



HAL
open science

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)

Tangui Barré, Hélène Fontaine, Clémence Ramier, Vincent Di Beo, Stanislas Pol, Patrizia Carrieri, Fabienne Marcellin, Carole Cagnot, Céline Dorival, Jessica Zucman-Rossi, et al.

► **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-03776967v1>

Submitted on 14 Sep 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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)

Tangui Barré¹, Hélène Fontaine², Clémence Ramier¹, Vincent Di Beo¹, Stanislas Pol², Patrizia Carrieri¹, Fabienne Marcellin¹, Carole Cagnot³, Céline Dorival⁴, Jessica Zucman-Rossi^{5,6}, Fabien Zoulim^{7,8,9}, Fabrice Carrat⁴, Camelia Protopopescu¹

¹ Aix Marseille Univ, Inserm, IRD, SESSTIM, Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale, ISSPAM, Marseille, France

Address: 27 Bd Jean Moulin 13385 Marseille Cedex 5, France

² Université de Paris; Département d'Hépatologie et Addictologie, Hôpital Cochin, APHP, Paris, France

Address: 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France

³ ANRS MIE (France Recherche Nord & Sud Sida-HIV Hépatites | Maladies Infectieuses Emergentes), Unit for Basic and Clinical Research on Viral Hepatitis, Paris, France

Address: 101 rue de Tolbiac, 75013 Paris, France

⁴ Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, Paris, France

Address: 27 rue Chaligny, 75012 Paris, France

⁵ Centre de Recherche des Cordeliers, Sorbonne Université, Inserm, USPC, Université Paris Descartes, Université Paris Diderot, Paris, France

Address: 15 Rue de l'École de Médecine, 75006 Paris, France

⁶ Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Paris, France

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Address: 20 Rue Leblanc, 75015 Paris, France

⁷ INSERM U1052, CNRS UMR-5286, Cancer Research Center of Lyon (CRCL), Lyon,
France

Address: 28 Rue Laennec, 69008 Lyon, France

⁸ University of Lyon, Université Claude-Bernard (UCBL), Lyon, France

Address: 43 Boulevard du 11 Novembre 1918, 69100 Villeurbanne, France

⁹ Hospices Civils de Lyon (HCL), Lyon, France

Address: 3 Quai des Célestins, 69002 Lyon, France

Corresponding author: Patrizia Carrieri, pmcarrieri@aol.com

TB: tangui.barre@inserm.fr

HF: helene.fontaine@aphp.fr

CR: clemence.ramier@inserm.fr

VDB: vincent.di-beo@inserm.fr

SP: stanislas.pol@aphp.fr

PC: pmcarrieri@aol.com

FM: fabienne.marcellin@inserm.fr

CC: carole.cagnot@anrs.fr

CD: celine.dorival@iplesp.upmc.fr

JZR: jessica.zucman-rossi@inserm.fr

FZ: fabien.zoulim@inserm.fr

FC: fabrice.carrat@iplesp.upmc.fr

CP: camelia.protopopescu@inserm.fr

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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 ≥ 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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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

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

10 Study population

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

19 Data collection

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

23 The questionnaire collected clinical and sociodemographic data including gender,
24 country of birth, age, time since HBV diagnosis, HBV treatment status, time since HBV
25 treatment initiation, cannabis use, tobacco use, current and past alcohol use (number of
26 standard drinks per day), current coffee consumption (number of cups per day), current tea
27

1 consumption (number of cups per day), living with a partner (yes/no), average monthly
2 household income, and educational level. Body height, weight and waist circumference were
3 measured. Data derived from blood samples included platelet count (platelets/L), aspartate
4 aminotransferase (AST, IU/L) and alanine aminotransferase (ALT, IU/L) levels, and gamma
5 glutamyltransferase (GGT, IU/L) level.
6
7
8
9

10 11 Liver fibrosis markers

12
13
14 Three non-invasive fibrosis markers were used as study outcomes: AST to platelet
15 ratio index (APRI) (18), FIB-4 (19), and GGT to platelet ratio (GPR). APRI was calculated as
16 $(AST \text{ (IU/L)} / (AST \text{ upper limit of normal (ULN)} \text{ (IU/L)}) / \text{platelet count (} 10^9 \text{/L)} \times 100$. AST ULN
17 was set at 40 IU/L. FIB-4 was calculated as $(\text{age (years)} \times \text{AST (IU/L)}) / (\text{platelets (} 10^9 \text{/L)} \times (\text{ALT}$
18 $(\text{IU/L})^{1/2})$, and GPR was calculated as $GPR = (\text{GGT (IU/L)} / \text{GGT ULN (IU/L)}) / \text{platelet count}$
19 $(10^9 \text{/L}) \times 100$. GGT ULN was set at 50 IU/L. The following cut-off values were used to rule in
20 significant liver fibrosis: APRI > 1.5 (18), FIB-4 > 3.25 (20,21) and GPR > 0.32 (22).
21
22
23
24
25
26
27
28
29
30

31 Explanatory variables

32
33
34 Time since HBV diagnosis (in years) was used for people not on treatment at
35 enrolment and with no treatment history. Instead, for people on treatment at enrolment, time
36 since treatment initiation (in years) was used. As these two variables were highly correlated
37 in the latter group, we chose the second variable for reasons related to interpretability.
38
39 Cannabis and tobacco use were categorized as current/former/never. Unhealthy alcohol use
40 was defined as > 2 and > 3 standard drinks per day for women and men, respectively, in
41 accordance with the French National Authority for Health (23). Both past and current
42 unhealthy use were taken into account. Current coffee consumption was tested alternatively
43 as a categorical variable (with 0, 1-2 and ≥ 3 cups per day as categories) and as a continuous
44 (number of cups per day) variable to test for a dose-response relationship. Current tea
45 consumption was tested as a dichotomized variable (daily vs. non-daily) in the main
46 analyses, and as a continuous variable (number of cups per day) in the sensitivity analyses.
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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

