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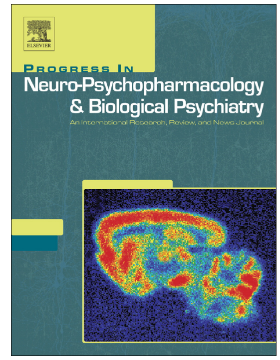

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Cannabis consumption and Non-Alcoholic Fatty Liver Disease. A three years longitudinal study in first episode non-affective psychosis patients.

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Abstract

Introduction: Increased incidence of obesity and excess weight leads to an increased incidence of nonalcoholic fatty liver disease (NAFLD). Recent evidence indicates a protective effect of cannabis consumption on weight gain and related metabolic alterations in psychosis patients. Overall, patients are at greater risk of presenting fatty diseases, such as NAFLD, partly due to lipid and glycemic metabolic disturbances. However, there are no previous studies on the likely effect of cannabis on liver steatosis. We aimed to explore if cannabis consumption had an effect on hepatic steatosis, in a sample of first-episode (FEP) non-affective psychosis.

Material and Methods: A total of 390 patients were evaluated at baseline and after 3 years of initiating the antipsychotic treatment. Anthropometric measurements and liver, lipid, and glycemic parameters were obtained at both time points. All but 6.7% of patients were drug-naïve at entry, and they self-reported their cannabis use at both time points. Liver steatosis and fibrosis were evaluated through validated clinical scores (Fatty Liver Index [FLI], Fibrosis-4 [FIB-4], and NAFLD).

Results: At 3-year follow-up, cannabis users presented significantly lower FLI scores than nonusers ($F = 13.874$; $p < 0.001$). Moreover, cannabis users less frequently met the criteria for liver steatosis than non-users ($X^2 = 7.97$, $p = 0.019$). Longitudinally, patients maintaining cannabis consumption after 3 years presented the smallest increment in FLI overtime, which was significantly smaller than the increment in FLI presented by discontinuers ($p = 0.022$) and never-users ($p = 0.016$). No differences were seen in fibrosis scores associated with cannabis.

Conclusions: Cannabis consumption may produce a protective effect against liver steatosis in psychosis, probably through the modulation of antipsychotic-induced weigh gain.

Highlights

- Cannabis consumption is associated with a lower risk of liver steatosis in psychosis.
- Cannabis use is not associated with liver fibrosis.
- The cannabis effect on liver tissue might be through the modulation of weight gain.
- A direct effect of cannabis on liver tissue has not been ruled out.

Keywords: liver steatosis; liver fibrosis; cannabis; antipsychotic treatment; treatment outcome; tolerability; medication naïve; first-episode psychosis.

1. Introduction

Patients with psychosis who are treated with antipsychotic medication are at greater risk of presenting altered liver function tests (Baeza et al., 2018), even from the early stages of psychosis (Erdogan et al., 2008), and an increased risk of chronic liver disease in the long term (Hsu et al., 2014). Although the mechanisms underlying the relation between antipsychotics and liver damage are not fully understood, previous studies demonstrated that treated schizophrenic patients (Gilles et al., 2010; Joseph et al., 2011; Konarzewska et al., 2014) exhibited an increased visceral and liver fat distribution compared with controls. In a recent study, we showed a significant incidence of nonalcoholic fatty liver disease (NAFLD) in a sample of patients with first-episode psychosis in the first 3 years of antipsychotic treatment (Morlán-Coarasa et al., 2016); in the same direction, a recent study reported a greater prevalence of NAFLD in patients with chronic schizophrenia (Yan et al., 2017). NAFLD, a condition of liver damage consisting of excessive accumulation of lipids in the hepatic tissue, has been associated with sedentary lifestyle and excess caloric diet (Romero-Gómez et al., 2017), among other factors leading to obesity and lipid/glycemic metabolic alterations (Targher, 2007). And these risk factors and metabolic disorders are frequently present in patients with psychosis (Vázquez-Bourgon et al., 2018). Interestingly, cannabis use, which is highly prevalent among psychotic patients (Green et al., 2005; Pelayo-Terán et al., 2008; Setien-Suero et al., 2017), has recently been associated with a protective effect against weight gain and obesity in psychosis (Vázquez-Bourgon et al., 2019 ; Scheffler et al., 2018).

However, to our knowledge, there are no previous studies exploring the possible effect of cannabis consumption on liver steatosis in psychosis.

Based on the evidence described above, we hypothesized that those patients with a first episode of non-affective psychosis who also use cannabis will present less frequently with NAFLD than psychotic patients who are non-users, suggesting a protective effect of cannabis on the liver.

The aim of this study was to explore, longitudinally, whether cannabis consumption has an effect on hepatic steatosis in a sample of patients with first-episode non-affective psychosis after 3 years of antipsychotic treatment.

2. Materials and methods

2.1. Study design

The sample population for the present study was recruited between 2001 and 2015 and formed part of a larger prospective longitudinal study on first-episode non-affective psychosis (Pelayo-Teran et al., 2008). Patients aged between 16 and 60 years who presented a first episode of non-affective psychosis with a confirmation diagnosis (at 6-month follow-up; *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition [DSM-IV] criteria) of schizophrenia, schizophreniform disorder, schizoaffective disorder, brief reactive psychosis, or psychosis not otherwise specified were included in the program. Patients were not admitted to the program if they presented any of the following: (1) intellectual disability, (2) neurological disorder, or (3) drug dependence (DSM-IV criteria). All subjects provided written informed consent prior to their inclusion in the study. The study was approved by the local ethics committee (University Hospital Marques de Valdecilla Ethics Committee).

2.2. Assessments

2.2.1. Patients

Patients attended clinical appointments with the same experienced psychiatrist on a regular basis and at least at baseline, 3 weeks, 6 weeks, 3 months, 6 months, and every 6 months thereafter until year 3. Patients were treated and maintained on antipsychotic treatment during the follow-up period. Certain concomitant medications were permitted if clinically needed, including lormetazepam and clonazepam (benzodiazepine receptor agonists, nonselective GABA-A receptor-positive allosteric modulators) for the management of agitation, general behavior disturbances, and/or insomnia; anticholinergic medication (biperiden at a dose of up to 8 mg/day) when clinically significant extrapyramidal signs occurred; or antidepressants (sertraline, a serotonin transporter reuptake inhibitor) and mood stabilizers (lithium, enzyme interactions).

