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Cannabis use is inversely associated with overweight and obesity in HBV-infected patients (ANRS CO22 Hepather cohort)

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Keywords

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Running title

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Author contributions

TB, CP, PC and FM designed the study.

VDB performed data curation.

CR performed the statistical analyses.

SP, FC, HF, MB, TA, LS, JB and CD contributed to the design of the study and participated in data collection.

TB wrote the original paper.

All authors reviewed the manuscript and approved the final version, including the authorship list.

Abstract

Background

Chronic hepatitis B virus (HBV) infection may evolve into cirrhosis and hepatocellular carcinoma, and this progression may be accelerated by specific risk factors including overweight and obesity. Although evidence for a protective effect of cannabis use on elevated body weight has been found for other populations, no data are available for HBV-infected patients.

Aims

We aimed to identify risk factors (including cannabis use) for overweight and obesity in patients with HBV chronic infection.

Methods

Using baseline data from the French ANRS CO22 Hepather cohort, we performed two separate analyses, one using 'central obesity' (based on waist circumference) and the other 'overweight' and 'obesity' (based on body mass index) as outcomes. Logistic and multinomial regressions were used to model central obesity and overweight/obesity, respectively.

Results

Among the 3706 patients in the study population, 50.8% had central obesity, 34.7% overweight, and 14.4% obesity. After multivariable adjustment, current cannabis use was associated with a 59% lower risk of central obesity compared with no lifetime use (adjusted odds ratio [95% confidence interval (CI)]: 0.41 [0.24–0.70]). It was also associated with a 54 and 84% lower risk of overweight (adjusted relative risk ratio [95% CI]: 0.46 [0.27–0.76]) and obesity (0.16 [0.04–0.67]), respectively.

Conclusions

Cannabis use was associated with lower risks of overweight and obesity in patients with HBV chronic infection. Future studies should test whether these potential benefits of cannabis and cannabinoid use translate into reduced liver diseases progression in this high-risk population.

Introduction

It has been estimated that HBV chronic infection accounted for a quarter of all global deaths caused by cirrhosis in 2017 ¹, and more than half of liver cancer cases in 2012 ². To date, despite the progress made with long-term nucleo(s)tide analogue therapy, HBsAg loss/seroconversion is rarely achieved, and most HBV-infected patients require therapy indefinitely ^{3,4}.

Hepatic steatosis, increased body mass index (BMI), diabetes, and combinations of these and other metabolic risk factors are associated with an increased risk of cirrhosis and hepatocellular carcinoma in HBV-infected patients ⁵. As obesity is a risk factor for hepatic steatosis ⁶ and mortality in this population ⁷, identifying clinical and socio-behavioural factors associated with obesity is crucial for optimal clinical management.

HBV vaccine has been compulsory for French newborns since 2018, and is recommended by the country's health authorities until 15 years of age. Although HBV prevalence is low in people born in France, it is higher in people living in France who were born in countries where HBV is endemic ⁸. In France and Europe, income is generally lower in immigrant households and the likelihood of poverty is higher ⁹. Given this context, where HBV carriers in France are expected to be mainly migrants with low socioeconomic status ⁸, and given that socioeconomic status is associated with obesity and weight gain ^{10,11}, we might expect that HBV-infected patients in France are at higher risk of obesity.

Cannabis use has been associated with reduced BMI and a lower likelihood of weight gain in the general population ^{12,13(p3),14}, with possible indirect preventive effects on cardiometabolic risk ¹⁵. However, while the potential benefits of cannabis use have been highlighted in patients with hepatitis C virus (HCV) infection ^{16,17}, neither its prevalence nor its

effects on anthropometric or clinical outcomes have yet been investigated in HBV-infected patients.

Cannabis use is still criminalized in France. Users may be punished with up to one year in prison and a fine of 3750€¹⁸; since 2020, an on-the-spot fine of 150€ can replace the normal procedure at the police's discretion¹⁹. Despite this criminalization, France has the highest prevalence of cannabis use among young people and adults in Europe²⁰, and indicators of cannabis use disorder and treatment for dependence are on the rise²¹. The demand for herbal cannabis is also growing, as is its potency²². While a national experimentation evaluating the putative circuit whereby medical cannabis would be made available for patients insufficiently relieved from other treatment is ongoing²³, there is still no legal framework for a therapeutic cannabis use in France.

Using data from the French ANRS CO22 Hepather cohort, we aimed to document cannabis use prevalence in HBV-infected patients followed in France, and to identify clinical and socio-behavioural (including cannabis use) risk factors for obesity and overweight in this population.

