (0.03%)	41 (0.22%)	8.63 (5.01-14.9)	<0.0001
Liver cancer (excl. viral hepatitis)	99.9%	6 (0.01%)	8 (0.04%)	5.35 (1.86-15.4)	0.0017
Liver cancer (any)	100%	6 (0.01%)	9 (0.05%)	6.01 (2.14-16.9)	0.0004
Hepatic complications: cirrhosis complications and/or liver cancer	100%	25 (0.03%)	49 (0.26%)	7.83 (4.84-12.7)	<0.0001

MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; UKBB, UK Biobank. p values are calculated using Fisher's exact test.

In the longitudinal analyses, we confirmed in the UKBB cohort, with a longer average follow-up duration (11.5 ± 1.0 years) than in CONSTANCES, that the incidence of liver outcomes was more frequent in the HBL group than in the control group (Fig. 2). The incidence of liver steatosis and/or fibrosis was approximately 1.5-fold higher (IDR 1.49, 95% CI 1.28-1.74) while complications of cirrhosis were more than 4-fold more frequent (IDR 4.50, 95% CI 3.57-5.67) in the HBL than in the control group.

Altogether, the data obtained in the UKBB were very similar to those observed in CONSTANCES and suggested that primary HBL is associated with an increased risk of hepatic complications.

Association between primary HBL and hepatic complications independently of classic risk factors

The critical question when considering the causal association between HBL and hepatic complications is the possibility of reverse causality, given that severe liver disease has been described as being associated with lower LDL-C concentrations.²¹ In order to mitigate the hypothesis of such reverse causality, we first performed the same analyses in our study population after excluding the individuals with classic risk factors for liver disease (i.e. obesity, excessive alcohol consumption, diabetes, viral hepatitis) or a personal history of hepatic complications at baseline. As shown in Fig. 3, the

