



**HAL**  
open science

## **Cannabis Use Is Inversely Associated with Overweight and Obesity in Hepatitis B Virus-Infected Patients (ANRS CO22 Hepather Cohort)**

Tangui Barré, Stanislas Pol, Clémence Ramier, Vincent Di Beo, Fabrice Carrat, Morgane Bureau, Marc Bourlière, Céline Dorival, Lawrence Serfaty, Tarik Asselah, et al.

### ► To cite this version:

Tangui Barré, Stanislas Pol, Clémence Ramier, Vincent Di Beo, Fabrice Carrat, et al.. Cannabis Use Is Inversely Associated with Overweight and Obesity in Hepatitis B Virus-Infected Patients (ANRS CO22 Hepather Cohort). Cannabis and Cannabinoid Research, 2021, 10.1089/can.2021.0094 . hal-03417059

**HAL Id: hal-03417059**

**<https://univ-angers.hal.science/hal-03417059v1>**

Submitted on 1 Mar 2023

**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.

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

Tangui Barré<sup>1</sup>, Stanislas Pol<sup>2</sup>, Clémence Ramier<sup>1</sup>, Vincent Di Beo<sup>1</sup>, Fabrice Carrat<sup>3</sup>, Morgane Bureau<sup>1</sup>, Marc Bourlière<sup>4, 1</sup>, Céline Dorival<sup>5</sup>, Lawrence Serfaty<sup>6</sup>, Tarik Asselah<sup>7, 8</sup>, Jérôme Boursier<sup>9</sup>, Fabienne Marcellin<sup>1</sup>, Patrizia Carrieri<sup>1</sup>, Hélène Fontaine<sup>2</sup>, Camelia Protopopescu<sup>1</sup> and the ANRS/AFEF Hepather study group

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

<sup>2</sup> Université Paris Centre; Département d'Hépatologie, Hôpital Cochin, APHP, Paris, France.

<sup>3</sup> Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, Département de Santé Publique, Hôpital Saint-Antoine, APHP, Paris, France.

<sup>4</sup> Hôpital St Joseph, Service d'Hépatogastroentérologie, Marseille, France.

<sup>5</sup> Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, Paris, France.

<sup>6</sup> Hepatology Department, Pôle des Pathologies Digestives, Hépatiques et de la Transplantation, Hôpital de Hautepierre-Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg, France.

<sup>7</sup> Université de Paris, Centre de recherche sur l'inflammation, INSERM UMR1149, F-75018, Paris, France.

<sup>8</sup> Department of Hepatology, AP-HP, Hôpital Beaujon, F-92110, Clichy, France.

<sup>9</sup> Hepato-Gastroenterology Department, Angers University Hospital, Angers, France; HIFIH Laboratory, UPRES 3859, SFR 4208, Angers University, Angers, France.

**Keywords**

Hepatitis B virus; cannabis; obesity; overweight; socioeconomic status

**Running title**

Cannabis use and obesity in hepatitis B infection

### **Contact info**

Patrizia Carrieri, pmcarrieri@aol.com, Faculté de Médecine de la Timone, Aile Bleue, 35 boulevard Jean Moulin, 13005 Marseille, France.

### **Word count**

3123

### **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 <sup>1</sup>, and more than half of liver cancer cases in 2012 <sup>2</sup>. 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 <sup>3,4</sup>.

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 <sup>5</sup>. As obesity is a risk factor for hepatic steatosis <sup>6</sup> and mortality in this population <sup>7</sup>, 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 <sup>8</sup>. In France and Europe, income is generally lower in immigrant households and the likelihood of poverty is higher <sup>9</sup>. Given this context, where HBV carriers in France are expected to be mainly migrants with low socioeconomic status <sup>8</sup>, and given that socioeconomic status is associated with obesity and weight gain <sup>10,11</sup>, 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 <sup>12,13(p3),14</sup>, with possible indirect preventive effects on cardiometabolic risk <sup>15</sup>. However, while the potential benefits of cannabis use have been highlighted in patients with hepatitis C virus (HCV) infection <sup>16,17</sup>, 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€<sup>18</sup>; since 2020, an on-the-spot fine of 150€ can replace the normal procedure at the police's discretion<sup>19</sup>. Despite this criminalization, France has the highest prevalence of cannabis use among young people and adults in Europe<sup>20</sup>, and indicators of cannabis use disorder and treatment for dependence are on the rise<sup>21</sup>. The demand for herbal cannabis is also growing, as is its potency<sup>22</sup>. While a national experimentation evaluating the putative circuit whereby medical cannabis would be made available for patients insufficiently relieved from other treatment is ongoing<sup>23</sup>, 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, 2012<sup>24</sup>. 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  $\geq 94$  cm for men (except for men born in Asia, Central or South America, for whom the cut-off was set at 90 cm) and  $\geq 80$  cm for women <sup>25</sup>. The second was a three-category BMI-status variable; specifically, participants with obesity (defined as a BMI  $\geq 30$  kg/m<sup>2</sup>), and those with overweight (defined as a BMI between 25 and 30 kg/m<sup>2</sup>), were compared with participants with no obesity or overweight <sup>26</sup>.