Materials and methods

Design and participants

The ANRS CO22 Hepather cohort is an ongoing French, national, multicentre, prospective, observational cohort study of patients with chronic active or inactive HBV or HCV infection. The cohort started in August, 2012²⁴. Eligible patients were invited to participate in the cohort during a medical follow-up visit in their hepatitis healthcare centre. Thirty-two centres were involved throughout France. Sociodemographic, clinical and biological data were collected at the enrolment visit. Patients were followed on a yearly basis, and supplemental data were collected during visits related to particular events (e.g., HBV or

HCV therapy initiation). Written informed consent was obtained from each cohort participant before enrolment. The Hepather protocol was designed in accordance with the Declaration of Helsinki and French law for biomedical research. It 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 main exclusion criterion in Hepather was HIV co-infection. For the present study, the study population comprised patients with chronic HBV infection at cohort enrolment (defined by positive HBsAg for at least six months). Patients with HCV coinfection (n=166) were excluded, as were patients with no data on cannabis use, and those with unavailable data for waist circumference or BMI.

Data collection

The present cross-sectional study is based on data retrieved from the enrolment visit. During this visit, physicians interviewed the participants face to face using a structured questionnaire. Anthropological measurements and urine and blood samples were also collected during the same visit.

The questionnaire collected clinical and sociodemographic data including gender, age, country of birth, educational level, average monthly household income, employment status (employed or not), time since HBV diagnosis, HBV treatment status, cannabis use, tobacco use, current and past alcohol consumption (number of standard drinks per day) and current coffee consumption (number of cups per day). Body height, weight and waist circumference were measured. Data derived from blood samples included platelet count ($10^9/L$), aspartate aminotransferase (AST, IU/L) and alanine aminotransferase (ALT, IU/L) levels.

Outcomes

We used two different obesity-related outcomes. The first was 'central' obesity, defined as having a waist circumference ≥ 94 cm for men (except for men born in Asia, Central or South America, for whom the cut-off was set at 90 cm) and ≥ 80 cm for women ²⁵. The second was a three-category BMI-status variable; specifically, participants with obesity (defined as a BMI ≥ 30 kg/m²), and those with overweight (defined as a BMI between 25 and 30 kg/m²), were compared with participants with no obesity or overweight ²⁶.

Explanatory variables

For both cannabis and tobacco use, participants were classified in the 'current', 'former' or 'never' category. For coffee consumption, a three-category variable was created based on the thresholds of no, one and three or more cups per day. The second threshold (i.e., 1 cup/day) was used to test for a potential dose-dependent relationship between coffee consumption and the outcomes. The third threshold (i.e., 3 cups or more/day) was chosen based on previous results showing a potential protective effect of coffee on liver stiffness and mortality in patients likely to develop liver disease ²⁷⁻²⁹. Alcohol consumption was categorized into four categories based on the threshold for unhealthy alcohol use (defined as > 2 standard drinks per day for women and > 3 standard drinks per day for men, in accordance with the French National Authority for Health ³⁰) as follows: abstinent i) with or ii) without a history of unhealthy alcohol use, iii) current unhealthy alcohol use, and iv) current moderate alcohol use (i.e., non-abstinent and non-unhealthy use). 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 diploma or not. Liver fibrosis was assessed using the FIB-4 index, which is a non-invasive marker of fibrosis calculated using age, AST level, ALT level, and platelet count with the following

formula: $\text{age [years]} * \text{AST [IU/L]} / (\text{platelet count [10}^9\text{/L]} * (\text{ALT [IU/L]})^{1/2}$. The presence of advanced fibrosis was defined as an FIB-4 index >3.25 ^{31,32}.

Statistical analyses

Two separate comparisons (i.e., one for each outcome) of study sample characteristics were made: one between participants with and without central obesity, and one according to the three-category BMI status variable (participants with obesity, those with overweight, and those without obesity or overweight). The Chi-square and Student's t test were used for categorical and continuous variables, respectively. Similarly, characteristics of excluded patients because of missing data on cannabis use, waist circumference or BMI were compared with those of included patients. Two separate analyses were performed to test for the association between cannabis use and the two study outcomes at cohort enrolment, after adjustment for other potential predictors. First, we estimated a logistic regression model with central obesity as the outcome. Second, we estimated a multinomial regression model with the three-category BMI-status outcome. Specifically, for the latter we took underweight or normal weight as the reference, and tested for the association between explanatory variables and both overweight and obesity. Associations were assessed by odds ratios (OR) for the logistic regression and by relative risk ratios (RRR) for the multinomial regression. The adjustment variables were considered eligible for inclusion in the multivariable analyses if they presented a P-value < 0.20 (Wald test) in the univariable analyses. A backward procedure based on the Wald test was used to select the adjustment variables to keep in each of the final two multivariable models (significance threshold set at $P \leq 0.05$). Variables eligible for multivariable analyses but not retained in the final models were reintroduced in these latter to test for potential changes in terms of the degree of significance of the associations and changes in OR or RRR estimates ³³. An effect of cannabis use on waist circumference and BMI as continuous variables was also tested using linear regression models, based on the same variable selection procedure.