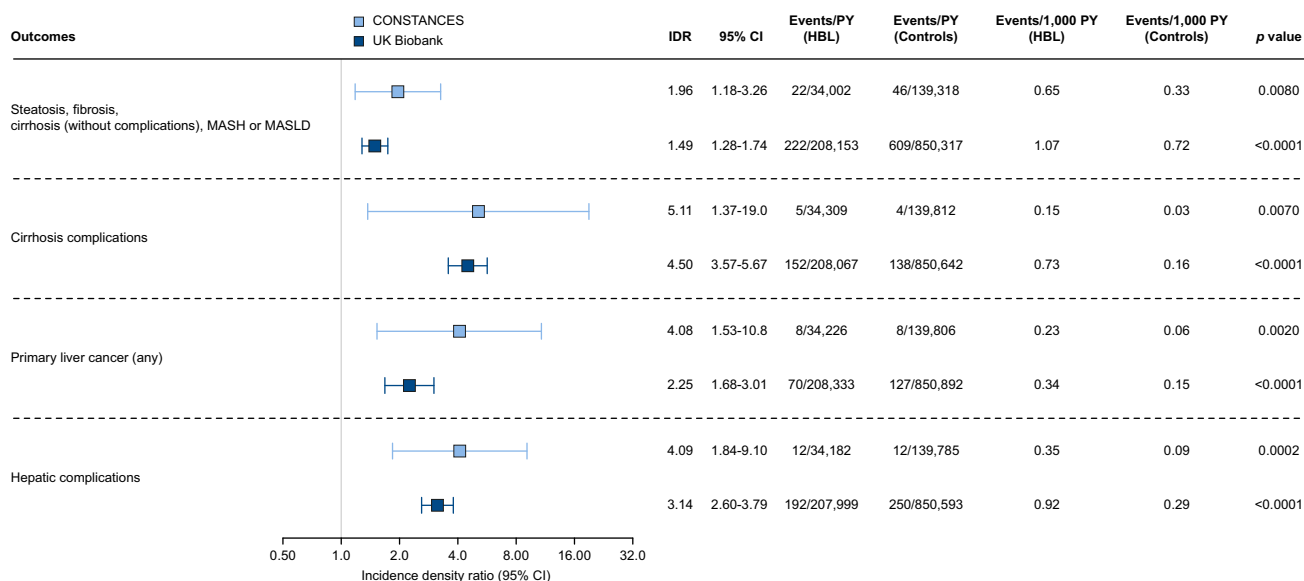


Fig. 2. Analysis of liver outcomes during follow-up in the HYPOBETA.fr and UKBB population, LDL-c <5th vs. 40th-60th percentiles. The results are expressed using incidence densities (events/total person-year) and the related between-group ratios. p values were calculated using Pearson's chi-squared test. Hepatic complications are defined as complications of cirrhosis and/or primary liver cancer. IDR, incidence density ratio; LDL-C, low-density lipoprotein-cholesterol; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; PY, person-year; UKBB, UK BioBank.

Association of hypocholesterolemia with hepatic complications

Table 3. Characteristics of the UKBB population (n = 94,666), according to baseline LDL-C levels (<5th vs. 40th-60th percentiles).

Characteristics	Data availability	40 th <LDL-c ≤60 th percentiles (n = 75,752)	LDL-c <5 th percentile (n = 18,914)	Difference*	p-value
Age	100%	56.0 [49.0; 62.0]	56.00 [49.0; 62.0]	-0.1 (-0.2-0.1)	NR
Women	100%	43,244 (57.1%)	10,794 (57.1%)	NR	NR
Clinical examination					
BMI (kg/m ²)	99.6%	27.1 (±4.61)	26.2 (±5.14)	-0.8 (-0.9 to -0.8)	<0.0001
BMI (categories)	99.6%				<0.0001
<18.5 kg/m ²		358 (0.5%)	281 (1.5%)		
18.5-24.9 kg/m ²		26,541 (35.1%)	8,662 (46.1%)		
25-29.9 kg/m ²		32,281 (42.7%)	6,310 (33.6%)		
≥30 kg/m ²		16,348 (21.6%)	3,536 (18.8%)		
Waist circ. (cm)	99.8%	88.9 (±13.0%)	86.8 (±14.5%)	-2.1 (-2.3 to -1.9)	<0.0001
Waist/Hip	99.8%	0.86 (±0.09)	0.85 (±0.09)	-0.01 (-0.01 to 0.01)	<0.0001
Diabetes	100%	953 (1.3%)	1,371 (7.2%)	5.44 (5.02-5.90)	<0.0001
Arterial hypertension	100%	46,001 (62.8%)	10,283 (58.0%)	0.93 (0.91-0.95)	<0.0001
Systolic BP (mmHg)	99.9%	138.9 (±19.5)	135.6 (±19.7)	-3.2 (-3.5 to -2.9)	<0.0001
Diastolic BP (mmHg)	99.9%	82.3 (±10.6)	79.6 (±10.8)	-2.7 (-2.9 to -2.5)	<0.0001
Smoking habits	100%				<0.0001
Never		43,624 (57.6%)	10,500 (55.6%)		
Former		24,799 (32.8%)	6,204 (32.9%)		
Current		7,279 (9.6%)	2,178 (11.5%)		
Prefer not to answer		50 (0.1%)	32 (0.2%)		
Alcohol Intake	100%				<0.0001