## 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 <sup>27-29</sup>. 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 <sup>30</sup>) 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  $>3.25$  <sup>31,32</sup>.

## 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 <sup>33</sup>. 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/m<sup>2</sup>), 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 <sup>14,15,34</sup>. 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 <sup>13</sup>. Finally, the largest genome-wide association study for lifetime cannabis use to date, revealed genetic overlap between lifetime cannabis use and low BMI <sup>12</sup>. 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 <sup>35</sup>. An effect of cannabis use on endocrine pathways related to appetite and metabolism (especially insulin concentration) has also been reported <sup>36</sup>. 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) <sup>37</sup>, 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 <sup>5–7</sup>. Conversely, improving BMI may have a beneficial effect on alanine aminotransferase normalization <sup>38,39</sup> and possibly long-term outcomes after viral suppression <sup>39</sup>. 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 <sup>40</sup>. The previous use of CB1 antagonists for treating obesity yielded promising results, but was stopped because of severe side effects <sup>41</sup>. 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 <sup>42–44</sup>, 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 <sup>45</sup>, especially as similar effects have already been suggested by studies conducted in HIV-HCV co-infected patients <sup>17,29,46,47</sup>. The potential protective effect of cannabis and cannabinoids on hepatic steatosis <sup>27,47-49</sup> is of particular interest for HBV-infected patients, as hepatic steatosis is a strong predictor of cancer and mortality in this population <sup>50</sup>.

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 <sup>16</sup>, but close to previous-month use in people aged 35-44 (5.9%) and 45-54 (2.9%) observed in France in 2017 <sup>51</sup>. 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 <sup>52</sup>. Low socioeconomic status has been associated with poorer diet quality <sup>53-55</sup>, and low income is a major barrier to healthy eating <sup>56</sup>. 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 <sup>57</sup>. Finally, specific psychosocial determinants may promote unhealthy dietary habits <sup>58</sup>.

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<sup>59,60</sup>. The protective effect of tobacco smoking on obesity (BMI $\geq$ 30 kg/m<sup>2</sup>) 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 expenditure<sup>61</sup>. As tobacco is frequently co-smoked with cannabis in Europe<sup>62</sup>, 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<sup>64–66</sup>. 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 mass<sup>67</sup>.

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.



## Acknowledgments

We would like to thank the participating patients and clinicians at each site. We also thank 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.

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

### 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-Noumbissie, Esmâ 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, Marine Faure, Bruno Froissart, Marie-Noëlle Hilleret, Jean-Pierre Zarski (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), Didier Samuel, Teresa Antonini, Audrey Coilly, Jean-Charles Duclos Vallée, 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

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, Florian Sebal, 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:*

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

## 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.

Fabrice Carrat reports receiving grants from INSERM-ANRS MIE during the implementation of the study, and personal fees from Imaxio, unrelated to the submitted work.

Marc Bourliere has served as a speaker, a consultant and an advisory board member for Gilead, Janssen, Roche, AbbVie, MSD, and Intercept, and has received research funding from Gilead, AbbVie, and Roche.

Tarik Asselah has served as a consultant, expert and speaker for Gilead, Abbvie, Bristol-Myers Squibb, Eiger BioPharmaceuticals, Janssen, Merck Sharp Dohme, MYR Pharmaceuticals, and Roche.

Tangui Barré, Clémence Ramier, Vincent Di Beo, Morgane Bureau, Céline Dorival, Lawrence Serfaty, Jérôme Boursier, Fabienne Marcellin, Patrizia Carrieri, Hélène Fontaine and Camelia Protopopescu have no competing financial interests.

## Funding

The Hepather cohort is funded by INSERM-ANRS MIE (France REcherche Nord&sud Sida-vih Hepatites | Maladies Infectieuses Emergentes), ANR Equipex and Cohort (Agence Nationale de la Recherche), DGS (Direction Générale de la Santé) and MSD, Janssen, Gilead, Abbvie, BMS, Roche. Those funding sources had no role in the writing of the manuscript or the decision to submit it for publication.

