



HAL
open science

Depressive symptoms after hepatitis C cure and socio-behavioral correlates in aging people living with HIV (ANRS CO13 HEPAVIH)

Fabienne Marcellin, Sylvie Bréigéon-Ronot, Clémence Ramier, Camelia Protopopescu, Camille Gilbert, Vincent Di Beo, Claudine Duvivier, Morgane Bureau-Stoltmann, Eric Rosenthal, Linda Wittkop, et al.

► To cite this version:

Fabienne Marcellin, Sylvie Bréigéon-Ronot, Clémence Ramier, Camelia Protopopescu, Camille Gilbert, et al.. Depressive symptoms after hepatitis C cure and socio-behavioral correlates in aging people living with HIV (ANRS CO13 HEPAVIH). JHEP Reports Innovation in Hepatology, 2022, 5 (1), pp.100614. 10.1016/j.jhepr.2022.100614 . inserm-04547481

HAL Id: inserm-04547481

<https://inserm.hal.science/inserm-04547481v1>

Submitted on 15 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

Depressive symptoms after hepatitis C cure and socio-behavioral correlates in aging people living with HIV (ANRS CO13 HEPAVIH)

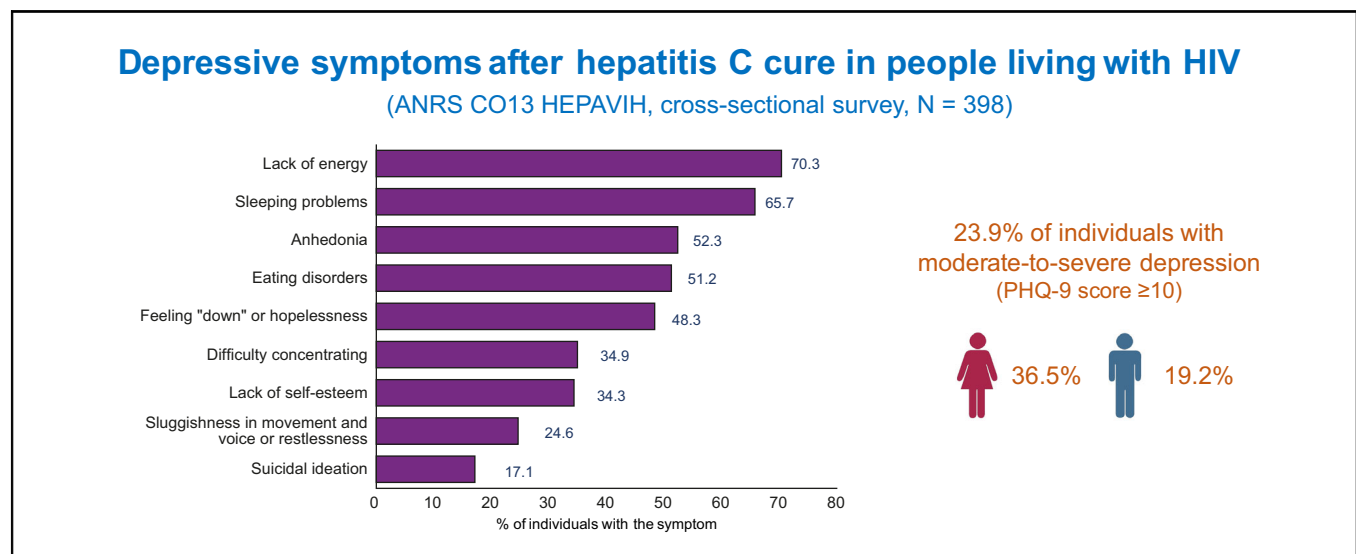
Authors

Fabienne Marcellin, Sylvie Bréigéon-Ronot, Clémence Ramier, Camelia Protopopescu, Camille Gilbert, Vincent Di Beo, Claudine Duvivier, Morgane Bureau-Stoltmann, Eric Rosenthal, Linda Wittkop, Dominique Salmon-Céron, Patrizia Carrieri, Philippe Sogni, Tangui Barré

Correspondence

pmcarrieri@aol.com (P. Carrieri).

Graphical abstract



Highlights

- Depressive symptoms are highly prevalent in people living with HIV (PLWH) after hepatitis C cure, especially in women.
- Lifestyle-related factors, including alcohol use, level of physical activity and nutrition, correlate with depression.
- A global care model is needed for PLWH living with or having a history of hepatitis C.

Lay summary

Despite potential improvements in mental health after successful treatment with direct-acting antivirals, many people living with HIV (PLWH) and hepatitis C virus (HCV) - even in older age classes - still face depressive symptoms after HCV cure. In this population, women and people reporting unhealthy alcohol use, sedentary lifestyle, or unhealthy eating behaviors are more prone to report depressive symptoms after HCV cure. Mental health and lifestyle-related issues should be integrated in a global care model for PLWH living with or having a history of hepatitis C.



Depressive symptoms after hepatitis C cure and socio-behavioral correlates in aging people living with HIV (ANRS CO13 HEPAVIH)

Fabienne Marcellin,¹ Sylvie Bréigéon-Ronot,² Clémence Ramier,¹ Camelia Protopopescu,¹ Camille Gilbert,³ Vincent Di Beo,¹ Claudine Duvivier,^{4,5,6,7} Morgane Bureau-Stoltmann,¹ Eric Rosenthal,^{1,8} Linda Wittkop,^{3,9} Dominique Salmon-Céron,^{10,11} Patrizia Carrieri,^{1,*} Philippe Sogni,^{11,12,13} Tangui Barré¹, on behalf of the ANRS CO13 HEPAVIH Study Group[†]

