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### **► To cite this version:**

Tangui Barré, Hélène Fontaine, Clémence Ramier, Vincent Di Beo, Stanislas Pol, et al.. Elevated coffee consumption is associated with a lower risk of elevated liver fibrosis biomarkers in patients treated for chronic hepatitis B (ANRS CO22 Hepather cohort). *Clinical Nutrition*, 2022, 41 (3), pp.610-619. 10.1016/j.clnu.2022.01.016 . hal-03776967

**HAL Id: hal-03776967**

**<https://hal.science/hal-03776967>**

Submitted on 14 Sep 2022

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**Elevated coffee consumption is associated with a lower risk of elevated liver fibrosis biomarkers in patients treated for chronic hepatitis B (ANRS CO22 Hepather cohort)**

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# Abstract

## Background and aims

Patients chronically infected with hepatitis B virus (HBV) are at high risk of liver fibrosis, cirrhosis and liver cancer, despite recent therapeutic advances. It is therefore crucial to find non-pharmaceutical options for liver fibrosis prevention in this population. Using cross-sectional data from the ANRS CO22 Hepather cohort, we aimed to identify socio-demographic and modifiable risk factors for significant fibrosis in chronic HBV patients.

## Methods

Logistic regression or Firth's penalized maximum likelihood logistic regression (according to outcome prevalence) multivariable models were used to test for associations between explanatory variables and significant fibrosis, as assessed by three non-invasive markers: AST to platelet ratio index (APRI), FIB-4, and gamma glutamyltransferase to platelet ratio (GPR). Analyses were stratified by HBV treatment status.

## Results

The study population comprised 2065 untreated and 1727 treated chronic HBV patients. Elevated coffee consumption was consistently associated with a lower risk of elevated fibrosis biomarkers in all three treated-participant models, suggesting a dose-response relationship (adjusted odds ratios for  $\geq 3$  cups/day versus 0 cups/day: 0.16, 0.35 and 0.62,  $p \leq 0.002$ , according to APRI, FIB-4 and GPR, respectively). Other modifiable risk factors included tobacco and alcohol use.

## Conclusion

Elevated coffee consumption was consistently associated with a lower risk of significant liver fibrosis, as assessed by three non-invasive markers in treated chronic HBV patients. This result can be immediately used in real-world situations, as increasing coffee consumption may be beneficial for patients at risk of advanced liver disease.

**Keywords:** coffee; hepatitis B; liver fibrosis; caffeine; France

## Introduction

Chronic hepatitis B virus (HBV) infection progresses to liver cirrhosis in up to 40% of untreated patients, and may lead to liver cancer and/or decompensated liver disease (1). It has been estimated that in 2017, chronic HBV infection accounted for a quarter of global deaths caused by cirrhosis (2), and more than half of liver cancer cases in 2012 (3). In this context, non-invasive tests for the assessment of liver fibrosis in patients with chronic HBV infection have proven relevant as they predict mortality and liver-related event incidence (4,5).

Despite the advance that nucleos(t)ide analogues represent, HBV cure rates remain low and most patients require therapy indefinitely (6,7). The presence of cirrhosis before hepatitis B surface antigen (HBsAg) seroclearance lessens the latter's benefits on hepatocellular carcinoma incidence (8). Cirrhosis regression is possible after HBV therapy, especially if cirrhosis is recent (9). It is crucial therefore to prevent and manage liver fibrosis in HBV-infected patients, and to identify risk factors for its occurrence and progression. Behavioural factors, such as smoking, are likely to impact fibrosis development and progression in chronic HBV patients (10). Socioeconomic status is also known to be associated with mortality among cirrhotic patients (11,12). In contrast, anti-fibrotic dietary components or patterns have been identified for other health conditions (13–16).

Using data from the ANRS CO22 Hepather cohort, we aimed to identify socio-demographic and behavioural risk factors for significant liver fibrosis, as assessed by several non-invasive tests in chronic HBV patients.

## Material and methods

### Design of the cohort

Data were taken from ANRS CO22 Hepather, an ongoing French national, multicentre, prospective, observational cohort of patients with chronic active or inactive HBV

or hepatitis C virus (HCV) infection, which started in August 2012 (17). HIV co-infected patients were excluded. Enrolment in the cohort took place in 32 hepatology centres throughout the country. Patients were recruited during a medical visit in their follow-up centre. Demographic, clinical and biological data were collected at the inclusion visit using e-CRF, and patients were followed up on a yearly basis. Written informed consent was obtained from each cohort participant before enrolment. The cohort protocol was designed in accordance with the Declaration of Helsinki and French law for biomedical research, and was approved by the 'Comité de Protection des Personnes (CPP) Ile de France 3' Ethics Committee (Paris, France) and the French Regulatory Authority (ANSM).

#### Study population

The present cross-sectional study population comprised participants with chronic HBV infection at enrolment, defined as a positive HBsAg for at least six months. We excluded patients co-infected with HCV and/or HDV. Participants with a history of HBV treatment but who were not on treatment at enrolment were also excluded, because they potentially represented a heterogeneous group with various reasons for not being on treatment. Consequently, the treatment's impact on clinical outcomes would have been difficult to characterize. Patients with unavailable data to calculate non-invasive fibrosis markers were also excluded.