## References

1. 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*. 2020;5(3):245-266. doi:10.1016/S2468-1253(19)30349-8
2. Maucort-Boulch D, de Martel C, Franceschi S, et al. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. *Int J Cancer*. 2018;142(12):2471-2477. doi:10.1002/ijc.31280
3. Asselah T, Loureiro D, Boyer N, et al. Targets and future direct-acting antiviral approaches to achieve hepatitis B virus cure. *Lancet Gastroenterol Hepatol*. 2019;4(11):883-892. doi:10.1016/S2468-1253(19)30190-6
4. Tout I, Loureiro D, Mansouri A, et al. Hepatitis B surface antigen seroclearance: Immune mechanisms, clinical impact, importance for drug development. *J Hepatol*. 2020;73(2):409-422. doi:10.1016/j.jhep.2020.04.013
5. Seto W-K. Chronic hepatitis B and metabolic risk factors: A call for rigorous longitudinal studies. *World J Gastroenterol*. 2019;25(3):282-286. doi:10.3748/wjg.v25.i3.282
6. Zhu L, Jiang J, Zhai X, et al. Hepatitis B virus infection and risk of non-alcoholic fatty liver disease: A population-based cohort study. *Liver Int Off J Int Assoc Study Liver*. 2019;39(1):70-80. doi:10.1111/liv.13933
7. Lin W-Y, Peng C-Y, Lin C-C, et al. General and Abdominal Adiposity and Risk of Death in HBV Versus Non-HBV Carriers. *Medicine (Baltimore)*. 2016;95(2). doi:10.1097/MD.0000000000002162
8. Brouard C, Saboni L, Gautier A, et al. HCV and HBV prevalence based on home blood self-sampling and screening history in the general population in 2016: contribution to the new French screening strategy. *BMC Infect Dis*. 2019;19(1):896. doi:10.1186/s12879-019-4493-2
9. Organisation for Economic Co-operation and Development, European Commission. *Settling In 2018, Indicators of Immigrant Integration*. OECD/EU; 2018. <https://www.oecd.org/publications/indicators-of-immigrant-integration-2018-9789264307216-en.htm>
10. Newton S, Braithwaite D, Akinyemiju TF. Socio-economic status over the life course and obesity: Systematic review and meta-analysis. *PloS One*. 2017;12(5):e0177151. doi:10.1371/journal.pone.0177151
11. Herzog B, Lacruz ME, Haerting J, et al. Socioeconomic status and anthropometric changes-A meta-analytic approach from seven German cohorts. *Obes Silver Spring Md*. 2016;24(3):710-718. doi:10.1002/oby.21366
12. Paman JA, Verweij KJH, Gerring Z, et al. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. *Nat Neurosci*. 2018;21(9):1161-1170. doi:10.1038/s41593-018-0206-1
13. Alshaarawy O, Anthony JC. Are cannabis users less likely to gain weight? Results from a national 3-year prospective study. *Int J Epidemiol*. 2019;48(5):1695-1700. doi:10.1093/ije/dyz044
14. Sidney S. Marijuana Use and Type 2 Diabetes Mellitus: a Review. *Curr Diab Rep*. 2016;16(11):117. doi:10.1007/s11892-016-0795-6
15. Meier MH, Pardini D, Beardslee J, et al. Associations Between Cannabis Use and Cardiometabolic Risk Factors: A Longitudinal Study of Men. *Psychosom Med*. 2019;81(3):281-288. doi:10.1097/PSY.0000000000000665