Cannabis consumption (past-year cannabis use) as well as alcohol and tobacco (yes or no) were assessed based on patients' self-reported information. Alcohol consumption was also recorded as a continuous variable in units and grams of alcohol per week. No distinction was made between the route of cannabis administration (smoking or ingestion), the part of the plant used, or potency. Information on daily quantity was collected, but as we were unable to quantify these data reliably, this was not included in the analyses.

The patients' weight and waist circumference were determined at baseline and at 3-year follow-up. The patients' height was measured at the time of enrollment. The patients' body mass index (BMI) was computed as their body weight (kg) divided by height in square meters.

2.2.2. Laboratory analyses

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Gamma-glutamyltransferase (GGT), alkaline phosphatase, bilirubin, serum albumin, and triglycerides, platelets count, leptin, and high-sensitivity C-reactive protein were determined from peripheral blood samples. All determinations were performed in our hospital. All measurements were obtained at the first visit and at the 3-year follow-up, after an overnight fast. Triglycerides were measured by an automated method on a TechniconDax (Technicon Instruments Corp, Tarrytown, NY, USA) using reagents supplied by Boehringer-Mannheim (Mannheim, Germany).

2.2.3. Liver steatosis and fibrosis assessments

The Fatty Liver Index (FLI) (Bedogni et al. 2006) was determined at baseline and 3 years. The FLI consists of an algorithm that predicts fatty liver disease based on BMI, waist circumference, and triglyceride and gammaglutamyl transferase levels, with an accuracy of 0.84 (95% confidence interval, 0.81–0.87). The FLI varies from 0 to 100. A score lower than 30 rules out fatty liver disease (negative likelihood ratio = 0.2), and a score greater than or equal to 60 suggests fatty liver disease (positive likelihood ratio = 4.3).

Liver fibrosis was evaluated also through validated clinical scores; the NAFLD fibrosis and Fibrosis-4 (FIB-4) scores (Angulo et al. 2007; Sterling et al. 2006). The NAFLD fibrosis score consists of an algorithm that predicts fibrosis based on age, BMI, the presence of diabetes and/or insulin resistance, the AST:ALT ratio, the platelet count, and albumin levels. A score ≤1.455 rules out liver fibrosis with a negative predictive value of 93%, whereas a score ≥0.676 predicts liver fibrosis with a positive predictive value of 90%. The FIB-4 score is another algorithm based on age, platelet count, and AST and ALT levels. A score ≤1.30 rules out liver fibrosis with a negative predictive value of 90%, whereas a score ≥2.67 predicts liver fibrosis with a positive predictive value of 80%.

2.3. Statistical analysis

2.3.1. Cross-sectional associations

We conducted separate cross-sectional analysis of covariance (ANCOVA) models for exploring the possible effect of cannabis use on liver health at baseline and at 3 years. For this purpose, the liver disease indexes (FLI, FIB-4, and NAFLD) and the liver and laboratory parameters listed above were the dependent variables, and cannabis consumption status (yes/no) was the independent variable. Age, sex, smoking status (yes/no), and alcohol intake (yes/no), were entered in the model as covariables to avoid their potential effect as confounding factors. Post hoc correction (Bonferroni) was applied.

2.3.2. Longitudinal examinations

To examine the longitudinal effects of cannabis, we divided patients into three trajectory consumption groups: "continuers" (cannabis users at baseline who continued smoking at the 3-year assessment), "discontinuers" (patients using cannabis upon entering the program but who did not at the 3-year follow-up), and "never-users" (patients who reported not using cannabis at either time point). A forth category ("cannabis starters") was not considered since only three patients (0.8% of the total sample) started consuming cannabis during the 3 years follow-up; these three patents were excluded from the study to enable the statistical comparisons between groups.

General lineal model (GLM) repeated-measures tests were conducted for each dependent variable of liver functioning separately (e.g.: FLI, FIB-4, or AST), with cannabis consumption groups ("continuers", "discontinuers", and "never-users") as the between-subject variable and time (baseline, 3-year follow-up) as within-subject variable. Effects of time (longitudinal dimension), and time by cannabis consumption group (interaction effect) were examined. Sex and age at baseline, and alcohol and tobacco longitudinal consumption groups were included as covariates. All post-hoc comparisons were Bonferroni corrected.

We additionally calculated the percentage of subjects with pathologic values for FLI and the main liver parameters, at baseline and at the 3-year follow-up, in each cannabis-consuming group (continuers, discontinuers, never-users). To evaluate significant changes over time in these percentages within groups, we used the McNemar test for repeated measures.

2.3.3. Post hoc analyses

Alcohol dependence was an exclusion criterion for entering the study. However, to maximize the avoidance of the effect of alcohol use on liver steatosis, we repeated the statistical analyses after excluding those patients with moderate-severe alcohol consumption at any of the time points. Moderate-severe alcohol use was defined using the accepted alcohol consumption thresholds for the diagnosis of NAFLD: 140 and 210 grams of alcohol per week in women and men, respectively (Leoni et al., 2018).

The Statistical Package for Social Science (SPSS) version 22.0 (IBM, Armonk, NY, USA) was used for the statistical analyses. All statistical tests were two-tailed, and the significance was determined at the 0.05 level.

3. Results

3.1. Sample characteristics

A total of 390 patients with data of cannabis consumption at both time points were included in this study. The sample had a mean age of 30.4 years, 44.4% (n = 173) were women, and 81.8% (n = 319) were diagnosed with schizophrenia or schizophreniform disorder. The mean duration of untreated psychosis was 12.8 months (SD = 29.7), and the mean Scale for the Assessment of Positive Symptoms–Scale for the Assessment of Negative Symptoms score was 20.3 (SD = 7.7). At baseline, 38.5% (n = 150) were cannabis users. All but 6.7% (n = 26) of patients included in the study were drug-naïve. Among those that were not drug-naïve, their mean duration of previous antipsychotic exposure was 1.6 weeks (SD = 1.5). In any case, those non-drug-naïve patients were not significantly (all $p > 0.1$) different from the drug-naïve group in any of the main variables studied at baseline. A more detailed description of the clinical and socio-demographic characteristics of the study sample, including the differences between cannabis consumption groups at baseline, is available in Vázquez-Bourgon et al., (submitted).

