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## **Cannabis use is associated with a lower risk of diabetes in chronic hepatitis C-infected patients (ANRS CO22 Hepather cohort)**

Tangui Barré, Marie Libérée Nishimwe, Camelia Protopopescu, Fabienne Marcellin, Fabrice Carrat, Céline Dorival, Elisabeth Delarocque-Astagneau, Dominique G. Larrey, Marc Bourlière, Ventzislava Petrov-Sanchez, et al.

### ► To cite this version:

Tangui Barré, Marie Libérée Nishimwe, Camelia Protopopescu, Fabienne Marcellin, Fabrice Carrat, et al.. Cannabis use is associated with a lower risk of diabetes in chronic hepatitis C-infected patients (ANRS CO22 Hepather cohort). *Journal of Viral Hepatitis*, 2020, 27 (12), pp.1473-1483. 10.1111/jvh.13380 . hal-03109215

**HAL Id: hal-03109215**

**<https://hal.science/hal-03109215>**

Submitted on 19 May 2021

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4 **Cannabis use is associated with a lower risk of diabetes in**  
5  
6 **chronic hepatitis C-infected patients (ANRS CO22 Hepather cohort)**  
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9 **Running title**  
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11 Cannabis use and diabetes in HCV patients  
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14  
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18 Hélène Fontaine<sup>\*10, 11</sup> and Patrizia Carrieri<sup>1,2</sup> on behalf of the ANRS/AFEF Hepather study  
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## 24 25 26 27 28 29 30 31 Acknowledgments

32  
33  
34  
35           The cohort received financial support from the INSERM-ANRS (France Recherche  
36  
37 Nord & Sud Sida-HIV Hépatites), the French ANR (Agence Nationale de la Recherche), the  
38  
39 French DGS (Direction Générale de la Santé), Merck Sharp and Dohme, Janssen-Cilag,  
40  
41 Gilead, Abbvie, Bristol-Myers Squibb, and Roche. Those funding sources had no role in the  
42  
43 writing of the manuscript or the decision to submit it for publication.

44  
45  
46           We thank the study participants and the participating clinicians at each site. We also  
47  
48 thank the INSERM-ANRS for sponsoring, funding and conducting the ANRS CO22 Hepather  
49  
50 cohort in collaboration with the French Association for the Study of the liver (Association  
51  
52 Française pour l'Etude du Foie: AFEF). Finally, our thanks to Jude Sweeney for the English  
53  
54 revision and editing of our manuscript.

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#### 37 **Financial support statement (authors):**

38  
39  
40 FC reports grants from INSERM-ANRS, during the conduct of the study; and personal fees  
41 from Imaxio, outside the submitted work. MB reports grants and personal fees from AbbVie  
42 and Gilead, outside the submitted work; and personal fees from MSD, Janssen, Boehringer  
43 Ingelheim, Intercept, and Bristol-Myers Squibb, outside the submitted work. SP has received  
44 consulting and lecturing fees from Bristol-Myers Squibb, Janssen, Gilead, Roche, MSD, MYR-  
45 Pharma, Shionogi, Biotest and Abbvie, as well as grants from Bristol-Myers Squibb, Gilead,  
46 Roche and MSD. HF reports personal fees and invitations for medical meetings from Gilead,  
47 AbbVie, Bristol-Myers Squibb, MSD, and Janssen, outside the submitted work. Other authors  
48 declare no financial support.

#### 59 **Trial statement**

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3 Data were derived from a trial registered with ClinicalTrials.gov, number NCT01953458.  
4  
5 Written informed consent was obtained from each cohort participant before enrolment. The  
6  
7 protocol was designed in accordance with the Declaration of Helsinki and French law for  
8  
9 biomedical research, and was approved by the 'Comité de Protection des Personnes (CPP)  
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11 Ile de France 3' Ethics Committee (Paris, France) and the French Regulatory Authority  
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13 (ANSM).  
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For Peer Review

## Abstract

**Background & Aims:** Chronic hepatitis C virus (HCV) infection is a risk factor of insulin resistance, and HCV-infected patients are at a high risk of developing diabetes. In the general population, research has shown the potential benefit of cannabis use for the prevention of diabetes and related metabolic disorders. We aimed to test whether cannabis use is associated with a lower risk of diabetes in chronic HCV-infected patients.

**Methods:** Chronic HCV-infected patients (n=10,445) were selected from the French national, multicenter, observational ANRS CO22 Hepather cohort. Cross-sectional data collected at cohort enrolment were used to assess the association between patients' clinical and behavioral characteristics and the risk of diabetes. Logistic regression model was performed with cannabis use as the main independent variable and a significance level set at 5%. A similar model stratified by the presence of advanced liver fibrosis (FIB-4>3.25) was also run.

**Results:** After multivariable adjustment, current (AOR [95%CI]: 0.49 [0.38-0.63]) and former (0.81 [0.67-0.98], p<.001) cannabis use were both associated with a reduced odds of diabetes. Conversely, male gender, tobacco use, elevated BMI, poverty, being a migrant and advanced fibrosis were associated with increased odds of diabetes. The association between cannabis use and diabetes was maintained in the stratified analysis.

**Conclusions:** In this large cross-sectional study of chronic HCV-infected patients, cannabis use was associated with a lower risk of diabetes independently of clinical and socio-behavioral factors. Further studies are needed to elucidate a potential

causal link and shed light on cannabis compounds and mechanisms involved in this relationship.

**Keywords:**

Hepatitis C, Chronic; Cannabis; Diabetes Mellitus; Marijuana Smoking; France.