Daily or almost daily		15,125 (20.0%)	3,879 (20.5%)		
3-4 times a week		18,164 (24.0%)	4,151 (21.9%)		
1-2 times a week		20,094 (26.5%)	4,718 (24.9%)		
1-3 times a month		8,624 (11.4%)	2,033 (10.7%)		
Special occasion		8,206 (10.8%)	2,262 (12.0%)		
Never		5,463 (7.2%)	1,823 (9.6%)		
Prefer not to answer		76 (0.1%)	48 (0.3%)		
Weekly average consumption (alcohol unit)	100%	1,413 (1.9%)	414 (2.2%)	1.17 (1.05-1.30)	0.0002
Alcohol consumption >5 units per day	100%	8,580 (11.3%)	2,314 (12.2%)	1.07 (1.02-1.12)	<0.0001
Alcohol consumption >14 (women) or >21 (men) units per week	100%	1,413 (1.9%)	414 (2.2%)	1.17 (1.05-1.30)	0.0002
Biology					
Total cholesterol (mg/dl)	100%	226 (±18)	158 (±22)	-67.9 (-68.3 to -67.6)	NR
HDL-c (mg/dl)	91.4%	57 (±15)	57 (±17)	-0.4 (-0.7 to -0.1)	0.0013
Triglycerides (mg/dl)	99.9%	148 (±85)	111 (±76)	-37.7 (-38.9 to -36.4)	<0.0001
LDL-c (mg/dl)	100%	142 (±9)	86 (±12)	-56.0 (-56.2 to -55.8)	NR
FPG (mg/dl)	92.3%	90 (±15)	92 (±26)	2.7 (2 to 3.1)	<0.0001
Plasma creatinine (µmol/L)	99.9%	71.4 (±15.0)	72.0 (±21.5)	0.6 (0.3 to 0.9)	<0.0001
eGFR (MDRD, ml/min)	99.9%	86.4 [76.8; 96.8]	86.9 [76.8; 98.3]	0.8 (0.5 to 1.1)	<0.0001
Hemoglobin (g/dl)	97.5%	14.1 [13.3; 15.0]	13.8 [13.0; 14.7]	-0.3 (-0.4 to -0.3)	<0.0001
White cell count (10 ⁶ /L)	97.4%	6,780 (±2,060)	6,780 (±2,330)	100 (-30 to -40)	0.6706
Platelets (10 ⁹ /L)	97.5%	254.2 (±58.8)	244.3 (±65.4)	-9.9 (-10 to -8.9)	<0.0001
GGT (IU/L)	99.9%	24.7 [17.8; 37.7]	22.4 [16.2; 34.9]	-0.5 (-1.2 to 0.2)	<0.0001
GGT (>ULN)	99.9%	11,029 (14.6%)	2,547 (13.5%)	0.93 (0.89-0.97)	0.0001
ALT (IU/L)	99.9%	19.3 [15.0; 26.0]	18.2 [14.1; 25.0]	-0.5 (-0.7 to -0.2)	<0.0001
ALT (>ULN)	99.9%	2,544 (3.4%)	723 (3.8%)	1.11 (1.04-1.23)	0.0017
FIB-4	97.1%	1.21 [0.96; 1.52]	1.29 [1.02; 1.67]	0.16 (0.12 to 0.20)	<0.0001
FIB-4 (thresholds)	97.1%				<0.0001
≤1.30		43,035 (58.5%)	9,280 (50.6%)		
1.30-2.67		29,246 (39.7%)	8,269 (45.1%)		
>2.67		1,307 (1.8%)	775 (4.2%)		
Apolipoprotein B (mg/dl)	99.5%	106 [100; 111]	67 [60; 73]	-39 (-39 to -39)	<0.0001

