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### ► **To cite this version:**

Patrizia Carrieri, Marc Bourlière, Vincent Di Beo, Clovis Lusivika-Nzinga, Clémence Ramier, et al.. Impaired health-related quality of life in the HCV cure era: who is concerned? (ANRS CO22 HEPATHER French cohort).. *Quality of Life Research*, 2023, 32 (12), pp.3427-3438. 10.1007/s11136-023-03496-w . hal-04191956

**HAL Id: hal-04191956**

**<https://hal.science/hal-04191956v1>**

Submitted on 30 Nov 2023

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**Impaired health-related quality of life in the HCV cure era: who is concerned? (ANRS CO22 HEPATHER French cohort)**

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**Word count:** 3,518

**No. of figures:** 2

**No. of tables:** 4

**Statements and declarations**

*Competing interests*

Patrizia Carrieri received research grants from MSD and Intercept unrelated to this work. Marc Bourlière reports grants and personal fees from AbbVie, grants and personal fees from Gilead, personal fees from MSD, personal fees from Janssen, personal fees from Boehringer Ingelheim, personal fees

from Intercept, and personal fees from BMS, all outside the submitted work. Stanislas Pol has served as a speaker, a consultant and an advisory board member for Janssen, Gilead, Roche, MSD, Abbvie, Biotest, Shinogi, Vivv, and LFB. He has received funding from Gilead, Abbvie, Roche and MSD for research not connected to the present work. H  l  ne Fontaine reports personal fees and invitations to medical meetings from Gilead, Abbvie, BMS, MSD, Janssen, MSD outside the present work. Fabrice Carrat reports grants from INSERM-ANRS during the implementation of this study and personal fees from Imaxio, outside the submitted work. The other authors have no conflict of interest to declare.

### *Funding*

The ANRS CO22 HEPATHER cohort received financial support from INSERM-ANRS MIE (France Recherche Nord & Sud Sida-VIH H  patites, Maladies Infectieuses Emergentes), the French ANR (Agence Nationale de la Recherche) ANR-11-EQPX-0021 and France 2030 #ANR-19-COHO-0002, the French DGS (Direction G  n  rale de la Sant  ), Merck Sharp and Dohme, Janssen-Cilag, Gilead, Abbvie, Bristol-Myers Squibb and Roche. These funding sources had no role in the writing of the manuscript or the decision to submit it for publication.

### *Author contributions*

Study concept and design: PC, FC, HF, MD; data acquisition: MB, CLN, SP, HF, FC, MD; data analysis and interpretation: PC, VdB, CR, SA, CP, JML, AM, MD, FM; drafting of the manuscript: PC, VdB, SA; critical revision of the manuscript for important intellectual content: PC, MB, VdB, CLN, CR, SA, CP, JML, SP, HF, AM, FC, MD, FM; statistical analysis: VdB, CR; obtaining of funding: PC, MD; administrative, technical, and material support: CLN; study supervision: PC, MD. All authors approved the final version of the manuscript.

### *Data availability*

Data are available upon request to the scientific committee of the ANRS CO22 HEPATHER cohort, which includes the authors of the manuscript (contact: [fabrice.carrat@iplesp.upmc.fr](mailto:fabrice.carrat@iplesp.upmc.fr)).

#### *Trial registration*

Trial registration with ClinicalTrials.gov NCT01953458.

#### **Acknowledgements**

We thank all of the members of the ANRS CO22 HEPATHER cohort Study Group, all the patients who participated in the HRQoL study, and all the healthcare staff involved in patient follow-up in each center. Our thanks also to the INSERM-ANRS MIE for sponsoring, funding and supervising the ANRS CO22 HEPATHER cohort in collaboration with the French Association for the Study of the Liver (Association Française pour l'Étude du Foie: AFEF). Finally, we thank Jude Sweeney (Milan, Italy) for the English revision and copyediting of our manuscript.

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**No. of words:** 247

## **ABSTRACT**

**Purpose:** Hepatitis C virus (HCV) cure after treatment with direct-acting antivirals (DAAs) can improve health-related quality of life (HRQoL). However, specific groups with chronic HCV may still exhibit worse post-cure HRQoL because of persisting severe liver fibrosis or social vulnerability factors (e.g., unhealthy alcohol use, living in poverty). We assessed the effect of such factors on longitudinal measures of HRQoL in chronic HCV patients.

**Methods:** ANRS CO22 HEPATHER is a prospective cohort of chronic HCV patients receiving DAAs, which included notably patients with social vulnerability factors, a population usually underrepresented in clinical trials. Multivariable mixed-effects linear regression models helped identify factors associated with longitudinal measures of HRQoL (PROQOL-HCV scores).

**Results:** At enrolment, 52.4% of the 2,740 participants were men, median age was 56 years [interquartile range: 50-64], and 21.5% had severe liver fibrosis (FIB-4 > 3.25). Twenty-eight percent reported current or past unhealthy alcohol use (>2(3) alcohol units per day for women (men)), and 28.1% were living in poverty (standard of living under 1,015€/month per household consumption unit). At first PROQOL-HCV completion, 54.0% of patients were HCV-cured. After multivariable adjustment, people with current or past unhealthy alcohol use, individuals living in poverty, those with severe liver fibrosis, and women had worse HRQoL in the dimensions explored. Conversely, HCV cure was associated with better HRQoL.

**Conclusions:** Specific socially vulnerable groups of patients with chronic HCV infection still experience impaired HRQoL, independently of HCV cure. Patient-centred interventions, including social support and referral for comorbidities, should be prioritized for them.

**Keywords:** alcohol; direct-acting antivirals; HCV cure; health-related quality of life; hepatitis C virus; vulnerable population.

**Key points**

- HCV cure with DAAs leads to better HRQoL.
- Specific socially vulnerable groups still experience impaired HRQoL, independently of HCV cure.
- Patient-centred interventions, including social support or referral for comorbidities, should be prioritized for these patients at higher risk of impaired HRQoL.

## Introduction

An estimated 58 million people worldwide have chronic hepatitis C virus (HCV) infection. In 2019, HCV infection was responsible for 290,000 (95% uncertainty interval: [230,000–580,000]) deaths per year, mainly from cirrhosis and hepatocellular carcinoma [1,2]. Chronic HCV infection - at any stage of severity - can significantly compromise patients' health-related quality of life (HRQoL), that is to say their subjective perception of physical, psychological and social well-being [3]. It has been reported that complications associated with advanced liver disease - such as encephalopathy, cirrhosis, extrahepatic manifestations, and fatigue - impair HRQoL in chronic HCV patients [4].