¹Aix Marseille Univ, Inserm, IRD, SESSTIM, Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale, ISSPAM, Marseille, France; ²Clinical Immunohematology Department, Marseille Public University Hospital System (AP-HM), Sainte-Marguerite Hospital, Aix-Marseille University, Marseille, France; ³ISPED, Inserm, Bordeaux Population Health Research Center, Team MORPH3EUS, UMR 1219, CIC-EC 1401, Université de Bordeaux, Bordeaux, France; ⁴Service de Maladies Infectieuses et Tropicales, Centre d'Infectiologie Necker-Pasteur, APHP-Hôpital Necker-Enfants Malades, Paris, France; ⁵IHU Imagine, Paris, France; ⁶Institut Cochin-CNRS 8104-INSERM U1016-RIL Team: Retrovirus, Infection and Latency, Université de Paris, Paris, France; ⁷Centre Médical de L'Institut Pasteur, Institut Pasteur, Paris, France; ⁸ANRS I Emerging infectious diseases, Paris, France; ⁹Service D'information Médicale, CHU de Bordeaux, Pôle de Santé Publique, Bordeaux, France; ¹⁰Service Maladies Infectieuses et Tropicales, APHP, Hôpital Cochin, Paris, France; ¹¹Université Paris Descartes, Paris, France; ¹²INSERM U1223, Institut Pasteur, Paris, France; ¹³Service d'Hépatologie, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, France

JHEP Reports 2023. <https://doi.org/10.1016/j.jhepr.2022.100614>

Background & Aims: A growing literature shows an improvement of chronic hepatitis C virus (HCV)-related depression after successful treatment with direct-acting antivirals. However, depression after HCV cure remains insufficiently documented in people living with HIV (PLWH) and HCV, a population with specific mental health challenges. This study aimed to (i) document the prevalence of moderate-to-severe depression (PHQ-9 score ≥ 10) across different age classes in HCV-cured PLWH; (ii) identify associated socio-behavioral correlates.

Methods: Descriptive analyses were performed on data collected during a cross-sectional survey (February 2018 - May 2019) nested in a prospective, multicenter cohort of individuals living with HIV and HCV (ANRS CO13 HEPAVIH). Socio-behavioral correlates of moderate-to-severe depression were identified using logistic regression.

Results: Among the 398 HCV-cured individuals in the study sample (median age [IQR]: 56 [53–59] years; 73.1% men), 23.9% presented with moderate-to-severe depression (PHQ-9 score ≥ 10). Depressive symptom prevalence rates were as follows: anhedonia: 52.3%; feeling 'down' or feelings of hopelessness: 48.3%; sleeping problems: 65.7%; lack of energy: 70.3%; eating disorders: 51.2%; lack of self-esteem: 34.3%; difficulty concentrating: 34.9%; sluggishness (in movement and voice) or restlessness: 24.6%; suicidal ideation: 17.1%. No significant difference was detected across age classes. Female sex, unhealthy alcohol use, sedentary lifestyle, and unhealthy eating behaviors were associated with increased odds of moderate-to-severe depression.

Conclusions: Depressive symptoms were common in this sample of HCV-cured PLWH. Unlike findings for the French general population, the prevalence of depression did not decrease with age class. Mental health remains a key issue for HIV-HCV-coinfected individuals, even after HCV cure, especially in women and in individuals with unhealthy behaviors.

Lay summary: Despite potential improvements in mental health after successful treatment with direct-acting antivirals, many people living with HIV (PLWH) and hepatitis C virus (HCV) - even in older age classes - still face depressive symptoms after HCV cure. In this population, women and people reporting unhealthy alcohol use, sedentary lifestyle, or unhealthy eating behaviors are more prone to report depressive symptoms after HCV cure. Mental health and lifestyle-related issues should be integrated in a global care model for PLWH living with or having a history of hepatitis C.

© 2022 The Author(s). Published by Elsevier B.V. on behalf of European Association for the Study of the Liver (EASL). This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Aging; Depression; Co-infection; HCV cure; HIV; Mental health.
Received 21 June 2022; received in revised form 6 October 2022; accepted 7 October 2022;
available online 28 October 2022

[†] Members of the collaboration group listed in Acknowledgements section.

* Corresponding author. Address: Inserm UMR 1252 SESSTIM, Aix-Marseille Univ, Faculté de Médecine, 27 Bd Jean Moulin, 13385 Marseille Cedex 5-France; Tel.: +33 4 13 73 22 81

E-mail address: pmcarrieri@aol.com (P. Carrieri).

Introduction

Mental health disorders, including depression, are highly prevalent in people living with HIV (PLWH), with negative consequences on individuals' perceived health and clinical outcomes.¹ The prevalence of depression is even higher in people living with HIV and hepatitis C virus (HCV).^{2,3} This is because of several factors, including the impact of HCV on the central nervous



system and, in many cases, vulnerabilities such as a history of injecting drug use and exposure to interferon-based therapy.

With life expectancy of PLWH approaching that of the general population, and HCV cure now possible for most individuals with HCV infection, addressing mental health needs has become a major challenge in the management of HIV-HCV coinfection. A growing literature shows significant improvements in mental health outcomes, including chronic HCV-related depression, after HCV cure thanks to successful treatment with direct-acting antivirals.^{4,5} However, depression after HCV cure remains insufficiently documented in individuals living with HIV and HCV, a population with specific mental health challenges. In addition, a recent survey showed a decline in the prevalence of depression with increasing age in the French general population.⁶ By contrast, in individuals living with HIV and HCV – who experience a faster aging process than the general population^{7,8} – there is a lack of data on the prevalence of depression across age classes. This study aimed to (i) document the prevalence of moderate-to-severe depression across different age classes in HCV-cured PLWH; (ii) identify associated socio-behavioral correlates.

Patients and methods

Data source

We used data from a multicenter cross-sectional survey conducted between February 2018 and May 2019 and nested in ANRS CO13 HEPAVIH, a French prospective cohort of people living with HIV and HCV.⁹ All patients enrolled in the ANRS CO13 HEPAVIH cohort study provided written informed consent. The cohort was designed and implemented in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Cochin University Hospital in Paris. Participation in the survey was proposed to all cohort patients. Survey participants answered a self-administered questionnaire to document their socio-behavioral characteristics, HCV status, and perceived health status. Information about cirrhosis status and time since HCV cure was also collected. The presence and severity of

depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9),¹⁰ a nine-item symptom checklist useable in routine HIV care¹¹ which reflects criteria for major depression as laid out in DSM-IV (Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders). The PHQ-9 begins with a general question (“Over the past two weeks, how often have you been bothered by any of the following problems?”). Then, for each item, respondents are invited to choose the best possible answer among the following four modalities: “Never” (0); “Several days” (1); “More than half the days” (2); and “Nearly every day” (3) (Table 1). A score ranging from 0 to 27 can be calculated by summing the values associated with each answer. The higher the score, the more severe the level of depression, as follows: 0–4, none or minimal; 5–9, mild; 10–14, moderate; 15–19, moderately severe; and 20–27, severe. A PHQ-9 score equal to or greater than 10 therefore denoted moderate-to-severe depression.¹⁰ Socio-behavioral information collected using the self-administered questionnaire included sex, age, HCV transmission group, alcohol and tobacco use, physical activity, and eating behaviors. Unhealthy alcohol use was defined as an AUDIT-c (Alcohol Use Disorders Identification Test-Consumption)¹² score above 4 for men, and above 3 for women. Not walking at least 10 consecutive minutes a day at least five days per week was considered a sedentary lifestyle. Eating behaviors were assessed using four questions addressing perceived unhealthy eating habits (eating too much, eating too fast, nibbling) and perceived diet balance. Reporting at least one unhealthy eating habit or unbalanced diet was considered reporting unhealthy eating behaviors. Plasma HIV viral load and CD4 T-cell count were described using data collected during the cohort follow-up visit closest to the date of the survey questionnaire administration.

Statistical analyses

Our study sample comprised HCV-cured survey participants with available data on depression (*i.e.*, who answered at least 5 of the 9 items in the PHQ-9). The main characteristics of patients were documented using descriptive statistics (number and percentage

Table 1. Characteristics of the study sample and socio-behavioral correlates of moderate-to-severe depression, defined as a PHQ-9 score ≥ 10 .

Variables (% of missing values)	% of individuals	Univariable logistic regression models, N = 398		Multivariable logistic regression model, n = 348	
		OR [95% CI]	p value	aOR [95% CI]	p value
Female sex (0)	26.9	2.41 [1.47–3.93]	<0.0001	2.90 [1.69–5.00]	<0.0001
Age in years (0)					
<53	20.6		1		0.667
53–59	55.3	1.13 [0.62–2.06]			0.683
≥ 60	24.1	0.87 [0.43–1.78]			0.708
HCV transmission group (0)					
Injecting drug use	54.5		1		0.526
Male-to-male sex	9.3	0.67 [0.28–1.61]			0.373
Heterosexual behaviors	10.8	1.11 [0.53–2.32]			0.775
Other	25.4	0.71 [0.40–1.26]			0.244
Unhealthy alcohol use ^a (1.3)	34.6	1.48 [0.92–2.38]	0.109	1.72 [1.01–2.92]	0.047
Tobacco use (3.0)	56.7	2.14 [1.30–3.53]	0.003		
Sedentary lifestyle ^b (11.3)	40.8	1.69 [1.03–2.78]	0.039	1.75 [1.05–2.94]	0.033
Unhealthy eating behaviors ^c (0.5)	47.2	2.04 [1.27–3.27]	0.003	2.08 [1.23–3.51]	0.006

Cross-sectional survey nested within the ANRS CO13 HEPAVIH cohort study, February 2018 - May 2019, N = 398.

Global p values are presented in bold for variables with more than two categories.

(a)OR (adjusted) odds ratios; CI, confidence interval; HCV, hepatitis C virus; PHQ-9, Patient Health Questionnaire-9.

^a AUDIT-c (Alcohol Use Disorders Identification Test-Consumption)¹² score ≥ 4 (3) for men (women).

^b Not walking at least 10 consecutive minutes a day at least five days per week was considered a sedentary lifestyle.

^c Eating behaviors were assessed using four questions addressing perceived unhealthy eating habits (eating too much, eating too fast, nibbling) and perceived diet balance. Reporting at least one unhealthy eating habit or unbalanced diet was considered reporting unhealthy eating behaviors.

of individuals for categorical variables, median and interquartile range (IQR) for continuous variables). Age and sex were compared between HCV-cured patients included in the study population and those excluded. Three age classes were built using the first and third quartiles of the distribution of age in the study sample as cut-off values. The PHQ-9 score was calculated with missing values in the checklist of symptoms recoded as zero. Based on previous studies in the cohort,^{9,13} we hypothesized that individuals may only have answered items which they felt concerned them. We therefore interpreted the absence of a response to a given item as the absence of the associated symptom. The PHQ-9 score and patients' answers to each item of the questionnaire were then compared between age classes. Comparisons were performed using either the Chi-square test or the exact Fisher test (if the sample size was lower than five for at least one variable category) for categorical variables, and the Kruskal-Wallis test for continuous variables. Univariable and multivariable logistic regression models were used to identify socio-behavioral correlates of moderate-to-severe depression (defined as a PHQ-9 score ≥ 10). We tested the variable 'center' as a random effect in logistic regression models in order to account for potential differences between centers participating in the study. In order to verify that different methods of handling missing PHQ-9 data provided the same results, we performed two sensitivity analyses. In the first, individuals with missing values in the checklist of symptoms were excluded. In the second, multiple imputation (MICE) was used. Lastly, we introduced clinical characteristics in logistic regression models in a final sensitivity analysis, using multiple imputation to account for missing data. Interactions between sex and the other variables were tested in the multivariable model. Finally, we performed sex-stratified analyses to describe the prevalence of moderate-to-severe depression for men and women in each age class. The significance threshold was set at 5%. Stata 16.1 for Windows (StataCorp, College Station, Texas, USA) software was used for the analyses.

Results

Characteristics of the study sample and prevalence of moderate-to-severe depression

Among the 435 cross-sectional survey participants, 425 were HCV-cured after successful treatment. Of the latter, those who did not answer any item in the PHQ-9 ($n = 23$) and those who answered fewer than 5 of the 9 items ($n = 4$) were excluded from the analyses. The remaining 398 individuals (91.5% of survey participants) constituted the study sample. No significant difference in terms of age class or sex was found between individuals in the study sample and excluded ones (data not shown). Most individuals in the study sample were men (73.1%), median [IQR] age was 56 [53–59] years (maximum: 75 years), and 54.5% had been HCV-infected through injecting drug use. More than one-third (34.6%) reported unhealthy alcohol use, 56.7% were tobacco smokers, 40.8% reported a sedentary lifestyle (to be noted, data were missing for 11.3% of individuals for the corresponding physical activity items), and 47.2% reported unhealthy eating behaviors (Table 1). Eight percent of individuals in the study sample had a detectable HIV viral load, 6.5% had a CD4 T-cell count lower than 200 cells/mm³, and 13.5% had cirrhosis. Median time since HCV cure [IQR] was 2 [2–4] years (data available for 223 individuals).