16. Barré T, Nishimwe ML, Protopopescu C, et al. Cannabis use is associated with a lower risk of diabetes in chronic hepatitis C-infected patients (ANRS CO22 Hepather cohort). *J Viral Hepat.* 2020;27(12):1473-1483. doi:<https://doi.org/10.1111/jvh.13380>
17. Adejumo AC, Adegbala OM, Adejumo KL, et al. Reduced Incidence and Better Liver Disease Outcomes among Chronic HCV Infected Patients Who Consume Cannabis. *Can J Gastroenterol Hepatol.* 2018;2018:9430953. doi:10.1155/2018/9430953
18. Massin S, Carrieri MP, Roux P. De jure decriminalisation of cannabis use matters: some recent trends from France. *Int J Drug Policy.* 2013;24(6):634-635. doi:10.1016/j.drugpo.2013.04.008
19. *LOI N° 2019-222 Du 23 Mars 2019 de Programmation 2018-2022 et de Réforme Pour La Justice (1).*; 2019.
20. European Monitoring Centre for Drugs and Drug Addiction. *European Drug Report 2019: Trends and Developments.* EMCDDA; 2019. [https://www.emcdda.europa.eu/publications/edr/trends-developments/2019\\_en](https://www.emcdda.europa.eu/publications/edr/trends-developments/2019_en)
21. Observatoire Français des Drogues et des Toxicomanies. *Drugs, Key Data 2019.* OFDT; 2019. <https://en.ofdt.fr/publications/drugs-key-data/8th-edition-june-2019/>
22. Gandilhon M, Spilka S, Masson C. *Les Mutations Du Marché Du Cannabis En France (Transformations of French Cannabis Market).* OFDT; 2019. <https://www.ofdt.fr/publications/collections/rapports/thema/les-mutations-du-marche-du-cannabis-en-france-thema/>
23. Agence Nationale de Sécurité du Médicament et des Produits de Santé. Cadre et mise en oeuvre de l'expérimentation (Framework and implementation of the experimentation). Published July 26, 2021. Accessed August 25, 2021. <https://ansm.sante.fr/dossiers-thematiques/cannabis-a-usage-medical/cadre-et-mise-en-oevre-de-lexperimentation-du-cannabis-medical>
24. Pol S, Bourliere M, Lucier S, et al. Safety and efficacy of daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients. *J Hepatol.* 2017;66(1):39-47. doi:10.1016/j.jhep.2016.08.021
25. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation.* 2005;112(17):2735-2752. doi:10.1161/CIRCULATIONAHA.105.169404
26. World Health Organization. Body mass index - BMI. Published July 9, 2019. Accessed July 9, 2019. <http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi>
27. Carrieri MP, Protopopescu C, Marcellin F, et al. The impact of coffee consumption on fibrosis and steatosis in HIV-HCV co-infected patients. *J Hepatol.* Published online November 2, 2017. doi:10.1016/j.jhep.2017.10.025
28. Carrieri MP, Protopopescu C, Marcellin F, et al. Protective effect of coffee consumption on all-cause mortality of French HIV-HCV co-infected patients. *J Hepatol.* 2017;67(6):1157-1167. doi:10.1016/j.jhep.2017.08.005
29. Protopopescu C, Santos ME, Sogni P, et al. Protective effect of cannabis and coffee consumption on HCV-related mortality in French HIV-HCV co-infected patients (ANRS CO13 HEPAVIH cohort). *J Hepatol.* 2018;68:S142-S143. doi:10.1016/S0168-8278(18)30501-4
30. 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).*; 2014. Accessed October 24, 2019. [https://www.has-sante.fr/jcms/c\\_1795221/fr/outil-d-aide-au-reperage-precoce-et-intervention-breve-alcool-cannabis-tabac-chez-l-adulte](https://www.has-sante.fr/jcms/c_1795221/fr/outil-d-aide-au-reperage-precoce-et-intervention-breve-alcool-cannabis-tabac-chez-l-adulte)

31. Sterling Richard K., Lissen Eduardo, Clumeck Nathan, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43(6):1317-1325. doi:10.1002/hep.21178
32. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatol Baltim Md*. 2007;46(1):32-36. doi:10.1002/hep.21669
33. Dunkler D, Plischke M, Leffondré K, et al. Augmented Backward Elimination: A Pragmatic and Purposeful Way to Develop Statistical Models. *PLOS ONE*. 2014;9(11):e113677. doi:10.1371/journal.pone.0113677
34. Ngueta G, Bélanger RE, Laouan-Sidi EA, et al. Cannabis use in relation to obesity and insulin resistance in the Inuit population. *Obes Silver Spring Md*. 2015;23(2):290-295. doi:10.1002/oby.20973
35. Clark TM, Jones JM, Hall AG, et al. Theoretical Explanation for Reduced Body Mass Index and Obesity Rates in Cannabis Users. *Cannabis Cannabinoid Res*. 2018;3(1):259-271. doi:10.1089/can.2018.0045
36. Farokhnia M, McDiarmid GR, Newmeyer MN, et al. Effects of oral, smoked, and vaporized cannabis on endocrine pathways related to appetite and metabolism: a randomized, double-blind, placebo-controlled, human laboratory study. *Transl Psychiatry*. 2020;10(1):1-11. doi:10.1038/s41398-020-0756-3
37. DiPatrizio NV. Endocannabinoids and the Gut-Brain Control of Food Intake and Obesity. *Nutrients*. 2021;13(4). doi:10.3390/nu13041214
38. Abd El-Kader SM, Al-Dahr MHS. Impact of weight reduction program on serum alanine aminotransferase activity and immunologic response in obese hepatitis B patients. *Afr Health Sci*. 2016;16(1):128-134. doi:10.4314/ahs.v16i1.17
39. Wang K, Lin W, Kuang Z, et al. Longitudinal Change of Body Mass Index Is Associated With Alanine Aminotransferase Elevation After Complete Viral Suppression in Chronic Hepatitis B Patients. *J Infect Dis*. 2019;220(9):1469-1476. doi:10.1093/infdis/jiz326
40. Silvestri C, Di Marzo V. The endocannabinoid system in energy homeostasis and the etiopathology of metabolic disorders. *Cell Metab*. 2013;17(4):475-490. doi:10.1016/j.cmet.2013.03.001
41. Di Marzo V, Després J-P. CB1 antagonists for obesity--what lessons have we learned from rimonabant? *Nat Rev Endocrinol*. 2009;5(11):633-638. doi:10.1038/nrendo.2009.197
42. Bielawiec P, Harasim-Symbor E, Chabowski A. Phytocannabinoids: Useful Drugs for the Treatment of Obesity? Special Focus on Cannabidiol. *Front Endocrinol*. 2020;11:114. doi:10.3389/fendo.2020.00114
43. Palomares B, Ruiz-Pino F, Garrido-Rodriguez M, et al. Tetrahydrocannabinolic Acid a (THCA-A) Reduces Adiposity and Prevents Metabolic Disease Caused by Diet-Induced Obesity. *bioRxiv*. Published online April 29, 2019:622035. doi:10.1101/622035
44. Palomares B, Ruiz-Pino F, Navarrete C, et al. VCE-004.8, A Multitarget Cannabinoquinone, Attenuates Adipogenesis and Prevents Diet-Induced Obesity. *Sci Rep*. 2018;8. doi:10.1038/s41598-018-34259-0
45. Gotfried J, Naftali T, Schey R. Role of Cannabis and Its Derivatives in Gastrointestinal and Hepatic Disease. *Gastroenterology*. 2020;159(1):62-80. doi:10.1053/j.gastro.2020.03.087
46. Barre T, Rojas Rojas T, Lacombe K, et al. Cannabis use and reduced risk of elevated fatty liver index in HIV-HCV co-infected patients: a longitudinal analysis (ANRS CO13 HEPAVIH). *Expert Rev Anti Infect Ther*. Published online February 4, 2021. doi:10.1080/14787210.2021.1884545
47. Nordmann S., Vilotitch A., Roux P., et al. Daily cannabis and reduced risk of steatosis in human immunodeficiency virus and hepatitis C virus-co-infected patients (ANRS CO13-HEPAVH). *J Viral Hepat*. 2017;25(2):171-179. doi:10.1111/jvh.12797