ALT, alanine aminotransferase; BP, blood pressure; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index; FPG, fasting plasma glucose; GGT, gamma-glutamyltransferase; NR, not relevant. ULN, upper limit normal.

Categorical data are expressed as n (%). Quantitative data are expressed as mean (±SD) or median [25th; 75th percentiles], according to the distribution.

*The differences are expressed as prevalence ratio (95% CI) for categorical parameters, and mean difference (95% CI) for all quantitative parameters. p values are calculated using Fisher's exact test or Student's t test for unpaired series.

increased risk of hepatic complications remained significant in the UKBB cohort, but not in the CONSTANCES cohort, probably owing to a lack of statistical power (lower number of events). It is important to note that with this approach, only

cirrhosis complications were significantly more frequent, whereas this was not the case for primary liver cancer.

However, in a time-to-event Cox analysis for primary liver cancer, a hazard ratio (HR) of 3.15 (95% CI, 2.61-3.80) was

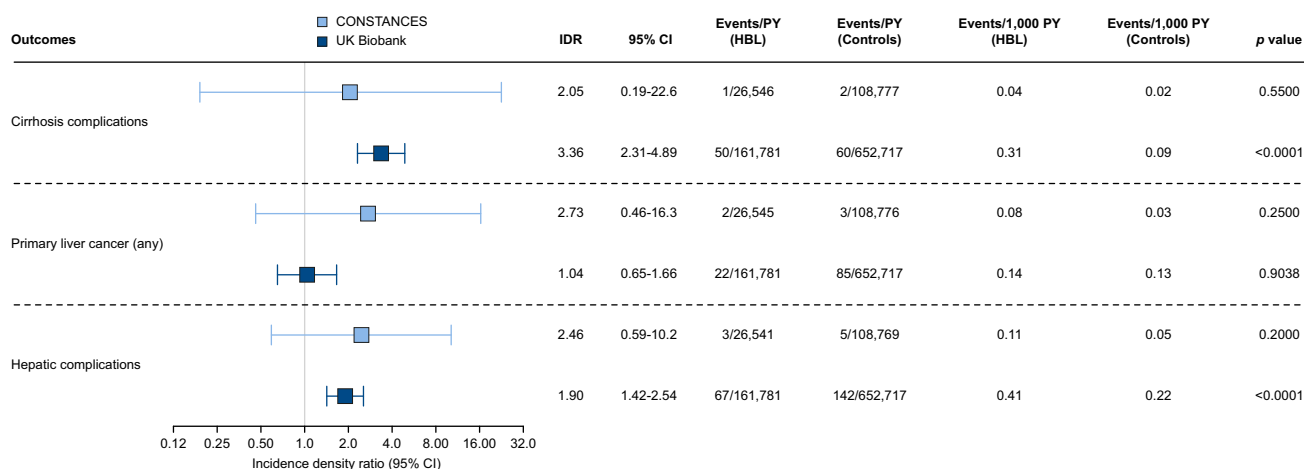


Fig. 3. Analysis of hepatic complications in the HYPOBETA.fr and UKBB population, restricted to population free of classic risk factors for liver disease; LDL-C <5th vs. 40th-60th percentiles. The results are expressed using incidence densities (events/total person-year) and the related between-group ratios. *p* values were calculated using Pearson’s chi-squared test. Classic risk factors for liver disease are defined as obesity, excessive alcohol consumption, diabetes, and history of viral hepatitis. Hepatic complications are defined as complications of cirrhosis and/or liver cancer. IDR, incidence density ratio; LDL-C, low-density lipoprotein-cholesterol; PY, person-year; UKBB, UK BioBank.

observed between the HBL and control groups on univariable analysis, while the HR was 2.60 (95% CI 2.13-3.17) on multivariable analysis adjusting for sex, age, alcohol consumption, diabetes, and history of viral hepatitis B and/or C in the UKBB (Table S2).

Finally, a 5-year landmark analysis of hepatic complications conducted in the UKBB population showed that the incidence of late hepatic complications was significantly increased in the HBL population with or without classic risk factors for liver disease at baseline (Fig. S3).

Taken together, these results confirmed the independent association between primary HBL and hepatic complications in the general population.

Sensitivity analyses with other thresholds for the definition of primary HBL

In order to strengthen our findings, we performed additional sensitivity analyses using other LDL-C thresholds or apoB instead of LDL-C to define our population with primary HBL.

We first investigated the association between very low LDL-C levels (LDL-C <1st percentile) and liver outcomes in both the CONSTANCES (mean LDL-C: 55 mg/dl) and the UKBB (mean LDL-C: 69 mg/dl) cohorts. As observed in patients with LDL-C <5th percentile, a history of liver disease is much more frequent in patients with LDL-C levels <1st percentile compared with controls (Table S3). As shown in Fig. 4, the IDR for liver outcomes was even more marked in individuals with very low LDL-