Ninety-five individuals (23.9%, 95% CI 19.8–28.4) presented moderate-to-severe depression (36.5% in women, 19.2% in men). Mild, moderate, moderately severe and severe depression concerned 31.2%, 14.8%, 6.5%, 2.5% of the study sample, respectively.

Socio-behavioral correlates of moderate-to-severe depression

Results of logistic regression models showed no significant relationship between age and the presence of moderate-to-severe depression (Table 1). In the multivariable analysis, being a woman (adjusted odds ratio [95% CI] 2.90 [1.69–5.00], $p < 0.0001$), unhealthy alcohol use (1.72 [1.01–2.92]; $p = 0.047$), sedentary lifestyle (1.75 [1.05–2.94], $p = 0.033$), and unhealthy eating behaviors (2.08 [1.23–3.51], $p = 0.006$) were identified as independent correlates of moderate-to-severe depression (Table 1). Inclusion of the variable 'center' as a random effect in the model confirmed the robustness of this multivariable analysis (no change in the list of variables retained in the model, no substantial modification of estimated adjusted odds ratios and associated confidence intervals). Interactions between sex and the other variables were tested in the multivariable model, but were not significant (data not shown).

Depressive symptoms across age classes

No significant difference was detected between age classes either for the prevalence of moderate-to-severe depression or for the level of depression (Table 2). Just over half (52.3%) of the study sample had anhedonia, 48.3% felt 'down' or had feelings of hopelessness, 65.7% had sleeping problems, 70.3% a lack of energy, 51.2% eating disorders, 34.3% a lack of self-esteem, 34.9% difficulty concentrating, 24.6% sluggishness (in movement and voice) or restlessness, and 17.1% suicidal ideation (Fig. 1). No significant difference was detected between age classes in terms of the frequency of these symptoms, or the percentage of patients receiving treatment for depression (Table 2). In the sex-stratified analyses, no significant difference was detected between age classes for the prevalence of moderate-to-severe depression (40.7%, 34.6%, and 35.7% of women with moderate-to-severe depression in the three age classes, $p = 0.862$; and 14.6%, 22.6%, and 14.7% of men with moderate-to-severe depression in the three age classes, $p = 0.233$).

Sensitivity analyses

In the sensitivity analysis, which excluded the 44 individuals with missing values in the PHQ-9 checklist of symptoms, the prevalence of moderate-to-severe depression was estimated at 23.5% (95% CI 19.3–28.2). In the multiple imputation sensitivity analysis, this prevalence was estimated at 23.9% (95% CI 19.9–28.4). The results of the main analysis concerning comparisons between age classes and identification of socio-behavioral correlates of moderate-to-severe depression were confirmed in these two sensitivity analyses (data not shown).

When included in the models, plasma HIV viral load detectability, CD4 T-cell count, time since HCV cure and cirrhosis status were not significantly associated with moderate-to-severe depression (data not shown).

Discussion

In this sample of HCV-cured PLWH with a median age of 56 years, the prevalence of depression was high, with more than one-quarter of the sample having moderate-to-severe depression. This is more than three times the prevalence of depression in the French general population (estimated at 7.03% according to a

Table 2. Depressive symptoms across age classes in HCV-cured people living with HIV.

Variables (% of missing values)	Whole study sample (N = 398)	Age classes (in years)			p value ^a
		Under 53 (n = 82)	Between 53 and 59 (n = 220)	Over 59 (n = 96)	
	No. of individuals (%) or median [IQR]				
PHQ-9¹⁰ depression score					
Continuous score (0)	5 [2–9]	5 [2–9]	6 [2–10]	4 [1–9]	0.612
Severity of depression^b (0)					0.802
None or minimal (0–4)	179 (45.0)	37 (45.1)	91 (41.4)	51 (53.1)	
Mild (5–9)	124 (31.2)	26 (31.7)	73 (33.2)	25 (26.0)	
Moderate (10–14)	59 (14.8)	12 (14.6)	36 (16.4)	11 (11.5)	
Moderately severe (15–19)	26 (6.5)	5 (6.1)	15 (6.8)	6 (6.3)	
Severe (20–27)	10 (2.5)	2 (2.4)	5 (2.3)	3 (3.1)	
Moderate-to-severe depression (score ≥10) (0)	95 (23.9)	19 (23.2)	56 (25.5)	20 (20.8)	0.666
Answers to the nine items in PHQ-9					
1. Little interest or pleasure in doing things (1.9)					0.598
Never	186 (47.7)	34 (43.0)	104 (47.7)	48 (51.6)	
Several days	117 (30.0)	26 (32.9)	67 (30.7)	24 (25.8)	
More than half the days	52 (13.3)	14 (17.7)	28 (12.8)	10 (10.8)	
Nearly every day	35 (9.0)	5 (6.3)	19 (8.7)	11 (11.8)	
2. Feeling 'down', depressed, or hopeless (2.2)					0.278
Never	201 (51.7)	40 (50.0)	113 (52.1)	48 (52.2)	
Several days	126 (32.4)	31 (38.8)	67 (30.9)	28 (30.4)	
More than half the days	41 (10.5)	6 (7.5)	28 (12.9)	7 (7.6)	
Nearly every day	21 (5.4)	3 (3.8)	9 (4.2)	9 (9.8)	
3. Trouble falling asleep or staying asleep, or sleeping too much (1.0)					0.467
Never	135 (34.3)	28 (34.2)	67 (30.5)	40 (43.5)	
Several days	131 (33.5)	29 (35.4)	77 (35.0)	25 (27.2)	
More than half the days	61 (15.5)	11 (13.4)	38 (17.3)	12 (13.0)	
Nearly every day	67 (17.0)	14 (17.1)	38 (17.3)	15 (16.3)	
4. Feeling tired or having little energy (1.7)					0.639
Never	116 (29.7)	23 (28.1)	62 (28.8)	31 (33.0)	
Several days	169 (43.2)	36 (43.9)	98 (45.6)	35 (37.2)	
More than half the days	63 (16.1)	16 (19.5)	29 (13.5)	18 (19.2)	
Nearly every day	43 (11.0)	7 (8.5)	26 (12.1)	10 (10.6)	
5. Poor appetite or overeating (2.2)					0.493
Never	190 (48.8)	33 (40.2)	107 (49.5)	50 (55.0)	
Several days	100 (25.7)	27 (32.9)	55 (25.5)	18 (19.8)	
More than half the days	47 (12.1)	11 (13.4)	24 (11.1)	12 (13.2)	
Nearly every day	52 (13.4)	11 (13.4)	30 (13.9)	11 (12.1)	
6. Feeling bad about yourself, or that you are a failure or have let yourself or your family down (1.4)					0.984
Never	258 (65.6)	56 (68.3)	138 (63.3)	64 (68.8)	
Several days	76 (19.3)	15 (18.3)	45 (20.6)	16 (17.2)	
More than half the days	36 (9.2)	7 (8.5)	21 (9.6)	8 (8.6)	
Nearly every day	23 (5.9)	4 (4.9)	14 (6.4)	5 (5.4)	
7. Difficulty concentrating on things, such as reading the newspaper or watching television (1.2)					0.479
Never	256 (65.1)	56 (69.1)	134 (61.5)	66 (70.2)	
Several days	85 (21.6)	18 (22.2)	51 (23.4)	16 (17.0)	
More than half the days	27 (6.9)	2 (2.5)	18 (8.3)	7 (7.5)	
Nearly every day	25 (6.4)	5 (6.2)	15 (6.9)	5 (5.3)	
8. Moving or speaking so slowly that people could have noticed. Or the opposite: being so fidgety or restless you have been moving around a lot more than usual (2.9)					0.813
Never	291 (75.4)	61 (78.2)	161 (75.6)	69 (72.6)	
Several days	48 (12.4)	8 (10.3)	29 (13.6)	11 (11.6)	
More than half the days	32 (8.3)	7 (9.0)	16 (7.5)	9 (9.5)	
Nearly every day	15 (3.9)	2 (2.6)	7 (3.3)	6 (6.3)	