48. Kaushal N, Dhadwal S, Kaur P. Ameliorative effects of hempseed (*Cannabis sativa*) against hypercholesterolemia associated cardiovascular changes. *Nutr Metab Cardiovasc Dis.* 2020;30(2):330-338. doi:10.1016/j.numecd.2019.09.006
49. Silvestri C, Paris D, Martella A, et al. Two non-psychoactive cannabinoids reduce intracellular lipid levels and inhibit hepatosteatosis. *J Hepatol.* 2015;62(6):1382-1390. doi:10.1016/j.jhep.2015.01.001
50. Peleg N, Issachar A, Sneh Arbib O, et al. Liver steatosis is a strong predictor of mortality and cancer in chronic hepatitis B regardless of viral load. *JHEP Rep Innov Hepatol.* 2019;1(1):9-16. doi:10.1016/j.jhepr.2019.02.002
51. Spilka S, Richard J-B, Le Nézet O, et al. *Les Niveaux d'usage Des Drogues Illicites En France En 2017 (Illegal Drug Use Levels in France in 2017)*. OFDT; 2018. <https://www.ofdt.fr/publications/collections/periodiques/lettre-tendances/les-niveaux-dusages-des-drogues-illicites-en-france-en-2017-tendances-128-novembre-2018/>
52. Loring B, Robertson A. *Obesity and Inequities. Guidance for Addressing Inequities in Overweight and Obesity*. World Health Organization; 2014. Accessed June 7, 2018. <http://www.euro.who.int/en/publications/abstracts/obesity-and-inequities.-guidance-for-addressing-inequities-in-overweight-and-obesity-2014>
53. Lewis M, Lee AJ. Dietary inequity? A systematic scoping review of dietary intake in low socio-economic groups compared with high socio-economic groups in Australia. *Public Health Nutr.* 2021;24(3):393-411. doi:10.1017/S1368980020003006
54. Kell KP, Judd SE, Pearson KE, et al. Associations between socio-economic status and dietary patterns in US black and white adults. *Br J Nutr.* 2015;113(11):1792-1799. doi:10.1017/S0007114515000938
55. Si Hassen W, Castetbon K, Cardon P, et al. Socioeconomic Indicators Are Independently Associated with Nutrient Intake in French Adults: A DEDIPAC Study. *Nutrients.* 2016;8(3):158. doi:10.3390/nu8030158
56. Darmon N, Drewnowski A. Contribution of food prices and diet cost to socioeconomic disparities in diet quality and health: a systematic review and analysis. *Nutr Rev.* 2015;73(10):643-660. doi:10.1093/nutrit/nuv027
57. Laraia BA, Leak TM, Tester JM, et al. Biobehavioral Factors That Shape Nutrition in Low-Income Populations: A Narrative Review. *Am J Prev Med.* 2017;52(2, Supplement 2):S118-S126. doi:10.1016/j.amepre.2016.08.003
58. INSERM. *Inégalités Sociales de Santé En Lien Avec l'alimentation et l'activité Physique.*; 2014:217-235. Accessed June 18, 2018. <http://www.ipubli.inserm.fr/handle/10608/6515>
59. Lovejoy JC, Sainsbury A, Stock Conference 2008 Working Group. Sex differences in obesity and the regulation of energy homeostasis. *Obes Rev Off J Int Assoc Study Obes.* 2009;10(2):154-167. doi:10.1111/j.1467-789X.2008.00529.x
60. Kanter R, Caballero B. Global gender disparities in obesity: a review. *Adv Nutr Bethesda Md.* 2012;3(4):491-498. doi:10.3945/an.112.002063
61. Audrain-McGovern J, Benowitz NL. Cigarette smoking, nicotine, and body weight. *Clin Pharmacol Ther.* 2011;90(1):164-168. doi:10.1038/clpt.2011.105
62. Hindocha C, Freeman TP, Ferris JA, et al. No Smoke without Tobacco: A Global Overview of Cannabis and Tobacco Routes of Administration and Their Association with Intention to Quit. *Front Psychiatry.* 2016;7. doi:10.3389/fpsyt.2016.00104
63. Traversy G, Chaput J-P. Alcohol Consumption and Obesity: An Update. *Curr Obes Rep.* 2015;4(1):122-130. doi:10.1007/s13679-014-0129-4