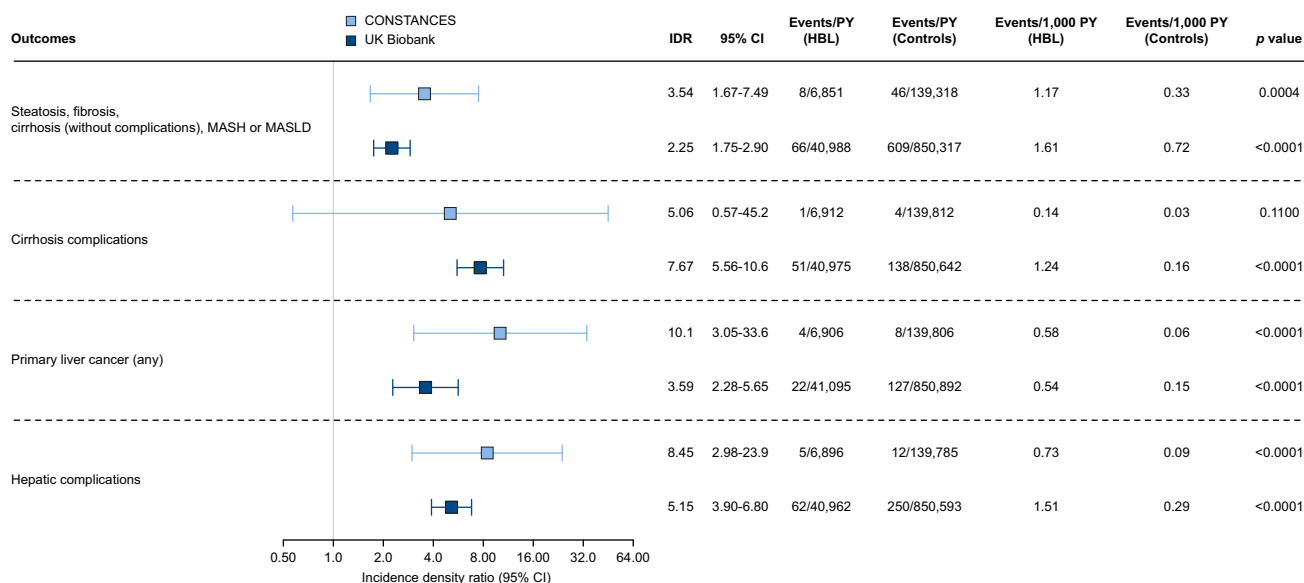


Fig. 4. Analysis of liver outcomes in the HYPOBETA.fr and UKBB population, population with LDL-C <1st vs. 40th-60th percentiles. The results are expressed using incidence densities (events/total person-year) and the related between-group ratios. *p* values were calculated using Pearson’s chi-squared test. IDR, incidence density ratio; LDL-C, low-density lipoprotein-cholesterol; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; PY, person-year; UKBB, UK BioBank.

C levels, with a ~8-fold increased risk of hepatic complications in CONSTANCES (IDR 8.45, 95% CI 2.98-23.9) and an ~5-fold increase in the UKBB (IDR 5.15, 95% CI 3.90-6.80). The increased risk of hepatic complications in the HBL group persisted after adjustment for confounding factors on multivariable analyses in the UKBB (HR 4.33, 95% CI 3.20-5.85) (Table S2) as well as in the population without classic risk factors for liver disease (Table S4). This observed "dose-dependent" effect (between the 5th and the 1st LDL-C percentiles) further reinforces the hypothesis of a mechanistic link between primary HBL and the development of liver complications. Furthermore, when the fixed LDL-C threshold of 70 mg/dl (1.81 mmol/L) was used to define the primary HBL population instead of the 5th percentile, the results were identical, with a significant increase in hepatic complications in populations without standard risk factors for liver disease at baseline (CONSTANCES: HR 3.29, 95% CI 0.64-16.9, *p* = 0.13; UKBB: HR 3.21, 95% CI 1.69-6.10, *p* <0.0001).

Finally, instead of LDL-C values, we used apoB plasma levels below the 5th percentile for individuals with HBL and between 40-60th percentile for the controls and observed similar results (Table S5, Fig. S4).

Association between monogenic HBL (FHBL) and hepatic complications

As a final approach, we focused on individuals with FHBL due to heterozygous variants in the *APOB* gene which induce a truncation of the protein and a defect in lipoprotein assembly (FHBL-SD2). As shown in Fig. 5, participants with FHBL in the UKBB cohort have an increased risk of developing hepatic complications during follow-up, even in the absence of classic risk factors for liver disease at baseline (IDR 4.19, 95% CI 1.74-10.1; *p* = 0.0077). This increase was statistically significant for cirrhosis complications (IDR 6.20, 95% CI 2.31-16.6; *p* = 0.0045) but not for primary liver cancer (IDR 3.66, 95% CI 0.84-13.5; *p* = 0.12).