1 potential changes in terms of the degree of significance of the associations and changes in
2 OR estimates (26). Stata version 14.2 for Windows (StataCorp, College Station, Texas, USA)
3
4 was used for all analyses.
5

6 7 Results

8 9 Study population characteristics

10
11 Among the 5213 patients with chronic HBV infection at enrolment in ANRS CO22
12 Hepather, 166 participants were excluded because of HCV co-infection, 175 because of HDV
13 co-infection, 262 because of a history of, but no current, HBV treatment, and 818 because of
14 missing data for non-invasive liver fibrosis markers. The study population therefore
15 comprised 3792 participants, among whom 2065 had no history of HBV treatment, and 1727
16 were on treatment at enrolment.
17
18

19
20 Participants were mainly men (57.2% and 72.8% of untreated and treated
21 participants, respectively), were predominantly from Africa (44.2%) and France (29.8%), and
22 were diagnosed with HBV for a median of 6.7 (untreated) and 11.9 years (treated) (**Table 1**).
23 More than half (54.6%) of untreated participants lived in poverty versus less than half
24 (41.4%) of treated participants. The overall proportion of participants with significant liver
25 fibrosis was 2.5, 4.4, and 36.4% according to the APRI, FIB-4, and GPR markers,
26 respectively. Proportions were higher in treated participants than in their untreated
27 counterparts (**Table 1**).
28
29

30 31 Factors associated with significant fibrosis

32 33 Untreated participants

34
35 After multiple adjustment, significant fibrosis in untreated participants was associated
36 with male gender (GPR), being born in Africa (vs. France, GPR), moderate and (current or
37 past) unhealthy alcohol use (GPR), and time since HBV diagnosis (APRI and FIB-4). It was
38 inversely associated with daily tea consumption (GPR) (**Table 2**).
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 Reintroducing variables into the final model for each outcome which were eligible for
2 each multivariable model but discarded during the stepwise procedure had no impact on
3
4 significance levels or magnitude of model estimates.
5

6 Treated participants

7
8 After multiple adjustment, significant fibrosis in treated participants was associated
9 with male gender (all markers), inversely associated with being born in Europe or Asia (vs.
10 France, GPR), inversely associated with ≥ 3 cups of coffee per day (all markers), inversely
11 associated with past or current cannabis use (GPR), associated with current tobacco use
12 (GPR) and current or past unhealthy alcohol use (FIB-4 and GPR), inversely associated with
13 having a secondary school certificate (FIB-4 and GPR), associated with living in poverty
14 (GPR), and finally, associated with time since HBV treatment initiation (APRI and GPR)
15
16
17
18
19
20
21
22
23
24 **(Table 3).**
25

26
27 Reintroducing variables into the final model for each outcome which were eligible for
28 each multivariable model but discarded during the stepwise procedure had no impact on
29
30 significance levels or magnitude of model estimates.
31

32 Sensitivity analyses

33
34 Sensitivity analyses with coffee or tea consumption as continuous variables gave
35 similar results in all models. The risk of fibrosis in untreated participants decreased by 22%
36 for each additional cup of tea ($p=0.020$) according to GPR. Instead, for coffee consumption in
37 treated participants, all three markers indicated a reduction in the risk of fibrosis for each
38 additional cup: 51% for APRI ($p<10^{-3}$), 38 for FIB-4 ($p<10^{-3}$), and 22% for GPR ($p=0.001$)
39
40
41
42
43
44
45
46
47
48
49 (data not shown).
50

51 Discussion

52
53
54
55
56 In a study sample of 3792 chronic HBV patients, we found that elevated coffee
57
58 consumption and alcohol abstinence were consistently inversely associated with significant
59
60
61
62
63
64
65

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 only one of the three non-invasive markers studied.
4
5

6
7 Stratification of patients according to HBV treatment status and the use of three
8 different non-invasive markers ensured a fine-grained analysis. The two subpopulations were
9 different for virtually all characteristics, with relevant absolute differences for gender,
10 socioeconomic status, duration of HBV infection and presence of significant fibrosis.
11 Untreated participants had a shorter duration of infection and lower prevalence of significant
12 fibrosis. This lower prevalence may be explained by the presence of significant fibrosis
13 having led to treatment initiation. Indeed, elevated ALT and/or the presence of fibrosis or
14 cirrhosis may have accelerated HBV diagnosis if not already diagnosed, and treatment
15 initiation in all those diagnosed, in accordance with current guidelines (27).
16
17
18
19
20
21
22
23
24
25
26

27 The relevance of the three markers we studied in predicting liver fibrosis or liver
28 disease progression has previously been reported for HBV-infected patients (4,20,22,28–30).
29 Their accuracy in predicting a specific fibrosis stage is still unknown, and different cut-off
30 values have been proposed to rule in/out different fibrosis stages (20,22,28). For instance,
31 Xiao et al. in their meta-analysis reported an area under the receiver operating characteristic
32 curve (AUROC) of 0.74 and 0.78 for significant fibrosis for APRI and FIB-4 respectively, as
33 validated against liver biopsy (20). Regarding GPR and using Fibroscan, Lemoine et al.
34 reported an AUROC of 0.72-0.73 for significant fibrosis (22). In our study, the fact that a
35 GPR>0.32 was found for more than 35% of patients in our population while elevated FIB-4
36 and APRI was found for less than 5% suggests that the threshold we used for GPR
37 corresponded to a less severe fibrosis stage than the two other markers.
38
39
40
41
42
43
44
45
46
47
48
49
50
51