#### Data collection

We used data collected during the cohort enrolment visit where physicians completed a structured questionnaire during a face-to-face interview with their patients. Anthropological measurements and urine and blood samples were also collected.

The questionnaire collected clinical and sociodemographic data including gender, country of birth, age, time since HBV diagnosis, HBV treatment status, time since HBV treatment initiation, cannabis use, tobacco use, current and past alcohol use (number of standard drinks per day), current coffee consumption (number of cups per day), current tea



consumption (number of cups per day), living with a partner (yes/no), average monthly household income, and educational level. Body height, weight and waist circumference were measured. Data derived from blood samples included platelet count (platelets/L), aspartate aminotransferase (AST, IU/L) and alanine aminotransferase (ALT, IU/L) levels, and gamma glutamyltransferase (GGT, IU/L) level.

#### Liver fibrosis markers

Three non-invasive fibrosis markers were used as study outcomes: AST to platelet ratio index (APRI) (18), FIB-4 (19), and GGT to platelet ratio (GPR). APRI was calculated as  $(AST \text{ (IU/L)} / (AST \text{ upper limit of normal (ULN) (IU/L)}) / \text{platelet count (} 10^9/\text{L)}) \times 100$ . AST ULN was set at 40 IU/L. FIB-4 was calculated as  $(\text{age (years)} \times AST \text{ (IU/L)}) / (\text{platelets (} 10^9/\text{L)}) \times (ALT \text{ (IU/L)})^{1/2}$ , and GPR was calculated as  $GPR = (GGT \text{ (IU/L)} / GGT \text{ ULN (IU/L)}) / \text{platelet count (} 10^9/\text{L)}) \times 100$ . GGT ULN was set at 50 IU/L. The following cut-off values were used to rule in significant liver fibrosis: APRI > 1.5 (18), FIB-4 > 3.25 (20,21) and GPR > 0.32 (22).

#### Explanatory variables

Time since HBV diagnosis (in years) was used for people not on treatment at enrolment and with no treatment history. Instead, for people on treatment at enrolment, time since treatment initiation (in years) was used. As these two variables were highly correlated in the latter group, we chose the second variable for reasons related to interpretability. Cannabis and tobacco use were categorized as current/former/never. Unhealthy alcohol use was defined as > 2 and > 3 standard drinks per day for women and men, respectively, in accordance with the French National Authority for Health (23). Both past and current unhealthy use were taken into account. Current coffee consumption was tested alternatively as a categorical variable (with 0, 1-2 and  $\geq 3$  cups per day as categories) and as a continuous (number of cups per day) variable to test for a dose-response relationship. Current tea consumption was tested as a dichotomized variable (daily vs. non-daily) in the main analyses, and as a continuous variable (number of cups per day) in the sensitivity analyses.

Poverty was defined as a standard of living lower than the 2015 French poverty threshold (1015€ per month). Standard of living was calculated as disposable income divided by the number of consumption units in the household. Educational level was dichotomized into having a secondary school certificate or not.

## Statistical analyses

As treatment is likely to impact fibrosis progression, the relationships between our explanatory variables and outcomes were also likely to be impacted. Moreover, treatment status may reflect access to treatment, which in turn may reflect socio-demographic and biographic factors. For these reasons, we stratified the analyses according to HBV treatment status at enrolment.

Study population characteristics were first compared between participants on and those not on HBV treatment using a Chi-square test (for categorical variables) or Student's t test (for continuous variables). Logistic regression with robust standard errors or Firth's penalized maximum likelihood logistic regression (24) (in cases where people with significant fibrosis represented less than 5% of the sub-population sample size) were then used to test for associations between explanatory variables and the three fibrosis outcomes. Only variables with a liberal p-value < 0.20 in the univariable analyses were considered eligible for each of the multivariable models (25). The final multivariable models were built using a backward stepwise procedure, and the likelihood ratio (Wald) test ( $p < 0.05$ ) was used to define the variables to be maintained in each model. Main analyses were run with the categorical coffee and tea variables, and sensitivity analyses were run with the continuous variables.

Results from regression models are presented as odds ratios (OR) and adjusted odds ratios (aOR, for the multivariable model), with corresponding 95% confidence intervals (CI). The level of significance was set at  $\alpha = 0.05$  in all tests. Variables eligible for multivariable analyses but not retained in the final models were reintroduced in the latter to test for

potential changes in terms of the degree of significance of the associations and changes in OR estimates (26). Stata version 14.2 for Windows (StataCorp, College Station, Texas, USA) was used for all analyses.

## Results

### Study population characteristics

Among the 5213 patients with chronic HBV infection at enrolment in ANRS CO22 Hepather, 166 participants were excluded because of HCV co-infection, 175 because of HDV co-infection, 262 because of a history of, but no current, HBV treatment, and 818 because of missing data for non-invasive liver fibrosis markers. The study population therefore comprised 3792 participants, among whom 2065 had no history of HBV treatment, and 1727 were on treatment at enrolment.