Discussion

Our study confirms in two separate large population-based cohorts that primary HBL is an independent risk factor for hepatic complications, including cirrhosis and primary liver cancer. These results therefore overturn the paradigm of the relationship between LDL-C and liver damage by reducing the probability of reverse causality. Indeed, this association between primary HBL and hepatic complications persists after adjustment for classic risk factors for liver disease such as obesity, excessive alcohol consumption, diabetes, and viral hepatitis, particularly in individuals with genetically proven FHBL. Although the frequency of hepatic complications may appear low, it should be noted that the individuals included in these cohorts were relatively young (45 years on average in CONSTANCES and 56 years in the UKBB). Altogether, these findings highlight the need for long-term liver monitoring in individuals with primary HBL.

Primary liver cancer characterized by the development of a malignant tumor in the digestive system is a common pathology and its incidence is increasing. Recent epidemiological data from the GLOBOCAN 2020 database, which includes 185 countries, indicate that primary liver cancers are one of the three most frequent causes of cancer death in 46 countries (and among the five most frequent causes of cancer death in 90 countries).²² In addition, this prevalence is expected to rise by more than 55% by 2040 and require a strengthening of prevention strategies. Among the modifiable risk factors for liver cancer, both metabolic syndrome, type 2 diabetes and obesity are becoming increasingly prevalent, notably predisposing to the risk of MASLD and MASH.²³ In the present study, we demonstrate that primary HBL is an independent risk factor for cirrhosis complications and primary liver cancer. It should be highlighted here that this increased risk is observed even though individuals with HBL have a lower BMI and waist circumference than controls, but with a significantly higher frequency of diabetes. Of note, this higher frequency of dia-

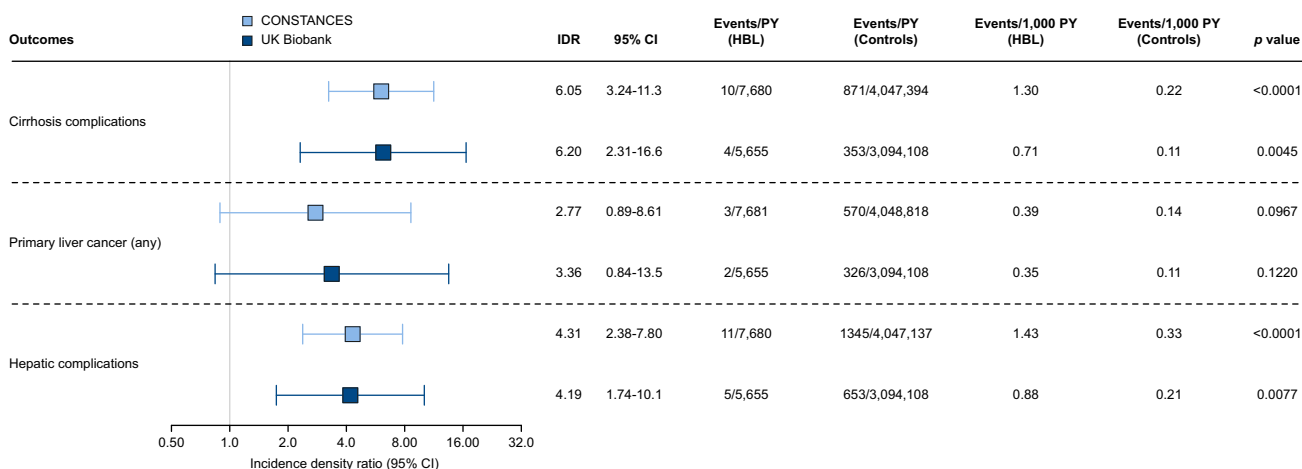


Fig. 5. Analysis of hepatic complications in the UKBB population, in the entire population and restricted to the population free of classic risk factors for liver disease, according to the presence of a truncating variant in the *APOB* gene. The results are expressed using incidence densities (events/total person-year) and the related between-group ratios. *p* values were calculated using Pearson's chi-squared test. Classic risk factors for liver disease are defined as obesity, excessive alcohol consumption, diabetes, and history of viral hepatitis. Hepatic complications are defined as complications of cirrhosis and/or primary liver cancer. IDR, incidence density ratio; PY, person-year; UKBB, UK BioBank.