The arrival of highly effective and well-tolerated direct-acting antivirals (DAAs) for the treatment of chronic HCV infection has radically decreased the disease burden in many countries [5], and has improved most HRQoL dimensions, in particular mobility, pain/discomfort, and mental health. These benefits have been observed both shortly after achieving sustained virological response (SVR) [6–8] and over the long term [9]. Improvements in HRQoL have also been observed in HIV-HCV co-infected patients [10]. However, in some specific groups, the effects of comorbidities seem to continue to compromise improvements in HRQoL dimensions even after HCV cure [11].

Real-world HRQoL data on patients with chronic HCV infection in the DAAs era are sparse. This is especially true for persons with social vulnerability factors (e.g., unhealthy alcohol use), as they are often listed among exclusion criteria in clinical trials assessing HRQoL. As defined in France's guidelines for the management of HCV infection [12], these groups include individuals at higher risk of infection (e.g., people who use drugs, individuals with unhealthy alcohol use, persons living in poverty, migrants, and men who have sex with men), a population that bears the burden of delayed diagnosis and delayed access to care [13,14]. People in these groups also experience stigma and discrimination [13], which might in turn affect several dimensions of HRQoL, even after HCV cure.

The arrival of DAAs highlights the need to use novel disease-sensitive HRQoL measures to capture the impact of HCV cure on HRQoL in chronic HCV patients. Most of the existing tools, such as the EQ-5D [15], the HCV-PRO [16,17] and the Chronic Liver Disease Questionnaire - Hepatitis C virus (CLDQ-HCV)

[18], are either not disease specific or may not be sensitive enough to capture all the benefits of DAAs. The Patient Reported Outcome Quality of Life survey for HCV (PROQOL-HCV) is the only HRQoL questionnaire developed for both HCV patients receiving DAAs or not which had been validated in several languages (English, French, Portuguese), in various countries (Australia, France, Brazil), and for different patient profiles [19,20].

This study aims at exploring the influence of specific social vulnerability factors - after adjustment for clinical characteristics such as severe liver fibrosis and HCV cure - on the evolution of HRQoL (PROQOL-HCV), in a real-world sample of chronic HCV patients followed-up in hospital centres.

## **Material and Methods**

### *Study setting*

ANRS CO22 HEPATHER is a French, national, multicentre, prospective, observational cohort study of patients with chronic hepatitis B or C virus infection whose follow-up is ongoing. Its main objective is to quantify the clinical effectiveness and safety of new hepatitis treatments in real-world situations. The main exclusion criteria were HIV co-infection, already receiving HCV treatment or having discontinued HCV treatment for less than three months at enrolment. The cohort design is described in detail elsewhere [21].

### *Ethical considerations*

HEPATHER is conducted in accordance with the ethical principles set out in the Helsinki Declaration (59<sup>th</sup> General Assembly of the World Medical Association, Seoul, Korea; October 2008) and with French law on biomedical research. It was approved by the Comité de Protection des Personnes (CPP) Ile de France 3 ethics committee (Paris, France) (#2943, 29/11/2011) and the French National Agency for the Safety of Medicines and Health Products (ANSM). Patients could be enrolled only after written informed consent and data were centralized using a dedicated information system.

### *Data collection*

Enrolment in the cohort (August 2012 - June 2018) took place in 32 hepatology centres throughout France. During the enrolment visit, detailed demographic, socio-behavioural, clinical, and biological data were collected using a dedicated electronic case report form and biological samples. Supplemental data related to particular events (e.g., initiation of HCV treatment, hospitalization) are collected yearly during follow-up visits. A self-administered questionnaire was proposed to cohort participants during annual follow-up visits and treatment-related visits (initiation, follow-up, end of treatment) between January 2015 and October 2019. It comprised items on sociodemographic characteristics, consumption of alcohol and drugs, quality of life (EQ-5D, SF-12 and PROQOL-HCV scales), as well as items on hepatitis B and C infection and associated treatments. In the present study, we focused exclusively on patients in HEPATHER with chronic HCV infection.

### *Assessment of HRQoL and definition of study outcomes*

In the present study, HRQoL was assessed using the PROQOL-HCV scale [19,20], which showed good reliability in patients with chronic HCV infection, and comprises 38 items spanning seven dimensions: Physical Health (6 items, Cronbach alpha:  $\alpha=0.90$ ), Emotional Health (9 items,  $\alpha=0.93$ ), Future Uncertainty (6 items,  $\alpha=0.79$ ), Intimate Relationships (3 items,  $\alpha=0.86$ ), Social Health (3 items,  $\alpha=0.47$ ), Cognitive Functioning (3 items,  $\alpha=0.80$ ), and Treatment Impact (8 items,  $\alpha=0.61$ ). Each dimension score has a 100-point range, and higher score values indicate better HRQoL. The scores associated with the first six PROQOL-HCV dimensions were the study outcomes. The seventh dimension, Treatment Impact, was not included in the analysis, as items for this dimension were not answered during visits without treatment.

### *Explanatory variables*

The following variables were tested as factors potentially associated with the study outcomes: sex, age, educational level ( $\geq$  or  $<$  upper secondary school certificate, which corresponds to the French

baccalaureate), body mass index (BMI), HCV cure, severe liver fibrosis, and social vulnerability factors. The latter included current or past unhealthy alcohol use, living in poverty, being a migrant, being a man who has sex with men (MSM), and current or past psychoactive substance use other than cannabis. BMI was categorized according to the following WHO classes [22]: <18.5, underweight; ≥18.5 and <25, normal weight; ≥25 and <30, overweight; ≥30, obesity. For each visit, the 'HCV cure' group comprised patients who had SVR (defined as undetectable HCV RNA 12 weeks or more after the end of treatment). Similarly, for each visit, the 'no HCV cure' group comprised i) patients who had not yet started DAAs treatment, ii) patients who had finished their DAAs treatment by the time of the visit but who had not achieved SVR, and iii) those still on DAAs at the visit. Liver fibrosis was assessed at enrolment by calculating the FIB-4 index, which was based on age, platelet count, and aspartate transaminase (AST) and alanine transaminase (ALT) levels, using the following formula:  $FIB-4 = \text{age [years]} * \text{AST [IU/L]} / (\text{platelet count [10}^9\text{/L]} * (\sqrt{\text{ALT [IU/L]}}))$ . A cut-off > 3.25 was used to define severe liver fibrosis [23]. Unhealthy alcohol use was defined as reporting more than 2 alcohol units per day for women, and more than 3 alcohol units per day for men [24]. Living in poverty was defined as a standard of living under a threshold set at 60% of the French population median income in 2015 (i.e. 1,015€ per month) [25]. Standard of living was calculated as disposable income divided by the number of consumption units in the household. Migrants were defined as individuals not born in France who reported having at least one parent of non-French origin. Men who answered that they had had sexual relationships with another man at least once in their life were considered MSM. Current or past psychoactive substance use was defined as reporting current or past use of non-prescribed psychoactive drugs (crack, cocaine, heroin, and other nasal or intravenous drugs) other than cannabis and/or taking having previously received at least one opioid substitution treatment (methadone, buprenorphine or other).