Participants were mainly men (57.2% and 72.8% of untreated and treated participants, respectively), were predominantly from Africa (44.2%) and France (29.8%), and were diagnosed with HBV for a median of 6.7 (untreated) and 11.9 years (treated) (**Table 1**). More than half (54.6%) of untreated participants lived in poverty versus less than half (41.4%) of treated participants. The overall proportion of participants with significant liver fibrosis was 2.5, 4.4, and 36.4% according to the APRI, FIB-4, and GPR markers, respectively. Proportions were higher in treated participants than in their untreated counterparts (**Table 1**).

### Factors associated with significant fibrosis

#### Untreated participants

After multiple adjustment, significant fibrosis in untreated participants was associated with male gender (GPR), being born in Africa (vs. France, GPR), moderate and (current or past) unhealthy alcohol use (GPR), and time since HBV diagnosis (APRI and FIB-4). It was inversely associated with daily tea consumption (GPR) (**Table 2**).

Reintroducing variables into the final model for each outcome which were eligible for each multivariable model but discarded during the stepwise procedure had no impact on significance levels or magnitude of model estimates.

#### Treated participants

After multiple adjustment, significant fibrosis in treated participants was associated with male gender (all markers), inversely associated with being born in Europe or Asia (vs. France, GPR), inversely associated with  $\geq 3$  cups of coffee per day (all markers), inversely associated with past or current cannabis use (GPR), associated with current tobacco use (GPR) and current or past unhealthy alcohol use (FIB-4 and GPR), inversely associated with having a secondary school certificate (FIB-4 and GPR), associated with living in poverty (GPR), and finally, associated with time since HBV treatment initiation (APRI and GPR) (**Table 3**).

Reintroducing variables into the final model for each outcome which were eligible for each multivariable model but discarded during the stepwise procedure had no impact on significance levels or magnitude of model estimates.

#### Sensitivity analyses

Sensitivity analyses with coffee or tea consumption as continuous variables gave similar results in all models. The risk of fibrosis in untreated participants decreased by 22% for each additional cup of tea ( $p=0.020$ ) according to GPR. Instead, for coffee consumption in treated participants, all three markers indicated a reduction in the risk of fibrosis for each additional cup: 51% for APRI ( $p<10^{-3}$ ), 38 for FIB-4 ( $p<10^{-3}$ ), and 22% for GPR ( $p=0.001$ ) (data not shown).

## Discussion

In a study sample of 3792 chronic HBV patients, we found that elevated coffee consumption and alcohol abstinence were consistently inversely associated with significant

1 liver fibrosis in the treated sub-population. Among untreated participants, daily tea  
2 consumption and alcohol abstinence were inversely associated with significant fibrosis for  
3  
4 only one of the three non-invasive markers studied.  
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7 Stratification of patients according to HBV treatment status and the use of three  
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9 different non-invasive markers ensured a fine-grained analysis. The two subpopulations were  
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11 different for virtually all characteristics, with relevant absolute differences for gender,  
12  
13 socioeconomic status, duration of HBV infection and presence of significant fibrosis.  
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15 Untreated participants had a shorter duration of infection and lower prevalence of significant  
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17 fibrosis. This lower prevalence may be explained by the presence of significant fibrosis  
18  
19 having led to treatment initiation. Indeed, elevated ALT and/or the presence of fibrosis or  
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21 cirrhosis may have accelerated HBV diagnosis if not already diagnosed, and treatment  
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23 initiation in all those diagnosed, in accordance with current guidelines (27).  
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28 The relevance of the three markers we studied in predicting liver fibrosis or liver  
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30 disease progression has previously been reported for HBV-infected patients (4,20,22,28–30).  
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32 Their accuracy in predicting a specific fibrosis stage is still unknown, and different cut-off  
33  
34 values have been proposed to rule in/out different fibrosis stages (20,22,28). For instance,  
35  
36 Xiao et al. in their meta-analysis reported an area under the receiver operating characteristic  
37  
38 curve (AUROC) of 0.74 and 0.78 for significant fibrosis for APRI and FIB-4 respectively, as  
39  
40 validated against liver biopsy (20). Regarding GPR and using Fibroscan, Lemoine et al.  
41  
42 reported an AUROC of 0.72-0.73 for significant fibrosis (22). In our study, the fact that a  
43  
44 GPR>0.32 was found for more than 35% of patients in our population while elevated FIB-4  
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46 and APRI was found for less than 5% suggests that the threshold we used for GPR  
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48 corresponded to a less severe fibrosis stage than the two other markers.  
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53 The seemingly protective effect of coffee consumption on liver fibrosis in this study  
54  
55 was previously highlighted in meta-analyses in patients with non-alcoholic fatty liver disease  
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57 (31,32), alcoholic liver disease, or HCV infection (33). Similar findings have also been  
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59 highlighted in HBV-infected patients (34,35). Our cross-sectional results are consistent with  
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1 those of Chen et al. who found lower AST, APRI and FIB-4 values for high-consumption  
2 coffee drinkers (4-7 days per week) at baseline in their survey of HB envelope antigen-  
3 negative chronically infected patients (35). This apparently dose-dependent effect may be  
4 due to caffeine content and/or antioxidant and anti-inflammatory properties of coffee (36,37)  
5 (polyphenols and diterpenes are probably responsible for these properties (38)). We  
6 confirmed this dose-response relationship by showing that only elevated coffee consumption  
7 ( $\geq 3$  cups/day) was associated with a lower risk of significant fibrosis in treated individuals,  
8 and by providing estimates of risk reduction associated with one-cup increases in coffee  
9 consumption. The consistency of our results in all the treated participant models in terms of  
10 coffee consumption suggests it may be a protective factor for a potentially extended range of  
11 fibrosis severity.  
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25 The lack of association between coffee consumption and liver fibrosis in untreated  
26 participants is intriguing. As for associations with other explanatory variables, it may be due  
27 to low statistical power, given that untreated individuals with significant fibrosis were less  
28 numerous. Differences in consumption habits – such as adding sucrose (a source of pro-  
29 fibrotic fructose (39)) to coffee - between the two sub-populations should also be considered,  
30 as well as the type of coffee used (40). Such behavioral differences related to cultural habits  
31 and/or or socio-economic differences between the two sub-groups may not have been  
32 sufficiently captured by the country of birth and socio-economic variables. Conversely, daily  
33 tea consumption was negatively associated with liver fibrosis in untreated participants only,  
34 and exclusively for the GPR marker, which suggests that the protective effect is probably  
35 exerted on less severe fibrosis stage. In treated participants, this association was only  
36 present in univariable analyses, which suggests that the effect of coffee consumption  
37 outweighed that of tea in this sub-population. We may expect tea to exert a weaker  
38 hepatoprotective effect than coffee because of its lower caffeine content and antioxidant  
39 activity per cup (41,42). The beneficial effect of tea consumption on fibrosis has been  
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inconsistently reported in population-based surveys (34), in patients with liver diseases (43), and in the HCV population (44).