To test for any potential bias introduced by the exclusion of participants with missing waist circumference measures, we performed a sensitivity analysis by including them in the analysis with the three-category BMI-status outcome, and compared the results with those of the main analysis.

All analyses were performed with Stata software version 14.1 for Windows (StataCorp LP, College Station, TX).

Results

Study population characteristics

The study population comprised 3706 participants (**Figure 1**). Their characteristics are presented in **Table 1**. Most were men (63.1%), median age was 42 years (interquartile range (IQR) [34 – 54]), and median time since HBV infection diagnosis was nine years (IQR [4 – 17]). Most (93.8%) declared they had never used cannabis, and only 2.6% were current users (**Table 1**). With regard to waist circumference and BMI, 50.8 and 14.4% of participants were classified as people with obesity, respectively, while 34.7% were classified as people with overweight. Among participants classified with obesity according to their BMI, 97.6% were classified with central obesity.

Excluded cohort patients differed from those included in the present study in terms of age (less than one-year difference in median), alcohol consumption, and employment status (data not shown).

Factors associated with central obesity

In multivariable analysis, participants reporting current cannabis use had a 59% lower risk of central obesity than those who never used it (adjusted odds ratio (aOR) [95% confidence interval (CI)]: 0.41 [0.24 – 0.70], $p=0.001$) (**Table 2**). Other protective factors were

being a man, younger age, not living in poverty and having a secondary school diploma. Current cannabis use was also associated with a lower waist circumference value after multiple adjustment (linear regression coefficient (coef.) [95% CI]: -5.65 [-7.89 – -3.41], $p < 10^{-3}$) (data not shown). None of the reintroductions of excluded explanatory variables in the final model had a relevant impact on the model estimates.

Factors associated with overweight and obesity as measured by BMI

In univariable analyses (**Table 3**), current cannabis use compared with no lifetime cannabis use was associated with lower risk of both overweight and obesity.

In multivariable analysis, current cannabis users had a 54% lower risk of overweight (adjusted relative risk ratio (aRRR) [95% CI]: 0.46 [0.27 – 0.76], $p = 0.002$) and an 84% lower risk of obesity (aRRR [95% CI]: 0.16 [0.04 – 0.67], $p = 0.013$) (**Table 4**). Current cannabis use was also associated with a lower BMI value after multiple adjustment (coef. [95% CI]: -1.87 [-2.62 – -1.12], $p < 10^{-3}$) (data not shown). None of the reintroductions of excluded explanatory variables in the final model had relevant impact on models' estimates.

The following variables were associated with both definitions of obesity in multivariable analyses (**Table 2 and Table 4**): current cannabis use, female gender, older age, living in poverty, and having no secondary school diploma.

Sensitivity analyses, performed on the population that included participants with no data on waist circumference, led to the same results as those in main analysis in terms of the level of significance and adjusted relative risk ratio magnitude (data not shown).

Discussion

Using cross-sectional data from 3706 chronically infected HBV patients, we found that current cannabis use was associated with a 59% lower risk of central obesity (elevated waist circumference), an 84% lower risk of obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), and a 54% lower risk of

overweight (BMI between 25 and 30 kg/m²), when compared with no lifetime cannabis use. To our knowledge, this is the first time that such associations have been highlighted for HBV-infected patients.