betes history in the HBL group may be attributed to a causal association, but it could also be explained by a selection bias. Indeed, individuals on statins were excluded from our analysis and it is expected that physicians will be less prone to prescribe statins to people with diabetes with spontaneously low LDL-C levels (HBL group) than to those with elevated or normal LDL-C levels.

Regarding other hepatic risk factors, it is important to note that both a history of viral hepatitis and excessive alcohol consumption were significantly more frequent in the HBL group. It has previously been reported that chronic HCV infection is associated with HBL, irrespective of hepatic damage and nutritional status.^{24,25} The observation of an increased prevalence of viral hepatitis in individuals with primary HBL is consistent with previous studies demonstrating that HCV increases LDL receptor expression at transcriptional and post-translational levels, via SREBPs and PCSK9, to promote lipid uptake and facilitate viral proliferation.^{26,27}

Despite these differences in the baseline prevalence of risk factors for liver disease in the two populations, the results of the multivariable analysis showed that the increased risk for hepatic complications in primary HBL remains statistically significant after adjustment for confounding factors.

However, it should be noted that, while the incidence of hepatic complications remained significantly increased in individuals with HBL with no history of liver disease and no classic risk factors for liver disease (obesity, diabetes, excessive alcohol consumption, viral hepatitis), this increase was mainly due to cirrhosis complications. Indeed, the incidence of primary liver cancer was not significantly increased in HBL groups. A possible explanation for this observation could be linked to the natural history of liver disease in HBL, with progression from steatosis to fibrosis, then cirrhosis and finally hepatocellular carcinoma. A study with a longer follow-up of participants with primary HBL would make it possible to confirm this hypothesis. The other explanation would be that HBL is a risk factor for liver cancer and that other associated factors (excessive alcohol consumption, diabetes, viral hepatitis) are needed to increase this risk, particularly over a short follow-up period.

A long standing question about the relationship between HBL and hepatic complications relates to the potential reverse causation since liver disease, particularly decompensated cirrhosis and liver cancer, can be accompanied by a drop in LDL-C concentrations.^{28,29} However, when censoring incident cancers within 3 to 5 years of the baseline survey (lag-time analyses), the inverse association of serum total cholesterol with primary liver cancer still persists in some studies,^{30,31} but not in others.^{32,33} Interestingly, we found in the UKBB cohort that the increased risk of hepatic complications persists in the HBL group after excluding the first 5 years of follow-up. Importantly, the fact that the incidence of hepatic complications increases when LDL-C concentration decreases (5th vs. 1st percentile) also supports a direct role for hypocholesterolemia in the pathophysiology of liver complications.

Previous Asian and European epidemiological studies in the general population had already highlighted a potential link between low cholesterol and liver cancer risk.^{30,31,34} Notably, the Japan public health center-based prospective study convincingly demonstrated that serum total cholesterol levels were

inversely associated with the risk of liver cancer, after adjustment for LLT, HCV infection and drinking habits.³⁰