All the explanatory variables were measured at cohort enrolment except HCV cure which was used as a time-varying variable in the analyses.

### *Study population*

Among HCV-chronic patients recruited in the ANRS CO22 HEPATHER cohort, patients who completed at least one PROQOL-HCV questionnaire during their follow-up were selected for the present study. We secondarily excluded those with no data available on social vulnerability factors.

### *Statistical analyses*

Descriptive statistics were given using numbers and percentages of patients for categorical variables, and median and interquartile range (IQR) for continuous variables. The main characteristics at enrolment were compared between patients included in the study population and those not included (Chi-square tests). We used mixed-effects linear regression models to estimate the effects of socio-behavioural and clinical factors on PROQOL-HCV scores in longitudinal analyses. Interactions between HCV cure and each social vulnerability factor were tested in these models. These models enabled us to account for within-participant correlation due to repeated assessments over time. Multicollinearity among the social vulnerability factors was tested using the variance inflation factors (VIF). Variables significantly associated with at least one score were considered eligible to enter all six multivariable analyses (each corresponding to a HRQoL dimension). Social vulnerability factors were systematically included in the multivariable analyses. The final six multivariable models were built using a backward selection procedure. To this end, variables which remained significantly ( $p < 0.05$ ) associated with at least one score after multivariable adjustment were kept in the six final multivariable models. Results were presented as crude and adjusted coefficients, with the corresponding 95% confidence intervals (CI). All analyses were performed using the Stata/SE 14.2 software (StataCorp LP, College Station, USA).

## **Results**

### *Study population and follow-up*

Among the 12,447 patients with chronic HCV infection at enrolment in the HEPATHER cohort, 5,440 completed the self-administered questionnaire at least once. Among them, 2,657 did not complete

the PROQOL-HCV and 43 had no information on social vulnerability factors. The study population thus comprised a total of 2,740 patients (Figure 1), for which PROQOL-HCV data were available at 4,521 visits. Of these, 2,148 (47.5%) were for 'no cure visits' (including 1,445 visits before treatment initiation, and 703 visits where treatment was ongoing or where treatment had ended but without SVR), and 2,373 (52.5%) were after HCV cure. Forty percent of patients (n=1,086) in the study population completed at least two PROQOL-HCV questionnaires; i.e. had at least two HRQoL assessments during their follow-up. The median [IQR] number of HRQoL assessments was 1 [1 - 2], with a maximum of 5 assessments. Median [IQR] time for each patient between the first and the last completed questionnaire was 10 [4 – 20] months, with a maximum time of 39 months, and median time between two consecutive questionnaires was 5 [1 – 11] months.

#### *Study population characteristics at cohort enrolment*

Forty-seven percent of patients in the study population were women, and median age at enrolment was 56 [IQR: 50 - 64] years (Table 1). Forty-eight percent had an educational level equal to or above upper secondary school certificate, and 21.5% had severe liver fibrosis at enrolment. With regard to social vulnerability factors, 28.3% of patients reported current or past unhealthy alcohol use, 28.1% were living in poverty, 34.8% reported current or past psychoactive substance use, 20.5% were migrants, and 2.2% were MSM. A total of 962 patients (35.1%) had no social vulnerability factor, and 1,003 (36.6%) had social vulnerability factors other than current or past unhealthy alcohol use. Among women (n=1,305), 345 (26.9%) were living in poverty, 285 (21.8%) had a history of drug use and 91 (6.9%) cumulated these two vulnerabilities.

Compared with excluded patients, the percentages of women and of individuals with higher education level were significantly higher in the study population, and the percentage of patients with severe liver fibrosis at enrolment was significantly lower. Slight differences in the distribution of the social vulnerability factors at enrolment were also observed, with a lower percentage of individuals living in



poverty and of migrants, but a higher percentage of MSM in the study population than in excluded patients (Supplementary Table 1).

#### *HCV status*

At the first administration of the PROQOL-HCV questionnaire, 1,479 patients (54.0%) in the study population were cured of HCV. The number of HCV cured patients reached 1907 (69.6%) at the last available visit with a completed PROQOL-HCV questionnaire.

#### *Distribution of PROQOL-HCV scores*

The distributions of the PROQOL-HCV scores are presented in Table 2. The dimensions with the highest median [IQR] values at both the first and the last administration of the questionnaire were Intimate Relationships (83.3 [58.3 – 100] and 91.7 [58.3 – 100], respectively) and Future Uncertainty (83.3 [66.7 – 95.8] and 87.5 [70.8 – 100], respectively). The Social Health dimension had the lowest score (66.7 [50.0 – 75.0] and 66.7 [58.3 – 75.0] at the first and the last administration of the questionnaire, respectively).

#### *Factors independently associated with PROQOL-HCV scores*

In the multivariable linear regression models (Tables 3 and 4), HCV cure was significantly associated with better PROQOL-HCV scores for all the six dimensions explored, with adjusted coefficients [95% CI] ranging from 2.74 [1.07; 4.42] (for the Intimate Relationships dimension) to 7.49 [5.91; 9.08] (for Physical Health). By contrast, severe liver fibrosis was associated with lower scores for all dimensions, with adjusted coefficients ranging from -4.78 [-6.64; -2.91] (for Social Health) to -8.48 [-11.1; -5.86] (for Physical Health). Compared with men, women had lower scores in all dimensions except Social Health, and greater differences were observed for Emotional Health (-5.74 [-7.75; -3.73]) and Physical Health (-5.09 [-7.14; -3.05]) (Table 4). Living with obesity was associated with lower scores in the Physical Health and Future Uncertainty dimensions (Table 3).

Independently of the factors above, the multivariable models also showed significant effects of social vulnerability factors on HRQoL. Current or past unhealthy alcohol use was associated with worse PROQOL-HCV for all dimensions, with the strongest association observed for Cognitive Functioning (Table 4). Living in poverty was associated with lower scores in all dimensions except Intimate Relationships, especially in the two dimensions related to physical and emotional health (Table 3). Current or past psychoactive substance use was associated with worse PROQOL-HCV for Emotional health, Intimate Relationships, and Cognitive Functioning dimensions. Being a migrant or a MSM was not significantly associated with PROQOL-HCV scores in the multivariable models (Tables 3 and 4). For each dimension explored, we found no significant interaction effect between HCV cure and the different social vulnerability factors studied (data not shown). No evidence of multicollinearity among the social vulnerability factors was detected, as all the VIF estimates were  $<1.11$ . The main results of the multivariable models are graphically presented in Figure 2.

## Discussion

This large, real-world, longitudinal cohort study provides new evidence on the pattern of factors associated with HRQoL in chronic HCV patients in the DAAs era. As expected, HCV cure had positive effects on all six HRQoL dimensions explored. Nevertheless, this study suggests that there are still specific groups of patients with impaired HRQoL levels for all dimensions, independently of HCV cure. Specifically, these groups are women, patients with current or past unhealthy alcohol use, and patients living in poverty.