Our results are consistent with findings for the general population. The negative relationship between cannabis use and BMI has been consistently reported in epidemiological studies ^{14,15,34}. A three-year national prospective study in the U.S. also found that cannabis users were less likely to gain weight than persons who never used it ¹³. Finally, the largest genome-wide association study for lifetime cannabis use to date, revealed genetic overlap between lifetime cannabis use and low BMI ¹². This effect of cannabis use on body weight may be mediated by an impact on the endocannabinoid system (ECS). It has been suggested that cannabis use may lead to a long-lasting downregulation of cannabinoid receptor 1 (CB1), which in turn reduces energy storage and increases metabolic rates ³⁵. An effect of cannabis use on endocrine pathways related to appetite and metabolism (especially insulin concentration) has also been reported ³⁶. Moreover, as the ECS in the gastrointestinal tract is a key component of the gut–brain axis that controls food intake (which is dysregulated in diet-induced obesity) ³⁷, we may expect that cannabis use also exerts a regulatory role in this local ECS and indirectly affect body weight.

Obesity or an elevated BMI are likely to foster hepatic steatosis, HCC and mortality in HBV-infected patients ^{5–7}. Conversely, improving BMI may have a beneficial effect on alanine aminotransferase normalization ^{38,39} and possibly long-term outcomes after viral suppression ³⁹. HBV-infected patients are therefore likely to benefit from overweight or obesity prevention and/or weight loss interventions, when overweight is already present. The major role of the ECS in energy homeostasis and metabolic disorders has been documented ⁴⁰. The previous use of CB1 antagonists for treating obesity yielded promising results, but was stopped because of severe side effects ⁴¹. However, the diversity of cannabinoids present in cannabis as well as their synthetic counterparts constitutes a promising field of research for alleviating elevated body weight-related disorders ^{42–44}, including in HBV-infected patients.

Further investigations should be carried out to test whether the seemingly beneficial effect of cannabis use on BMI in HBV-infected patients also translates into metabolic or hepatic benefits. Moreover, as the ECS influences gastrointestinal homeostasis, direct effects of cannabis use (and/or its derivatives) on hepatic diseases should also be investigated further ⁴⁵, especially as similar effects have already been suggested by studies conducted in HIV-HCV co-infected patients ^{17,29,46,47}. The potential protective effect of cannabis and cannabinoids on hepatic steatosis ^{27,47-49} is of particular interest for HBV-infected patients, as hepatic steatosis is a strong predictor of cancer and mortality in this population ⁵⁰.

Data on cannabis use in HBV-infected people are scarce. In the present study, 2,6% of the study population reported current cannabis use, which is much lower than self-reported prevalence for HCV-infected people in France ¹⁶, but close to previous-month use in people aged 35-44 (5.9%) and 45-54 (2.9%) observed in France in 2017 ⁵¹. Cannabis use might have been under-reported because the face-to-face data collection methodology in Hepather may have led to desirability bias.

Poverty and low educational level were strongly associated with obesity in our study. This reflects a WHO report which estimated that in the EU, 26% of obesity in men and 50% of obesity in women can be attributed to inequalities in educational level, with persons with a low socioeconomic status being approximately twice as likely to become obese ⁵². Low socioeconomic status has been associated with poorer diet quality ⁵³⁻⁵⁵, and low income is a major barrier to healthy eating ⁵⁶. Furthermore, low-income households are exposed to diverse sources of stress and short sleep duration which enhance the preference for highly palatable foods and emotional eating ⁵⁷. Finally, specific psychosocial determinants may promote unhealthy dietary habits ⁵⁸.

The gender effect which we found, where women were more likely to have obesity than men, reflects widely reported findings, and may be explained by factors including the influence of gonadal steroids on body composition and appetite, chromosomal factors, and

myriad sociocultural dynamics^{59,60}. The protective effect of tobacco smoking on obesity (BMI \geq 30 kg/m²) which we found is also in line with findings elsewhere. It has been suggested that this effect is related to both decreased food intake and increased energy expenditure⁶¹. As tobacco is frequently co-smoked with cannabis in Europe⁶², it is possible that the effect of cannabis on body weight which we observed was in reality related to tobacco. However, as it is likely that cannabis users are also tobacco cigarette users, we are confident that our adjusting for tobacco use in the analysis isolated the effect strictly due to cannabis.

The main strength of the present study is its large sample size (n= 3706), which allowed us to highlight an effect of cannabis use on obesity. However, the low self-reported prevalence of use prevented us from drawing firm conclusions, and replication studies are needed. The consistent results between the two models (i.e., BMI- and waist circumference-based) attest to the robustness of our conclusions. BMI is a simple marker that has previously been associated with progression of hepatitis B and associated fibrosis^{64–66}. It has previously been highlighted that a measure of waist circumference provides both independent and complementary information to BMI values when predicting morbidity and mortality. This is likely to be at least partly due to its ability to identify adults with increased visceral adipose tissue mass⁶⁷.