(continued on next page)

Table 2 (continued)

Variables (% of missing values)	Whole study sample (N = 398)	Age classes (in years)			p value ^a
		Under 53 (n = 82)	Between 53 and 59 (n = 220)	Over 59 (n = 96)	
9. Thoughts that you would be better off dead, or of hurting yourself in some way (1.4)		No. of individuals (%) or median [IQR]			0.719
Never	325 (82.9)	65 (81.3)	183 (84.3)	77 (81.1)	
Several days	42 (10.7)	11 (13.8)	18 (8.3)	13 (13.7)	
More than half the days	17 (4.3)	3 (3.8)	11 (5.1)	3 (3.2)	
Nearly every day	8 (2.0)	1 (1.3)	5 (2.3)	2 (2.1)	
Treatment for depression					
Receiving treatment for depression (5.8)	60 (16.0)	11 (14.3)	34 (16.0)	15 (17.4)	0.860

Cross-sectional survey nested within the ANRS CO13 HEPAVIH cohort study, February 2018 - May 2019, N = 398.

HCV, hepatitis C virus; IQR, interquartile range; PHQ-9, Patient Health Questionnaire-9.

^a Comparison between age classes using the Chi-square or Fisher's exact test (for categorical variables) and the Kruskal-Wallis test (for continuous variables).

^b PHQ-9 score range for the different degrees of depression severity: none or minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), severe (20-27).

recent European survey using the PHQ¹⁴). Interestingly, unlike findings in a recent general population-based survey led in France,⁶ neither the prevalence nor severity of depression varied significantly with age. In that survey, prevalence decreased linearly after 45 years of age. Our results reflect clinical mental health data collected in a previous study on the same cohort.¹⁵ However, comparisons are difficult due to differences in the scales used to assess depression and in the HCV treatments available at the time of each study. Our results are consistent with those of a recent review study³ which showed that people living with HIV and HCV were significantly more likely to report depressive symptoms than HIV- or HCV-monoinfected people. We found no significant difference between age classes in terms of the presence of each depressive symptom studied. These findings confirm that mental health remains a key issue for individuals living with HIV and HCV, even after HCV cure. Promising results from the literature demonstrate that depressive symptoms decrease in many individuals with chronic HCV infection successfully treated with direct-acting antiviral therapy.^{4,5} However, real-life data are still lacking to document depression after HCV cure in previously HIV-HCV-coinfected individuals.

In the present study, the odds of having moderate-to-severe depression were nearly three times higher in women compared with men. This is in line with what is observed in the French general population.⁶ Differences in the prevalence of depression between men and women are well-reported, with both psychosocial and biological mechanisms potentially at play.¹⁶⁻¹⁸ Findings from sex-stratified analyses suggested a potential decrease in the prevalence of moderate-to-severe depression with age among women (as observed in the French general population). However, sex-stratified comparisons of prevalence rates between age classes showed no statistically significant difference.

Our study also identified several behavioral correlates of depressive symptoms, including unhealthy alcohol use, sedentary lifestyle, and unhealthy eating behaviors. While we may hypothesize the existence of a bidirectional relationship between such behavioral factors and depression, our findings underline the need for a global care model for the follow-up of PLWH treated and cured of hepatitis C. Since HCV cure is associated with significant improvements in quality of life, the period post-HCV cure may be an opportunity to manage addictive behaviors and adopt healthier lifestyles.^{9,19-21}

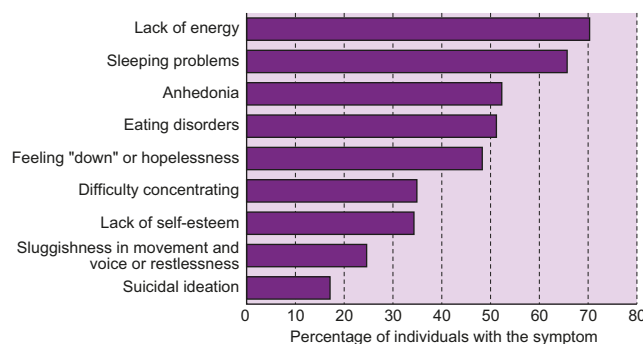


Fig. 1. Percentage of HCV-cured people living with HIV affected by the nine depressive symptoms assessed by the PHQ-9. PHQ-9, Patient Health Questionnaire-9 (cross-sectional survey nested within the ANRS CO13 HEPAVIH cohort study, February 2018–May 2019, N = 398).