Our results for HCV cure are consistent with the previous literature [6,7,9,26–28] including a recent meta-analysis [29] which showed that HCV cure was significantly associated with better HRQoL for all its dimensions. Interestingly, we found significant beneficial effects of HCV cure not only for the physical dimensions of HRQoL, but also for mental and social dimensions. In our study population, the effect of HCV cure on HRQoL was greater for the Emotional Health, Physical Health and Future Uncertainty dimensions of the PROQOL-HCV. The better HRQoL values for the Future Uncertainty dimension in HCV-cured patients may be partially explained by the change in their disease status (i.e. from ill to cured). It may also be related to reduced fatigue following HCV cure [7,27], something which might be beneficial for all HRQoL dimensions (i.e. physical, mental and social). Moreover, the positive effect of HCV cure on systemic inflammation may result in a reduction of the symptom burden of extrahepatic manifestations, which are known to impair HRQoL [4,27]. In our study, it is important to note that the magnitude of the positive effects of HCV cure on HRQoL dimensions was relatively small compared with the variability (interquartile ranges) observed for the PROQOL-HCV scores (Table 2). To better understand the interest of HCV cure effect on HRQoL, it would be important to translate absolute difference values into minimal clinically important differences (MCID) to be able to better interpret variations over time, or after HCV cure [30] or corresponding to specific events.

In our study, having severe liver fibrosis was associated with impaired HRQoL, independently of HCV cure. This result is in line with previous research showing that some patients may continue to have altered liver test results and remain at a higher risk of fibrosis progression even after achieving

SVR [31]. This result highlights the need for extended follow-up after cure and appropriate referral for potential persistent liver-related comorbidities.

Our study revealed that specific groups at higher risk of stigma and social inequity [13] also experienced impaired HRQoL, independently of HCV cure and severe liver fibrosis. The most affected groups were women, people with current or past unhealthy alcohol use, and those living in poverty, as they exhibited worse HRQoL for all six PROQOL-HCV dimensions studied. Our results suggest that patients with social vulnerability factors may require a different approach to clinical follow-up, where both somatic and psychiatric care are integrated irrespective of where clinical follow-up occurs (i.e. in hepatology or primary care services).

The association between current or past unhealthy alcohol use and impaired HRQoL is of particular interest, given that the burden of alcohol use may continue to affect access to treatment [32] and liver health, even after HCV cure [33]. This would also suggest that patients with current or past unhealthy alcohol use should not be discharged after HCV cure (which is in line with EASL guidelines [34]) because of their double risk of liver disease progression and HRQoL impairment. Encouraging reduced alcohol use and referral to services providing alcohol reduction interventions may result in benefits on liver health [33], mortality risk [35], and quality of life [36].

Another important result of our study was the worse HRQoL scores in women and patients living in poverty.

To our knowledge, this association between female sex and impaired HRQoL in the DAAs era is a novel result, and is possibly due to the fact that women are more likely to be HCV-infected through drug use, thereby accumulating multiple sources of stigma and discrimination (i.e. drug use, female sex, and low socio-economic status) [13]. HCV-infected women with a history of drug use have fewer opportunities to receive HCV treatment and longer waiting times for access to HCV care [37]. Given that our models were adjusted for severe liver fibrosis, we presume that it was more the impact of stigma than liver disease which affected the different dimensions of HRQoL in the women in our study. The association between living in poverty and impaired HRQoL in our model, which was also adjusted

for HCV cure and liver fibrosis, is consistent with previous research which found that health insurance status affected HRQoL levels [11].

Our study has several strengths. First, its large sample size allowed us to adequately represent groups generally under-represented in previous studies. Second, we used the PROQOL-HCV, which is a disease-specific and internationally validated psychometric scale to assess HRQoL. This questionnaire is likely to be more sensitive than other tools to changes in patient-reported outcomes after HCV cure following DAAs treatment. Third, this is one of the first longitudinal studies [17] to explore the extent to which belonging to a specific group concerned by social vulnerability factors – which often coincide with socially deprived populations – can affect the different dimensions of HRQoL.

With regard to the study's limitations, behavioural data related to the use of alcohol and other psychoactive substances were based on self-reports, which could be affected by social desirability bias. Patients with a liver disease such as HCV infection may underreport alcohol use, as suggested by results of a previous study in HIV-HCV co-infected patients [38]. However, any such possible underreporting is more likely to have affected the association found in a conservative manner. Some missing data in the country of origin of migrants, along with lack of data concerning the country of origin of migrants, along with data on individuals' ethnicity (which collection is not authorized in France) is another limitation of our study. In addition, the slight differences in the percentage of women and in the percentages of patients with severe liver fibrosis, of those living in poverty and of migrants observed between included and excluded patients might have biased the associations found in our study. However, these differences were of limited magnitude.

Our study's findings suggest the need to monitor HRQoL in patients with chronic HCV infection, in particular women, people with current or past unhealthy alcohol use, and people living in poverty. This monitoring should be extended after HCV cure, especially in the new clinical setting of DAAs, where lasting therapeutic relationships and contact with healthcare providers are sometimes less frequent.

To conclude, although HCV cure with DAAs leads to better HRQoL, specific socially vulnerable groups still experience impaired HRQoL, independently of HCV cure. Patient-centred interventions to improve HRQoL, including social support or referral for comorbidities, should be prioritized for patients at higher risk of impaired HRQoL.