Another study strength is the fact that we statistically adjusted for socio-behavioural and clinical factors; it is widely recognized that these factors strongly impact body weight.

Some limitations must also be mentioned. First, data on cannabis use were based on self-report, which may imply desirability bias and there underreporting. However, any such underreporting would be unlikely to be different between the two groups (i.e., with and without obesity). Second, data on the principal behavioural factors related to body weight - such as dietary intake and physical activity - were unavailable. However, we believe that the impact of this was minimized as these factors are also related to socioeconomic status, for which we had data.

Conclusions

To conclude, we found that current cannabis use was consistently associated with lower risk of both obesity and overweight in patients with chronic HBV infection. Further studies should investigate the mechanisms leading to this effect, so that cannabinoid-based treatments against elevated body weight can be developed. Moreover, future studies should test whether this potential benefit of cannabis and cannabinoid use translates into a reduction in the high risk of liver disease progression in this population.

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

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Author/Conflict of Interest Disclosure Statement

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, and has received research funding from Gilead, Abbvie, Roche and MSD with no connection to the present work.

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Figure 1: Flow chart of the study population (ANRS CO22 Hepather cohort)

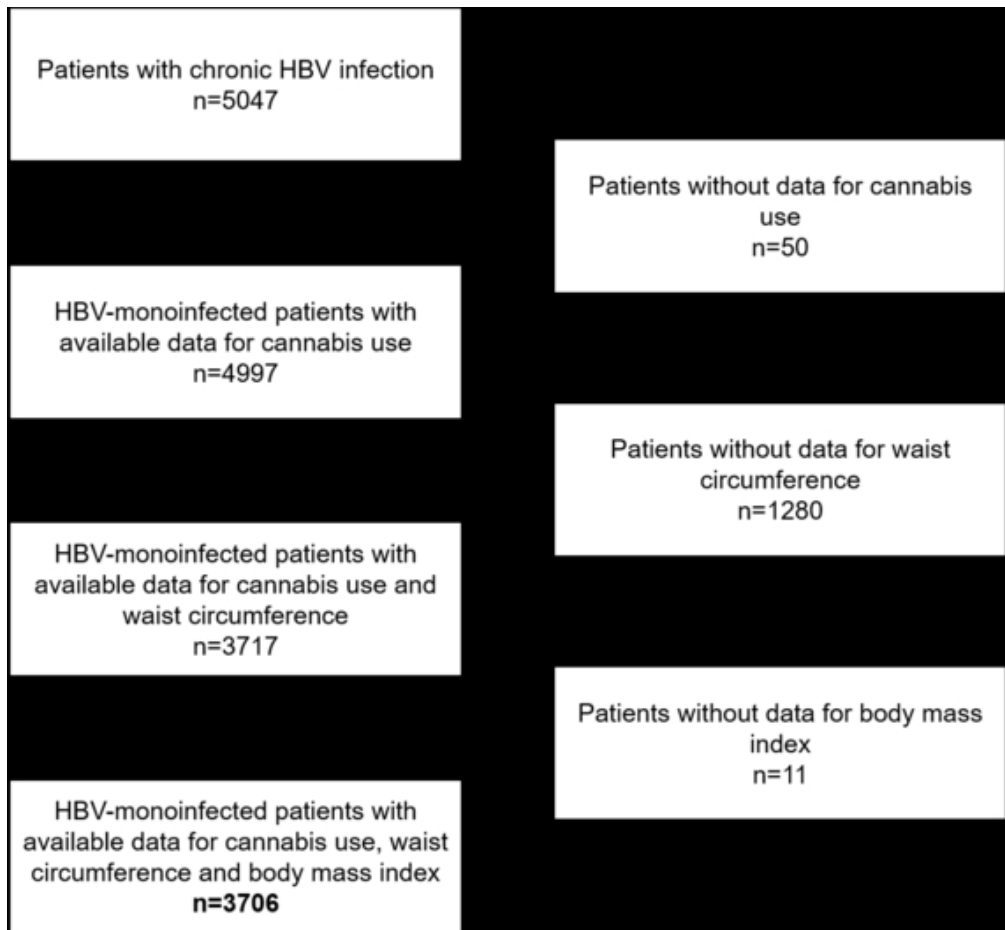


Figure 1: Flow chart of the study population (ANRS CO22 Hepather cohort)

48x44mm (300 x 300 DPI)

Table 1: Study population characteristics according to obesity status (ANRS CO22 Hepather cohort, n=3706)