This study is limited by its cross-sectional nature. Future studies should characterize the clinical profile of PLWH with moderate-to-severe depression after HCV cure, and investigate whether the observed sex effect on the prevalence of depression may be partially attributable to HIV- or HCV-related characteristics. Despite this limitation, our results are timely and provide a warning about the high prevalence of depression after HCV cure in HIV-HCV-coinfected individuals. The use of the PHQ-9 – a depression scale not specifically developed for aging people⁶ – may constitute another study limitation. However, a previous study found it was a valid instrument in aging and geriatric populations.²² Finally, the low number of women in the study sample prevented analysis of sex-specific correlates of moderate-to-severe depression. Larger studies are needed to identify potential differences between men and women in the patterns of correlates of depression after HCV cure.

To conclude, our results highlight the heavy burden of depression in aging PLWH with a history of hepatitis C, even after HCV cure, especially in women. Though bidirectional relationships exist between behavioral factors and depression, specific lifestyle-related behaviors such as unhealthy alcohol use, lack of physical activity, and nutrition should be addressed during post-cure follow-up, and integrated together with mental health in a global care model.

Abbreviations

HCV, hepatitis C virus; PHQ-9, Patient Health Questionnaire-9; PLWH, people living with HIV.

Financial support

This work was supported by the ANRS Emerging Infectious Diseases, with the participation of SIDACTION; Abbott France; Glaxo-Smith-Kline; Roche; Schering-Plough, BMS, Merck-Serono).

Conflict of interest

The authors have no conflict of interest to declare concerning this work. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: FM, PC, TB. Data curation: FM, CR, CP. Formal analysis: CR. Funding acquisition: FM, MBS, LW, DS, PC, PS. Investigation: SB, CG, CD, ER, DS, PS. Methodology: FM, CR, VdB, CP. Project administration: MBS, LW, DS, PC, PS. Resources: SB, CG, CD, ER, LW, DS, PS. Software: CR, VdB. Supervision: FM, CP, PC. Validation: FM, CR, CP, TB. Visualization: FM, CR, TB. Writing—original draft: FM, CR, TB. Writing—review and editing: FM, SB, CR, CP, CG, VdB, CD, MBS, ER, LW, DS, PC, PS, TB.

Data availability statement

Data are available upon request to the scientific committee of the ANRS CO13 HEPATHER cohort, which includes the authors of the manuscript (contact: pmcARRIER@aol.com).

Acknowledgements

The ANRS CO13 HEPATHVH cohort and the nested cross-sectional survey presented here were sponsored and funded by ANRS Emerging Infectious Diseases. Our thanks to all the members of the ANRS-CO13-HEPAVH study group, the physicians and nurses involved in the cohort follow-up, and the patients who participated in the present survey. We also thank Jude Sweeney (Milan, Italy) for the English revision and copy-editing of the manuscript.

The ANRS CO13 HEPATHVH Study Group:

Scientific Committee: D.Salmon (co-Principal investigator), L.Wittkop (co-Principal Investigator & Methodologist), P.Sogni (co-Principal Investigator), L. Esterle (project manager), P.Trimoulet, J.Lzopet, L.Serfaty, V.Paradis, B.Spire, P.Carrieri, M.A.Valantin, G.Pialoux, J.Chas, O.Zaegel-Faucher, K.Barange, A.Naqvi, E.Rosenthal, A.Bicart-See, O.Bouchaud, A.Gervais, C.Lascoux-Combe, C.Goujard, K.Lacombe, C.Duvivier, D.Neau, P.Morlat, F.Bani-Sadr, L.Meyer, F.Boufassa, B.Autran, A.M.Roque, C.Solas, H.Fontaine, D.Costagliola, L.Piroth, A.Simon, D.Zucman, F.Boué, P.Miaillhes, E.Billaud, H.Aumaître, D.Rey, G.Peytavin, V.Petrov-Sanchez, A. Levier.

Clinical Centers (ward: participating physicians): APHP, Hôpitaux Universitaires Paris Centre, Paris (Médecine Interne et Maladies Infectieuses: D. Salmon, R.Usubillaga; Hépatogastro-entérologie: P.Sogni; Anatomopathologie: B.Terris; Virologie: P.Tremeaux); APHP Pitié-Salpêtrière, Paris (Maladies Infectieuses et Tropicales: C.Katlama, M.A.Valantin, H.Stitou; Médecine Interne: A.Simon, P.Cacoub, S.Nafissa; Hépatogastro-entérologie: Y.Benhamou; Anatomopathologie: F.Charlotte; Virologie: S.Fourati); AP-HM Sainte-Marguerite, Marseille (Service d'Immunologie-Hématologie Clinique: I.Poizot-Martin, O.Zaegel, H.Laroche; Virologie: C.Tamalet); APHP Tenon, Paris (Maladies Infectieuses et Tropicales: G.Pialoux, J.Chas; Anatomopathologie: P.Callard, F.Bendjaballah; Virologie: C.Amiel, C.Le Pendeven); CHU Purpan, Toulouse (Maladies Infectieuses et Tropicales: B. Marchou; Médecine interne: L.Alrice; Hépatogastro-entérologie: K.Barange, S.Metivier; Anatomopathologie: J.Selves; Virologie: F.Larroquette); CHU Archet, Nice (Médecine Interne: E.Rosenthal; Infectiologie: A.Naqvi, V.Rio; Anatomopathologie: J.Haudebourg, M.C.Saint-Paul; Virologie: A. De Monte, V.Giordanengo, C.Partouche); APHP Avicenne, Bobigny (Médecine Interne-Unité VIH: O.Bouchaud; Anatomopathologie: A.Martin, M.Ziol; Virologie: Y.Baazia, V.Iwaka-Bande, A.Gerber); Hôpital Joseph Duguin, Toulouse (Médecine Interne: M.Uzan, A.Bicart-See, D.Garipuy, M.J.Ferro-Collados; Anatomopathologie: J.Selves; Virologie: F.Nicot); APHP Bichat-Claude-Bernard, Paris (Maladies Infectieuses: A.Gervais, Y.Yazdanpanah; Anatomopathologie: H.Adle-Biasette; Virologie: G.Alexandre, Pharmacologie: G.Peytavin); APHP Saint-Louis, Paris (Maladies infectieuses: C.Lascoux-Combe, J.M.Molina; Anatomopathologie: P.Bertheau; Virologie:

M.L.Chaix, C. Delauger, S. Maylin); APHP Saint-Antoine (Maladies Infectieuses et Tropicales: K. Lacombe, J. Bottero, J. Krause, P.M. Girard, Anatomopathologie: D. Wendum, P. Cervera, J. Adam; Virologie: C. Viala); APHP, Hôpitaux Paris Sud, Bicêtre, Paris (Maladies Infectieuses et Tropicales: D. Vittecoq; Médecine Interne: C. Goujard, Y. Quertainmont, E. Teicher; Virologie: C. Pallier); APHP Necker, Paris (Maladies Infectieuses et Tropicales: O. Lortholary, C. Duvivier, C. Rouzaud, J. Lourenco, F. Touam, C. Louisin; Virologie: V. Avettand-Fenoel, E. Gardienet, A. Mélard); CHU Bordeaux Hôpital Pellegrin, Bordeaux (Maladies Infectieuses et Tropicales: D. Neau, A. Ochoa, E. Blanchard, S. Castet-Lafarie, C. Cazanave, D. Malvy, M. Dupon, H. Dutronc, F. Dauchy, L. Lacaze-Buzy, A. Desclaux; Anatomopathologie: P. Bioulac-Sage; Virologie: P. Trimoulet, S. Reigadas); CHU Bordeaux Hôpital Saint-André, Bordeaux (Médecine Interne et Maladies Infectieuses: P. Morlat, D. Lacoste, F. Bonnet, N. Bernard, M. Hessemfar, J. F. Paccalin, C. Martell, M. C. Pertusa, M. Vandenhende, P. Mercié, D. Malvy, T. Pistone, M.C. Receveur, M. Méchain, P. Duffau, C. Rivoisy, I. Faure, S. Caldato; Anatomopathologie: P. Bioulac-Sage; Virologie: P. Trimoulet, S. Reigadas, P. Bellocave, C. Tumiotto); CHU Bordeaux Hôpital du Haut-Levêque, Bordeaux (Médecine Interne: J.L. Pellegrin, J.F. Viillard, E. Lazzaro, C. Greib; Anatomopathologie: P. Bioulac-Sage; Virologie: P. Trimoulet, S. Reigadas); Hôpital FOCH, Suresnes (Médecine Interne: D. Zucman, C. Majerholc; Virologie: M. Brollo, E. Farfour); APHP Antoine Bécélère, Clamart (Médecine Interne: F. Boué, J. Polo Devoto, I. Kansau, V. Chambrin, C. Pignon, L. Berrouche, R. Fior, V. Martinez, S. Abgrall, M. Favier; Virologie: C. Deback); CHU Henri Mondor, Créteil (Immunologie Clinique: Y. Lévy, S. Dominguez, J.D. Lelièvre, A.S. Lascaux, G. Melica); CHU Nantes Hôpital Hôtel Dieu, Nantes (Maladies Infectieuses et Tropicales: E. Billaud, F. Raffi, C. Allavena, V. Reliquet, D. Boutoille, C. Biron; M. Lefebvre, N. Hall, S. Bouche; Virologie: A. Rodallec, L. Le Guen, C. Hemon); Hôpital de la Croix Rousse, Lyon (Maladies Infectieuses et Tropicales: P. Miaillhes, D. Peyramond, C. Chidiac, F. Ader, F. Biron, A. Boibieux, L. Cotte, T. Ferry, T. Perpoint, J. Koffi, F. Zoulim, F. Bailly, P. Lack, M. Maynard, S. Radenne, M. Amiri, F. Valour; Hépatogastro-entérologie: J. Koffi, F. Zoulim, F. Bailly, P. Lack, M. Maynard, S. Radenne, C. Augustin-Normand; Virologie: C. Scholtes, T.T. Le-Thi); CHU Dijon, Dijon (Département d'infectiologie: L. Piroth, P. Chavanet, M. Duong Van Huyen, M. Buisson, A. Waldner-Combernoux, S. Mahy, A. Salmon Rousseau, C. Martins); CH Perpignan, Perpignan (Maladies infectieuses et tropicales: H. Aumaître, Virologie: S. Galim); CHU Robert Debré, Reims (Médecine interne, maladies infectieuses et immunologie clinique: F. Bani-Sadr, D. Lambert, Y. Nguyen, J.L. Berger, M. Hentzien, Virologie: V. Brodard); CHRU Strasbourg (Le Trait d'Union: D. Rey, M. Partisani, M.L. Batard, C. Che-neau, M. Priester, C. Bernard-Henry, E. de Mautort, P. Fischer, Virologie: P. Gantner et S. Fafi-Kremer).

Data collection: F.Roustant, P. Platterier, I. Kmiec, L. Traore, S. Lepuil, S. Parlier, V. Sicart-Payssan, E. Bedel, S. Anriamiandrisoa, C. Pomes, F. Touam, C. Louisin, M. Mole, C. Bolliot, P. Catalan, M. Mebarki, A. Adda-Lievain, P. Thilbaut, Y. Ousidhoum, F.Z. Makhoukhi, O. Braik, R. Bayoud, C. Gatey, M.P. Pietri, V. Le Baut, R. Ben Rayana, D. Bornarel, C. Chesnel, D. Beniken, M. Pauchard, S. Akel, S. Caldato, C. Lions, A. Ivanova, A-S. Ritleg, C. Debreux, L. Chalal, J.Zelie, H. Hue, A. Soria, M. Cavellec, S. Breau, A. Joulie, P. Fisher, S. Gohier, D. Croisier-Bertin, S. Ogoudjobi, C. Brochier, V. Thoirain-Galvan, M. Le Cam.