**Abbreviations:**

ALT, alanine transaminase

AST, aspartate transaminase

BMI, body mass index

CLDQ-HCV, Chronic Liver Disease Questionnaire - Hepatitis C Virus

DAAs, direct-acting antivirals

HBV, hepatitis B virus

HCV, hepatitis C virus

HIV, human immunodeficiency virus

HRQoL, health-related quality of life

IQR, interquartile range

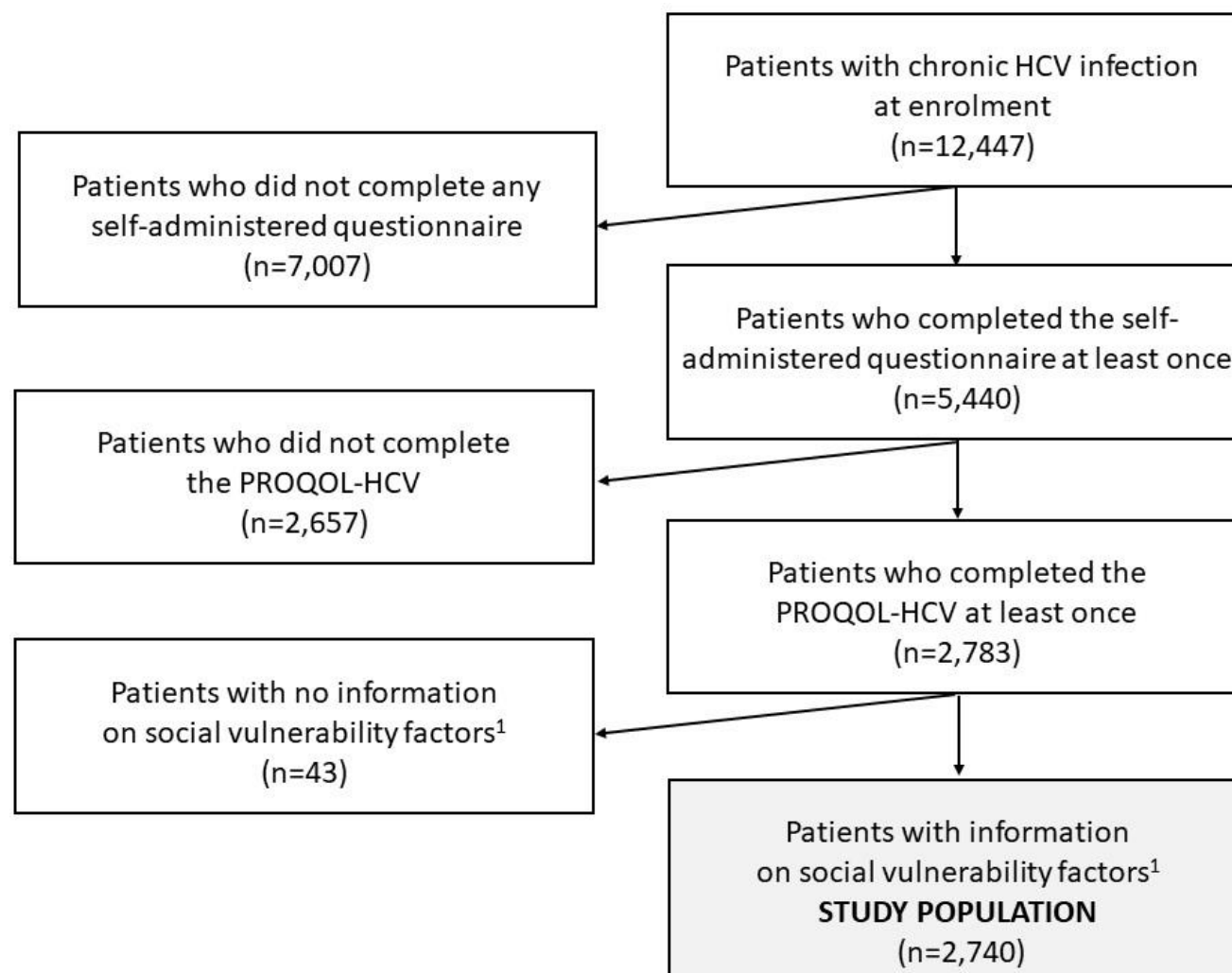
MSM, man who has sex with men

PROQOL-HCV, Patient Reported Outcome Quality of Life survey for HCV

RNA, ribonucleic acid

SVR, sustained virological response

Figure 1. Flow chart of the study population (ANRS CO22 HEPATHER cohort)



<sup>1</sup> Social vulnerability factors included: current or past unhealthy alcohol use, being a migrant, being a man who has sex with men (MSM), living in poverty, and reporting current or past psychoactive substance use other than cannabis (unhealthy alcohol use was defined as drinking more than 2(3) alcohol units per day for women (men)[24]; being a migrant was defined as being born outside France and having at least one parent also born outside France; being a MSM was defined as being a man who had sexual relations with another man at least once during his lifetime; living in poverty was defined as a standard of living lower than the 2015 French poverty threshold (1,015€ per month per household consumption unit) [25]; reporting current or past psychoactive substance use other than cannabis was defined as reporting past or current use of non-prescribed psychoactive drugs (crack, cocaine, heroin, and other nasal or intravenous drugs) other than cannabis and/or taking at least one opioid substitution treatment (methadone, buprenorphine or other)).



**Table 1. Characteristics of the study population at enrolment in the ANRS CO22 HEPATHER cohort (n=2,740)**

| <b>Characteristic</b> (% of missing values)                         | <b>No. of individuals (%) or median [IQR]</b> |
|---|---|
| <b>Male sex</b> (0)   | 1,435 (52.4%)                                 |
| <b>Age</b> (years) (0.2)  | 56 [50 – 64]                                  |
| <b>Educational level</b> ≥ upper secondary school certificate (0.9) | 1,305 (48.0%)                                 |
| <b>BMI<sup>a</sup></b> (kg/m <sup>2</sup> ) (0.6)                   |   |
| Underweight   | 83 (3.0%)                                     |
| Normal weight   | 1,420 (52.1%)                                 |
| Overweight  | 899 (33.0%)                                   |
| Obesity   | 321 (11.8%)                                   |
| <b>Severe liver fibrosis<sup>b</sup></b> (8.7)                      | 537 (21.5%)                                   |

|   |             |
|---|-------------|
| <b>Current or past unhealthy alcohol use<sup>c</sup></b>                                | 775 (28.3%) |
| <b>Current or past psychoactive substance use (other than cannabis)<sup>d</sup> (0)</b> | 953 (34.8%) |
| <b>Living in poverty<sup>e</sup> (2.0)</b>  | 755 (28.1%) |
| <b>Being a migrant<sup>f</sup> (0.2)</b>  | 561 (20.5%) |
| <b>Being a MSM<sup>g</sup> (0)</b>  | 60 (2.2%)   |

IQR, interquartile range; HCV, hepatitis C virus; BMI, body mass index; MSM, man who has sex with men.

<sup>a</sup> Categorized according to the following WHO classes [22]: <18.5, underweight; ≥18.5 and <25, normal weight; ≥25 and <30, overweight; ≥30, obesity.

<sup>b</sup> Severe liver fibrosis defined as an FIB-4 > 3.25 [23].

<sup>c</sup> Defined as drinking more than 2(3) alcohol units per day for women (men)[24].

<sup>d</sup> Defined as reporting past or current use of non-prescribed psychoactive drugs (crack, cocaine, heroin, and other nasal or intravenous drugs) other than cannabis and/or taking at least one opioid substitution treatment (methadone, buprenorphine or other).

<sup>e</sup> Defined as a standard of living lower than the 2015 French poverty threshold (1,015€ per month per household consumption unit) [25].

<sup>f</sup> Defined as being born outside France and having at least one parent also born outside France.

<sup>g</sup> Defined as reporting sexual relationships with men at least once during lifetime.