64. Yu M-W, Shih W-L, Lin C-L, et al. Body-mass index and progression of hepatitis B: a population-based cohort study in men. *J Clin Oncol Off J Am Soc Clin Oncol*. 2008;26(34):5576-5582. doi:10.1200/JCO.2008.16.1075
65. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet Lond Engl*. 2013;381(9865):468-475. doi:10.1016/S0140-6736(12)61425-1
66. Seto W-K, Fung J, Cheung K-S, et al. Body-mass index is associated with fibrosis regression during long-term nucleoside analogue therapy in chronic hepatitis B. *Aliment Pharmacol Ther*. 2016;44(10):1071-1079. doi:10.1111/apt.13804
67. Ross R, Neeland IJ, Yamashita S, et al. Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol*. 2020;16(3):177-189. doi:10.1038/s41574-019-0310-7



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

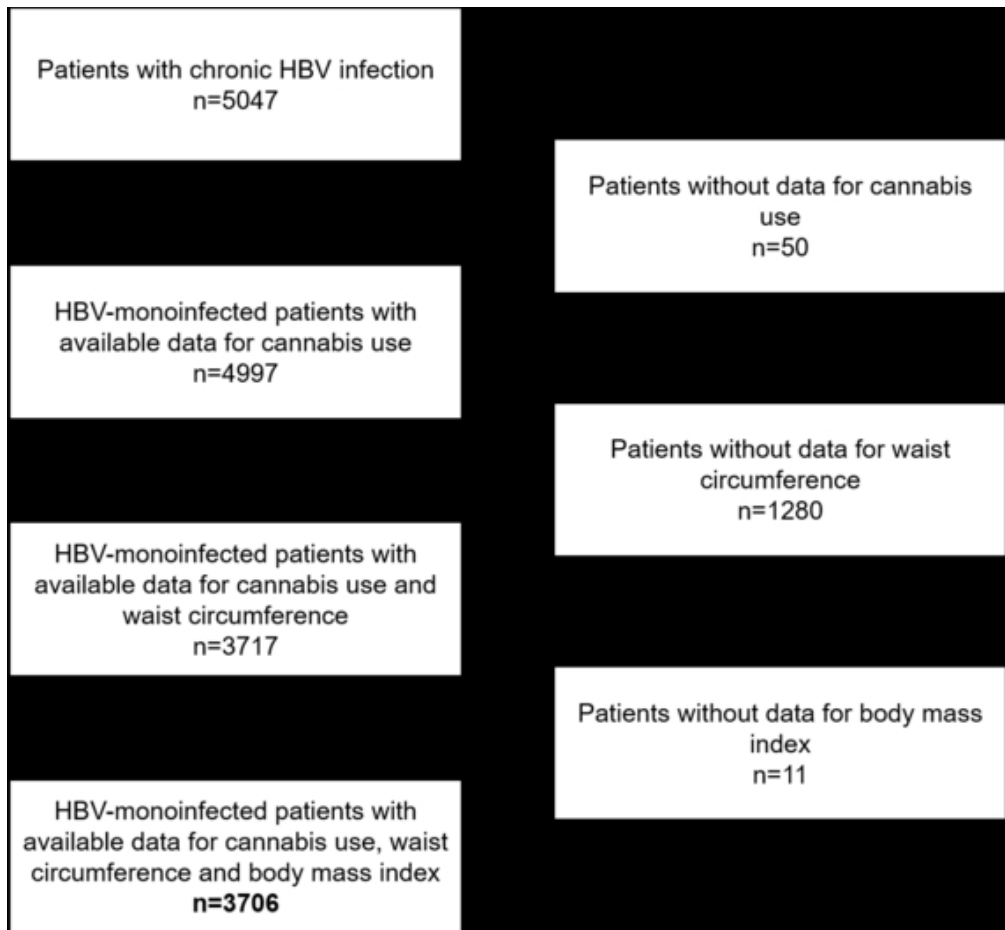


Figure 1: Flow chart of the study population (ANRS CO22 Hepather cohort)

48x44mm (300 x 300 DPI)

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

Variable			Central obesity <sup>†</sup>					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		
<b>Cannabis use</b>																
Never	3475	93.8	1731	91.9	1744	95.7	< 10 <sup>-3</sup>	1747	92.6	1217	94.6	511	95.7	< 10 <sup>-3</sup>		
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			
<b>Gender</b>																
Male	2338	63.1	1389	73.7	949	52.1	< 10 <sup>-3</sup>	1171	62.1	897	69.8	270	50.6	< 10 <sup>-3</sup>		
Female	1368	36.9	495	26.3	873	47.9		715	37.9	389	30.2	264	49.4			
<b>Age at baseline (years)</b>																
Median [IQR]	42 [34–54]	/	39 [31–49]	/	46 [37–58]	/	< 10 <sup>-3</sup>	40 [32–51]	/	44 [35–55]	/	46 [37–58]	/	< 10 <sup>-3</sup>		
<b>Coffee consumption</b>																
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														
<b>Tobacco smoking</b>																
Never	2429	65.5	1229	65.2	1200	65.9	< 10 <sup>-3</sup>	1256	66.6	814	63.3	359	67.2	< 10 <sup>-3</sup>		
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			
<b>Alcohol consumption</b>																
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												
<b>Living in poverty</b>														
No	1865	50.3	1002	54.8	863	48.8	< 10 <sup>-3</sup>	1003	55.0	641	51.3	221	42.3	< 10 <sup>-3</sup>
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												
<b>Education level</b>														