Finally, the strongest argument in favor of a causal role for HBL in hepatic complications probably comes from genetics. Indeed, concordant studies have demonstrated that individuals with FHBL present an increased prevalence of liver steatosis and MASLD.^{6,11} Here, we confirmed that patients with genetically proven FHBL with *APOB* truncating variants had a significant increase in the incidence of hepatic complications, even in the absence of other risk factors. From a mechanistic perspective, this can be explained by a defect in hepatic VLDL secretion linked to apoB truncated protein.⁵ It is important to note, however, that all FHBL are probably not comparable in terms of risk of liver complications. Unlike class I FHBL owing to lipoprotein assembly and secretion defects (FHBL-SD), class II FHBL, owing to enhanced lipoprotein catabolism (FHBL-EC), appears to be more neutral with respect to the risk of liver complications.^{35,36} Notably, loss-of-function variants in *PCSK9* have been found to have (i) neutral effects on plasma liver enzymes and MASLD in the UKBB and eMERGE cohorts³⁵ or even (ii) protective effects against liver damage in individuals with MASLD.³⁶ To the best of our knowledge, only one genetic study, using apolipoprotein E genotype (PROSPER trial, including 2,913 participants), assessed the association between plasma total cholesterol and the risk of cancer.³⁷ Although this study suggests that low cholesterol levels are not causally related to increased cancer risk, additional investigations taking into account the different genetic causes of FHBL (FHBL-SD vs. FHBL-EC) are required to obtain more insight into the pathophysiology of MASLD/MASH and liver complications linked to FHBL.

Our study presents some limitations that should be acknowledged. The diagnosis of HBL was made on a single LDL-C measurement and we had no information on the duration and degree of exposure of each patient to hypocholesterolemia. However, we carefully excluded secondary causes of HBL such as vegan diet or LLT. Apart from FIB-4, which we could calculate in the UKBB cohort, we had no non-invasive markers of liver fibrosis and in particular no fibroscan data. Similarly, no imaging data were available for the diagnosis of hepatic steatosis. Moreover, the quality of MASLD and MASH diagnosis based on ICD-10th codes was highly questionable owing to the lack of uniform coding, even if this lack of sensitivity was expected to be balanced between the HBL and control groups. Finally, due to the observational design, the associations presented could be due to a lack of control of the confounding factors, either missing or difficult to fully capture, such as alcohol consumption and hepatitis.

The major strength of our study lies in the population-based study design, the large population size, the systematic data collection and the substantial follow-up of the two cohorts, CONSTANCES and the UKBB, which provided real-life evidence. Above all, despite significant differences in population definition and data collection, the analyses were replicated in two independent cohorts with perfectly concordant results, which reinforces our conclusions.

Primary HBL, characterized by a primary decrease in LDL-C, is independently associated with a markedly increased risk of hepatic complications, including primary liver cancer. The value of systematic liver monitoring for prevention or early detection of liver diseases in people with HBL must be further studied.

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Abbreviations

ALT, alanine aminotransférase; apoB, apolipoprotein B; CONSTANCES, « CONSulTANts des Centres d'Examens de Santé » (French) cohort or Consultants of health examination centers; FIB-4, fibrosis-4 index; FHBL, familial HBL; HBL, hypobetalipoproteinemia; HDL-C, high-density lipoprotein-cholesterol; HR, hazard ratio; HSC, health screening center; IDR, incidence density ratio; LDL-C, low-density lipoprotein-cholesterol; LLT, lipid-lowering therapy; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NHS, National Health Service; PY, patient-year; SNDS, French National Healthcare System; TG, triglycerides; UKBB, United Kingdom Biobank; VLDL, very low-density lipoprotein.

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Conflict of interest

The authors have no conflict of interest to disclose related to the current manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

BC and MW conceived and designed the study. BC supervised and funded the project. MG, SK and MZ provided their expertise regarding the CONSTANCES cohort. AL and AR provided their expertise regarding the UK Biobank cohort. CL provided his expertise in the field of French hospital administrative data. TG, AR, SK and MW performed the data management. TG and MW performed the data analyses. BC, TG, AR and MW wrote the first draft of the manuscript. All of the authors discussed the study design, the interpretation of the results, and reviewed and approved the final manuscript.

Data availability statement

Data associated with the manuscript are not publicly available. For CONSTANCES data, access can be provided by the CASD (Malakoff, France) and requested from the scientific committee here:

<https://www.constances.fr/espace-scientifique/proposer-projet.php>

For UK Biobank data, access via the Access Management System can be requested here:

<https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access>

The computer codes that enabled this work to be carried out can be sent on request.

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Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2024.01.030>.

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Author names in bold designate shared co-first authorship

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