**Table 2. Distribution of PROQOL-HCV scores at first and last administration of the questionnaire in the study population (ANRS CO22 HEPATHER cohort, n=2,740)**

| PROQOL-HCV scores <sup>1</sup> | Distribution at first administration of the questionnaire |                                  | Distribution at last administration of the questionnaire |                                  |
|--------------------------------|---|----------------------------------|--|----------------------------------|
|                                | Median [IQR]  | % of missing values <sup>2</sup> | Median [IQR]   | % of missing values <sup>2</sup> |
| <b>Emotional health</b>        | 75.0 [52.8 – 94.4]  | 10.9                             | 75.0 [55.6 – 97.2]                                       | 9.1                              |
| <b>Physical health</b>         | 70.8 [45.8 – 91.7]  | 13.6                             | 70.8 [50.0 – 91.7]                                       | 12.8                             |
| <b>Future uncertainty</b>      | 83.3 [66.7 – 95.8]  | 10.4                             | 87.5 [70.8 – 100]  | 10.5                             |
| <b>Intimate relationships</b>  | 83.3 [58.3 – 100]   | 12.0                             | 91.7 [58.3 – 100]  | 13.0                             |
| <b>Social health</b>           | 66.7 [50.0 – 75.0]  | 7.6                              | 66.7 [58.3 – 75.0]                                       | 8.6                              |
| <b>Cognitive functioning</b>   | 75.0 [58.3 – 100]   | 4.5                              | 83.3 [58.3 – 100]  | 5.3                              |

IQR, interquartile range; PROQOL-HCV, Patient Reported Outcome Quality of Life survey for HCV.

<sup>1</sup> Each PROQOL-HCV score has a 100-point range, and higher score values indicate better HRQoL.

<sup>2</sup> The percentages correspond to missing values for at least one item contributing to the PROQOL-HCV score calculation.

**Table 3. Factors associated with PROQOL-HCV scores in patients with chronic HCV infection, multivariable mixed-effects linear regression models (ANRS CO22 HEPATHER cohort, n=2,740 patients, 4,521 visits)**

**Models for the Emotional Health, Physical Health, and Future Uncertainty dimensions of the PROQOL-HCV**

|   | Emotional Health<br>(n=2,269) |                | Physical Health<br>(n=2,211) |                | Future Uncertainty<br>(n=2,250) |                |
|---|-------------------------------|----------------|------------------------------|----------------|---------------------------------|----------------|
|   | Coeff [95% CI]                | <i>p-value</i> | Coeff [95% CI]               | <i>p-value</i> | Coeff [95% CI]                  | <i>p-value</i> |
| <b>SOCIO-DEMOGRAPHIC CHARACTERISTICS</b>                                  |                               |                |                              |                |                                 |                |
| <b>Female sex</b>   | -5.74 [-7.75;-3.73]           | <0.001         | -5.09 [-7.14;-3.05]          | <0.001         | -1.72 [-3.36;-0.08]             | 0.040          |
| <b>Age (years)</b>  | -0.08 [-0.18;0.01]            | 0.493          | -0.20 [-0.29;-0.11]          | <0.001         | 0.18 [0.11;0.26]                | <0.001         |
| <b>Educational level ≥ upper secondary school certificate<sup>a</sup></b> | 0.73 [-1.24;2.69]             | 0.468          | 1.48 [-0.49;3.45]            | 0.141          | 1.73 [0.11;3.35]                | 0.036          |
| <b>CLINICAL CHARACTERISTICS</b>   |                               |                |                              |                |                                 |                |
| <b>HCV cure</b>   | 5.07 [3.64;6.51]              | <0.001         | 7.49 [5.91;9.08]             | <0.001         | 6.38 [5.16;7.59]                | <0.001         |
| <b>BMI<sup>b</sup> (kg/m<sup>2</sup>)</b>                                 |                               |                |                              |                |                                 |                |
| Normal weight (ref)   | 0                             |                | 0                            |                | 0                               |                |
| Underweight   | -1.36 [-7.04;4.32]            | 0.639          | -4.31 [-10.27;1.64]          | 0.155          | 0.12 [-4.58;4.82]               | 0.959          |

|   |                      |        |                      |        |                     |        |
|---|----------------------|--------|----------------------|--------|---------------------|--------|
| Overweight  | 0.29 [-1.82;2.40]    | 0.788  | 0.29 [-1.79;2.37]    | 0.786  | -0.86 [-2.62;0.91]  | 0.342  |
| Obesity   | -2.06 [-5.29;1.16]   | 0.210  | -4.99 [-8.37;-1.60]  | 0.004  | -3.75 [-6.44;-1.06] | 0.006  |
| <b>Severe liver fibrosis<sup>c</sup></b>  | -5.05 [-7.55;-2.55]  | <0.001 | -8.48 [-11.10;-5.86] | <0.001 | -5.39 [-7.50;-3.29] | <0.001 |
| <b>SOCIAL VULNERABILITY FACTORS</b>   |                      |        |                      |        |                     |        |
| <b>Current or past unhealthy alcohol use<sup>d</sup></b>                                | -3.92 [-6.27;-1.57]  | 0.001  | -2.50 [-4.84;-0.17]  | 0.036  | -3.04 [-5.00;-1.09] | 0.002  |
| <b>Current or past psychoactive substance use<br/>(other than cannabis)<sup>e</sup></b> | -2.84 [-5.12;-0.56]  | 0.015  | -1.12 [-3.38;1.14]   | 0.330  | -0.19 [-2.08;1.71]  | 0.848  |
| <b>Living in poverty<sup>f</sup></b>  | -7.80 [-10.18;-5.42] | <0.001 | -8.18 [-10.55;-5.81] | <0.001 | -4.49 [-6.43;-2.55] | <0.001 |
| <b>Being a migrant<sup>g</sup></b>  | 0.96 [-1.71;3.64]    | 0.480  | 0.17 [-2.54;2.88]    | 0.903  | -0.69 [-2.89;1.51]  | 0.539  |
| <b>Being a MSM<sup>h</sup></b>  | -1.54 [-7.52;4.45]   | 0.614  | 0.77 [-5.35;6.88]    | 0.806  | 2.07 [-2.68;6.81]   | 0.393  |

BMI, body mass index; Coeff, adjusted regression coefficient; CI, confidence interval; HCV, hepatitis C virus; MSM, man who has sex with men; PROQOL-HCV, Patient Reported Outcome Quality of Life survey for HCV; ref=reference category.

<sup>a</sup> Educational level was based on upper secondary school certificate (i.e. the French baccalaureate).

<sup>b</sup> Categorized according to the following WHO classes [22]: <18.5, underweight; ≥18.5 and <25, normal weight; ≥25 and <30, overweight; ≥30, obesity.

<sup>c</sup> Defined as an FIB-4 value > 3.25 [23].

<sup>d</sup> Defined as drinking more than 2(3) alcohol units per day for women (men)[24].

