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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.

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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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Trial statement

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3 Data were derived from a trial registered with ClinicalTrials.gov, number NCT01953458.
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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

1
2
3 causal link and shed light on cannabis compounds and mechanisms involved in this
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5 relationship.
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8 **Keywords:**
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11 Hepatitis C, Chronic; Cannabis; Diabetes Mellitus; Marijuana Smoking; France.
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17 **Introduction**
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21 With a global prevalence of over 500 million cases in 2018, type 2 diabetes is
22 a growing health and economic burden^{1,2}, associated with increased all-cause
23 mortality³. In 2015, the number of hepatitis C virus (HCV) viremic infections was
24 estimated at more than 71 million worldwide. HCV is a leading cause of death and
25 disability, especially through cirrhosis^{4,5}. HCV and diabetes are reciprocally
26 intertwined: HCV infection triggers diabetes (mostly type 2) and diabetes worsens
27 HCV outcomes, for instance by increasing the risk for cirrhosis⁶. Furthermore, the
28 treatment of diabetes in cirrhotic patients is complex⁷. Diabetes is the second most
29 common extrahepatic manifestation of HCV infection⁸. HCV infection is assumed to
30 lead to hepatic insulin resistance through direct impairment of the hepatocyte insulin
31 signaling pathway and to peripheral insulin resistance through hepatic production of
32 mediators⁹. Insulin resistance constitutes the pathological background for type 2
33 diabetes development, and may also trigger hepatic steatosis, the latter being also
34 promoted directly by HCV infection¹⁰. A difference is sometimes made between type
35 2 diabetes and a state of impaired glucose regulation caused by loss of liver function
36 as a consequence of cirrhosis (referred to as 'hepatogenous diabetes')⁷.
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3 In high-income countries, the HCV burden is mainly felt in marginalized
4 populations¹¹ such as people who inject drugs and homeless people. In Europe,
5 injecting drug use is the main route of HCV transmission¹². Moreover, people who
6 inject drugs face many barriers to access to care^{13,14}. A higher HCV prevalence is
7 associated with lower income, lower education level and less employment¹⁵. In
8 parallel, a low socioeconomic status is associated with poorer health in general¹⁶,
9 and with higher type 2 diabetes incidence in particular¹⁷. 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 conclusive¹⁸. 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 confounders¹⁹. In chronic HCV-infected
21 patients, cannabis use was also associated with better liver disease outcomes²⁰.
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 elsewhere²¹. 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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43 1).

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.
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7 Body height and weight were measured. Data derived from blood samples included
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9 platelet count (platelets/mm³), 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
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30 classified into the 'current use' category. Among people who answered 'no', those
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32 who reported lifetime cannabis use were classified into the "lifetime use" category.
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34 Finally, people who answered 'no' to both questions (current/lifetime use) were
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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 day²². 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 increase²³. Poverty was defined
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46 as a standard of living lower than the 2015 French poverty threshold (1,015€ per
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48 month). Standard of living was calculated as disposable income divided by the
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50 number of consumption units in the household. Being a migrant was defined as being
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52 born outside France and having at least one parent also born outside France. Liver
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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 [10⁹/L])
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3 * (ALT [IU/L])^{1/2}. A cut-off >3.25 was used to define advanced fibrosis²⁴. The
4
5 following variables were also tested as explanatory variables: gender, age, current
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7 tobacco use (yes/no), current alcohol consumption (abstinent, moderate, elevated),
8
9 and body mass index (BMI) with the following WHO classes²⁵: <18.5, underweight;
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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 Health²⁶.
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20 Statistical analyses

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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
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26 variables). Similarly, the characteristics of the study population were compared
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28 between cannabis use status (using Fisher's test for continuous variables). Logistic
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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
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34 with a liberal p-value <0.20 in the univariable analyses were considered eligible for
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36 the multivariable model²⁷. 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
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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
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44 associated with a lower BMI¹⁸. Because cirrhosis is diabetogenic⁷, similar logistic
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46 regressions stratified by fibrosis status were also performed to test whether the
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48 relationship between cannabis use and diabetes may differ between patients with
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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%
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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 (≥ 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 ≥ 4
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37 cups/day did not change this result ($p=0.30$). Accordingly, this variable was removed
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39 from the final model. Results for the final model are given in Table 3. When artificially
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41 maintained in the model, it did not change other relationships between the explicative
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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
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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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When comparing individuals included in the multivariable analysis with those excluded ($n=1,230$) because of missing values, the former were older (56.8 vs. 54.8 years, $p<0.001$), more likely to be male (55.7 vs. 52.3%, $p=0.023$), less likely to be current smokers (37.2 vs. 40.5%, $p=0.028$), and more likely to have elevated coffee consumption (69.3 vs. 64.6%, $p<0.001$). When stratifying by fibrosis status, current cannabis use was associated with a lower odds of diabetes (compared with 'no lifetime use') in patients with and without advanced fibrosis (Supporting tables 1 & 2).