52 The seemingly protective effect of coffee consumption on liver fibrosis in this study
53 was previously highlighted in meta-analyses in patients with non-alcoholic fatty liver disease
54 (31,32), alcoholic liver disease, or HCV infection (33). Similar findings have also been
55 highlighted in HBV-infected patients (34,35). Our cross-sectional results are consistent with
56
57
58
59
60
61
62
63
64
65

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 (≥ 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.
12
13
14
15
16
17
18
19
20
21
22
23
24

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
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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).
9

10
11 All these results have practical implications. As HBV-infected patients have an excess
12 mortality risk, and a high risk of both liver disease and liver-related mortality (4,5,62,63),
13 increasing coffee consumption for non-users or light users may represent a simple, cost-
14 effective prevention strategy for improved liver health. Indeed, for those patients, the benefits
15 of increasing consumption are likely to exceed potential harms (64). Although decaffeinated
16 coffee may also have (probably to a lesser extent) hepatoprotective properties (36,65,66),
17 the potential harms and side effects associated with elevated coffee consumption are
18 substantially reduced (64). Our findings also highlight the need for further research
19 investigating mechanisms at play the beneficial effect which coffee consumption provides, as
20 it seems feasible (and desirable) to develop drugs for fibrosis prevention based on active
21 compounds from coffee to expand the therapeutic arsenal currently available.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42

43 Conclusion

44 Elevated coffee consumption was consistently associated with a lower risk of significant liver
45 fibrosis, as assessed by three non-invasive markers in chronic HBV patients on treatment.
46
47 This result can be immediately used in real-world situations, as increasing coffee
48 consumption may be beneficial for patients at risk of advanced liver disease.
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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.

ANRS/AFEF Hepather Study group

Investigators

Laurent Alric, Delphine Bonnet, Virginie Payssan-Sicart, Chloe Pomes (CHU Purpan, Toulouse, France), Fabien Zoulim, Marianne Maynard, Roxane Bai, Lucie Hucault, François Bailly (Hospices Civils de Lyon, Lyon, France), François Raffi, Eric Billaud, David Boutoille, Maeva Lefebvre, Elisabeth André-Garnier (Hôpital Hôtel-Dieu, Nantes, France), Paul Cales, Isabelle Hubert, Adrien Lannes, Françoise Lunel, Jérôme Boursier (CHU Angers, Angers, France), Tarik Asselah, Nathalie Boyer, Nathalie Giuily, Corinne Castelnau, Giovanna Scoazec (Hôpital Beaujon, Clichy, France), Stanislas Pol, Hélène Fontaine, Emilie Rousseaud, Anaïs Vallet-Pichard, Philippe Sogni (Hôpital Cochin, Paris, France), Victor de Ledinghen, Juliette Foucher, Jean-Baptiste Hiriart, Jancell M'Bouyou, Marie Irlès-Depé (Hôpital Haut-Lévêque, Pessac, Bordeaux, France), Marc Bourlière, Si Nafa Si Ahmed, Valérie Oules (Hôpital Saint Joseph, Marseille, France), Albert Tran, Rodolphe Anty, Eve Gelsi, Régine Truchi (CHU de Nice, Nice, France), Dominique Thabut, Saloua Hammeche, Joseph Moussali (Hôpital de la Pitié Salpêtrière, Paris, France), Xavier Causse, Barbara De Dieuleveult, Brahim Ouarani, Damien Labarrière (CHR La Source, Orléans, France), Nathalie Ganne, Véronique Grando-Lemaire, Pierre Nahon, Séverine Brulé, Betul ULKER (Hôpital Jean Verdier, Bondy, France), Dominique Guyader, Caroline Jezequel, Audrey Brener, Anne Laligant, Aline Rabot, Isabelle Renard (CHU Rennes, Rennes, France), François Habersetzer, Thomas F. Baumert, Michel Doffoel, Catherine Mutter, Pauline Simo-

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Noumbissie, Esma Razi (Hôpitaux Universitaires de Strasbourg, Strasbourg, France), Jean-Pierre Bronowicki, Hélène Barraud, Mouni Bensenane, Abdelbasset Nani, Sarah Hassani-Nani, Marie-Albertine Bernard (CHU de Nancy, Nancy, France), Georges-Philippe Pageaux, Dominique Larrey, Magda Meszaros (Hôpital Saint Eloi, Montpellier, France), Sophie Metivier, Christophe Bureau, Thibault Morales, Jean Marie Peron, Marie Angèle Robic (CHU Purpan, Toulouse, France), Thomas Decaens, Bruno Froissart, Marie-Noelle Hilleret, Charlotte Costentin, Théophile Gerster (CHU de Grenoble, Grenoble, France), Ghassan Riachi, Odile Gorla, Fatima Paris, Hélène Montialoux (CHU Charles Nicolle, Rouen, France), Vincent Leroy, Giuliana Amaddeo, Anne Varaut, Mélanie Simoes, Rachida Amzal (Hôpital Henri Mondor, Créteil, France), Olivier Chazouillères, Tony Andreani, Bénédicte Angoulevant, Azeline Chevance, Lawrence Serfaty (Hôpital Saint-Antoine, Paris, France), Jean-Charles Duclos Vallée, Didier Samuel, Teresa Antonini, Audrey Coilly, Mariagrazia Tateo (Hôpital Paul Brousse, Villejuif, France), Armand Abergel, Maud Reymond, Chanteranne Brigitte, Buchard Benjamin, Léon Muti (Hôpital Estaing, Clermont-Ferrand, France), Claire Geist, Guillaume Conroy, Raphaëlle Riffault (Centre Hospitalier Régional, Metz, France), Isabelle Rosa, Camille Barrault, Laurent Costes, Hervé Hagège (Centre Hospitalier Intercommunal, Créteil, France), Véronique Loustaud-Ratti, Paul Carrier, Maryline Debette-Gratien, (CHU Limoges, Limoges, France), Philippe Mathurin, Guillaume Lassailly, Elise Lemaitre, Valérie Canva, Sébastien Dharancy, Alexandre Louvet (CHRU Claude Huriez, Lille, France), Anne Minello, Marianne Latournerie, Marc Bardou, Thomas Mouillot (Dijon University Hospital, Dijon, France), Louis D'Alteroche, Didier Barbereau, Charlotte Nicolas, Laure Elkrief, Anaïs Jaillais (CHU Trousseau, 37044 Tours, France), Jérôme Gournay, Caroline Chevalier, Isabelle Archambeaud, Sarah Habes (CHU de Nantes, Nantes, France), Isabelle Portal (CHU Timone, Marseille, France), Moana Gelu-Simeon, Eric Saillard, Marie-Josée Lafrance, Lucie Catherine (CHU de Pointe-à-Pitre, Pointe-à-Pitre, Guadeloupe).