3.2. Baseline and 3-year liver differences between cannabis users and nonusers

When comparing cross-sectionally cannabis users and nonusers (Table 1), the ANCOVA models showed a significant association only with leptin at both time points. Thus, cannabis users presented significant lower leptin levels before and 3 years after initiating antipsychotic treatment as compared with nonusers. No other liver or laboratory parameters studied were significantly associated with cannabis consumption at baseline or 3 years. However, the results also showed a significantly lower mean FLI among cannabis users at 3-year follow-up compared with nonusers (11.8 vs 40.3; $F = 13.784$, $p < 0.001$). Subsequent, X^2 tests showed that cannabis users at 3-year follow-up presented less frequently an FLI score equal to or greater than 60 than nonusers (11.1% vs. 28.3%; $X^2 = 7.97$, $p = 0.019$). This association remained significant after Yates's correction ($X^2 = 6.01$, $p = 0.049$).

3.3. Comparison of longitudinal changes in liver steatosis between cannabis users, nonusers, and discontinuers.

We found a significant interaction between cannabis consumption trajectories (users, discontinuers, and never-users) and time in FLI score ($F = 4.42$; $p = 0.014$) (Table 2). Additionally, we found a trend-level interaction between cannabis consumption trajectories and time in BMI (F=2.72; p=0.067). Post-hoc analyses revealed that patients who maintained the cannabis consumption (n=14) did not presented significant changes in FLI scores (p=0.892; estimated mean difference = 0.9), over a 3-year period. On the other hand, patients that abandoned the cannabis consumption (n=40) and those that never smoked cannabis (n=104) exhibited significant increments in FLI scores over the 3-year follow-up period (both p <0.001; estimated mean differences = 20.8 and 21.7, respectively).

3.4. Incidence of high levels of liver parameters and indexes over 3 years of antipsychotic treatment and cannabis use.

McNemar tests (Table 3) showed significant increments in the percentage of patients with liver parameters above the normal limits (ALT >40, GGT >32; %difference = 6, $p = 0.021$; and %difference = 11.4, $p < 0.001$, respectively). Unexpectedly, with regard to AST, the significant association was in the inverse direction; there was a significant reduction over time in the proportion of patients scoring above the upper-normal limit (AST >35; %difference = –6.3, $p = 0.013$).

When analyzing other laboratory tests, we also observed significant increments in the percentage of patients scoring above the upper-normal limit for leptin and high-sensitivity C-reactive protein (%difference = 25.1, $p < 0.001$; and %difference = 14.6, $p < 0.001$, respectively).

Finally, regarding the FLI score, we observed a significant increment in the percentage of patients with a score suggestive of liver steatosis (FLI >60; %difference = 18.9, p < 0.001).

Only one patient presented an FIB-4 score suggestive of liver fibrosis (FIB-4 score = 3.00). None of the patients presented an FIB-4 score greater than 2.67 at 3-year follow-up. Similarly, no patients presented a high NAFLD fibrosis score at any time point. Therefore, we were unable to analyze the association between liver fibrosis and cannabis consumption in our sample.

When comparing the changes in the proportion of patients with values above the normal limits, in each of the cannabis-consuming trajectories (users, discontinuers, and never-users; Table 3), we observed that, for most of the parameters, the group of cannabis consumers presented smaller increments than the discontinuers and never-users.

3.5. Post hoc analyses.

Thirty (7.7%) patients at baseline and 20 (5.1%) at 3-year follow-up reported elevated alcohol consumption (>210 g per week in men and >140 g per week in women). The results from statistical analyses, after excluding these patients (n = 40), remained the same; for a detailed description of these results see Tables 2-4 in Vázquez-Bourgon et al. (submitted). In the same direction, when FLI was analyzed as a qualitative variable, the significant association between cannabis use and FLI remained significant, where cannabis users presented less frequently an FLI ≥60 than nonusers (6.7% vs. 26.1%; X^2 = 9.89, p = 0.007) after 3 years of antipsychotic treatment. This association remained significant after Yates's correction (X^2 = 7.46, p = 0.024).

4. Discussion

We present the first study exploring the effect of cannabis consumption on liver health in a sample of patients with a first episode of psychosis. The results showed that those patients who reported continuing cannabis use were at lower risk of developing NAFLD in the first 3 years after the illness onset.

Cannabis consumers presented significantly lower mean FLI scores than non-users at the 3-year follow-up. This association was also seen using FLI as a qualitative measure of steatosis; thus, among cannabis users, there were significantly fewer patients meeting the criteria for NAFLD than among non-users after 3 years of antipsychotic treatment. When analyzing this relationship in detail longitudinally, we observed that those patients discontinuing cannabis consumption during the 3-year follow-up period presented a similar increase in mean FLI as never-users, with the increments in mean FLI in these two groups significantly greater than the increment observed in the continuers group.

These differences between groups in mean scores of FLI had clinical relevance, since there were important differences in the percentage of patients reaching a FLI score predictive of steatosis after 3 years of treatment: 7% of consumers versus 30% and 27% of discontinuers and never-users, respectively.

These results are in line with previous studies in the general population (Adejumo et al., 2017), in which cannabis users showed significantly lower NAFLD prevalence compared with non-users. This association between cannabis consumption and lower NAFLD prevalence has also been identified in subgroups of patients with other pathologies. For instance, cannabis consumption among patients with abusive alcohol use significantly reduced the odds of developing alcoholic steatosis, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (Adejumo et al., 2018). In the same direction, those patients co-infected by the human immunodeficiency and hepatitis C viruses, and reporting the use of cannabis, showed a a reduced risk of steatosis (Nordmann et al., 2018), and did not accelerate the progression of liver disease (Brunet et al., 2013). Similarly, cannabis use was associated with a decreased incidence of liver cirrhosis among hepatitis C virus patients (Adejumo et al., 2018b). However, some studies showed contrary evidence. Using imaging techniques in a small sample of 30 patients of chronic cannabis smokers, Muniyappa and colleagues (2013) found no association between cannabis and hepatic steatosis. In addition, daily cannabis use was associated with steatosis (Hezode et al., 2008) and liver fibrosis (Ishida et al., 2008) in patients with chronic hepatitis C disease.

Regarding fibrosis, our results found no significant differences when analyzing the fibrosis scores (FIB-4 and NAFLD fibrosis) between groups, which may be explained by the young mean age of the sample and the insufficient follow-up (3 years) for the development of liver fibrosis.