Management, statistical analyses: P. Carrieri, M. Chalouni, V. Conte, L. Dequae-Merchadou, M. Desvallées, L. Esterle, C. Gilbert, S. Gillet, Q. Guillochon, C. Khan, R. Knight, F. Marcellin, L. Michel, M. Mora, C. Protopopescu, P. Roux, B. Spire, T. Barré, C. Ramier, A. Sow, C. Lions, V. Di Beo, M. Bureau, L. Wittkop.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2022.100614>.

References

- [1] Remien RH, Stirratt MJ, Nguyen N, Robbins RN, Pala AN, Mellins CA. Mental health and HIV/AIDS: the need for an integrated response. *AIDS Lond Engl* 2019;33(9):1411–1420.
- [2] Adinolfi LE, Nevala R, Rinaldi L, Romano C, Giordano M. Chronic hepatitis C virus infection and depression. *Clin Liver Dis* 2017;21(3):517–534.
- [3] Fialho R, Pereira M, Rusted J, Whale R. Depression in HIV and HCV co-infected patients: a systematic review and meta-analysis. *Psychol Health Med* 2017;22(9):1089–1104.

- [4] Kaur H, Dhiman RK, Kulkarni AV, Premkumar M, Singh V, Duseja AK, et al. Improvement of chronic HCV infection-related depression, anxiety, and neurocognitive performance in persons achieving SVR-12: a real-world cohort study. *J Viral Hepat* 2022;29(5):395–406.
- [5] Pericot-Valverde I, Heo M, Niu J, Norton BL, Akiyama MJ, Agyemang L, et al. Declines in depressive symptoms among people who inject drugs treated with direct-acting antivirals while on opioid agonist therapy. *Open Forum Infect Dis* oct 2020;7(10):ofaa380.
- [6] Léon C, Chan Chee C, du Roscoät E, le groupe Baromètre, santé. 2017. La dépression en France chez les 18-75 ans: résultats du Baromètre santé 2017 [in French] *Bull Epidemiol Hebd* 2018;32–33:637–644; http://invs.santepubliquefrance.fr/beh/2018/32-33/2018_32-33_1.html.
- [7] Pfefferbaum A, Zahr NM, Sassoos SA, Kwon D, Pohl KM, Sullivan EV. Accelerated and premature aging characterizing regional cortical volume loss in human immunodeficiency virus infection: contributions from alcohol, substance use, and hepatitis C coinfection. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2018;3(10):844–859.
- [8] De Francesco D, Wit FW, Bürkle A, Oehlke S, Kootstra NA, Winston A, et al. Do people living with HIV experience greater age advancement than their HIV-negative counterparts? *AIDS Lond Engl* 01 2019;33(2):259–268.
- [9] Marcellin F, Di Beo V, Esterle L, Abgrall S, Pialoux G, Barré T, et al. Post-HCV cure self-reported changes in physical activity, eating behaviours, and fatigue in people living with HIV (ANRS CO13 HEPAVIH). *J Viral Hepat* nov 2021;28(11):1665–1667.
- [10] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* sept 2001;16(9):606–613.
- [11] Edwards M, Quinlivan EB, Bess K, Gaynes BN, Heine A, Zinski A, et al. Implementation of PHQ-9 depression screening for HIV-infected patients in a real-world setting. *J Assoc Nurses AIDS Care JANAC* juin 2014;25(3):243–252.
- [12] Bush K, Kivlahan DR, McDonnell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med* 1998;158(16):1789–1795.
- [13] Barré T, Mercié P, Lions C, Mialhes P, Zucman D, Aumaître H, et al. HCV cure: an appropriate moment to reduce cannabis use in people living with HIV? (ANRS CO13 HEPAVIH data). *AIDS Res Ther* 15 mars 2022;19(1):15.
- [14] Arias-de la Torre J, Vilagut G, Ronaldson A, Serrano-Blanco A, Martín V, Peters M, et al. Prevalence and variability of current depressive disorder in 27 European countries: a population-based study. *Lancet Public Health* oct 2021;6(10):e729–38.
- [15] Michel L, Lions C, Winnock M, Lang JP, Loko MA, Rosenthal E, et al. Psychiatric and substance use disorders in HIV/hepatitis C virus (HCV)-coinfected patients: does HCV clearance matter? [Agence Nationale de Recherche sur le SIDA et les Hépatites Virales (ANRS) HEPAVIH CO13 cohort]. *HIV Med* nov 2016;17(10):758–765.
- [16] Shi P, Yang A, Zhao Q, Chen Z, Ren X, Dai Q. A hypothesis of gender differences in self-reporting symptom of depression: implications to solve under-diagnosis and under-treatment of depression in males. *Front Psychiatry* 2021;12:589687.
- [17] Labaka A, Goñi-Balentiaga O, Lebeña A, Pérez-Tejada J. Biological sex differences in depression: a systematic review. *Biol Res Nurs* juill 2018;20(4):383–392.
- [18] Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: meta-analyses of diagnoses and symptoms. *Psychol Bull* août 2017;143(8):783–822.
- [19] Knight R, Roux P, Vilotitch A, Marcellin F, Rosenthal E, Esterle L, et al. Significant reductions in alcohol use after hepatitis C treatment: results from the ANRS CO13-HEPAVICH cohort. *Addict Abingdon Engl* sept 2017;112(9):1669–1679.
- [20] Kim HP, Edwards A, Reeve BB, Golin CE, Evon DM. Symptoms and functioning improve after chronic hepatitis C cure as assessed by the memorial symptom assessment scale and PROMIS measures. *J Viral Hepat* 29 Juin 2021.
- [21] Evon DM, Sarkar S, Amador J, Lok AS, Sterling RK, Stewart PW, et al. Patient-reported symptoms during and after direct-acting antiviral therapies for chronic hepatitis C: the PROP UP study. *J Hepatol* sept 2019;71(3):486–497.
- [22] Zhang H, Wang S, Wang L, Yi X, Jia X, Jia C. Comparison of the geriatric depression scale-15 and the patient health questionnaire-9 for screening depression in older adults. *Geriatr Gerontol Int* févr 2020;20(2):138–143.