< secondary school diploma	1759	47.5	791	42.6	968	54.0	< 10 <sup>-3</sup>	822	44.4	618	48.7	319	60.3	< 10 <sup>-3</sup>
≥ 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												
<b>Employed</b>														
No	1543	41.6	698	37.3	845	46.8	< 10 <sup>-3</sup>	750	40.1	522	40.9	271	51.1	< 10 <sup>-3</sup>
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												
<b>Advanced liver fibrosis<sup>‡</sup></b>														
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												
<b>Time since HBV diagnosis (years)</b>														
Median [IQR]	9 [4–17]	/	8 [3–16]	/	10 [5–18]	/	< 10 <sup>-3</sup>	9 [4–17]	/	10 [4–17]	/	10 [4–16]	/	0.116
<b>HBV treatment status</b>														
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	

<sup>‡</sup>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)**

<b>Variables</b>	<b>Univariable analysis (n=3706)</b>		<b>Multivariable analysis (n=3587)</b>	
	<b>OR [95% CI]</b>	<b>P-value</b>	<b>aOR [95% CI]</b>	<b>P-value</b>
<b>Cannabis use</b>				
Never (ref.)	1	< 10 <sup>-3</sup>	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 <sup>-3</sup>	0.41 [0.24 – 0.70]	0.001
<b>Gender</b>				
Male (ref.)	1		1	
Female	2.58 [2.25 – 2.96]	< 10 <sup>-3</sup>	2.92 [2.51 – 3.40]	< 10 <sup>-3</sup>
<b>Age at baseline (years)</b>	1.04 [1.03 – 1.05]	< 10 <sup>-3</sup>	1.05 [1.04 – 1.05]	< 10 <sup>-3</sup>
<b>Coffee consumption</b>				
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		
<b>Tobacco smoking</b>				
Never (ref.)	1	< 10 <sup>-3</sup>		
Former	1.33 [1.12 – 1.59]	0.002		
Current	0.72 [0.60 – 0.85]	< 10 <sup>-3</sup>		
<b>Alcohol consumption</b>				
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		
<b>Living in poverty</b>				
No (ref.)	1		1	
Yes	1.28 [1.12 – 1.45]	< 10 <sup>-3</sup>	1.47 [1.26 – 1.70]	< 10 <sup>-3</sup>
<b>Education level</b>				
< secondary school diploma (ref.)	1		1	
≥ secondary school diploma	0.63 [0.55 – 0.72]	< 10 <sup>-3</sup>	0.83 [0.72 – 0.96]	0.013
<b>Employed</b>				
No (ref.)	1			
Yes	0.68 [0.59 – 0.77]	< 10 <sup>-3</sup>		
<b>Advanced liver fibrosis<sup>†</sup></b>				
No (ref.)	1			
Yes	1.30 [0.94 – 1.81]	0.113		
<b>Time since HBV diagnosis (years)</b>	1.02 [1.01 – 1.02]	< 10 <sup>-3</sup>		
<b>HBV treatment status</b>				
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)