Other risk factors identified in our models included male gender, unhealthy alcohol use, tobacco use and lower educational level. Male gender has previously been identified as a risk factor for more severe liver disease in HBV-infected patients (45–48), and is believed to be related to sex-specific hormones (48). Unhealthy alcohol use is a well-known risk factor for liver fibrosis (49); the detrimental effect of alcohol during HBV infection is recognized, although not fully understood (50). The positive association we found between tobacco use and fibrosis is consistent with results from Xiong et al. who found that tobacco smoking in male HBV-infected patients aggravated liver fibrosis prior to antiviral therapy and delayed fibrosis regression in persons on antiviral therapy (10). Tobacco use has also been identified as a risk factor for hepatocellular carcinoma in HBV-infected patients (51), with a mediation effect through HBV viral load being suggested (52). Consistently with our results, no association was found between current tobacco use and FIB-4 values in a large cohort of untreated HBV-infected patients (53). Finally, we found that treated patients with a lower educational level were more likely to have high FIB-4 and GPR scores. We may suppose that participants with a lower socioeconomic status adopt healthy behaviours to a lower degree (54), especially regarding physical activity and diet quality (55,56), two factors that play a role in liver disease progression (14,57). The protective effect of cannabis use we found in treated individuals (for GPR only) despite low prevalence of use in this sub-population is noteworthy. While cannabis and cannabinoids may have a protective effect on liver steatosis (58), results for liver fibrosis among HCV-infected patients remain inconclusive (59,60).

The main strength of our study was its large sample size. With more than 3700 patients included in the analyses, we were able to identify several risk factors for significant fibrosis, and stratify the analyses by HBV treatment status. The use of multiple outcomes partially offset limitations inherent to the use of non-invasive markers as opposed to the gold

1 standard (i.e., liver biopsy) for assessing the presence of fibrosis. Given the dynamic nature  
2 of liver fibrosis, which is subject to progression or regression, the cross-sectional nature of  
3 our study would appear to be a limitation. We were not able to assess the potential role of  
4 coffee consumption in fibrosis progression. Chen et al. did not find any effect of coffee  
5 consumption on fibrosis progression or hepatocellular carcinoma risk (35). The availability of  
6 various socio-behavioural variables was another study strength, although physical activity  
7 and diet quality assessments were not available. However, we can suppose that both were  
8 associated with socioeconomic status and behaviours (55,56,61).  
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10 All these results have practical implications. As HBV-infected patients have an excess  
11 mortality risk, and a high risk of both liver disease and liver-related mortality (4,5,62,63),  
12 increasing coffee consumption for non-users or light users may represent a simple, cost-  
13 effective prevention strategy for improved liver health. Indeed, for those patients, the benefits  
14 of increasing consumption are likely to exceed potential harms (64). Although decaffeinated  
15 coffee may also have (probably to a lesser extent) hepatoprotective properties (36,65,66),  
16 the potential harms and side effects associated with elevated coffee consumption are  
17 substantially reduced (64). Our findings also highlight the need for further research  
18 investigating mechanisms at play the beneficial effect which coffee consumption provides, as  
19 it seems feasible (and desirable) to develop drugs for fibrosis prevention based on active  
20 compounds from coffee to expand the therapeutic arsenal currently available.  
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## 22 Conclusion

23 Elevated coffee consumption was consistently associated with a lower risk of significant liver  
24 fibrosis, as assessed by three non-invasive markers in chronic HBV patients on treatment.  
25 This result can be immediately used in real-world situations, as increasing coffee  
26 consumption may be beneficial for patients at risk of advanced liver disease.  
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## Acknowledgements

We thank the study participants and the participating clinicians at each site. We also thank the INSERM-ANRS MIE for sponsoring, funding and conducting the ANRS CO22 Hepather cohort in collaboration with the French Association for the Study of the liver (Association Française pour l'Etude du Foie: AFEF). Finally, our thanks to Jude Sweeney (Milan, Italy) for the English revision and copyediting of our manuscript.