Cannabis users presented significantly lower levels of leptin compared with non-users, before and 3 years after initiating antipsychotic treatment. In addition, the proportion of patients with a leptin level above the upper normal limit significantly increased, after the first 3 years of psychosis, among the discontinuers and never-users, but not in the cannabis users group. These results are in line with recent data on cannabis use in the general population (Moreira et al., 2018) where cannabis smokers presented significantly lower levels of leptin than nonsmokers, in a population-based study. Leptin, a hormone that is mainly produced by the adipocytes, and acting on the hypothalamus, exerts a crucial role in energy balance and food intake. Leptin levels have been described to be elevated in schizophrenia patients (Kim et al., 2017; Pérez-Iglesias et al., 2008) and in those exposed to antipsychotic treatment (Ragguett et al., 2017). However, it has been proposed that the increase of leptin levels in these antipsychotic-exposed populations, is a consequence of augmented fat mass rather than being induced directly by antipsychotic treatment (Perez-Iglesias et al., 2008). It appears that at increasing concentrations, leptin induces target cells to become resistant to its own action (Lustig et al., 2004), leading to a "leptin-resistance" state in which leptin loses its satiating effect at the central level. Therefore, impaired leptin signaling does not seem to be the primary mechanism implicated in weight gain induced by antipsychotics; subsequently, the differences in leptin levels observed in our results, associated with cannabis use, appear to be secondary to the effect of cannabis on weight (Vázquez-Bourgon et al,. 2019; Scheffler et al., 2018). This would explain the contradictory data in the literature regarding the effect of cannabis on the liver, with a previous study reporting a profibrogenic effect of cannabis (Ishida et al., 2008).

The effects of cannabis use on weight and lipid/glycemic metabolism may be explained by its interaction with the endocannainoid system (ECS). The ECS includes two main receptors, cannabinoid type 1 and 2 receptors (CB1R and CB2R), whose major ligands are endogenous cannabinoids. These receptors are found in the central nervous system and various peripheral tissues, including the liver (Pertwee, 2008; Gong et al., 2006; Galiègue et al., 1995; Spigelman, 2010) playing a possible role in its functionality. Under healthy conditions, cannabinoid receptors are weakly expressed in the liver; CB1R in hepatocytes and endothelial cells, and CB2R in Kupffer cells. However, hepatic damage is associated with an increase in the expression of both receptors (Mallat & Lotersztajn, 2008). Thus, it is likely that cannabis plays a role in liver disease. CB1R seems to promote liver damage (Hsiao et al., 2015; Osei-Hyiaman et al., 2005; Osei-Hyiaman et al., 2008), while CB2R might have a protective effect (Di Marzo 2008; Mallat et al., 2007; Kunos et al., 2006). Thus, cannabis may promote a beneficial balance between CB1R and CB2R agonism in psychotic patients. It is interesting to note that Δ^9-tetrahydrocannabivarin and cannabidiol, two of the main cannabis components, were able to increase lipid mobilization and inhibit the development of hepatosteatosis, in *in vitro* and *in vivo* (animal models) experiments (Silvestri et al., 2015). In line with this, we observed a lower mean FLI among cannabis users compared with non-users. Thus, further studies testing the role of cannabinoids and cannabinoid receptors could help to elucidate the mechanisms involved in the possible protective role of cannabis on liver damage (Begg et al., 2005).

On the other hand, Kim and colleagues (2017) also showed a protective role of marijuana against body weight gain, attributed to a lower fasting insulin level. Liver diseases are often associated with insulin resistance and occur when the liver accumulates too much fat, altering the metabolism of glucose. Interestingly, rimonabant, a CB1R antagonist, improved insulin sensitivity in an experimental model (Ganesh & Rustgi, 2016), and similarly, cannabidiol can act as a CB1R antagonist, providing the possible link of insulin in our results (Thomas et al., 2007; Tam et al., 2011). In addition, cannabis users tend to consume higher calories and alcohol than nonusers and nonetheless seem to have a lower prevalence of body weight gain. Therefore, cannabis could protect the liver, even in the face of the dietary risks that cannabis users often show. This possible protective effect could be exerted through an intermediate beneficial effect on lipid and glycemic metabolism; in fact, previous studies (Bruins et al., 2016; Vázquez-Bourgon et al., 2019) showed that the discontinuation of cannabis use increased the metabolic risk.

Strengths and limitations

This study has several relevant limitations. First, the data regarding cannabis use were self-reported, and no confirmation by toxicological urinalysis was performed, which may have introduced information bias. However, information and self-reports given by subjects tend to be relatively accurate (Buchan et al., 2002; Harrison et al., 1993). Notably, the patients who were enrolled in our program went through a process in which both clinical and behavioral data were collected from both themselves and their relatives. We thus feel confident as to the utility of the self-reported measurements of substance use in our sample. Despite of this, we acknowledge that the study lacks some relevant information regarding cannabis use; frequency, amount, and lifetime duration of cannabis use. No distinction was made about the parts of the plant used or the cannabinoid potency; however, there are currently more than 100 known cannabinoids with diverse effects and action mechanisms, at both cannabinoid and non-cannabinoid receptors (Elsohly & Slade, 2005; Hill et al., 2012). Therefore, further studies in animal models would be helpful to determine the mechanisms underlying the possible protective role of cannabis in NAFLD.

Second, the mean age of the sample (30.4 years) hinders the occurrence of liver steatosis, since it is a pathological process that requires a longer period of time to develop.

Third, the definition and diagnosis of NAFLD through the FLI score may be too weighted by BMI, and it is possible that we are just observing a proxy of a protective effect of cannabis on BMI changes, as we have previously described in the same sample (Vázquez-Bourgon et al., 2019). However, the FLI score and fibrosis scores (NAFLD and FIB-4) are considered to be validated, noninvasive tools for the screening and diagnosis of liver damage (Leoni et al., 2018). Despite this, our results should be further explored and confirmed using imaging techniques, liver stiffness, and/or liver biopsy.

Fourth, the impact of diet and physical activity on our findings herein cannot be ruled out, since a thorough description of these variables in our sample during follow-up was not available. In addition, concomitant medication may potentially interfere with the endocannabinoid system and might play a significant role in our findings. It is remarkable that chronic antidepressant treatment (serotonin and norepinephrine reuptake inhibitors and serotonin reuptake inhibitors) produces changes in cannabinoid receptors, modifying their expression (Smaga et al., 2017).

Despite these limitations, the study has several strengths. First, it is to our knowledge the first study to explore the possible impact of cannabis on liver steatosis in a sample of patients with psychosis. Second, its design as a pragmatic clinical trial facilitates the generalization of the results to other clinical populations. Third, using a well-characterized sample of drug-naïve patients recently diagnosed with a first episode of non-affective psychosis helps to avoid the confounding effect of chronicity and long-term exposure to medications. Fourth, the long-term follow-up period (3 years) facilitates the detection of early liver alterations such as steatosis.