<sup>†</sup>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)**

<b>Variables</b>	<b>Overweight (<math>25 \leq \text{BMI} &lt; 30</math>) RRR [95% CI]</b>	<b>P- value</b>	<b>Obesity (<math>\text{BMI} \geq 30</math>) RRR [95% CI]</b>	<b>P- value</b>
<b>Cannabis use</b>				
Never (ref.)	1	<b>0.006</b>	1	<b>0.005</b>
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
<b>Gender</b>				
Male (ref.)	1		1	
Female	0.71 [0.61 – 0.83]	$< 10^{-3}$	1.60 [1.32 – 1.94]	$< 10^{-3}$
<b>Age at baseline (years)</b>	1.02 [1.01 – 1.02]	$< 10^{-3}$	1.03 [1.02 – 1.03]	$< 10^{-3}$
<b>Coffee consumption</b>				
0 cup/day (ref.)	1	<b>0.057</b>	1	<b>0.509</b>
1-2 cups/day	1.05 [0.89 – 1.24]	0.552	1.04 [0.83 – 1.31]	0.713
$\geq 3$ cups/day	1.24 [1.03 – 1.48]	0.020	1.15 [0.90 – 1.48]	0.250
<b>Tobacco smoking</b>				
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
<b>Alcohol consumption</b>				
Abstinent without past unhealthy use (ref.)	1	<b>0.182</b>	1	<b>0.002</b>
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
<b>Living in poverty</b>				
No (ref.)	1		1	
Yes	1.16 [1.00 – 1.34]	0.047	1.66 [1.37 – 2.02]	$< 10^{-3}$
<b>Education level</b>				
$<$ secondary school diploma (ref.)	1		1	
$>$ secondary school diploma	0.84 [0.73 – 0.97]	0.018	0.53 [0.43 – 0.64]	$< 10^{-3}$
<b>Employed</b>				
No (ref.)	1		1	
Yes	0.97 [0.83 – 1.12]	0.631	0.64 [0.53 – 0.78]	$< 10^{-3}$
<b>Advanced liver fibrosis<sup>†</sup></b>				
No (ref.)	1		1	
Yes	0.86 [0.59 – 1.24]	0.416	1.19 [0.76 – 1.87]	0.438



<b>Time since HBV diagnosis (years)</b>	1.01 [1.00 – 1.01]	0.189	1.00 [0.99 – 1.01]	0.727
<b>HBV treatment status</b>				
Never treated (ref.)	1	<b>0.264</b>	1	<b>0.254</b>
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)**

<b>Variables</b>	<b>Overweight (25 ≤ BMI &lt; 30)</b>		<b>Obesity (BMI ≥ 30)</b>	
	<b>aRRR [95% CI]</b>	<b>P-value</b>	<b>aRRR [95% CI]</b>	<b>P-value</b>
<b>Cannabis use</b>				
Never (ref.)	1	<b>0.011</b>	1	<b>0.017</b>
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
<b>Gender</b>				
Male (ref.)	1		1	
Female	0.72 [0.62 – 0.85]	< 10 <sup>-3</sup>	1.71 [1.39 – 2.11]	< 10 <sup>-3</sup>
<b>Age at baseline (years)</b>	1.02 [1.01 – 1.02]	< 10 <sup>-3</sup>	1.03 [1.02 – 1.03]	< 10 <sup>-3</sup>
<b>Tobacco smoking</b>				
Never (ref.)	1	<b>0.149</b>	1	<b>0.015</b>
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
<b>Alcohol consumption</b>				
Abstinent without past unhealthy use (ref.)	1	<b>0.851</b>	1	<b>0.015</b>
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
<b>Living in poverty</b>				
No (ref.)	1		1	
Yes	1.28 [1.10 – 1.50]	0.002	1.77 [1.42 – 2.20]	< 10 <sup>-3</sup>
<b>Education level</b>				
< secondary school diploma (ref.)	1		1	
> secondary school diploma	0.93 [0.80 – 1.09]	0.381	0.68 [0.55 – 0.84]	< 10 <sup>-3</sup>

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