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#### Sponsor

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## Funding statement

Hepather cohort is funded by INSERM-ANRS MIE (France REcherche Nord&sud Sida-vih Hépatites | Maladies Infectieuses Emergentes), ANR Equipex and Cohort (Agence Nationale de la Recherche), DGS (Direction Générale de la Santé) and MSD, Janssen, Gilead, Abbvie, BMS, and Roche.

## Conflicts of interest

Stanislas Pol has served as a speaker, a consultant and an advisory board member for Janssen, Gilead, Roche, MSD, Abbvie, Biotest, Shinogi, Vivv, and LFB. He has received research funding from Gilead, Abbvie, Roche and MSD not connected to the present work.

Fabrice Carrat reports grants from INSERM-ANRS during the implementation of this study and personal fees from Imaxio, outside the submitted work.

The other authors have no conflict of interest to declare.

## Authors' contributions

TB, HF and CP designed the study.

VDB cleaned the data.

CR performed the statistical analyses.

HF, SP, CC, CD, JZR, FZ and FC contributed to the design of the study and participated in data collection.

TB wrote the original paper.

All authors reviewed the manuscript.

All authors approved the final version of the article, including the authorship list.

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Table 1: Study population characteristics according to HBV treatment status at enrolment (ANRS CO22 Hepather cohort, N = 3792)

Variables	Study sample		Patients not on HBV treatment at enrolment		Patients on HBV treatment at enrolment		
	N = 3792	%	N = 2065	%	N = 1727	%	p-value <sup>1</sup>
<b>Gender</b>							
Male	2438	64.3	1181	57.2	1257	72.8	< 10 <sup>-3</sup>
Female	1354	35.7	884	42.8	470	27.2	
<b>Place of birth</b>							
France	1131	29.8	515	24.9	616	35.7	< 10 <sup>-3</sup>
Europe (excl. France)	380	10.0	199	9.6	181	10.5	
Africa	1675	44.2	1077	52.2	598	34.6	
Asia	557	14.7	248	12.0	309	17.9	
Caribbean & South America	48	1.3	25	1.2	23	1.3	
Missing	1	0.0					

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<b>Living with a partner</b>							
No	1333	35.2	782	38.0	551	32.0	< 10 <sup>-3</sup>
Yes	2446	64.5	1274	62.0	1172	68.0	
<i>Missing</i>	13	0.3					
<b>Coffee consumption</b>							
0 cups/day	1331	35.1	810	39.9	521	30.8	< 10 <sup>-3</sup>
1-2 cups/day	1404	37.0	728	35.9	676	40.0	
≥ 3 cups/day	985	26.0	492	24.2	493	29.2	
<i>Missing</i>	72	1.9					
<b>Coffee consumption</b>							
Median [IQR]	1 [0 – 3]	-	1 [0 – 2]	-	1 [0 – 3]	-	< 10 <sup>-3</sup>
<b>Tea consumption</b>							
Non-daily	2250	59.3	1200	59.3	1050	62.4	0.055
Daily	1459	38.5	825	40.7	634	37.6	
<i>Missing</i>	83	2.2					
<b>Cannabis use</b>							
Never	3535	93.2	1915	93.3	1620	94.6	0.068

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Former	139	3.7	77	3.8	62	3.6	
Current	92	2.4	61	3.0	31	1.8	
Missing	26	0.7					
<b>Tobacco use</b>							
Never	2423	63.9	1399	67.8	1024	59.3	< 10 <sup>-3</sup>
Former	698	18.4	298	14.4	400	23.2	
Current	669	17.6	366	17.7	303	17.5	
Missing	2	0.1					
<b>Alcohol use</b>							
Abstinent with no history of unhealthy use	2156	56.9	1203	58.6	953	55.4	0.017
Moderate use	1398	36.9	749	36.5	649	37.7	
Current or past unhealthy use <sup>2</sup>	221	5.8	102	5.0	119	6.9	
Missing	17	0.4					
<b>Living in poverty<sup>3</sup></b>							
No	1877	49.5	902	45.4	975	58.6	< 10 <sup>-3</sup>