Methodology and Coordinating Centre

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Fabrice Carrat (coordinator), Frederic Chau, Céline Dorival, Isabelle Goderel, Clovis Lusivika-Nzinga, Marc-Antoine Bellance, Jonathan Bellet, Priscilla Monfalet, Jessica Chane-Teng, Sephora Bijaoui, Grégory Pannetier, François Téoulé, Jérôme Nicol, Rafika Bekhti (Sorbonne University & INSERM U1136 - IPLESP, Paris, France).

Sponsor

Carole Cagnot, Anaïs Boston, Laura Nailler, Guillaume Le Meut (INSERM-ANRS-MIE, Paris, France), Alpha Diallo (Pharmacovigilance coordinator), Ventzislava Petrov-Sanchez (coordinator).

Scientific Committee

- Voting members:

Marc Bourlière (Hôpital St Joseph, Marseille), Jérôme Boursier (CHU Angers, Angers, France), Fabrice Carrat (Scientific Coordinator, Hôpital Saint-Antoine, Paris, France), Patrizia Carrieri (INSERM U912, Marseille, France), Elisabeth Delarocque-Astagneau (Inserm UMR1181, Paris), Victor De Ledinghen (Hôpital Haut-Lévêque, Pessac, Bordeaux, France), Céline Dorival (UPMC & INSERM U1136, Paris, France), Hélène Fontaine (Hôpital Cochin, Paris, France), Slim Fourati (Hôpital Henri Mondor, Créteil, France), Chantal Housset (Inserm UMR-S938 1 IFR65, Paris), Dominique Larrey (Hôpital Saint Eloi, Montpellier, France), Pierre Nahon (Hôpital Jean Verdier, Bondy, France), Georges-Philippe Pageaux (Hôpital Saint Eloi, Montpellier, France), Ventzislava Petrov-Sanchez (ANRS, Paris, France), Stanislas Pol (Principal Investigator, Hôpital Cochin, Paris, France), Mathias Bruyand (Agence Nationale de Santé Publique, Saint Maurice, France), Linda Wittkop (ISPED-INSERM U897, Bordeaux, France), Fabien Zoulim (Hospices Civils de Lyon, Lyon, France), Jessica Zucman-Rossi (Inserm U674/1162, Paris).

- Non-voting members:

1 Marianne L'hennaff (ARCAT-TRT-5-CHV, France), Michèle Sizorn (SOS hépatites, France);
2 one representative of INSERM-ANRS-MIE Pharmacovigilance team, Paris, France (Anaïs
3 Boston, Alpha Diallo), Carole Cagnot (INSERM-ANRS-MIE, Paris, France), one member of
4 Inserm Transfert, Paris, France (Alice Bousselet, Mireille Caralp), and one representative of
5
6
7
8
9 each pharmaceutical company (MSD, Gilead, Abbvie).

10 11 12 Funding statement

13
14
15
16 Hepather cohort is funded by INSERM-ANRS MIE (France REcherche Nord&sud
17 Sida-vih Hépatites | Maladies Infectieuses Emergentes), ANR Equipex and Cohort (Agence
18 Nationale de la Recherche), DGS (Direction Générale de la Santé) and MSD, Janssen,
19
20
21
22
23 Gilead, Abbvie, BMS, and Roche.

24 25 26 Conflicts of interest

27
28
29
30 Stanislas Pol has served as a speaker, a consultant and an advisory board member for
31 Janssen, Gilead, Roche, MSD, Abbvie, Biotest, Shinogi, Vivv, and LFB. He has received
32 research funding from Gilead, Abbvie, Roche and MSD not connected to the present work.

33
34
35
36 Fabrice Carrat reports grants from INSERM-ANRS during the implementation of this study
37 and personal fees from Imaxio, outside the submitted work.

38
39
40
41 The other authors have no conflict of interest to declare.

42 Authors' contributions

43
44
45
46 TB, HF and CP designed the study.

47
48
49
50 VDB cleaned the data.

51
52
53
54 CR performed the statistical analyses.

55
56
57
58 HF, SP, CC, CD, JZR, FZ and FC contributed to the design of the study and participated in
59 data collection.

60
61
62
63
64
65
66 TB wrote the original paper.