Conclusions

Our results suggest that using cannabis could have a protective effect on liver steatosis. The beneficial effect of cannabis at the level of the development of steatosis seems to be secondary to its modulation effect on weight gain and the reduced development of obesity, although a direct effect of cannabis on the hepatic tissue has not been ruled out. These results, although obtained from a sample of patients with psychosis, could be generalized; the hepatic alterations that may occur associated with the rapid increase in weight produced in our sample may be seen as an appropriate pragmatic experimental model for the study of steatosis.

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Declaration of interest

The authors declare no conflicts of interest in the present study or in preparing the manuscript.

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Author Agreement/Declaration

All authors have seen and approved the final version of the manuscript being submitted. We warrant that the article is an original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Author contribution:

The authors have contributed to the manuscript as follows: JV-B and BC-F designed the study and wrote the protocol. ES-S, MG-R and RA-A evaluated the patients and collected the study variables. VO-G build and maintained the database and helped with the statistical analyses. PI, MTA-L, IS-P and JV-B managed the literature searches. JV-B undertook the statistical analysis, and wrote the first draft of the manuscript. JC, PI, MTA-L, and BC-F contributed to the interpretation of the data and revised the manuscript critically. All authors contributed to and have approved the final manuscript.

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References

Adejumo AC, Alliu S, Ajayi TO, et al. Cannabis use is associated with reduced prevalence of non-alcoholic fatty liver disease: A cross-sectional study. PLoS One. 2017;12(4):e0176416.

Adejumo AC, Ajayi TO, Adegbala OM, et al. Cannabis use is associated with reduced prevalence of progressive stages of alcoholic liver disease. Liver Int. 2018 (a). doi: 10.1111/liv.13696.

Adejumo AC, Adegbala OM, Adejumo KL, Bukong TN. Reduced Incidence and Better Liver Disease Outcomes among Chronic HCV Infected Patients Who Consume Cannabis. Can J Gastroenterol Hepatol. 2018 (b);2018:9430953. doi: 10.1155/2018/9430953. eCollection 2018

Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Saksena S, Burt AD, Bida JP, Lindor K, Sanderson SO, Lenzi M, Adams LA, Kench J, Therneau TM, Day CP. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846-54.

Baeza I, de la Serna E, Calvo-Escalona R, Merchán-Naranjo J, Rodríguez-Latorre P, Martínez-Cantarero MC, Andrés P, Alda JA, Muñoz-Samons D, Ilzarbe D, Arango C, Castro-Fornieles J. One-Year Prospective Study of Liver Function Tests in Children and Adolescents on Second-Generation Antipsychotics: Is There a Link with Metabolic Syndrome? J Child Adolesc Psychopharmacol. 2018;28(7):463-473.

Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, Tiribelli C. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006;6:33.

Begg M, Pacher P, Bátkai S, Osei-Hyiaman D, Offertáler L, Mo FM, Liu J, Kunos G. Evidence for novel cannabinoid receptors. Pharmacol Ther. 2005;106(2):133-45.

Bruins J, Bruggeman R, Visser E, Bartels A, Van den Heuvel E, Pijnenborg M, Jörg F. Cannabis Use in Psychosis: the Effects On Metabolic Health. European Psychiatry. 2015;30:240.

Brunet L, Moodie EE, Rollet K, Cooper C, Walmsley S, Potter M, Klein MB; Canadian Co-infection Cohort Investigators. Marijuana smoking does not accelerate progression of liver disease in HIV-hepatitis C coinfection: a longitudinal cohort analysis. Clin Infect Dis. 2013;57(5):663-70.

Buchan BJ, Dennis,ML, Tims FM, & Diamond GS. Cannabis use: consistency and validity of selfreport, on-site urine testing and laboratory testing. Addiction. 2002; 97: 98–108. doi:10.1046/j.1360-0443.97.s01.1.x.

Di Marzo V. Targeting the endocannabinoid system: to enhance or reduce? Nat Rev Drug Discov. 2008 May;7(5):438-55. doi: 10.1038/nrd2553.

Elsohly MA, Slade D. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. Life Sci. 2005 Dec 22;78(5):539-48. Epub 2005 Sep 30.

Erdogan A, Atasoy N, Akkurt H, Ozturk D, Karaahmet E, Yalug I, Yalug K, Ankarali H, Balcioglu I. Risperidone and liver function tests in children and adolescents: a short-term prospective study. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(3):849-57. doi: 10.1016/j.pnpbp.2007.12.032

Galiègue S, Mary S, Marchand J, Dussossoy D, Carrière D, Carayon P, Bouaboula M, Shire D, Le Fur G, Casellas P. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. Eur J Biochem. 1995 Aug 15;232(1):54-61.

Ganesh S, Rustgi VK. Current Pharmacologic Therapy for Nonalcoholic Fatty Liver Disease. Clin Liver Dis. 2016 May;20(2):351-64. doi: 10.1016/j.cld.2015.10.009. Epub 2016 Feb 19.

Gilles M, Hentschel F, Paslakis G, Glahn V, Lederbogen F, Deuschle M. Visceral and subcutaneous fat in patients treated with olanzapine: a case series. ClinNeuropharmacol. 2010 Sep-Oct;33(5):248-9.

Gong JP, Onaivi ES, Ishiguro H, Liu QR, Tagliaferro PA, Brusco A, Uhl GR. Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. Brain Res. 2006 Feb 3;1071(1):10-23.

Green B, Young R, Kavanagh D. Cannabis use and misuse prevalence among people with psychosis.Br J Psychiatry. 2005;187:306-13.

Harrison ER, Haaga J, Richards T. Self-reported drug use data: what do they reveal? Am J Drug Alcohol Abuse. *1993;* 19(4): 423-41.

Hézode C, Zafrani ES, Roudot-Thoraval F, Costentin C, Hessami A, Bouvier-Alias M, Medkour F, Pawlostky JM, Lotersztajn S, Mallat A. Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. Gastroenterology. 2008;134(2):432-9.

Hill AJ, Williams CM, Whalley BJ, Stephens GJ. Phytocannabinoids as novel therapeutic agents in CNS disorders. Pharmacol Ther. 2012 Jan;133(1):79-97. doi: 10.1016/j.pharmthera.2011.09.002. Epub 2011 Sep 6.