<sup>e</sup> Defined as reporting past or current use of non-prescribed psychoactive drugs (crack, cocaine, heroin, and other nasal or intravenous drugs) other than cannabis and/or taking at least one opioid substitution treatment (methadone, buprenorphine or other).

<sup>f</sup> Defined as a standard of living lower than the 2015 French poverty threshold (1,015€ per month per household consumption unit) [25].

<sup>g</sup> Defined as being born outside France and having at least one parent also born outside France.

<sup>h</sup> Defined as reporting sexual relations with men at least once during lifetime.

**Table 4. Factors associated with PROQOL-HCV scores in patients with chronic HCV infection, multivariable mixed-effects linear regression models (ANRS CO22 HEPATHER cohort, n=2,740 patients, 4,521 visits)**

**Models for the Intimate Relationships, Social Health, and Cognitive Functioning dimensions of the PROQOL-HCV**

|  | Intimate Relationships<br>(n=2,209) |                | Social Health<br>(n=2,298) |                | Cognitive Functioning<br>(n=2,250) |                |
|--|-------------------------------------|----------------|----------------------------|----------------|------------------------------------|----------------|
|  | Coeff [95% CI]                      | <i>P-value</i> | Coeff [95% CI]             | <i>P-value</i> | Coeff [95% CI]                     | <i>P-value</i> |
| <b>SOCIO-DEMOGRAPHIC CHARACTERISTICS</b>                                   |                                     |                |                            |                |                                    |                |
| <b>Female sex</b>  | -2.61 [-4.92;-0.31]                 | 0.026          | -0.45 [-1.90;0.99]         | 0.540          | -4.34 [-6.34;-2.35]                | <0.001         |
| <b>Age (years)</b>   | 0.02 [-0.08;0.12]                   | 0.712          | -0.06 [-0.13;0.00]         | 0.062          | -0.10 [-0.19;-0.01]                | 0.039          |
| <b>Educational level ≥ upper secondary school certificate <sup>a</sup></b> | -0.06 [-2.22;2.10]                  | 0.957          | -1.67 [-3.09;-0.26]        | 0.021          | 1.07 [-0.91;3.05]                  | 0.290          |
| <b>CLINICAL CHARACTERISTICS</b>  |                                     |                |                            |                |                                    |                |
| <b>HCV cure</b>  | 2.74 [1.07;4.42]                    | 0.001          | 3.01 [1.87;4.16]           | <0.001         | 4.01 [2.57;5.45]                   | <0.001         |
| <b>BMI<sup>b</sup> (kg/m<sup>2</sup>)</b>                                  |                                     |                |                            |                |                                    |                |
| Normal weight (ref)  | 0                                   |                | 0                          |                | 0                                  |                |
| Underweight  | -3.35 [-10.57;3.87]                 | 0.362          | -1.73 [-6.24;2.77]         | 0.451          | -1.06 [-7.70;5.57]                 | 0.753          |



|   |                     |        |                     |        |                      |        |
|---|---------------------|--------|---------------------|--------|----------------------|--------|
| Overweight  | -0.19 [-2.53;2.16]  | 0.875  | 0.58 [-0.96;2.12]   | 0.458  | 1.10 [-1.00;3.20]    | 0.303  |
| Obesity   | -1.11 [-4.74;2.52]  | 0.548  | -1.00 [-3.32;1.31]  | 0.369  | -1.29 [-4.56;1.99]   | 0.441  |
| <b>Severe liver fibrosis<sup>c</sup></b>  | -6.01 [-8.88;-3.14] | <0.001 | -4.78 [-6.64;-2.91] | <0.001 | -7.65 [-10.23;-5.07] | <0.001 |
| <b>SOCIAL VULNERABILITY FACTORS</b>   |                     |        |                     |        |                      |        |
| <b>Current or past unhealthy alcohol use<sup>d</sup></b>                                | -3.33 [-5.97;-0.70] | 0.013  | -4.00 [-5.68;-2.31] | <0.001 | -7.1 [-12.62;-1.59]  | 0.012  |
| <b>Current or past psychoactive substance use<br/>(other than cannabis)<sup>e</sup></b> | -3.00 [-5.49;-0.51] | 0.018  | -1.32 [-2.92;0.27]  | 0.103  | -3.93 [-6.11;-1.76]  | <0.001 |
| <b>Living in poverty<sup>f</sup></b>  | -2.55 [-5.23;0.12]  | 0.062  | -5.61 [-7.38;-3.84] | <0.001 | -5.61 [-8.05;-3.17]  | <0.001 |
| <b>Being a migrant<sup>g</sup></b>  | 0.39 [-2.55;3.34]   | 0.793  | 1.69 [-0.23;3.61]   | 0.084  | 2.00 [-0.67;4.67]    | 0.142  |
| <b>Being a MSM<sup>h</sup></b>  | -0.55 [-6.38;5.29]  | 0.855  | 0.83 [-3.49;5.16]   | 0.705  | -2.96 [-9.31;3.38]   | 0.360  |

BMI, body mass index; Coeff, adjusted regression coefficient; CI, confidence interval; HCV, hepatitis C virus; MSM, man who has sex with men; PROQOL-HCV, Patient Reported Outcome Quality of Life survey for HCV; ref=reference category.

<sup>a</sup> Educational level was based on upper secondary school certificate (i.e. the French baccalaureate).

<sup>b</sup> Categorized according to the following WHO classes [22]: <18.5, underweight; ≥18.5 and <25, normal weight; ≥25 and <30, overweight; ≥30, obesity.

<sup>c</sup> Defined as an FIB-4 value > 3.25 [23].

<sup>d</sup> Defined as drinking more than 2(3) alcohol units per day for women (men)[24].