Variable			Central obesity [†]					Underweight or normal weight			Overweight			Obesity		
	Study population (n=3706)	%	No (n=1884)	%	Yes (n=1822)	%	P-value	BMI < 25 (n=1886)	%	25 ≤ BMI < 30 (n=1286)	%	BMI ≥ 30 (n=534)	%	P-value		
Cannabis use																
Never	3475	93.8	1731	91.9	1744	95.7	< 10 ⁻³	1747	92.6	1217	94.6	511	95.7	< 10 ⁻³		
Former	134	3.6	74	3.9	60	3.3		67	3.6	46	3.6	21	3.9			
Current	97	2.6	79	4.2	18	1.0		72	3.8	23	1.8	2	0.4			
Gender																
Male	2338	63.1	1389	73.7	949	52.1	< 10 ⁻³	1171	62.1	897	69.8	270	50.6	< 10 ⁻³		
Female	1368	36.9	495	26.3	873	47.9		715	37.9	389	30.2	264	49.4			
Age at baseline (years)																
Median [IQR]	42 [34–54]	/	39 [31–49]	/	46 [37–58]	/	< 10 ⁻³	40 [32–51]	/	44 [35–55]	/	46 [37–58]	/	< 10 ⁻³		
Coffee consumption																
0 cup/day	1363	36.8	726	38.8	637	35.4	0.076	717	38.4	454	35.6	192	36.4	0.204		
1-2 cups/day	1323	35.7	666	35.6	657	36.5		680	36.4	453	35.5	190	36.1			
≥ 3 cups/day	982	26.5	478	25.6	504	28.0		469	25.1	368	28.9	145	27.5			
Missing	38	1.0														
Tobacco smoking																
Never	2429	65.5	1229	65.2	1200	65.9	< 10 ⁻³	1256	66.6	814	63.3	359	67.2	< 10 ⁻³		
Former	630	17.0	274	14.5	356	19.5		268	14.2	253	19.7	109	20.4			
Current	647	17.5	381	20.2	266	14.6		362	19.2	219	17.0	66	12.4			
Alcohol consumption																
Abstinent without past unhealthy use	2112	57.0	1063	56.7	1049	57.7	0.001	1104	58.8	719	56.0	289	54.5	0.014		
Abstinent with past unhealthy use	141	3.8	56	3.0	85	4.7		55	2.9	53	4.1	33	6.2			

Moderate use	1385	37.4	737	39.3	648	35.6		695	37.0	493	38.4	197	37.2	
Unhealthy use	56	1.5	20	1.1	36	2.0		25	1.3	20	1.6	11	2.1	
<i>Missing</i>	12	0.3												
Living in poverty														
No	1865	50.3	1002	54.8	863	48.8	< 10 ⁻³	1003	55.0	641	51.3	221	42.3	< 10 ⁻³
Yes	1731	46.7	825	45.2	906	51.2		822	45.0	608	48.7	301	57.7	
<i>Missing</i>	110	3.0												
Education level														
< secondary school diploma	1759	47.5	791	42.6	968	54.0	< 10 ⁻³	822	44.4	618	48.7	319	60.3	< 10 ⁻³
≥ secondary school diploma	1891	51.0	1067	57.4	824	46.0		1030	55.6	651	51.3	210	39.7	
<i>Missing</i>	56	1.5												
Employed														
No	1543	41.6	698	37.3	845	46.8	< 10 ⁻³	750	40.1	522	40.9	271	51.1	< 10 ⁻³
Yes	2133	57.6	1173	62.7	960	53.2		1121	59.9	753	59.1	259	48.9	
<i>Missing</i>	30	0.8												
Advanced liver fibrosis[‡]														
No	3114	84.0	1589	95.9	1525	94.7	0.112	1573	95.2	1091	95.9	450	94.3	0.399
Yes	153	4.1	68	4.1	85	5.3		79	4.8	47	4.1	27	5.7	
<i>Missing</i>	439	11.8												
Time since HBV diagnosis (years)														
Median [IQR]	9 [4–17]	/	8 [3–16]	/	10 [5–18]	/	< 10 ⁻³	9 [4–17]	/	10 [4–17]	/	10 [4–16]	/	0.116
HBV treatment status														
Never treated	1909	51.5	959	50.9	950	52.1	0.281	946	50.2	683	53.1	280	52.4	0.295
History of treatment	219	5.9	103	5.5	116	6.4		119	6.3	76	5.9	24	4.5	
Ongoing treatment	1578	42.6	822	43.6	756	41.5		821	43.5	527	41.0	230	43.1	