Hsiao WC, Shia KS, Wang YT, Yeh YN, Chang CP, Lin Y, Chen PH, Wu CH, Chao YS, Hung MS.A novel peripheral cannabinoid receptor 1 antagonist, BPR0912, reduces weight independently of food intake and modulates thermogenesis. Diabetes Obes Metab. 2015 May;17(5):495-504.

Hsu JH, Chien IC, Lin CH, Chou YJ, Chou P. Increased risk of chronic liver disease in patients with schizophrenia: a population-based cohort study. Psychosomatics. 2014;55(2):163-71.

Ishida JH, Peters MG, Jin C, Louie K, Tan V, Bacchetti P, Terrault NA. Influence of cannabis use on severity of hepatitis C disease. Clin Gastroenterol Hepatol. 2008;6(1):69-75.

Joseph AM, Venkatasubramanian G, Sharma PS. A six-to-ten weeks' follow-up study on the effects of olanzapine on abdominal fat and other metabolic parameters in patients with psychoses--an imaging-based study with controls. East Asian Arch Psychiatry. 2011 Mar;21(1):10-6.

Kim JH, Kim JH, Park PW, Machann J, Roden M, Lee SW, Hwang JH. Body and liver fat content and adipokines in schizophrenia: a magnetic resonance imaging and spectroscopy study. Psychopharmacology (Berl). 2017 Jun;234(12):1923-1932.

Kim D, Kim W, Kwak MS, Chung GE, Yim JY, Ahmed A. Inverse association of marijuana use with nonalcoholic fatty liver disease among adults in the United States. PLoS One. 2017 Oct 19;12(10):e0186702. doi: 10.1371/journal.pone.0186702.

Konarzewska B, Stefańska E, Wendołowicz A, Cwalina U, Golonko A, Małus A, et al. Visceral obesity in normal-weight patients suffering from chronic schizophrenia. BMC Psychiatry. 2014 Feb 8;14:35. doi: 10.1186/1471-244X-14-35.

Kunos G, Osei-Hyiaman D, Bátkai S, Gao B. Cannabinoids hurt, heal in cirrhosis. Nat Med. 2006 Jun;12(6):608-10.

Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. World J Gastroenterol. 2018 Aug 14;24(30):3361-3373. doi: 10.3748/wjg.v24.i30.3361.

Lustig RH, Sen S, Soberman JE, et al. Obesity, leptin resistance, and the effects of insulin reduction. Int J Obes Relat Metab Disord. 2004;28: 1344–1348.

Mallat A, Teixeira-Clerc F, Deveaux V, Lotersztajn S. Cannabinoid receptors as new targets of antifibrosing strategies during chronic liver diseases. Expert Opin Ther Targets. 2007 Mar;11(3):403-9.

Mallat A, Lotersztajn S. Cannabinoid receptors as therapeutic targets in the management of liver diseases. Drug News Perspect. 2008 Sep;21(7):363-8. doi: 10.1358/dnp.2008.21.7.1255306.

Moreira FP, Wiener CD, Oliveira JF, Souza LDM, da Silva RA, Portela LV, Lara DR, Jansen K, Oses JP. Gender differences of cannabis smoking on serum leptin levels: population-based study. Braz J Psychiatr. 2018;40(2):216-219.

Morlán-Coarasa MJ, Arias-Loste MT, Ortiz-García de la Foz V, Martínez-García O, Alonso-Martín C, Crespo J, Romero-Gómez M, Fábrega E, Crespo-Facorro B. Incidence of non-alcoholic fatty liver disease and metabolic dysfunction in first episode schizophrenia and related psychotic disorders: a 3-year prospective randomized interventional study. Psychopharmacology (Berl). 2016 Dec;233(23-24):3947-3952.

Muniyappa R, Sable S, Ouwerkerk R, Mari A, Gharib AM, Walter M, Courville A, Hall G, Chen KY, Volkow ND, Kunos G, Huestis MA, Skarulis MC. Metabolic effects of chronic cannabis smoking. Diabetes Care. 2013;36(8):2415-22. doi: 10.2337/dc12-2303.

Nordmann S, Vilotitch A, Roux P1,2, Esterle L, Spire B, Marcellin F, Salmon-Ceron D, Dabis F, Chas J, Rey D, Wittkop L, Sogni P, Carrieri P; ANRS CO13 HEPAVIH Study Group. Daily cannabis and reduced risk of steatosis in human immunodeficiency virus and hepatitis C virus-co-infected patients (ANRS CO13-HEPAVIH). J Viral Hepat. 2018 Feb;25(2):171-179.

Osei-Hyiaman D, DePetrillo M, Pacher P, Liu J, Radaeva S, Bátkai S, Harvey-White J, Mackie K, Offertáler L, Wang L, Kunos G. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. J Clin Invest. 2005 May;115(5):1298-305.

Osei-Hyiaman D, Liu J, Zhou L, Godlewski G, Harvey-White J, Jeong WI, Bátkai S, Marsicano G, Lutz B, Buettner C, Kunos G. Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. J Clin Invest. 2008 Sep;118(9):3160-9. doi: 10.1172/JCI34827.

Pelayo-Terán JM, Pérez-Iglesias R, Ramírez-Bonilla M, González-Blanch C, Martínez-García O, Pardo-García G, Rodríguez-Sánchez JM, Roiz-Santiáñez R, Tordesillas-Gutiérrez D, Mata I, Vázquez-Barquero JL, Crespo-Facorro B. Epidemiological factors associated with treated incidence of first-episode non-affective psychosis in Cantabria: insights from the Clinical Programme on Early Phases of Psychosis. Early Interv Psychiatry. 2008 Aug;2(3):178-87.

Perez-Iglesias R, Vazquez-Barquero JL, Amado JA, Berja A, Garcia-Unzueta MT, Pelayo-Terán JM, Carrasco-Marín E, Mata I, Crespo-Facorro B. Effect of antipsychotics on peptides involved in energy balance in drug-naive psychotic patients after 1 year of treatment. J Clin Psychopharmacol. 2008;28(3):289-95.

Pertwee RG. Ligands that target cannabinoid receptors in the brain: from THC to anandamide and beyond. Addict Biol. 2008 Jun;13(2):147-59. doi: 10.1111/j.1369-1600.2008.00108.x.