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Yes	1775	46.8	1086	54.6	689	41.4	
Missing	140	3.7					
<b>Educational level</b>							
< secondary school certificate	1842	48.6	965	47.7	877	51.7	0.014
≥ secondary school certificate	1877	49.5	1059	52.3	818	48.3	
Missing	73	1.9					
<b>Time since HBV diagnosis</b>							
– in years							
Median [IQR]	9.18 [3.82 – 16.86]	-	6.67 [2.36 – 12.95]	-	11.94 [6.41 – 19.92]	-	< 10 <sup>-3</sup>
<b>Time since first HBV treatment – in years</b>							
Median [IQR]	6.22 [2.51 – 10.88]	-	-	-	6.22 [2.51 – 10.88]	-	-
<b>FIB-4 score</b>							
≤ 3.25	3625	95.6	2026	98.1	1599	92.6	< 10 <sup>-3</sup>
> 3.25	167	4.4	39	1.9	128	7.4	
<b>GPR score</b>							
≤ 0.32	2413	63.6	1425	69.0	988	57.2	< 10 <sup>-3</sup>

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> 0.32	1379	36.4	640	31.0	739	42.8	
<b>APRI score</b>							
≤ 1.5	3699	97.5	2031	98.4	1668	96.6	< 10 <sup>-3</sup>
> 1.5	93	2.5	34	1.6	59	3.4	

<sup>1</sup>p-values for Chi-square test (categorical variables) or Student's t test (continuous variables).

<sup>2</sup>Unhealthy alcohol use was defined as > 2 and > 3 standard drinks per day for women and men, respectively.

<sup>3</sup>Poverty was defined as a standard of living lower than the 2015 French poverty threshold (1015€ per month per household consumption unit).

APRI, aspartate aminotransferase to platelet ratio index; GPR, gamma glutamyltransferase to platelet ratio; HBV, hepatitis B virus; IQR, interquartile range.

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**Table 2: Factors associated with significant fibrosis according to three non-invasive fibrosis markers for patients not on HBV treatment at enrolment (logistic and Firth's penalized maximum likelihood logistic regressions, ANRS CO22 Hepather cohort, N = 2064)**

	APRI>1.5 <sup>1</sup>				FIB-4>3.25 <sup>1</sup>				GPR>0.32 <sup>1</sup>			
Variable	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
			N = 2005				N = 2037				N = 2017	
	OR [95% CI]	p-value	aOR [95% CI]	p-value	OR [95% CI]	p-value	aOR [95% CI]	p-value	OR [95% CI]	p-value	aOR [95% CI]	p-value
Gender												
Male (ref.)	1				1				1		1	



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Female	0.57 [0.27 – 1.18]	0.127			0.53 [0.27 – 1.06]	0.074			0.19 [0.15 – 0.23]	< 10 <sup>-3</sup>	0.22 [0.17 – 0.28]	< 10 <sup>-3</sup>
Place of birth		0.508				0.302				< 10 <sup>-3</sup>		< 10 <sup>-3</sup>
France (ref.)	1				1				1		1	
Europe (excl. France)	0.61 [0.15 – 2.44]	0.485			0.54 [0.17 – 1.73]	0.299			0.90 [0.62 – 1.31]	0.589	0.99 [0.66 – 1.50]	0.972
Africa	0.70 [0.32 – 1.55]	0.381			0.50 [0.25 – 0.99]	0.046			1.53 [1.21 – 1.93]	< 10 <sup>-3</sup>	1.69 [1.30 – 2.20]	< 10 <sup>-3</sup>
Asia	1.50 [0.58 – 3.86]	0.406			0.43 [0.13 – 1.38]	0.157			0.94 [0.66 – 1.33]	0.724	1.05 [0.72 – 1.53]	0.812

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Caribbe												
an &	0.94				0.59				0.87		0.85	
South	[0.05 –				[0.03 –				[0.34 –		[0.33 –	
America	16.56]	0.969			10.17]	0.719			2.23]	0.774	2.23]	0.743
Living												
with a												
partner												
No (ref.)	1				1				1			
Yes	0.87				0.97				1.02			
	[0.44 –				[0.51 –				[0.84 –			
	1.71]	0.678			1.84]	0.926			1.24]	0.804		
Coffee		0.098				0.967				0.527		
consum												
ption												
0									1			
cups/da												
y (ref.)	1				1							

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1-2 cups/day	0.45 [0.20 – 1.02]	0.055			0.91 [0.44 - 1.88]	0.796			0.88 [0.71 – 1.10]	0.258		
≥ 3 cups/day	0.52 [0.21 – 1.25]	0.144			0.95 [0.42 – 2.12]	0.873			0.94 [0.74 – 1.20]	0.639		
Tea consumption												
Non-daily (ref.)	1				1				1		1	
Daily	1.03 [0.57 – 1.88]	0.924			0.77 [0.39 – 1.49]	0.432			0.68 [0.56 – 0.83]	< 10 <sup>-3</sup>	0.78 [0.63 – 0.96]	0.020
Cannabis use		0.854				0.573				0.078		

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Never (ref.)	1				1				1			
Former	1.10 [0.21 – 5.75]	0.908			0.31 [0.02 – 5.03]	0.408			1.03 [0.63 – 1.69]	0.900		
Current	0.46 [0.03 – 7.54]	0.584			0.39 [0.02 – 6.36]	0.506			1.81 [1.08 – 3.03]	0.024		
<b>Tobacco use</b>		<b>0.623</b>				<b>0.047</b>				<b>&lt; 10<sup>-3</sup></b>		
Never (ref.)	1				1				1			
Former	0.94 [0.34 – 2.59]	0.898			2.34 [1.14 – 4.80]	0.020			1.79 [1.38 – 2.32]	< 10 <sup>-3</sup>		