All authors reviewed the manuscript.

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

References

1. Tang LSY, Covert E, Wilson E, Kottlil S. Chronic Hepatitis B Infection: A Review. *JAMA*. 1 mai 2018;319(17):1802- 13.
2. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 22 janv 2020;5(3):245- 66.
3. Maucort-Boulch D, de Martel C, Franceschi S, Plummer M. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. *Int J Cancer*. 15 juin 2018;142(12):2471- 7.
4. Tseng T-C, Liu C-J, Su T-H, Yang W-T, Chen C-L, Yang H-C, et al. Fibrosis-4 index predicts cirrhosis risk and liver-related mortality in 2075 patients with chronic HBV infection. *Aliment Pharmacol Ther*. juin 2018;47(11):1480- 9.
5. Kim JH, Kim JW, Seo JW, Choe WH, Kwon SY. Noninvasive Tests for Fibrosis Predict 5-Year Mortality and Hepatocellular Carcinoma in Patients With Chronic Hepatitis B. *J Clin Gastroenterol*. déc 2016;50(10):882- 8.
6. Asselah T, Loureiro D, Boyer N, Mansouri A. Targets and future direct-acting antiviral approaches to achieve hepatitis B virus cure. *Lancet Gastroenterol Hepatol*. nov 2019;4(11):883- 92.
7. Tout I, Loureiro D, Mansouri A, Soumelis V, Boyer N, Asselah T. Hepatitis B surface antigen seroclearance: Immune mechanisms, clinical impact, importance for drug development. *J Hepatol*. août 2020;73(2):409- 22.
8. Song A, Wang X, Lu J, Jin Y, Ma L, Hu Z, et al. Durability of hepatitis B surface antigen seroclearance and subsequent risk for hepatocellular carcinoma: A meta-analysis. *J Viral Hepat*. avr 2021;28(4):601- 12.
9. Bedossa P. Reversibility of hepatitis B virus cirrhosis after therapy: who and why? *Liver Int*. janv 2015;35 Suppl 1:78- 81.
10. Xiong M, Li J, Yang S, Zeng F, Ji Y, Liu J, et al. Impacts of cigarette smoking on liver fibrosis and its regression under therapy in male patients with chronic hepatitis B. *Liver Int*. août 2019;39(8):1428- 36.
11. Vaz J, Strömberg U, Eriksson B, Buchebner D, Midlöv P. Socioeconomic and marital status among liver cirrhosis patients and associations with mortality: a population-based cohort study in Sweden. *BMC Public Health* [Internet]. 30 nov 2020 [cité 11 juin 2021];20. Disponible sur: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7706059/>
12. Jepsen P, Vilstrup H, Andersen PK, Sørensen HT. Socioeconomic status and survival of cirrhosis patients: A Danish nationwide cohort study. *BMC Gastroenterol*. 18 mai 2009;9:35.
13. Bae M, Park Y-K, Lee J-Y. Food components with antifibrotic activity and implications in prevention of liver disease. *J Nutr Biochem*. mai 2018;55:1- 11.

14. Soleimani D, Ranjbar G, Rezvani R, Goshayeshi L, Razmpour F, Nematy M. Dietary patterns in relation to hepatic fibrosis among patients with nonalcoholic fatty liver disease. *Diabetes Metab Syndr Obes.* 2019;12:315- 24.
15. Aller R, Sigüenza R, Pina M, Laserna C, Antolín B, Burgueño B, et al. Insulin resistance is related with liver fibrosis in type 2 diabetic patients with non-alcoholic fatty liver disease proven biopsy and Mediterranean diet pattern as a protective factor. *Endocrine.* juin 2020;68(3):557- 63.
16. Carrieri MP, Protopopescu C, Marcellin F, Wittkop L, Lacombe K, Esterle L, et al. The impact of coffee consumption on fibrosis and steatosis in HIV-HCV co-infected patients. *J Hepatol.* 2 nov 2017;
17. Pol S, Bourliere M, Lucier S, Hezode C, Dorival C, Larrey D, et al. Safety and efficacy of daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients. *J Hepatol.* 2017;66(1):39- 47.
18. Wai C-T, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology.* août 2003;38(2):518- 26.
19. Sterling Richard K., Lissen Eduardo, Clumeck Nathan, Sola Ricard, Correa Mendes Cassia, Montaner Julio, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology.* 25 mai 2006;43(6):1317- 25.
20. Xiao G, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. *Hepatology.* janv 2015;61(1):292- 302.
21. Mallet V, Dhalluin-Venier V, Roussin C, Bourliere M, Pettinelli ME, Giry C, et al. The accuracy of the FIB-4 index for the diagnosis of mild fibrosis in chronic hepatitis B. *Aliment Pharmacol Ther.* 15 févr 2009;29(4):409- 15.
22. Lemoine M, Shimakawa Y, Nayagam S, Khalil M, Suso P, Lloyd J, et al. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. *Gut.* 1 août 2016;65(8):1369- 76.
23. Haute Autorité de Santé (French National Authority for Health). Screening tool for early detection and brief intervention (Outil d'aide au repérage précoce et à l'intervention brève) [Internet]. 2014 [cité 24 oct 2019]. Disponible sur: https://www.has-sante.fr/jcms/c_1795221/fr/outil-d-aide-au-reperage-precoce-et-intervention-breve-alcool-cannabis-tabac-chez-l-adulte
24. FIRTH D. Bias reduction of maximum likelihood estimates. *Biometrika.* 1 mars 1993;80(1):27- 38.
25. Hosmer D W, Lemeshow S. *Applied Logistic Regression* [Internet]. Second edition. John Wiley & Sons, Inc.; [cité 8 oct 2019]. Disponible sur: <https://onlinelibrary.wiley.com/doi/book/10.1002/0471722146>
26. Dunkler D, Plischke M, Leffondré K, Heinze G. Augmented Backward Elimination: A Pragmatic and Purposeful Way to Develop Statistical Models. *PLOS ONE.* 21 nov 2014;9(11):e113677.

27. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *Journal of Hepatology*. 1 août 2017;67(2):370- 98.
28. Lee J, Kim MY, Kang SH, Kim J, Uh Y, Yoon KJ, et al. The gamma-glutamyl transferase to platelet ratio and the FIB-4 score are noninvasive markers to determine the severity of liver fibrosis in chronic hepatitis B infection. *Br J Biomed Sci*. juill 2018;75(3):128- 32.
29. Ben Ayed H, Koubaa M, Yaich S, Rekik K, Ben Jemaa T, Maaloul I, et al. A new combined predicting model using a non-invasive score for the assessment of liver fibrosis in patients presenting with chronic hepatitis B virus infection. *Med Mal Infect*. nov 2019;49(8):607- 15.
30. Zhu Y-F, Tan Y-F, Xu X, Zheng J-L, Zhang B-H, Tang H-R, et al. Gamma-glutamyl transpeptidase-to-platelet ratio and the fibrosis-4 index in predicting hepatitis B virus-related hepatocellular carcinoma development in elderly chronic hepatitis B patients in China: A single-center retrospective study. *Medicine (Baltimore)*. déc 2019;98(50):e18319.
31. Wijarnpreecha K, Thongprayoon C, Ungprasert P. Coffee consumption and risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol*. févr 2017;29(2):e8- 12.
32. Hayat U, Siddiqui AA, Okut H, Afroz S, Tasleem S, Haris A. The effect of coffee consumption on the non-alcoholic fatty liver disease and liver fibrosis: A meta-analysis of 11 epidemiological studies. *Ann Hepatol*. févr 2021;20:100254.
33. Liu F, Wang X, Wu G, Chen L, Hu P, Ren H, et al. Coffee Consumption Decreases Risks for Hepatic Fibrosis and Cirrhosis: A Meta-Analysis. *PLOS ONE*. 10 nov 2015;10(11):e0142457.
34. Hodge A, Lim S, Goh E, Wong O, Marsh P, Knight V, et al. Coffee Intake Is Associated with a Lower Liver Stiffness in Patients with Non-Alcoholic Fatty Liver Disease, Hepatitis C, and Hepatitis B. *Nutrients*. 1 janv 2017;9(1):56.
35. Chen C-L, Chang W-C, Yi C-H, Hung J-S, Liu T-T, Lei W-Y, et al. Association of coffee consumption and liver fibrosis progression in patients with HBeAg-negative chronic hepatitis B: A 5-year population-based cohort study. *J Formos Med Assoc*. févr 2019;118(2):628- 35.
36. Dranoff JA. Coffee Consumption and Prevention of Cirrhosis: In Support of the Caffeine Hypothesis. *Gene Expr*. 21 mars 2018;18(1):1- 3.
37. Dranoff JA, Feld JJ, Lavoie ÉG, Fausther M. HOW DOES COFFEE PREVENT LIVER FIBROSIS? BIOLOGICAL PLAUSIBILITY FOR RECENT EPIDEMIOLOGICAL OBSERVATIONS. *Hepatology*. août 2014;60(2):464- 7.
38. Contaldo F, Santarpia L, Pasanisi F. Chronic inflammatory liver diseases and coffee intake. *Curr Opin Clin Nutr Metab Care*. sept 2019;22(5):389- 92.
39. Federico A, Rosato V, Masarone M, Torre P, Dallio M, Romeo M, et al. The Role of Fructose in Non-Alcoholic Steatohepatitis: Old Relationship and New Insights. *Nutrients*. 16 avr 2021;13(4):1314.
40. Miłek M, Młodecki Ł, Dżugan M. Caffeine content and antioxidant activity of various brews of specialty grade coffee. *Acta Sci Pol Technol Aliment*. juin 2021;20(2):179- 88.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
41. Gilbert RM, Marshman JA, Schwieder M, Berg R. Caffeine content of beverages as consumed. *Can Med Assoc J.* 7 févr 1976;114(3):205- 8.
42. Richelle M, Tavazzi I, Offord E. Comparison of the antioxidant activity of commonly consumed polyphenolic beverages (coffee, cocoa, and tea) prepared per cup serving. *J Agric Food Chem.* juill 2001;49(7):3438- 42.
43. Alferink LJM, Fittipaldi J, Kieft-de Jong JC, Taimr P, Hansen BE, Metselaar HJ, et al. Coffee and herbal tea consumption is associated with lower liver stiffness in the general population: The Rotterdam study. *J Hepatol.* 2017;67(2):339- 48.
44. Khalaf N, White D, Kanwal F, Ramsey D, Mittal S, Tavakoli-Tabasi S, et al. Coffee and Caffeine Are Associated With Decreased Risk of Advanced Hepatic Fibrosis Among Patients With Hepatitis C. *Clin Gastroenterol Hepatol.* août 2015;13(8):1521-1531.e3.
45. Stroffolini T, Esvan R, Biliotti E, Sagnelli E, Gaeta GB, Almasio PL. Gender differences in chronic HBsAg carriers in Italy: Evidence for the independent role of male sex in severity of liver disease. *J Med Virol.* nov 2015;87(11):1899- 903.
46. Xiong M, Li J, Yang S, Zeng F, Ji Y, Liu J, et al. Influence of Gender and Reproductive Factors on Liver Fibrosis in Patients With Chronic Hepatitis B Infection. *Clin Transl Gastroenterol.* oct 2019;10(10):e00085.
47. Lee M-H, Yang H-I, Liu J, Batrla-Utermann R, Jen C-L, Iloeje UH, et al. Prediction models of long-term cirrhosis and hepatocellular carcinoma risk in chronic hepatitis B patients: risk scores integrating host and virus profiles. *Hepatology.* août 2013;58(2):546- 54.
48. Sun J, Robinson L, Lee NL, Welles S, Evans AA. No contribution of lifestyle and environmental exposures to gender discrepancy of liver disease severity in chronic hepatitis b infection: Observations from the Haimen City cohort. *PLoS One.* 2017;12(4):e0175482.
49. Cubero FJ, Urtasun R, Nieto N. Alcohol and liver fibrosis. *Semin Liver Dis.* mai 2009;29(2):211- 21.
50. Ganesan M, Eikenberry A, Poluektova LY, Kharbanda KK, Osna NA. Role of alcohol in pathogenesis of hepatitis B virus infection. *World J Gastroenterol.* 7 mars 2020;26(9):883- 903.
51. Liu X, Baecker A, Wu M, Zhou J-Y, Yang J, Han R-Q, et al. Interaction between tobacco smoking and hepatitis B virus infection on the risk of liver cancer in a Chinese population. *Int J Cancer.* 15 avr 2018;142(8):1560- 7.
52. Wang Y-H, Chuang Y-H, Wu C-F, Jan M-C, Wu W-J, Lin C-L, et al. Smoking and Hepatitis B Virus-Related Hepatocellular Carcinoma Risk: The Mediating Roles of Viral Load and Alanine Aminotransferase. *Hepatology.* avr 2019;69(4):1412- 25.
53. Brahmania M, Liu S, Wahed AS, Yim C, Hansen BE, Khalili M, et al. Alcohol, tobacco and coffee consumption and liver disease severity among individuals with Chronic Hepatitis B infection in North America. *Ann Hepatol.* août 2020;19(4):437- 45.
54. Stringhini S, Sabia S, Shipley M, Brunner E, Nabi H, Kivimaki M, et al. Association of socioeconomic position with health behaviors and mortality. *JAMA.* 24 mars 2010;303(12):1159- 66.

- 1 55. O'Donoghue G, Kennedy A, Puggina A, Aleksovska K, Buck C, Burns C, et al. Socio-economic
2 determinants of physical activity across the life course: A « DETERMINANTS OF DIET AND PHYSICAL
3 ACTIVITY » (DEDIPAC) umbrella literature review. PLoS One. 2018;13(1):e0190737.
- 4 56. Darmon N, Drewnowski A. Contribution of food prices and diet cost to socioeconomic
5 disparities in diet quality and health: a systematic review and analysis. Nutr Rev. oct
6 2015;73(10):643- 60.
- 7 57. Schneider CV, Zandvakili I, Thaiss CA, Schneider KM. Physical activity is associated with reduced
8 risk of liver disease in the prospective UK Biobank cohort. JHEPReport [Internet]. 1 juin 2021
9 [cité 18 juin 2021];3(3). Disponible sur: [https://www.jhep-reports.eu/article/S2589-
10 5559\(21\)00039-2/abstract](https://www.jhep-reports.eu/article/S2589-5559(21)00039-2/abstract)
- 11 58. Berk K, Bzdega W, Konstanynowicz-Nowicka K, Charytoniuk T, Zywno H, Chabowski A.
12 Phytocannabinoids-A Green Approach toward Non-Alcoholic Fatty Liver Disease Treatment. J
13 Clin Med. 20 janv 2021;10(3).
- 14 59. Farooqui MT, Khan MA, Cholankeril G, Khan Z, Mohammed Abdul MK, Li AA, et al. Marijuana is
15 not associated with progression of hepatic fibrosis in liver disease: a systematic review and
16 meta-analysis. European Journal of Gastroenterology & Hepatology. févr 2019;31(2):149.
- 17 60. Wijarnpreecha K, Panjawatnan P, Ungprasert P. Use of cannabis and risk of advanced liver
18 fibrosis in patients with chronic hepatitis C virus infection: A systematic review and meta-
19 analysis. J Evid Based Med. nov 2018;11(4):272- 7.
- 20 61. Hiscock R, Bauld L, Amos A, Fidler JA, Munafò M. Socioeconomic status and smoking: a review.
21 Ann N Y Acad Sci. févr 2012;1248:107- 23.
- 22 62. Iloeje UH, Yang H-I, Jen C-L, Su J, Wang L-Y, You S-L, et al. Risk and Predictors of Mortality
23 Associated With Chronic Hepatitis B Infection. Clinical Gastroenterology and Hepatology. 1 août
24 2007;5(8):921- 31.
- 25 63. Si J, Yu C, Guo Y, Bian Z, Meng R, Yang L, et al. Chronic hepatitis B virus infection and total and
26 cause-specific mortality: a prospective cohort study of 0.5 million people. BMJ Open. 9 avr
27 2019;9(4):e027696.
- 28 64. O'Keefe JH, DiNicolantonio JJ, Lavie CJ. Coffee for Cardioprotection and Longevity. Prog
29 Cardiovasc Dis. juin 2018;61(1):38- 42.
- 30 65. Xiao Q, Sinha R, Graubard BI, Freedman ND. Inverse associations of total and decaffeinated
31 coffee with liver enzyme levels in NHANES 1999–2010. Hepatology. déc 2014;60(6):2091- 8.
- 32 66. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Coffee, including
33 caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic
34 review and dose–response meta-analysis. BMJ Open. 1 mai 2017;7(5):e013739.

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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 ¹
Gender							
Male	2438	64.3	1181	57.2	1257	72.8	< 10 ⁻³
Female	1354	35.7	884	42.8	470	27.2	
Place of birth							
France	1131	29.8	515	24.9	616	35.7	< 10 ⁻³
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	
<i>Missing</i>	1	0.0					

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Living with a partner								
No	1333	35.2	782	38.0	551	32.0	< 10 ⁻³	
Yes	2446	64.5	1274	62.0	1172	68.0		
<i>Missing</i>	13	0.3						
Coffee consumption								
0 cups/day	1331	35.1	810	39.9	521	30.8	< 10 ⁻³	
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						
Coffee consumption								
Median [IQR]	1 [0 – 3]	-	1 [0 – 2]	-	1 [0 – 3]	-	< 10 ⁻³	
Tea consumption								
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						
Cannabis use								
Never	3535	93.2	1915	93.3	1620	94.6	0.068	

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Former	139	3.7	77	3.8	62	3.6	
Current	92	2.4	61	3.0	31	1.8	
<i>Missing</i>	26	0.7					
Tobacco use							
Never	2423	63.9	1399	67.8	1024	59.3	< 10 ⁻³
Former	698	18.4	298	14.4	400	23.2	
Current	669	17.6	366	17.7	303	17.5	
<i>Missing</i>	2	0.1					
Alcohol use							
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 ²	221	5.8	102	5.0	119	6.9	
<i>Missing</i>	17	0.4					
Living in poverty³							
No	1877	49.5	902	45.4	975	58.6	< 10 ⁻³

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Yes	1775	46.8	1086	54.6	689	41.4	
<i>Missing</i>	140	3.7					
Educational level							
< 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	
<i>Missing</i>	73	1.9					
Time since HBV diagnosis							
– <i>in years</i>							
Median [IQR]	9.18 [3.82 – 16.86]	-	6.67 [2.36 – 12.95]	-	11.94 [6.41 – 19.92]	-	< 10 ⁻³
Time since first HBV treatment – <i>in years</i>							
Median [IQR]	6.22 [2.51 – 10.88]	-	-	-	6.22 [2.51 – 10.88]	-	-
FIB-4 score							
≤ 3.25	3625	95.6	2026	98.1	1599	92.6	< 10 ⁻³
> 3.25	167	4.4	39	1.9	128	7.4	
GPR score							
≤ 0.32	2413	63.6	1425	69.0	988	57.2	< 10 ⁻³

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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

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

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

³Poverty 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.

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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>1.5¹				FIB-4>3.25¹				GPR>0.32¹			
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	

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Female	0.57 [0.27 – 1.18]	0.127			0.53 [0.27 – 1.06]	0.074			0.19 [0.15 – 0.23]	< 10 ⁻³	0.22 [0.17 – 0.28]	< 10 ⁻³
Place of birth		0.508				0.302				< 10⁻³		< 10⁻³
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 ⁻³	1.69 [1.30 – 2.20]	< 10 ⁻³
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

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1-2 cups/da y	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/da y	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 consum ption												
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 ⁻³	0.78 [0.63 – 0.96]	0.020
Cannab is use		0.854				0.573				0.078		

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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		
Tobacco use		0.623				0.047				< 10⁻³		
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 ⁻³		

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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		0.606				0.255				< 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

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Current or past unhealth y use ²	1.69 [0.44 – 6.45]	0.445			2.25 [0.71 – 7.19]	0.170				3.92 [2.59 – 5.92]	< 10 ⁻³	3.18 [2.04 – 4.94]	< 10 ⁻³
Living in poverty³													
No (ref.)	1				1					1			
Yes	0.78 [0.40 – 1.54]	0.473			0.70 [0.37 – 1.34]	0.286				1.03 [0.85 – 1.24]	0.787		
Educati onal level													
< Second	1				1					1			

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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		

¹For 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.

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

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

³Poverty 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.

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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	Univariate analysis		Multivariate analysis N = 1721		Univariate analysis		Multivariate analysis N = 1735		Univariate analysis		Multivariate 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 ⁻³	0.23 [0.18 – 0.31]	< 10 ⁻³
Place of birth		0.423				0.732				0.001		0.002

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

France (ref.)	1				1				1		1	
Europe (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		

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Coffee consumption		0.00		0.00		0.00		0.00		0.15		0.00
		2		2		5		1		8		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 ³	0.16 [0.06 – 0.44]	< 10 ³	0.43 [0.25 – 0.73]	0.00 2	0.35 [0.20 – 0.61]	< 10 ³	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		

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Cannabis use		0.91				0.64				0.16		0.00
		9				3				8		2
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
Tobacco use		0.14				0.01				< 10⁻³		0.02
		8				5				3		0
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]	< 10 ⁻³	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
Alcohol use		0.07				< 10⁻³		0.00		0.00		0.01
		8				3		2		1		8

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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 ²	2.09 [0.96 – 4.56]	0.06 2			2.79 [1.64 – 4.75]	< 10 ³	2.60 [1.46 – 4.64]	0.00 1	2.04 [1.39 – 3.00]	< 10 ³	1.66 [1.07 – 2.57]	0.02 3
Living in poverty ³												
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

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Educational level												
< 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]	3	0.73 [0.60 – 0.89]	0.00 2	0.77 [0.62 – 0.96]	0.02 2
Time since the first HBV treatment – in years	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

¹For 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.

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

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

³Poverty 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.