[‡]Central obesity was defined as having a waist circumference ≥ 94 cm for men (except for men born in Asia, Central or South America, for whom the cut-off was set at 90 cm) and ≥ 80 cm for women (24)

‡Advanced liver fibrosis was defined as a FIB-4 score >3.25 (21)

BMI, body mass index; HBV, hepatitis B virus; IQR, interquartile range

Table 2: Factors associated with central obesity in univariable and multivariable analyses (logistic regression, ANRS CO22 Hepather cohort, n=3706)

Variables	Univariable analysis (n=3706)		Multivariable analysis (n=3587)	
	OR [95% CI]	P-value	aOR [95% CI]	P-value
Cannabis use				
Never (ref.)	1	< 10 ⁻³	1	0.002
Former	0.80 [0.57 – 1.14]	0.220	1.20 [0.84 – 1.72]	0.322
Current	0.23 [0.13 – 0.38]	< 10 ⁻³	0.41 [0.24 – 0.70]	0.001
Gender				
Male (ref.)	1		1	
Female	2.58 [2.25 – 2.96]	< 10 ⁻³	2.92 [2.51 – 3.40]	< 10 ⁻³
Age at baseline (years)	1.04 [1.03 – 1.05]	< 10 ⁻³	1.05 [1.04 – 1.05]	< 10 ⁻³
Coffee consumption				
0 cup/day (ref.)	1	0.076		
1-2 cups/day	1.12 [0.97 – 1.31]	0.129		
≥ 3 cups/day	1.20 [1.02 – 1.42]	0.028		
Tobacco smoking				
Never (ref.)	1	< 10 ⁻³		
Former	1.33 [1.12 – 1.59]	0.002		
Current	0.72 [0.60 – 0.85]	< 10 ⁻³		
Alcohol consumption				
Abstinent without past unhealthy use (ref.)	1	0.002		
Abstinent with past unhealthy use	1.54 [1.09 – 2.18]	0.015		
Moderate use	0.89 [0.78 – 1.02]	0.096		
Unhealthy use	1.82 [1.05 – 3.17]	0.033		
Living in poverty				
No (ref.)	1		1	
Yes	1.28 [1.12 – 1.45]	< 10 ⁻³	1.47 [1.26 – 1.70]	< 10 ⁻³
Education level				
< secondary school diploma (ref.)	1		1	
≥ secondary school diploma	0.63 [0.55 – 0.72]	< 10 ⁻³	0.83 [0.72 – 0.96]	0.013
Employed				
No (ref.)	1			
Yes	0.68 [0.59 – 0.77]	< 10 ⁻³		
Advanced liver fibrosis[†]				
No (ref.)	1			
Yes	1.30 [0.94 – 1.81]	0.113		
Time since HBV diagnosis (years)	1.02 [1.01 – 1.02]	< 10 ⁻³		
HBV treatment status				
Never treated (ref.)	1	0.282		
History of treatment	1.14 [0.86 – 1.50]	0.369		
Ongoing treatment	0.93 [0.81 – 1.06]	0.275		

Central obesity was defined as having a waist circumference ≥ 94 cm for men (except for men born in Asia, Central or South America, for whom the cut-off was set at 90 cm) and ≥ 80 cm for women (24)

[†]Advanced liver fibrosis was defined as a FIB-4 score >3.25 (21)

aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; OR, odds ratio

Table 3: Factors associated with overweight and obesity in univariable analyses (multinomial logistic regression, ANRS CO22 Hepather cohort, n=3706)