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Current	1.45 [0.65 – 3.22]	0.360			0.89 [0.35 – 2.27]	0.809			1.37 [1.08 – 1.76]	0.011		
Alcohol use		<b>0.606</b>				<b>0.255</b>				$< 10^{-3}$		$< 10^{-3}$
Abstinen t with no history of unhealth y use (ref.)	1				1				1		1	
Moderat e use	1.34 [0.66 – 2.70]	0.418			1.53 [0.79 – 2.96]	0.206			1.68 [1.38 – 2.05]	$< 10^{-3}$	1.52 [1.22 – 1.89]	$< 10^{-3}$

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Current										< 10 <sup>-3</sup>		< 10 <sup>-3</sup>
or past	1.69				2.25				3.92		3.18	
unhealth	[0.44 –				[0.71 –				[2.59 –		[2.04 –	
y use <sup>2</sup>	6.45]	0.445			7.19]	0.170			5.92]		4.94]	
Living												
in												
poverty												
3												
No (ref.)	1				1				1			
Yes	0.78	0.473			0.70	0.286			1.03			
	[0.40 –				[0.37 –				[0.85 –			
	1.54]				1.34]				1.24]	0.787		
Educational												
level												
<												
Second	1				1				1			

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ary school certificat e (ref.)												
≥ Second ary school	1.15 [0.59 – 2.25]	0.685			0.63 [0.34 – 1.20]	0.160			1.01 [0.84 – 1.22]	0.888		
Time since HBV diagnos is – in years	1.03 [1.00 – 1.07]	0.038	1.03 [1.00 – 1.07]	0.038	1.05 [1.02 – 1.08]	0.002	1.05 [1.02 – 1.08]	0.002	0.98 [0.97 – 1.00]	0.007		

<sup>1</sup>For the outcomes based on APRI and FIB-4, Firth’s penalized maximum likelihood logistic regressions were used. For the outcome based on GPR, logistic regressions were used.

<sup>2</sup>Unhealthy alcohol use was defined as > and > 3 standard drinks per day for women and men, respectively.

<sup>3</sup>Poverty was defined as a standard of living lower than the 2015 French poverty threshold (1015€ per month per household consumption unit).

aOR, adjusted odds ratio; APRI, aspartate aminotransferase to platelet ratio index; CI, confidence interval; GPR, gamma glutamyltransferase to platelet ratio; HBV, hepatitis B virus.



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**Table 3: Factors associated with significant fibrosis as assessed by three non-invasive fibrosis markers, for patients on HBV treatment at enrolment (logistic and Firth's penalized maximum likelihood logistic regressions, ANRS CO22 Hepather cohort, N = 1727)**

	APRI>1.5				FIB-4>3.25				GPR>0.32			
Variables	Univariable analysis		Multivariable analysis N = 1721		Univariable analysis		Multivariable analysis N = 1735		Univariable analysis		Multivariable analysis N = 1583	
	OR [95% CI]	p-value	aOR [95% CI]	p-value	OR [95% CI]	p-value	aOR [95% CI]	p-value	OR [95% CI]	p-value	aOR [95% CI]	p-value
Gender												
Male (ref.)	1		1		1		1		1		1	
Female	0.62 [0.33 – 1.20]	0.156	0.39 [0.19 – 0.80]	0.010	0.63 [0.40 – 0.99]	0.044	0.49 [0.29 – 0.81]	0.005	0.25 [0.20 – 0.32]	< 10 <sup>-3</sup>	0.23 [0.18 – 0.31]	< 10 <sup>-3</sup>
Place of birth		0.423				0.732				0.001		0.002

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France (ref.)	1				1				1		1	
Europe												0.00
(excl. France)	0.87 [0.30 – 2.48]	0.79 2			1.00 [0.55 – 1.83]	0.99 7			0.64 [0.45 – 0.91]	0.01 2	0.51 [0.34 – 0.76]	1
Africa	1.65 [0.90 – 3.03]	0.10 8			0.84 [0.55 – 1.28]	0.41 1			1.20 [0.96 – 1.50]	0.11 7	1.02 [0.77 – 1.35]	0.86 7
Asia	1.20 [0.55 – 2.61]	0.64 4			0.73 [0.42 – 1.25]	0.25 0			0.73 [0.55 – 0.97]	0.03 1	0.73 [0.53 – 1.00]	0.05 0
Caribbean & South America	2.28 [0.41 – 12.75]	0.34 7			0.50 [0.07 – 3.81]	0.50 7			0.99 [0.43 – 2.30]	0.98 6	1.35 [0.55 – 3.32]	0.51 3
Living with a partner												
No (ref.)	1				1				1			
Yes	0.84 [0.49 – 1.43]	0.51 8			1.14 [0.77 – 1.70]	0.51 4			1.09 [0.89 – 1.34]	0.40 4		

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Coffee consumption		0.00 2		0.00 2		0.00 5		0.00 1		0.15 8		0.00 4
0 cups/day (ref.)	1		1		1		1		1		1	
1-2 cups/day	0.73 [0.42 – 1.26]	0.26 4	0.73 [0.42 – 1.27]	0.27 1	0.93 [0.62 – 1.39]	0.72 0	0.81 [0.52 – 1.24]	0.32 6	0.96 [0.76 – 1.21]	0.72 0	0.88 [0.68 – 1.15]	0.34 7
≥ 3 cups/day	0.17 [0.06 – 0.45]	< 10 <sup>3</sup>	0.16 [0.06 – 0.44]	< 10 <sup>3</sup>	0.43 [0.25 – 0.73]	0.00 2	0.35 [0.20 – 0.61]	< 10 <sup>3</sup>	0.79 [0.62 – 1.02]	0.07 2	0.62 [0.46 – 0.83]	0.00 2
Tea consumption												
Non-daily (ref.)	1				1				1			
Daily	1.17 [0.68 – 2.00]	0.57 2			0.89 [0.61 – 1.31]	0.57 0			0.81 [0.66 – 0.98]	0.03 4		

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<b>Cannabis use</b>		<b>0.91</b> <b>9</b>				<b>0.64</b> <b>3</b>				<b>0.16</b> <b>8</b>		<b>0.00</b> <b>2</b>
Never (ref.)	1				1				1		1	
Former	1.14 [0.31 – 4.17]	0.83 8			0.84 [0.30 – 2.35]	0.73 9			0.67 [0.39 – 1.14]	0.14 2	0.42 [0.23 – 0.76]	0.00 4
Current	1.36 [0.26 – 7.17]	0.71 5			0.41 [0.05 – 3.00]	0.37 7			0.62 [0.29 – 1.33]	0.22 2	0.38 [0.16 – 0.89]	0.02 6
<b>Tobacco use</b>		<b>0.14</b> <b>8</b>				<b>0.01</b> <b>5</b>				<b>&lt; 10<sup>-3</sup></b>		<b>0.02</b> <b>0</b>
Never (ref.)	1				1				1		1	
Former	1.47 [0.83 – 2.59]	0.18 5			1.57 [1.06 – 2.35]	0.02 6			1.57 [1.24 – 1.98]	<b>&lt; 10<sup>-3</sup></b>	1.27 [0.96 - 1.68]	0.08 8
Current	0.63 [0.27 – 1.46]	0.28 1			0.70 [0.39 – 1.24]	0.22 0			1.35 [1.04 – 1.74]	0.02 4	1.56 [1.13 – 2.15]	0.02 3
<b>Alcohol use</b>		<b>0.07</b> <b>8</b>				<b>&lt; 10<sup>-3</sup></b>		<b>0.00</b> <b>2</b>		<b>0.00</b> <b>1</b>		<b>0.01</b> <b>8</b>

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Abstinent with no history of unhealthy use (ref.)	1				1		1		1		1	
Moderate use	0.80 [0.45 – 1.43]	0.46 1			0.83 [0.55 – 1.25]	0.37 6	0.96 [0.62 – 1.47]	0.84 5	1.23 [1.01 – 1.51]	0.04 1	1.32 [1.04 – 1.67]	0.02 4
Current or past unhealthy use <sup>2</sup>	2.09 [0.96 – 4.56]	0.06 2			2.79 [1.64 – 4.75]	< 10 <sup>–3</sup>	2.60 [1.46 – 4.64]	0.00 1	2.04 [1.39 – 3.00]	< 10 <sup>–3</sup>	1.66 [1.07 – 2.57]	0.02 3
Living in poverty <sup>3</sup>												
No (ref.)	1				1				1		1	
Yes	1.28 [0.75 – 2.19]	0.36 3			1.17 [0.80 – 1.70]	0.42 3			1.21 [0.99 – 1.47]	0.05 9	1.27 [1.00 – 1.61]	0.04 9

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60  
61  
62  
63  
64  
65

<b>Educational level</b>												
< secondary school certificate (ref.)	1				1		1		1		1	
≥ secondary school certificate	0.75 [0.44 – 1.28]	0.29 3			0.51 [0.34 – 0.75]	1	0.54 [0.36 – 0.81]	0.00 3	0.73 [0.60 – 0.89]	0.00 2	0.77 [0.62 – 0.96]	0.02 2
<b>Time since the first HBV treatment – in years</b>	0.92 [0.87 – 0.97]	0.00 4	0.93 [0.88 – 0.98]	0.00 7	0.97 [0.94 – 1.01]	0.14 5			0.98 [0.96 – 1.00]	0.01 9	0.98 [0.96 – 0.99]	0.01 1

<sup>1</sup>For the outcome based on APRI, Firth's penalized maximum likelihood logistic regressions were used. For the outcomes based on FIB-4 and GPR, logistic regressions were used.

<sup>2</sup>Unhealthy alcohol use was defined as > 2 and > 3 standard drinks per day for women and men, respectively.

<sup>3</sup>Poverty was defined as a standard of living lower than the 2015 French poverty threshold (1015€ per month per household consumption unit).

aOR, adjusted odds ratio; APRI, aspartate aminotransferase to platelet ratio index; CI, confidence interval; GPR, gamma glutamyltransferase to platelet ratio; HBV, hepatitis B virus.