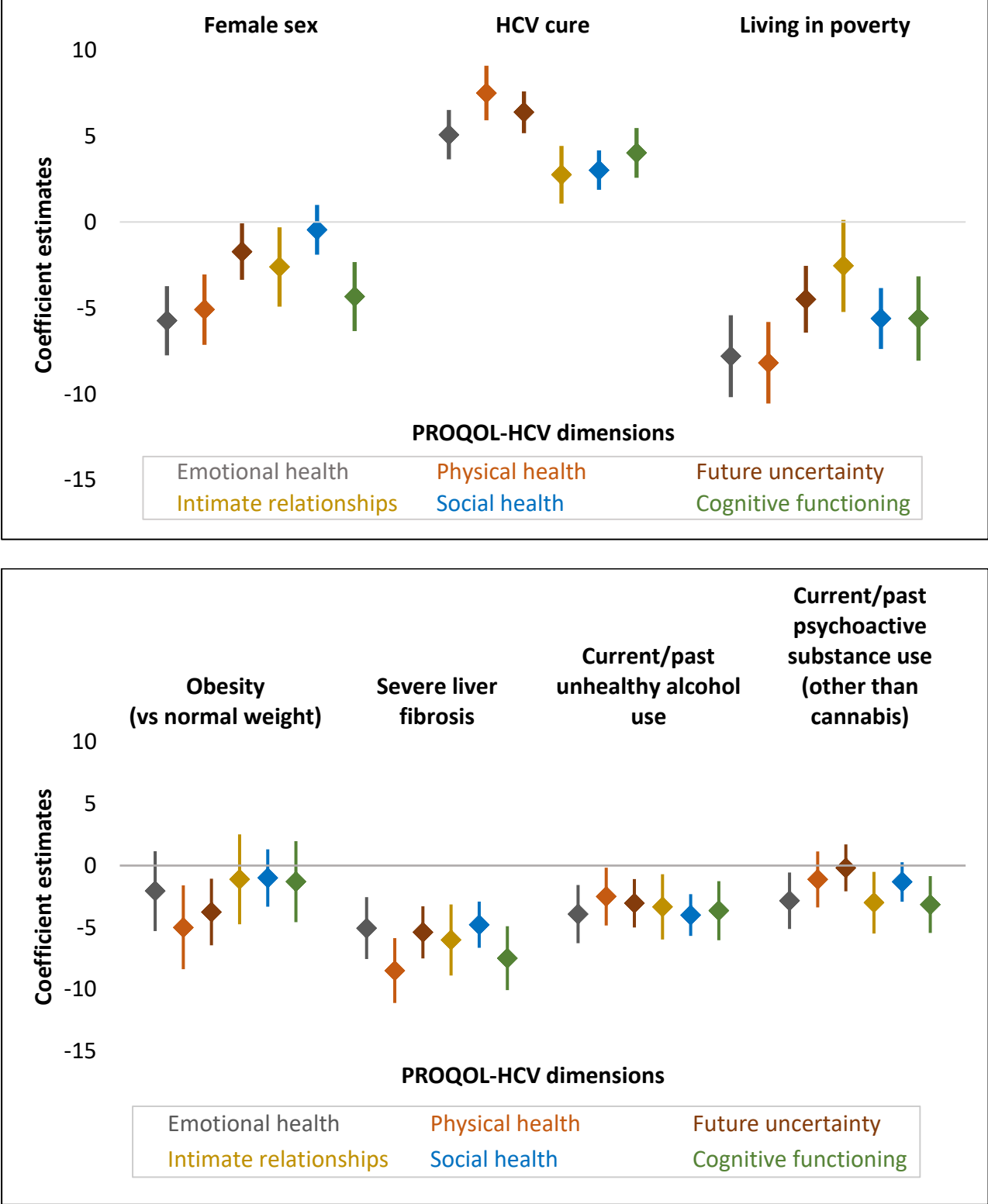
<sup>e</sup> Defined as reporting past or current use of non-prescribed psychoactive drugs (crack, cocaine, heroin, and other nasal or intravenous drugs) other than cannabis and/or taking at least one opioid substitution treatment (methadone, buprenorphine or other).

<sup>f</sup> Defined as a standard of living lower than the 2015 French poverty threshold (1,015€ per month per household consumption unit) [25].

<sup>g</sup> Defined as being born outside France and having at least one parent also born outside France.

<sup>h</sup> Defined as reporting sexual relations with men at least once during lifetime.

Figure 2. Coefficient estimates and their 95% confidence intervals for the main correlates of PROQOL-HCV scores, multivariable mixed-effects linear regression models (ANRS CO22 HEPATHER cohort, n=2,740 patients, 4,521 visits)



The multivariable models were adjusted for age, educational level, being a migrant, and being a MSM.

## Supplementary Table 1

### Main characteristics of patients at enrolment in the ANRS CO22 HEPATHER cohort: Comparison between patients included in the study population and those excluded

|   | <b>Excluded patients</b><br>(n = 9,707) | <b>Included patients</b><br>(n = 2,740) | <i>p-value</i> <sup>1</sup> |
|---|---|---|-----------------------------|
|   | No. of individuals (%)                  |   |                             |
| <b>Female sex</b>   | 4,159 (42.8)                            | 1,305 (47.6)                            | <0.001                      |
| <b>Educational level ≥ upper secondary school certificate<sup>a</sup></b>           | 4,291 (45.0)                            | 1,305 (47.6)                            | 0.005                       |
| <b>Severe liver fibrosis<sup>b</sup></b>  | 2,640 (27.2)                            | 537 (21.5)                              | <0.001                      |
| <b>Hepatocellular carcinoma</b>   | 165 (1.7)                               | 31 (1.1)                                | 0.001                       |
| <b>BMI<sup>c</sup></b>  |   |   | 0.081                       |
| Normal weight   | 4,849 (50.5)                            | 1,420 (52.1)                            |                             |
| Underweight   | 324 (3.4)                               | 83 (3.1)                                |                             |
| Overweight  | 3,133 (32.6)                            | 899 (33.0)                              |                             |
| Obesity   | 1,305 (13.6)                            | 321 (11.8)                              |                             |
| <b>SOCIAL VULNERABILITY FACTORS</b>   |   |   |                             |
| <b>Current or past unhealthy alcohol use<sup>d</sup></b>                            | 2,912 (30.2)                            | 774 (28.3)                              | 0.054                       |
| <b>Current or past psychoactive substance use (other than cannabis)<sup>e</sup></b> | 3,359 (34.6)                            | 954 (34.9)                              | 0.775                       |
| <b>Living in poverty<sup>f</sup></b>  | 3,161 (33.9)                            | 754 (28.1)                              | <0.001                      |
| <b>Being a migrant<sup>g</sup></b>  | 2,742 (28.3)                            | 560 (20.5)                              | <0.001                      |
| <b>Being a MSM<sup>h</sup></b>  | 113 (1.2)                               | 60 (2.2)                                | <0.001                      |

BMI, body mass index.

<sup>1</sup> Chi-square test.

<sup>a</sup> Educational level was based on upper secondary school certificate (i.e. the French baccalaureate).

<sup>b</sup> Defined as an FIB-4 value > 3.25 [23].

<sup>c</sup> Categorized according to the following WHO classes [22]: <18.5, underweight; ≥18.5 and <25, normal weight; ≥25 and <30, overweight; ≥30, obesity.

<sup>d</sup> Defined as drinking more than 2(3) alcohol units per day for women (men) [24].

<sup>e</sup> Defined as reporting past or current use of non-prescribed psychoactive drugs (crack, cocaine, heroin, and other nasal or intravenous drugs) other than cannabis and/or taking at least one opioid substitution treatment (methadone, buprenorphine or other).

<sup>f</sup> Defined as a standard of living lower than the 2015 French poverty threshold (1,015€ per month per household consumption unit) [25].

<sup>g</sup> Defined as being born outside France and having at least one parent also born outside France.

<sup>h</sup> Defined as reporting sexual relations with men at least once during lifetime.

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