Discussion

Using cross-sectional data from more than 9,000 HCV-infected patients, we found that former and current cannabis use were associated with, respectively, a 19% and 51% lower risk of diabetes when compared with no lifetime cannabis use. To our knowledge, this is the first time that such an association has been highlighted for HCV-infected patients. Under the assumption that the pattern of cannabis use differs only in terms of duration between former (shorter exposure) and current users (longer exposure), our results suggest that the potential protective effect of cannabis displays a dose-dependent relationship.

Our results are consistent with a meta-analysis in the U.S general population based on the National Health and Nutrition Examination Surveys (NHANES) and the

1
2
3 National Surveys on Drug Use and Health²⁸. 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 use²⁹.
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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^{30,31}, while cannabis
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18 use in young adulthood was associated with prediabetes incidence in middle age³¹.

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 low³⁰.

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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^{18,32}. 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 diabetes³³. Exogenous cannabinoids from cannabis are likely to interact with the
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54
55 endocannabinoid system and its control of energy balance. For instance, cannabidiol,
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58 a major non-psychotropic constituent of cannabis, decreases both body weight and
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61 food intake in rats^{34,35}.

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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 inflammation³⁶, this latter being a likely contributor to
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5 type 2 diabetes occurrence^{37,38}. As cannabidiol found in cannabis possesses anti-
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7 inflammatory properties³⁹, this indirect action may lead to a stronger effect of
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9 cannabis on diabetes in HCV-infected patients. Moreover, HCV-infected patients are
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11 at greater risk of liver disease, and cirrhosis is diabetogenic⁷. Accordingly, we found
12
13 that advanced liver fibrosis is a risk factor for diabetes. Based on a large database of
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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 patients²⁰. 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
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23 users. This is in line with our results showing a lower risk of diabetes among current
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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
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29 progression of liver fibrosis in HCV and HIV-HCV co-infected patients⁴⁰, 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- β , but no impact was found on
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41 insulin resistance⁴¹. In the era of direct-acting antivirals for HCV, SVR rates of almost
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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 history⁴². 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 unclear⁴³.
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8 The endocannabinoid system is present in the liver and is involved in the
9 control of various hepatic functions⁴⁴. 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 receptors⁴⁵. 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 β -cell function without
17 affecting body weight or appetite⁴⁶. 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 factors⁴⁷. The increased
38 risk of diabetes associated with current tobacco use has already been shown in the
39 general population⁴⁸ and seems to be mediated through an impact on body weight,
40 body composition, peripheral insulin sensitivity and pancreatic beta cell function⁴⁹.
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 unknown⁵⁰. Given the positive association previously found between
44 alcohol consumption and physical activity, the former may be a proxy of healthy
45 behavior⁵¹, 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 income¹⁷. 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 outcomes¹⁶. For instance, it has been shown that poor people covered by
9 complementary universal health cover are frequently denied care in France⁵². With
10 regards to immigrants, in France in 2015, approximately 31% were from the
11 European Union, while 45% were from Africa⁵³. 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 decile⁵⁴. 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 others⁵⁵. 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 population²³. Given that
22 elevated coffee consumption seems to protect HIV-HCV co-infected patients from
23 liver fibrosis²² 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 development⁶. 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 diabetes⁶. 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 unequivocal⁵⁶, 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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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	%	
Gender				
Female	4668 (44.7)	4129	88.5	11.6 <.001
Male	5777 (55.3)	4859	84.1	15.9
Cannabis use				
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
Tobacco use				
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

Coffee consumption									
Low (<3 cups/day)	7185 (68.8)	6097	84.9	1088	15.1	<.001			
Elevated (≥3 cups/day)	3260 (31.2)	2891	88.7	369	11.3				
Body mass index									
Underweight (<18.5)	346 (3.3)	325	93.9	21	6.1	<.001			
Normal (≥18.5 and <25)	5259 (50.3)	4779	90.9	480	9.1				
Overweight (≥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				
Alcohol consumption†									
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				
Poverty‡									
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	
Being a migrant[¶]						
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	
Advanced liver fibrosis (FIB-4>3.25)						
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	
Age (mean years (STD))(missing=14)	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	%	
Gender							
Female	300	6.4	545	11.7	3823	81.9	<.001
Male	1159	20.1	1411	24.4	3207	55.5	
Cannabis use							
Never	7030	100.0	
Former	.	.	1956	100.0	.	.	
Current	1459	100.0	
Tobacco use							
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	
Coffee consumption							

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	
Body mass index							
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	
Alcohol consumption[‡]							
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	
Poverty^s							
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	
Being a migrant†							
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	
Advanced liver fibrosis (FIB-4>3.25)							
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	
Age (mean years, (STD))(missing=14)	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
Gender						
Female	1			1		
Male	1.45	1.29-1.62	<.001	1.86	1.61-2.14	<.001
Cannabis use						
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
Tobacco use						
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 (≥ 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 (≥ 18.5 and <25)	1			1		
Overweight (≥ 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[†]

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[‡]

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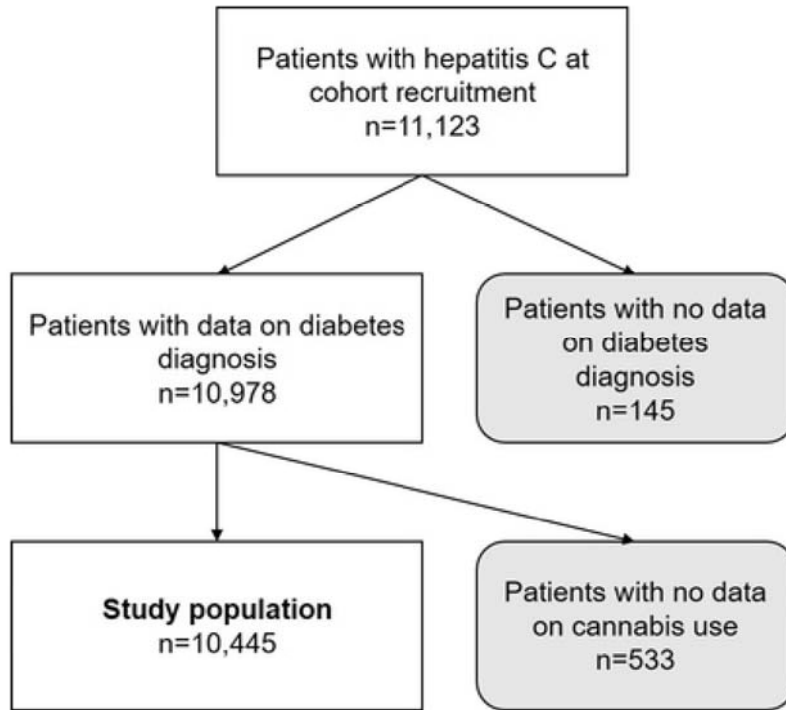


Figure 1: Flowchart of the study population (ANRS CO22 Hepather cohort).

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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
Gender						
Female	1		<.001	1		<.001
Male	1.38	1.19-1.60		1.83	1.53-2.19	
Cannabis use						
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	
Tobacco use						
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	
Coffee consumption						
Low (<3 cups/day)	1		0.010			

Elevated (≥ 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 (≥ 18.5 and < 25) 1 1

Overweight (≥ 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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7 **Age (years)** 1.05 1.04-1.05 <.001 1.05 1.04-
8 1.06 <.001
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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
Gender						
Female	1		<.001	1		<.001
Male	1.39	1.15-1.69		1.87	1.50-2.33	
Cannabis use						
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	
Tobacco use						
No lifetime use or former use	1		<.001			
Current	0.72	0.60-0.87				
Coffee consumption						
Low (<3 cups/day)	1		0.214			

Elevated (≥ 3 cups/day)	0.85	0.66-1.20				
Body mass index						
Underweight (< 18.5)	0.88	0.45-1.69	$< .001$	1.14	0.56-2.31	$< .001$
Normal (≥ 18.5 and < 25)	1			1		
Overweight (≥ 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	
Alcohol consumption†						
Abstinent	1		0.101			
Moderate	0.89	0.73-1.10				
Elevated	0.64	0.41-1.00				
Poverty‡						
No	1		0.008	1		0.011
Yes	1.30	1.07-1.58		1.34	1.07-1.67	
Being a migrant§						
No	1		$< .001$	1		0.001

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3					1.16-	
4	Yes	1.89	1.55-2.29		1.45	
5						1.81
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7						
8						1.04-
9	Age (years)	1.02	1.01-1.03	<.001	1.05	0.001
10						1.06
11						
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† 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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