Ragguett RM, Hahn M, Messina G, Chieffi S, Monda M, De Luca V. Association between antipsychotic treatment and leptin levels across multiple psychiatric populations: An updated meta-analysis. Hum Psychopharmacol. 2017;32(6)

Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol. 2017 Oct;67(4):829-846.

Scheffler F, Kilian S, Chiliza B, Asmal L, Phahladira L, du Plessis S, Kidd M, Murray RM, Di Forti M, Seedat S, Emsley R. Effects of cannabis use on body mass, fasting glucose and lipids during the first 12 months of treatment in schizophrenia spectrum disorders. Schizophr Res. 2018 Sep;199:90-95. doi: 10.1016/j.schres.2018.02.050

Setién-Suero E, Neergaard K, Ramírez-Bonilla M, Correa-Ghisays P, Fañanás L, Crespo-Facorro B, Ayesa-Arriola R. Cannabis use in male and female first episode of non-affective psychosis patients: Long-term clinical, neuropsychological and functional differences. PLoS One. 2017 Aug 23;12(8):e0183613. doi: 10.1371/journal.pone.0183613. eCollection 2017.

Silvestri C, Paris D, Martella A, Melck D, Guadagnino I, Cawthorne M, Motta A, Di Marzo V. Two non-psychoactive cannabinoids reduce intracellular lipid levels and inhibit hepatosteatosis. J Hepatol. 2015 Jun;62(6):1382-90. doi: 10.1016/j.jhep.2015.01.001.

Smaga I, Zaniewska M, Gawliński D, Faron-Górecka A, Szafrański P, Cegła M, Filip M. Changes in the cannabinoids receptors in rats following treatment with antidepressants. Neurotoxicology. 2017 Dec;63:13-20. doi: 10.1016/j.neuro.2017.08.012.

Spigelman I. Therapeutic Targeting of Peripheral Cannabinoid Receptors in Inflammatory and Neuropathic Pain States. In: Kruger L, Light AR, editors. Translational Pain Research: From Mouse to Man. Boca Raton, FL: CRC Press/Taylor & Francis; 2010. Chapter 5.

Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, S Sulkowski M, Torriani FJ, Dieterich DT, Thomas DL, Messinger D, Nelson M; APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317-25.

Tam J, Liu J, Mukhopadhyay B, Cinar R, Godlewski G, Kunos G. Endocannabinoids in liver disease. Hepatology. 2011 Jan;53(1):346-55. doi: 10.1002/hep.24077.

Targher G. Non-alcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: the plot thickens. Diabet Med. 2007;24:1–6.

Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Br J Pharmacol. 2007 Mar;150(5):613-23.

Vázquez-Bourgon J, Pérez-Iglesias R, Ortiz-García de la Foz V, et al. Long-term metabolic effects of aripiprazole, ziprasidone and quetiapine: a pragmatic clinical trial in drug-naïve patients with a first-episode of psychosis. Psychopharmacology (Berl). 2018;235(1):245-255.

Vázquez-Bourgon J, Setién-Suero E, Pilar-Cuéllar F, Romero Jiménez R, Ortiz-García de la Foz V, Castro E, Crespo-Facorro B. Effect of cannabis on weight and metabolism in first-episode non-affective psychosis: results from a 3-years longitudinal study. Journal of Psychopharmacology. 2019;33(3):284-294..

Vázquez-Bourgon J, Ortiz-García de la Foz V, Suarez-Pereira I, Iruzubieta P, Arias-Loste MT, Setién-Suero E, Ayesa-Arriola R, Gómez-Revuelta M, Crespo J, Crespo Facorro B. Data regarding the effect of cannabis consumption on liver function in the prospective PAFIP cohort of first episode psychosis. *Data in Brief*. 2019; *submitted*

Yan J, Hou C, Liang Y. The prevalence and risk factors of young male schizophrenics with non-alcoholic fatty liver disease. Neuropsychiatric disease and treatment. 2017;13:1493-1498.

Table 1. Baseline and 3-years liver function tests in first episode psychosis.

	Baseline					3-years				
	Cannabis users	No cannabis users	Stats*			Cannabis users	No cannabis users	Stats*		
	Mean (SE)	Mean (SE)	*df*	*F*	*P*	Mean (SE)	Mean (SE)	*df*	*F*	*P*
FLI algorithm factors										
BMI (kg/m^2)	**22.2 (0.4)**	**24.0 (0.3)**	**1; 377**	**11.098**	**0.001**	**24.8 (0.8)**	**27.3 (0.3)**	**1; 369**	**9.205**	**0.003**
Waist circumference (cm)	81.7 (1.5)	84.2 (1.1)	1; 190	1.342	0.248	**79.7 (2.9)**	**91.4 (0.8)**	**1; 221**	**13.942**	**<0.001**
Triglycerides	84.6 (4.2)	80.9 (3.0)	1; 316	0.383	0.536	91.5 (15.8)	119.6 (5.1)	1; 369	2.764	0.097
Liver laboratory tests										
AST	24.4 (1.8)	28.3 (1.3)	1; 350	2.473	0.117	26.6 (1.7)	24.4 (0.6)	1; 370	1.342	0.247

ALT	23.5 (2.6)	30.3 (1.9)	1; 373	3.405	0.066	30.3 (3.6)	30.4 (1.2)	1; 371	0.001	0.977
GGT	26.9 (4.2)	17.8 (3.1)	1; 353	2.405	0.122	28.5 (8.0)	28.4 (2.6)	1; 370	0.000	0.990
AP	79.1 (7.8)	89.2 (6.5)	1; 139	0.754	0.387	66.4 (4.4)	65.5 (1.7)	1; 140	0.034	0.854
Bilirubin	0.71 (0.08)	0.89 (0.06)	1; 119	0.726	0.396	0.66 (0.07)	0.59 (0.03)	1; 137	0.746	0.389
Albumin	4.54 (0.04)	4.54 (0.03)	1; 305	0.006	0.939	4.56 (0.04)	4.54 (0.01)	1; 364	0.248	0.619
Other laboratory tests										
Platelets	252.3 (6.9)	246.8 (4.8)	1; 300	0.350	0.555	253.9 (10.6)	243.7 (3.6)	1; 362	0.798	0.372
Leptin	**6.4 (0.9)**	**9.5 (0.7)**	**1; 292**	**4.887**	**0.028**	**10.2 (1.8)**	**14.3 (0.6)**	**1; 359**	**4.293**	**0.039**
hsCRP	0.17 (0.08)	0.16 (0.05)	1; 161	0.012	0.912	0.18 (0.11)	0.29 (0.03)	1; 212	0.916	0.340
Hepatic disease indexes										
FLI	15.7 (3.1)	19.0 (2.1)	1; 161	0.640	0.425	**11.8 (7.3)**	**40.3 (2.0)**	**1; 216**	**13.874**	**<0.001**
FIB-4 score	0.69 (0.04)	0.69 (0.03)	1; 276	0.001	0.979	0.73 (0.04)	0.68 (0.01)	1; 353	1.141	0.286
NAFDL score	-3.57 (0.12)	-3.39 (0.08)	1; 266	1.238	0.267	-3.36 (0.16)	-3.06 (0.05)	1; 344	3.269	0.072

* ANCOVA model: parameter was used as the dependent variable, cannabis use was the fixed factor and age, sex, and tobacco and alcohol consumption use were used as covariates.

Abbreviations: FLI, fatty liver Index; BMI, body mass index; GGT, Gamma-glutamyltransferase ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase; AP, alkaline phosphatase; hsCRP, high sensitivity C-reactive protein; FIB-4, fibrosis 4 score; NAFLD, non-alcoholic fatty liver disease fibrosis score.

Table 2. Longitudinal differences in liver function tests, after 3 years of antipsychotic treatment.

	Baseline				3 years				Time x canna	
	Users	Discontinuers	Non	Stats	Users	Discontinuers	Non	Stats	Stats.	
	Mean	Mean	Me	F; p	Me	Mean	Me	*F;*	*F; p*	*df*
FLI algorith										
BMI	21.9	22.7 (3.1)	23.	**6.5**	25.	27.2 (4.3)	27.	**5.3**	2.73;	2;

Waist circumf.	79.2 (8.0)	82.4 (11.5)	83. 8	2.2 3;	83. 5	90.9 (11.4)	90. 7	**5.4 6;**	1.59; 0.207	2; 18
Triglycer	83.8	82.2	80.	0.2	101	133.6	115	1.4	1.64;	2;
Laborato ry tests										
AST	30.7	26.1	26.	1.7	27.	22.9 (9.6)	24.	2.2	0.38;	2;
ALT	30.9	25.4	28.	2.7	34.	29.2	30.	1.5	0.32;	2;
GGT	16.6	24.6	20.	1.6	25.	31.3	28.	0.7	0.08;	2;
AP	75.7	85.4	88.	0.6	67.	67.4	63.	0.3	1.10;	2;
Bilirubin	0.96	0.67	0.7	2.8	0.6	0.58	0.5	0.6	2.54;	2;
Albumin	4.7	4.6 (0.4)	4.5	0.0	4.6	4.6 (0.2)	4.5	0.0	0.01;	2;
Platelets	261.5	245.8	248	1.4	248	242.9	239	1.3	0.67;	2;
Leptin	2.96	5.5 (8.0)	10.	2.9	5.3	10.8 (9.9)	16.	2.2	0.40;	2;
hsCRP	0.13	0.15	0.1	0.1	0.1	0.32	0.2	0.6	0.16;	2;
Hepatic disease										
FLI	10.3	14.9	19.	1.3	18.	40.4	38.	**5.7**	**4.42;**	2;
FIB-4	0.54	0.61	0.7	0.1	0.5	0.60	0.7	0.1	0.36;	2;
NAFDL	-4.08	-3.75	-	1.1	-	-3.25	-	**5.1**	1.43;	2;

* GLM repeated-measure model.

Abbreviations: FLI, fatty liver Index; BMI, body mass index; GGT, Gamma-glutamyltransferase ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase; AP, alkaline phosphatase; hsCRP, high sensitivity C-reactive protein; FIB-4, fibrosis 4 score; NAFLD, non-alcoholic fatty liver disease fibrosis score.

Table 3. Comparison of proportion of subjects with pathological liver functions tests, at baseline and at 3-years in each cannabis consumption group.

	Baseline	3 year follow-up			
	% (n)	% (n)	% difference	N	p*
AST, >35 UI/L					
Continuer	23.7 (9)	13.2 (5)	-10.5	38	0.344
Discontinuers	13.3 (12)	8.9 (8)	-4.4	90	0.454
Non-users	15.0 (33)	8.6 (19)	-8.4	220	0.054
Total	15.5 (54)	9.2 (32)	-6.3	348	0.013
ALT, >40 UI/L					
Continuer	17.5 (7)	22.5 (9)	5	40	0.727
Discontinuers	9.0 (9)	20.0 (20)	11	100	0.027
Non-users	13.9 (32)	17.7 (41)	3.8	231	0.281
Total	12.9 (48)	18.9 (70)	6	371	0.021
GGT, >32 UI/L					
Continuer	2.6 (1)	20.5 (8)	17.9	39	0.016
Discontinuers	7.6 (7)	20.7 (19)	13.1	92	0.004
Non-users	11.8 (26)	21.4 (47)	11.6	220	0.001
Total	9.7 (34)	21.1 (74)	11.4	351	<0.001
Leptin, >10 ng/ml					
Continuer	3.8 (1)	11.5 (3)	7.7	26	0.500
Discontinuers	12.0 (9)	37.3 (28)	25.3	75	<0.001

Non-users	36.5 (66)	64.1 (116)	27.6	181	<0.001
Total	27.0 (76)	52.1 (147)	25.1	282	<0.001
hsCRP, >0.3 ng/dL					
Continuer	11.1 (1)	0 (0)	-11.1	9	-
Discontinuers	6.7 (3)	22.2 (10)	15.1	45	0.039
Non-users	7.7 (8)	24.0 (25)	16.3	104	0.002
Total	7.6 (12)	22.2 (35)	14.6	158	<0.001
FLI ≥60					
Continuer	0 (0)	7.1 (1)	7.1	14	-
Discontinuers	5.0 (2)	30.0 (12)	25	40	0.002
Non-users	8.7 (9)	26.9 (28)	18.2	104	<0.001
Total	7.0 (11)	25.9 (41)	18.9	158	<0.001

**McNemar test for repeated measures.*

Abbreviations: FLI, fatty liver Index; GGT, Gamma-glutamyltransferase ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase; hsCRP, high sensitivity C-reactive protein.

Highlights

- Cannabis consumption is associated with a lower risk of liver steatosis in psychosis.
- Cannabis use is not associated with liver fibrosis.
- The cannabis effect on liver tissue might be through the modulation of weight gain.
- A direct effect of cannabis on liver tissue has not been ruled out.