## Introduction

With a global prevalence of over 500 million cases in 2018, type 2 diabetes is a growing health and economic burden<sup>1,2</sup>, associated with increased all-cause mortality<sup>3</sup>. In 2015, the number of hepatitis C virus (HCV) viremic infections was estimated at more than 71 million worldwide. HCV is a leading cause of death and disability, especially through cirrhosis<sup>4,5</sup>. HCV and diabetes are reciprocally intertwined: HCV infection triggers diabetes (mostly type 2) and diabetes worsens HCV outcomes, for instance by increasing the risk for cirrhosis<sup>6</sup>. Furthermore, the treatment of diabetes in cirrhotic patients is complex<sup>7</sup>. Diabetes is the second most common extrahepatic manifestation of HCV infection<sup>8</sup>. HCV infection is assumed to lead to hepatic insulin resistance through direct impairment of the hepatocyte insulin signaling pathway and to peripheral insulin resistance through hepatic production of mediators<sup>9</sup>. Insulin resistance constitutes the pathological background for type 2 diabetes development, and may also trigger hepatic steatosis, the latter being also promoted directly by HCV infection<sup>10</sup>. A difference is sometimes made between type 2 diabetes and a state of impaired glucose regulation caused by loss of liver function as a consequence of cirrhosis (referred to as 'hepatogenous diabetes')<sup>7</sup>.



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3 In high-income countries, the HCV burden is mainly felt in marginalized  
4 populations<sup>11</sup> such as people who inject drugs and homeless people. In Europe,  
5 injecting drug use is the main route of HCV transmission<sup>12</sup>. Moreover, people who  
6 inject drugs face many barriers to access to care<sup>13,14</sup>. A higher HCV prevalence is  
7 associated with lower income, lower education level and less employment<sup>15</sup>. In  
8 parallel, a low socioeconomic status is associated with poorer health in general<sup>16</sup>,  
9 and with higher type 2 diabetes incidence in particular<sup>17</sup>. HCV-infected patients'  
10 susceptibility to diabetes may therefore be exacerbated by socioeconomic factors.  
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15 In the general population, studies examining the association between  
16 cannabis use and the risk of diabetes have yielded inconclusive results, while results  
17 showing the protective effect of cannabis in terms of other metabolic disorders seem  
18 more conclusive<sup>18</sup>. In a cross-sectional analysis of HIV-HCV co-infected patients,  
19 cannabis use, irrespective of frequency, was associated with lower odds of insulin  
20 resistance after adjustment for known confounders<sup>19</sup>. In chronic HCV-infected  
21 patients, cannabis use was also associated with better liver disease outcomes<sup>20</sup>.  
22 However, there is still a lack of data regarding the association between cannabis use  
23 and the risk of type 2 diabetes in HCV mono-infected patients. Using data from the  
24 French ANRS CO22 Hepather cohort, we aimed to test whether cannabis use is  
25 inversely associated with type 2 diabetes in HCV-infected patients.  
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## 48 Material and methods

### 49 Participants

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52 ANRS CO22 Hepather is a French national, multicenter, prospective,  
53 observational cohort of adult hepatitis B (HBV)- and HCV-infected patients  
54 (registered with ClinicalTrials.gov, number NCT01953458). The cohort design has  
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3 been extensively described elsewhere<sup>21</sup>. Set up in 2012, enrolment in the study took  
4 place in 32 centers throughout France. Patients were recruited during a medical  
5 follow-up visit in their center (eligible patients were proposed to participate in the  
6 cohort). Demographic, clinical and biological data were collected at the inclusion visit.  
7  
8 Patients were followed-up on a yearly basis, and supplemental data were also  
9 collected during visits related to particular events (e.g., initiation of HBV or HCV  
10 therapy). Written informed consent was obtained from each cohort participant before  
11 enrolment. The protocol was designed in accordance with the Declaration of Helsinki  
12 and French law for biomedical research, and was approved by the 'Comité de  
13 Protection des Personnes (CPP) Ile de France 3' Ethics Committee (Paris, France)  
14 and the French Regulatory Authority (ANSM).  
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29 The present study population comprised patients with chronic HCV (defined as  
30 positive HCV-RNA and anti-HCV antibodies) at cohort recruitment. The main  
31 exclusion criteria in Hepather were HIV co-infection, being on HCV-treatment or  
32 having stopped HCV treatment for less than 3 months at recruitment. We also  
33 excluded patients with no data on diabetes diagnosis (n=145) and patients with no  
34 cannabis use data (n=533), leaving us with a study sample of 10,445 patients (Figure  
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#### 44 45 Data collection

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48 At the enrolment visit, patients completed a face-to-face interview with their physician  
49 based on a structured questionnaire. Anthropological measurements and urine and  
50 blood samples were also taken.  
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55 Data collected in the questionnaire included: lifetime (yes/no) and current (yes/no)  
56 cannabis use, current tobacco use (yes/no), current alcohol consumption (number of  
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3 standard drinks per day), current coffee consumption (number of cups per day),  
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5 household income (average monthly income) and own and parents' country of birth.  
6  
7 Body height and weight were measured. Data derived from blood samples included  
8  
9 platelet count (platelets/mm<sup>3</sup>), aspartate aminotransferase (AST, IU/L) and alanine  
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11 aminotransferase (ALT, IU/L).  
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## 14 Outcome

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17 The variable 'presence of diabetes' was used as the outcome. Diabetes diagnosis  
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19 ('Yes/No') was established based on a confirmed fasting blood sugar level of at least  
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21 126 mg/dL (7.0 mmol/L) and/or uptake of antidiabetic drugs.  
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## 25 Explanatory variables

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28 People who answered 'yes' to the question concerning current use of cannabis were  
29  
30 classified into the 'current use' category. Among people who answered 'no', those  
31  
32 who reported lifetime cannabis use were classified into the "lifetime use" category.  
33  
34 Finally, people who answered 'no' to both questions (current/lifetime use) were  
35  
36 classified into the 'no lifetime use' category. We therefore ended up with a three-level  
37  
38 cannabis variable. According to previous studies in HIV-HCV co-infected patients,  
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40 elevated coffee consumption was defined as 3 or more cups of coffee per day<sup>22</sup>. A  
41  
42 second threshold at 4 cups of coffee was also tested. A meta-analysis highlighted a  
43  
44 decrease in relative risk of diabetes by 1 cup per day increase<sup>23</sup>. Poverty was defined  
45  
46 as a standard of living lower than the 2015 French poverty threshold (1,015€ per  
47  
48 month). Standard of living was calculated as disposable income divided by the  
49  
50 number of consumption units in the household. Being a migrant was defined as being  
51  
52 born outside France and having at least one parent also born outside France. Liver  
53  
54 fibrosis was assessed through FIB-4 calculation, based on age, platelet count, AST  
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56 and ALT using the following formula: (age [years] \* AST [IU/L]) / (platelet count [10<sup>9</sup>/L])  
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3 \* (ALT [IU/L])<sup>1/2</sup>. A cut-off >3.25 was used to define advanced fibrosis<sup>24</sup>. The  
4  
5 following variables were also tested as explanatory variables: gender, age, current  
6  
7 tobacco use (yes/no), current alcohol consumption (abstinent, moderate, elevated),  
8  
9 and body mass index (BMI) with the following WHO classes<sup>25</sup>: <18.5, underweight;  
10  
11 ≥18.5 and <25, normal weight; ≥25 and <30, overweight; ≥30, obese. Elevated  
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13 alcohol consumption was defined as >2 standard drinks per day for women and >3  
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15 standard drinks per day for men, according to French National Authority for Health<sup>26</sup>.  
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## 20 Statistical analyses

21  
22 The characteristics of diabetic patients were compared with those of non-diabetic  
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24 patients using a Chi-square test (categorical variables) or Student's t-test (continuous  
25  
26 variables). Similarly, the characteristics of the study population were compared  
27  
28 between cannabis use status (using Fisher's test for continuous variables). Logistic  
29  
30 regression models were used to test the association between cannabis use and  
31  
32 diabetes at cohort entry, after adjustment for other potential predictors. Only variables  
33  
34 with a liberal p-value <0.20 in the univariable analyses were considered eligible for  
35  
36 the multivariable model<sup>27</sup>. The final multivariable model was built using a backward  
37  
38 stepwise procedure and the likelihood ratio test (p<0.05) was used to define the  
39  
40 variables to be maintained in the model. An interaction between cannabis use and  
41  
42 BMI was tested for in the final model because cannabis use is known to be  
43  
44 associated with a lower BMI<sup>18</sup>. Because cirrhosis is diabetogenic<sup>7</sup>, similar logistic  
45  
46 regressions stratified by fibrosis status were also performed to test whether the  
47  
48 relationship between cannabis use and diabetes may differ between patients with  
49  
50 advanced fibrosis and other patients. Results from logistic regression models were  
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52 presented as odds ratios and adjusted odds ratios (for the multivariable model), with  
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3 the corresponding 95% confidence intervals. The level of significance was set at  
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5  $\alpha=0.05$  in all tests. SAS version 9.4 software was used for all analyses.  
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## 8 9 Results

### 10 11 12 Study population characteristics

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16 The characteristics of the study population are presented in Tables 1 and 2.

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19 The study population was mainly male (56.6%). Median age was 56 years and 13.7%  
20  
21 of the patients had diabetes. A majority of the study population had never used  
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23 cannabis (67.3%), 18.7% were former users and 14.0% were current users.  
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### 26 27 28 Multivariable analyses

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31 Despite being significantly associated with diabetes in univariable analysis, elevated  
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33 coffee consumption ( $\geq 3$  cups/day) was not significantly associated with the presence  
34  
35 of diabetes ( $p=0.54$ ) in the multivariable analysis. Increasing the threshold to  $\geq 4$   
36  
37 cups/day did not change this result ( $p=0.30$ ). Accordingly, this variable was removed  
38  
39 from the final model. Results for the final model are given in Table 3. When artificially  
40  
41 maintained in the model, it did not change other relationships between the explicative  
42  
43 and dependent variables.  
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48 Current and former cannabis use were both associated with a lower odds of  
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50 diabetes (compared with 'no lifetime use') (adjusted odds-ratio (OR), 95% confidence  
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52 interval (CI): 0.49 [0.38-0.63] and 0.81 [0.67-0.98], respectively). The lower odds of  
53  
54 diabetes in current users than in former users was statistically significant (0.60 [0.46-  
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56 0.80],  $p=0.0003$ ). Older age and being a man were positively associated with higher  
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58 odds of diabetes. BMI classes displayed a dose-dependent relationship with the odds  
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3 of diabetes. Moderate alcohol consumption was associated with a 23% lower odds of  
4 diabetes (compared with abstinence), while current tobacco use was associated with  
5 a 17% increased odds (Table 3). Both poverty and being a migrant were positively  
6 associated with the odds of diabetes, while individuals with advanced liver fibrosis  
7 had a 71% increased odds of diabetes. The interaction term between cannabis use  
8 and BMI was not statistically significant ( $p=0.23$ ).  
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18 When comparing individuals included in the multivariable analysis with those  
19 excluded ( $n=1,230$ ) because of missing values, the former were older (56.8 vs. 54.8  
20 years,  $p<0.001$ ), more likely to be male (55.7 vs. 52.3%,  $p=0.023$ ), less likely to be  
21 current smokers (37.2 vs. 40.5%,  $p=0.028$ ), and more likely to have elevated coffee  
22 consumption (69.3 vs. 64.6%,  $p<0.001$ ). When stratifying by fibrosis status, current  
23 cannabis use was associated with a lower odds of diabetes (compared with 'no  
24 lifetime use') in patients with and without advanced fibrosis (Supporting tables 1 & 2).  
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## 34 Discussion

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38 Using cross-sectional data from more than 9,000 HCV-infected patients, we  
39 found that former and current cannabis use were associated with, respectively, a  
40 19% and 51% lower risk of diabetes when compared with no lifetime cannabis use.  
41  
42 To our knowledge, this is the first time that such an association has been highlighted  
43 for HCV-infected patients. Under the assumption that the pattern of cannabis use  
44 differs only in terms of duration between former (shorter exposure) and current users  
45 (longer exposure), our results suggest that the potential protective effect of cannabis  
46 displays a dose-dependent relationship.  
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58 Our results are consistent with a meta-analysis in the U.S general population  
59 based on the National Health and Nutrition Examination Surveys (NHANES) and the  
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3 National Surveys on Drug Use and Health<sup>28</sup>. In that meta-analysis, recently active  
4 cannabis smoking and diabetes were inversely associated (compared with no lifetime  
5 cannabis use), with a summary odds-ratio of 0.7 [0.6-0.8]. This confirmed previous  
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8 results from NHANES data which compared lifetime use with no lifetime use<sup>29</sup>.  
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12 However, the only longitudinal analyses available revealed no association between  
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15 cannabis use and incidence of diabetes in the general population<sup>30,31</sup>, while cannabis  
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18 use in young adulthood was associated with prediabetes incidence in middle age<sup>31</sup>.

19 Beyond specificities due to HCV infection, differences in lifestyle or cannabis material  
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22 and practices may impair comparability between those studies coming from Sweden  
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25 and the U.S. Moreover, in the Swedish study the prevalence of current cannabis use  
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28 was very low<sup>30</sup>.

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31 Insulin resistance is closely related to other metabolic dysregulations and to  
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34 metabolic syndrome. The effects of cannabis use on BMI, obesity and other  
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37 metabolic dysregulations are still controversial but tend to indicate that there is a  
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40 beneficial effect<sup>18,32</sup>. Several cannabis compounds exerting potential beneficial  
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43 effects on these risk factors for diabetes have been identified. The endocannabinoid  
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46 system controls energy intake via both central and peripheral mechanisms, as well as  
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49 energy storage and expenditure, with direct implications for the development of type  
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52 2 diabetes<sup>33</sup>. Exogenous cannabinoids from cannabis are likely to interact with the  
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55 endocannabinoid system and its control of energy balance. For instance, cannabidiol,  
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58 a major non-psychoactive constituent of cannabis, decreases both body weight and  
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61 food intake in rats<sup>34,35</sup>.

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57 Given that diabetes pathogenesis in HCV-infected patients involves specific  
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60 mechanisms, the effects of cannabis use we found may be partly mediated by  
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63 mechanisms different from those observed in the general population. For instance,

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3 HCV infection causes systemic inflammation<sup>36</sup>, this latter being a likely contributor to  
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5 type 2 diabetes occurrence<sup>37,38</sup>. As cannabidiol found in cannabis possesses anti-  
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7 inflammatory properties<sup>39</sup>, this indirect action may lead to a stronger effect of  
8  
9 cannabis on diabetes in HCV-infected patients. Moreover, HCV-infected patients are  
10  
11 at greater risk of liver disease, and cirrhosis is diabetogenic<sup>7</sup>. Accordingly, we found  
12  
13 that advanced liver fibrosis is a risk factor for diabetes. Based on a large database of  
14  
15 USA hospital discharge records, Adejumo *et al.* found that cannabis use was  
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17 associated with a lower prevalence of liver cirrhosis among chronic HCV-infected  
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19 patients<sup>20</sup>. Among users, while the difference was not statistically different,  
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21 dependent users had an even lower prevalence of liver cirrhosis than non-dependent  
22  
23 users. This is in line with our results showing a lower risk of diabetes among current  
24  
25 cannabis users than in former users. While a recent systematic review and meta-  
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27 analysis concluded that there is no association between cannabis use and  
28  
29 progression of liver fibrosis in HCV and HIV-HCV co-infected patients<sup>40</sup>, the  
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31 mediating effect of fibrosis and/or cirrhosis between cannabis and diabetes deserves  
32  
33 further investigation. However, as the analyses in the present study were adjusted for  
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35 advanced liver fibrosis, we hypothesize that other mechanisms are involved. Patients  
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37 achieving sustained virological response (SVR) after interferon-based therapy  
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39 exhibited improvements in HOMA-IR and HOMA- $\beta$ , but no impact was found on  
40  
41 insulin resistance<sup>41</sup>. In the era of direct-acting antivirals for HCV, SVR rates of almost  
42  
43 100% are being reached, inducing clear benefits on the alteration of homeostasis of  
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45 glucose metabolism associated with HCV infection, including improvement of insulin  
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47 resistance and reduced onset of *de novo* insulin resistance and type 2 diabetes in  
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49 patients without advanced cirrhosis or long-term diabetic history<sup>42</sup>. For HCV patients  
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51 with type 2 diabetes, whether the beneficial short-term outcomes of DAA-induced  
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3 HCV clearance are maintained and of clinical significance in the long term remains  
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5 unclear<sup>43</sup>.  
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8 The endocannabinoid system is present in the liver and is involved in the  
9 control of various hepatic functions<sup>44</sup>. Noticeably, hepatic cannabinoid receptor CB1  
10 activation contributes to obesity-related insulin resistance. Endocannabinoids may  
11 also be directly involved in diabetes development, given that they may favor beta cell  
12 failure through peripheral CB1 receptors<sup>45</sup>. One can hypothesize that exogenous  
13 cannabinoids from cannabis interact with peripheral and/or hepatic endocannabinoid  
14 systems. For instance, chronic administration in patients with type 2 diabetes of  
15 delta-9-tetrahydrocannabivarin (THCV), which is found in cannabis, leads to a  
16 reduction of fasting plasma glucose and improved pancreatic  $\beta$ -cell function without  
17 affecting body weight or appetite<sup>46</sup>. These effects could explain the seemingly  
18 protective effect of cannabis use on diabetes development, even if other cannabis  
19 compounds may be involved, directly or through interaction with one another.  
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36 The gender difference in the risk of diabetes observed in our study is well-  
37 known and is mediated through endocrine and behavioral factors<sup>47</sup>. The increased  
38 risk of diabetes associated with current tobacco use has already been shown in the  
39 general population<sup>48</sup> and seems to be mediated through an impact on body weight,  
40 body composition, peripheral insulin sensitivity and pancreatic beta cell function<sup>49</sup>.  
41 Moderate alcohol consumption has previously been identified as protecting against  
42 type 2 diabetes in the general population, although the exact biological mechanisms  
43 involved are still unknown<sup>50</sup>. Given the positive association previously found between  
44 alcohol consumption and physical activity, the former may be a proxy of healthy  
45 behavior<sup>51</sup>, while abstinent persons may include individuals who stop drinking  
46 because of previous health problems.  
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3 Agardh *et al.* in their meta-analysis found an overall higher risk of diabetes in  
4 groups with a low socioeconomic status, specifically in terms of educational level,  
5 occupation and income<sup>17</sup>. This is in line with the associations we found between  
6 poverty and the risk of diabetes. There is now mounting evidence that socioeconomic  
7 factors such as income or education are risk factors for a wide range of health  
8 outcomes<sup>16</sup>. For instance, it has been shown that poor people covered by  
9 complementary universal health cover are frequently denied care in France<sup>52</sup>. With  
10 regards to immigrants, in France in 2015, approximately 31% were from the  
11 European Union, while 45% were from Africa<sup>53</sup>. We therefore expect that a majority  
12 of patients identified as migrants in our study were African. The most recent data  
13 indicate that immigrant households have a higher prevalence of poverty, are  
14 overrepresented in the less wealthy half of France population, and that almost a third  
15 of immigrant households where the head of the household was born in Africa have a  
16 standard of living lower than the first decile<sup>54</sup>. The association we found between  
17 being born outside France and the risk of diabetes is therefore certainly related to  
18 socioeconomic factors, but genetic contributions may make the burden heavier for  
19 some sub-populations than for others<sup>55</sup>. We did not find a significant association  
20 between elevated coffee consumption and the risk of diabetes after multivariable  
21 adjustment, despite robust evidence found in the general population<sup>23</sup>. Given that  
22 elevated coffee consumption seems to protect HIV-HCV co-infected patients from  
23 liver fibrosis<sup>22</sup> and that cirrhosis is a cause of diabetes, we may hypothesize that  
24 adjusting for fibrosis, as we did, lessens the protective effect of coffee on diabetes.  
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54 The main strength of the present study is the sample size and the sampling  
55 procedure likely to provide data representative of HCV-infected French patients.  
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58 Despite its cross-sectional nature, with more than 9,000 patients and a significant  
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3 proportion of cannabis users, it provides the first evidence of the potential protective  
4 effect of cannabis use on diabetes among HCV-infected patients. As diabetes  
5 diagnosis is more likely to encourage more health-conscious behavior, it is unlikely  
6 that reverse causality is involved in the association we found between cannabis use  
7 and diabetes. Longitudinal studies are nonetheless required to confirm these  
8 findings. Multivariable adjustment for clinical, behavioral and socio-economic  
9 variables is another strength of the study. It is now well-recognized that these  
10 variables impact to a great extent health outcomes. This study has limitations.  
11 Collection of cannabis data during face-to-face interviews with physicians may have  
12 led to underreporting of use. However, such underreporting would be unlikely to be  
13 different between the two groups (i.e., with and without diabetes). Furthermore, such  
14 a bias is less likely for former cannabis users. To further assess the dose-dependent  
15 nature of the relationship, more precise data regarding cannabis use would have  
16 been valuable. We did not have data regarding diet quality or physical activity, which  
17 are known risk factor for diabetes development. However, they are related to BMI  
18 which was included, and if they were available, reverse causality would have  
19 impaired the interpretation (diabetic patients may be more attentive to their lifestyle).  
20 Being able to take into account history of HCV treatment (information which was not  
21 available in our study) would have been beneficial given that interferon-based  
22 therapeutic regimens may be involved in type 1 diabetes development<sup>6</sup>. The lack of  
23 data differentiating type 2 from type 1 diabetes also impairs the interpretation of the  
24 results. However, HCV is recognized as triggering mostly type 2 diabetes and only  
25 occasionally type 1 diabetes<sup>6</sup>. Therefore, given the high prevalence of type 2  
26 diabetes among HCV infected patients and that the relationship between type 2  
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3 diabetes and HCV is unequivocal<sup>56</sup>, we may expect that the vast majority of diabetes  
4 cases were type 2.  
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## 8 9 Conclusions

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11 In conclusion, we found that cannabis use is associated with a lower risk of  
12 diabetes in HCV-infected patients. Further studies are needed to longitudinally  
13 confirm these results and investigations into cannabis compounds and their biological  
14 effects hold great promise for the treatment and prevention of diabetes.  
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For Peer Review

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## Tables

**Table 1: Characteristics of the study population according to diabetes status (ANRS CO22 Hepather cohort, n=10,445).**

	All participants N=10,445	No diabetes N=8,988 (86.1%)	Diabetes N=1,457 (13.9%)	P-value†
	N (%)	N	%	
<b>Gender</b>				
Female	4668 (44.7)	4129	88.5	11.6 <.001
Male	5777 (55.3)	4859	84.1	15.9
<b>Cannabis use</b>				
Never	7030 (67.3)	5883	83.7	16.3 <.001
Former	1956 (18.7)	1740	89.0	11.0
Current	1459 (14.0)	1365	93.6	6.4
<b>Tobacco use</b>				
No or former	3928 (37.6)	3312	84.3	15.7 <.001
Current	6515 (62.4)	5674	87.1	12.9
Missing	2 (0.02)	2	100.0	0.0

<b>Coffee consumption</b>									
Low (<3 cups/day)	7185 (68.8)	6097	84.9	1088	15.1	<.001			
Elevated ( $\geq 3$ cups/day)	3260 (31.2)	2891	88.7	369	11.3				
<b>Body mass index</b>									
Underweight (<18.5)	346 (3.3)	325	93.9	21	6.1	<.001			
Normal ( $\geq 18.5$ and <25)	5259 (50.3)	4779	90.9	480	9.1				
Overweight ( $\geq 25$ and <30)	3332 (31.9)	2773	83.2	559	16.8				
Obese (>30)	1414 (13.5)	1032	73.0	382	27.0				
Missing	94 (0.9)	79	84.0	15	16.0				
<b>Alcohol consumption<sup>‡</sup></b>									
Abstinent	5972 (57.2)	5002	83.8	970	16.2	<.001			
Moderate	3980 (38.1)	3545	89.1	435	10.9				
Elevated	441 (4.2)	400	90.7	41	9.3				
Missing	52 (0.5)	41	78.9	11	21.2				
<b>Poverty<sup>s</sup></b>									
No	6742 (64.5)	5896	87.5	846	12.6	<.001			

Yes	3360 (32.2)	2800	83.3	560	16.7	
Missing	343 (3.3)	292	85.1	51	14.9	
<b>Being a migrant<sup>¶</sup></b>						
No	7563 (72.4)	6691	88.5	872	11.5	<.001
Yes	2869 (27.5)	2285	79.6	584	20.4	
Missing	13 (0.1)	12	92.3	1	7.7	
<b>Advanced liver fibrosis (FIB-4&gt;3.25)</b>						
No	7106 (68.0)	6291	88.5	815	11.5	<.001
Yes	2511 (24.0)	1956	77.9	555	22.1	
Missing	828 (7.9)	741	89.5	87	10.5	
<b>Age (mean years (STD))(missing=14)</b>	56.6 (11.6)	55.9 (11.6)		60.9 (10.2)		<.001

† Chi-square test (categorical variables) or Student's t-test (continuous variable, i.e. age).

‡ Elevated alcohol consumption was defined as >2 standard drinks per day for women and >3 standard drinks per day for men. §Poverty was defined as a standard of living lower than the 2015 French poverty threshold (1,015€ per month per household consumption unit). ¶Being a migrant was defined as being born outside France and having at least one parent also born outside France. STD, standard deviation.

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**Table 2: Characteristics of the study population according to cannabis use (ANRS CO22 Hepather cohort, n=10,445).**

	Current use		Former use		No lifetime use		P-value†
	N	%	N	%	N	%	
<b>Gender</b>							
Female	300	6.4	545	11.7	3823	81.9	<.001
Male	1159	20.1	1411	24.4	3207	55.5	
<b>Cannabis use</b>							
Never	.	.	.	.	7030	100.0	
Former	.	.	1956	100.0	.	.	
Current	1459	100.0	.	.	.	.	
<b>Tobacco use</b>							
No or former	51	1.3	80	2.0	3797	96.7	<.001
Current	1408	21.6	1876	28.8	3231	49.6	
Missing	.	.	.	.	2	100.0	
<b>Coffee consumption</b>							

Low (<3 cups/day)	786	10.9	1166	16.2	5233	72.8	<.001
Elevated (≥3 cups/day)	673	20.6	790	24.2	1797	55.1	
<b>Body mass index</b>							
Underweight (<18.5)	103	29.8	69	19.9	174	50.3	<.001
Normal (≥18.5 and <25)	927	17.6	1053	20.0	3279	62.4	
Overweight (≥25 and <30)	335	10.1	613	18.4	2384	71.6	
Obese (>30)	89	6.2	201	14.2	1124	79.5	
Missing	5	5.3	20	21.3	69	73.4	
<b>Alcohol consumption<sup>‡</sup></b>							
Abstinent	650	10.9	968	16.2	4354	72.9	<.001
Moderate	624	15.7	866	21.8	2490	62.6	
Elevated	171	38.8	107	24.3	163	37.0	
Missing	14	26.9	15	28.9	23	44.2	
<b>Poverty<sup>s</sup></b>							
No	792	11.8	1292	19.2	4658	69.1	<.001

Yes	634	18.9	621	18.5	2105	62.7	
Missing	33	9.6	43	12.5	267	77.8	
<b>Being a migrant†</b>							
No	1255	16.6	1658	21.9	4650	61.5	<.001
Yes	203	7.1	296	10.3	2370	82.6	
Missing	1	7.7	2	15.4	10	76.9	
<b>Advanced liver fibrosis (FIB-4&gt;3.25)</b>							
No	1063	15.0	1351	19.0	4692	66.0	<.001
Yes	295	11.8	441	17.6	1775	70.7	
Missing	101	12.2	164	19.8	563	68.0	
<b>Age (mean years, (STD))(missing=14)</b>	50.6 (7.8)		52.2 (7.2)		59.0 (12.4)		<.001

† Chi-square test (categorical variables) or Fisher's test (continuous variable, i.e. age).



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3 † Elevated alcohol consumption was defined as >2 standard drinks per day for women and >3 standard drinks per day for men. §Poverty was  
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5 defined as a standard of living lower than the 2015 French poverty threshold (1,015€ per month per household consumption unit). ¶Being a  
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7 migrant was defined as being born outside France and having at least one parent also born outside France. STD, standard deviation.  
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**Table 3: Factors associated with the presence of diabetes, logistic regression models, univariable and multivariable analyses (ANRS CO22 Hepather cohort, n=10,445)**

	Univariable analyses (n=10,445)			Multivariable analysis (n=9,215)		
	OR	95% CI	P-value	AOR	95% CI	P-value
<b>Gender</b>						
Female	1			1		
Male	1.45	1.29-1.62	<.001	1.86	1.61-2.14	<.001
<b>Cannabis use</b>						
No lifetime use	1			1		
Former	0.64	0.55-0.74	<.001	0.81	0.67-0.98	0.031
Current	0.35	0.28-0.44	<.001	0.49	0.38-0.63	<.001
<b>Tobacco use</b>						
No lifetime use or former use	1			1		

Current	0.80	0.71-0.89	<.001	1.17	1.01- 1.36	0.036
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### Coffee consumption

Low (<3 cups/day)	1					
Elevated ( $\geq 3$ cups/day)	0.72	0.63-0.81	<.001			

### Body mass index

Underweight (<18.5)	0.64	0.41-1.01	0.056	0.92	0.57- 1.46	0.708
Normal ( $\geq 18.5$ and <25)	1			1		
Overweight ( $\geq 25$ and <30)	2.01	1.76-2.29	<.001	1.65	1.43- 1.91	<.001
Obese (>30)	3.69	3.17-4.28	<.001	3.33	2.82- 3.92	<.001

### Alcohol consumption<sup>†</sup>

Abstinent	1			1		
Moderate	0.63	0.56-0.71	<.001	0.77	0.68- 0.89	<.001
Elevated	0.53	0.38-0.73	<.001	0.72	0.50- 1.03	0.075

### Poverty<sup>‡</sup>

No	1			1		
Yes	1.39	1.24-1.57	<.001	1.32	1.15- 1.51	<.001
<b>Being a migrants§</b>						
No	1			1		
Yes	1.96	1.75-2.20	<.001	1.51	1.31- 1.74	<.001
<b>Advanced liver fibrosis (FIB-4&gt;3.25)</b>						
No	1			1		
Yes	2.19	1.94-2.47	<.001	1.71	1.50- 1.95	<.001
<b>Age (years)</b>						
	1.04	1.03-1.05	<.001	1.04	1.03- 1.05	<.001

† Elevated alcohol consumption was defined as >2 standard drinks per day for women and >3 standard drinks per day for men. ‡Poverty was defined as a standard of living lower than the 2015 French poverty threshold (1,015€ per month per household consumption unit). §Being a migrant was defined as being born outside France and having at least one parent also born outside France. (A)OR, (adjusted) odds ratio; CI, confidence interval.

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**Figure 1: Flowchart of the study population (ANRS CO22 Hepather cohort).**

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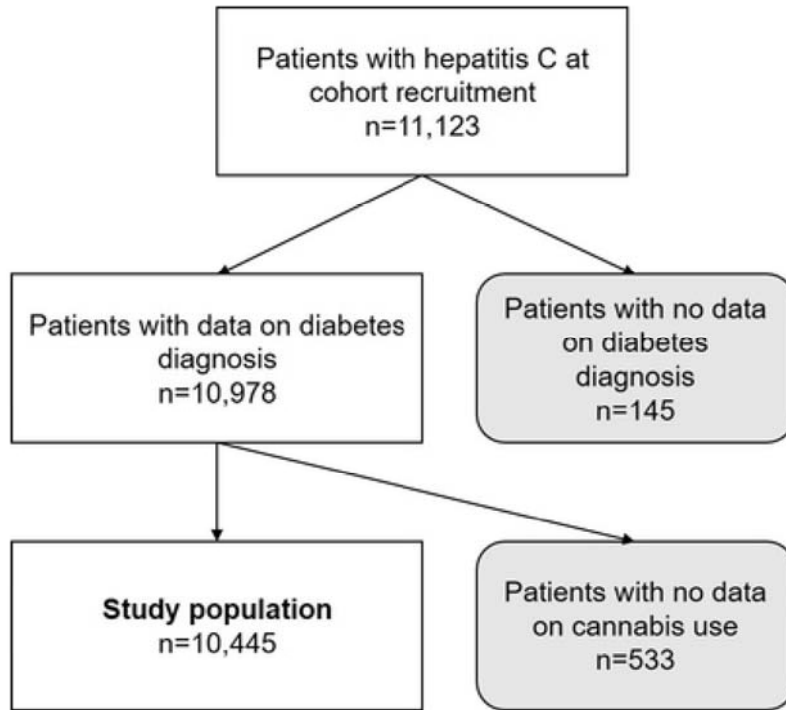


Figure 1: Flowchart of the study population (ANRS CO22 Hepather cohort).

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**Supporting table 1: Factors associated with the presence of diabetes in patients without advanced fibrosis, logistic regression models, univariable and multivariable analyses (ANRS CO22 Hepather cohort, n=7,106)**

	Univariable analyses (n=7,106)			Multivariable analysis (n=6,813)		
	OR	95% CI	P-value	AOR	95% CI	P-value
<b>Gender</b>						
Female	1		<.001	1		<.001
Male	1.38	1.19-1.60		1.83	1.53-2.19	
<b>Cannabis use</b>						
No lifetime use	1		<.001	1		0.001
Former	0.66	0.54-0.80		0.89	0.70-1.14	
Current	0.34	0.26		0.55	0.40-0.75	
<b>Tobacco use</b>						
No lifetime use or former use	1		0.011	1		0.006
Current	0.83	0.71-0.96		1.30	1.08-1.57	
<b>Coffee consumption</b>						
Low (<3 cups/day)	1		0.010			

Elevated ( $\geq 3$  cups/day) 0.82 0.70-0.95

### Body mass index

Underweight ( $< 18.5$ )	0.63	0.34-1.16	$< .001$	0.79	0.42- 1.49	$< .001$
Normal ( $\geq 18.5$ and $< 25$ )	1			1		
Overweight ( $\geq 25$ and $< 30$ )	2.37	1.20-2.82		1.89	1.57- 2.28	
Obese ( $> 30$ )	4.55	3.75-5.54		3.94	3.20- 4.87	

### Alcohol consumption†

Abstinent	1		$< .001$	1		$< .001$
Moderate	0.56	0.48-0.66		0.66	0.55- 0.78	
Elevated	0.41	0.25-0.67		0.52	0.30- 0.89	

### Poverty‡

No	1		$< .001$	1		0.008
Yes	1.33	1.15-1.55		1.27	1.06- 1.52	

### Being a migrant§

No	1		$< .001$	1		$< .001$
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3	Yes	2.00	1.72-2.32		1.56	1.3-1.87
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6						1.04-
7	<b>Age (years)</b>	1.05	1.04-1.05	<.001	1.05	<.001
8						1.06
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11 † Elevated alcohol consumption was defined as >2 standard drinks per day for women and  
 12 >3 standard drinks per day for men. ‡Poverty was defined as a standard of living lower than  
 13 the 2015 French poverty threshold (1,015€ per month per household consumption unit).  
 14 §Being a migrant was defined as being born outside France and having at least one parent  
 15 also born outside France. (A)OR, (adjusted) odds ratio; CI, confidence interval.

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**Supporting table 2: Factors associated with the presence of diabetes in patients with advanced fibrosis, logistic regression models, univariable and multivariable analyses (ANRS CO22 Hepather cohort, n=2,511)**

	Univariable analyses (n=2,511)			Multivariable analysis (n=2,410)		
	OR	95% CI	P-value	AOR	95% CI	P-value
<b>Gender</b>						
Female	1		<.001	1		<.001
Male	1.39	1.15-1.69		1.87	1.50-2.33	
<b>Cannabis use</b>						
No lifetime use	1		<.001	1		<.001
Former	0.62	0.47-0.81		0.66	0.49-0.89	
Current	0.330	0.23-0.50		0.39	0.25-0.60	
<b>Tobacco use</b>						
No lifetime use or former use	1		<.001			
Current	0.72	0.60-0.87				
<b>Coffee consumption</b>						
Low (<3 cups/day)	1		0.214			

Elevated ( $\geq 3$ cups/day)	0.85	0.66-1.20				
<b>Body mass index</b>						
Underweight ( $< 18.5$ )	0.88	0.45-1.69	$< .001$	1.14	0.56-2.31	$< .001$
Normal ( $\geq 18.5$ and $< 25$ )	1			1		
Overweight ( $\geq 25$ and $< 30$ )	1.50	1.21-1.85		1.31	1.04-1.64	
Obese ( $> 30$ )	2.57	1.99-3.31		2.43	1.85-3.19	
<b>Alcohol consumption†</b>						
Abstinent	1		0.101			
Moderate	0.89	0.73-1.10				
Elevated	0.64	0.41-1.00				
<b>Poverty‡</b>						
No	1		0.008	1		0.011
Yes	1.30	1.07-1.58		1.34	1.07-1.67	
<b>Being a migrant§</b>						
No	1		$< .001$	1		0.001

Yes	1.89	1.55-2.29		1.45	1.16-1.81	
<b>Age (years)</b>	1.02	1.01-1.03	<.001	1.05	1.04-1.06	0.001

† Elevated alcohol consumption was defined as >2 standard drinks per day for women and >3 standard drinks per day for men. ‡Poverty was defined as a standard of living lower than the 2015 French poverty threshold (1,015€ per month per household consumption unit). §Being a migrant was defined as being born outside France and having at least one parent also born outside France. (A)OR, (adjusted) odds ratio; CI, confidence interval.

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