Variables	Overweight ($25 \leq \text{BMI} < 30$) RRR [95% CI]	P- value	Obesity ($\text{BMI} \geq 30$) RRR [95% CI]	P- value
Cannabis use				
Never (ref.)	1	0.006	1	0.005
Former	0.99 [0.67 – 1.44]	0.941	1.07 [0.65 – 1.77]	0.786
Current	0.46 [0.29 – 0.74]	0.001	0.09 [0.02 – 0.39]	0.001
Gender				
Male (ref.)	1		1	
Female	0.71 [0.61 – 0.83]	$< 10^{-3}$	1.60 [1.32 – 1.94]	$< 10^{-3}$
Age at baseline (years)	1.02 [1.01 – 1.02]	$< 10^{-3}$	1.03 [1.02 – 1.03]	$< 10^{-3}$
Coffee consumption				
0 cup/day (ref.)	1	0.057	1	0.509
1-2 cups/day	1.05 [0.89 – 1.24]	0.552	1.04 [0.83 – 1.31]	0.713
≥ 3 cups/day	1.24 [1.03 – 1.48]	0.020	1.15 [0.90 – 1.48]	0.250
Tobacco smoking				
Never (ref.)	1	$< 10^{-3}$	1	$< 10^{-3}$
Former	1.46 [1.20 – 1.77]	$< 10^{-3}$	1.42 [1.10 – 1.83]	0.006
Current	0.93 [0.77 – 1.13]	0.477	0.64 [0.48 – 0.85]	0.002
Alcohol consumption				
Abstinent without past unhealthy use (ref.)	1	0.182	1	0.002
Abstinent with past unhealthy use	1.48 [1.00 – 2.18]	0.048	2.29 [1.46 – 3.60]	$< 10^{-3}$
Moderate use	1.09 [0.94 – 1.26]	0.261	1.08 [0.88 – 1.33]	0.446
Unhealthy use	1.23 [0.68 – 2.23]	0.498	1.68 [0.82 – 3.46]	0.158
Living in poverty				
No (ref.)	1		1	
Yes	1.16 [1.00 – 1.34]	0.047	1.66 [1.37 – 2.02]	$< 10^{-3}$
Education level				
$<$ secondary school diploma (ref.)	1		1	
$>$ secondary school diploma	0.84 [0.73 – 0.97]	0.018	0.53 [0.43 – 0.64]	$< 10^{-3}$
Employed				
No (ref.)	1		1	
Yes	0.97 [0.83 – 1.12]	0.631	0.64 [0.53 – 0.78]	$< 10^{-3}$
Advanced liver fibrosis[†]				
No (ref.)	1		1	
Yes	0.86 [0.59 – 1.24]	0.416	1.19 [0.76 – 1.87]	0.438

Time since HBV diagnosis (years)	1.01 [1.00 – 1.01]	0.189	1.00 [0.99 – 1.01]	0.727
HBV treatment status				
Never treated (ref.)	1	0.264	1	0.254
History of treatment	0.88 [0.65 – 1.20]	0.429	0.68 [0.43 – 1.08]	0.101
Ongoing treatment	0.89 [0.77 – 1.03]	0.117	0.95 [0.78 – 1.15]	0.586

†Advanced liver fibrosis was defined as a FIB-4 score >3.25 (21)

BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; RRR, relative risk ratio

Table 4: Factors associated with overweight and obesity in multivariable analyses (multinomial logistic regression, ANRS CO22 Hepather cohort, n=3578)

Variables	Overweight (25 ≤ BMI < 30)		Obesity (BMI ≥ 30)	
	aRRR [95% CI]	P-value	aRRR [95% CI]	P-value
Cannabis use				
Never (ref.)	1	0.011	1	0.017
Former	0.96 [0.64 – 1.45]	0.853	1.41 [0.83 – 2.40]	0.206
Current	0.46 [0.27 – 0.76]	0.002	0.16 [0.04 – 0.67]	0.013
Gender				
Male (ref.)	1		1	
Female	0.72 [0.62 – 0.85]	< 10 ⁻³	1.71 [1.39 – 2.11]	< 10 ⁻³
Age at baseline (years)	1.02 [1.01 – 1.02]	< 10 ⁻³	1.03 [1.02 – 1.03]	< 10 ⁻³
Tobacco smoking				
Never (ref.)	1	0.149	1	0.015
Former	1.18 [0.95 – 1.46]	0.129	1.25 [0.94 – 1.66]	0.123
Current	0.92 [0.75 – 1.14]	0.444	0.72 [0.52 – 0.99]	0.043
Alcohol consumption				
Abstinent without past unhealthy use (ref.)	1	0.851	1	0.015
Abstinent with past unhealthy use	1.12 [0.74 – 1.68]	0.595	1.84 [1.13 – 2.98]	0.014
Moderate use	1.07 [0.91 – 1.25]	0.434	1.29 [1.03 – 1.60]	0.025
Unhealthy use	1.10 [0.59 – 2.05]	0.766	1.89 [0.85 – 4.22]	0.120
Living in poverty				
No (ref.)	1		1	
Yes	1.28 [1.10 – 1.50]	0.002	1.77 [1.42 – 2.20]	< 10 ⁻³
Education level				
< secondary school diploma (ref.)	1		1	
> secondary school diploma	0.93 [0.80 – 1.09]	0.381	0.68 [0.55 – 0.84]	< 10 ⁻³

aRRR, adjusted relative risk ratio; BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus