

# Predictors of Poor Mental and Physical Health Status Among Patients With Chronic Hepatitis C Infection: The Chronic Hepatitis Cohort Study (CHeCS)

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**Our objective was to assess the extent and risk factors for depression and poor physical health among patients with chronic hepatitis C virus (HCV) infection. We surveyed HCV-infected patients seen at four large healthcare systems participating in the Chronic Hepatitis Cohort Study (CHeCS). Survey data included demographics, depression and physical health measures, substance use history, current social support, recent stressor exposures, and, from the electronic medical record, treatment history, and Charlson Comorbidity Index scores. There were 4,781 respondents, who were a mean of 56.7 years old, 71% White, and 57% male. Altogether, 51.4% reported past injection drug use, 33.9% were current smokers, and 17.7% had abused alcohol in the previous year. Additionally, 47.4% had been previously treated for HCV and 14.8% had a 12-week sustained viral response (SVR) following HCV therapy. Overall, 29.7% of patients met criteria for current depression and 24.6% were in poor physical health. In multivariate analyses, significant predictors of depression and poor health included: male gender (versus female, odds ratios [ORs], 0.70 and 0.81), Black race (versus white, ORs, 0.60 and 0.61), having education less than high school (versus college, ORs, 1.81 and 1.54), being employed (versus not, ORs, 0.36 and 0.25), having high life stressors (versus low, ORs, 2.44 and 1.64), having low social support (versus high, ORs = 2.78 and 1.40), and having high Charlson scores (versus none, ORs = 1.58 and 2.12). Achieving a 12-week SVR was found to be protective for depression. **Conclusion:** This large survey of U.S. HCV patients indicates the extent of adverse health behaviors and mental and physical comorbidities among these patients. (HEPATOLOGY 2014;00:000-000)**

Currently, an estimated 2.7 million persons in the United States have chronic hepatitis C virus (HCV) infection.<sup>1</sup> Despite its prevalence, more needs to be learned about the spectrum of disease, access to care, effectiveness of therapies, and the quality of life for persons living with HCV infection.

To assess the impact of chronic hepatitis infection, the Chronic Hepatitis Cohort Study (CHeCS) is being carried out to assess the burden of care, modes of transmission, effectiveness of hepatitis screening, barriers to care, and appropriate treatments and their impact on mortality, morbidity, and the quality of

*Abbreviations:* CHeCS, Chronic Hepatitis Cohort Study; EHRs, electronic health records; HCV, hepatitis C virus; IDU, injection drug use; SVR, sustained viral response.

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**Ethical Considerations:** The investigation followed the guidelines of the U.S. Department of Health and Human Services regarding protection of human subjects. The study protocol was approved and renewed annually by each participating institution's Institutional Review Board. A version of this article was presented at the HMO Research Network National Conference, Phoenix, AZ, April 2014.

life.<sup>2,3</sup> As part of CHeCS, surveys were conducted among all chronic hepatitis C patients known to be alive at the time of the survey.<sup>4</sup> The purpose of the survey was to assess hepatitis risk factors, treatment exposures, additional demographic variables, and key psychosocial measures in the course and outcome of chronic hepatitis disease, data important for public health and medical management of HCV disease.

The focus of the current study is to assess the quality of life of patients with chronic hepatitis C infection, especially the prevalence of current depression and poor health status as these relate to HCV treatment history and the course of disease,<sup>5-9</sup> in the largest sample of U.S. patients to date. This research was guided, in part, by a psychosocial-stressor model used in previous investigations.<sup>10,11</sup> This conceptualization supposes that exposure to environmental stressors and/or the availability of psychosocial resources impact health outcomes.<sup>12-15</sup>

## Materials and Methods

The CHeCS study methods have been previously described in detailed elsewhere.<sup>2,3</sup> Briefly, the cohort was created based on electronic health records (EHRs) of patients 18 years or older who had healthcare services provided between January 1, 2006 and December 31, 2010 at one of four sites: Geisinger Health System, Danville, PA; Henry Ford Health System, Detroit MI (data coordinating center); Kaiser Permanente-Northwest, Portland, OR; and Kaiser Permanente-Hawaii, Honolulu, HI. The electronic data collected included patient demographic information, medical encounter data, laboratory results, diagnosis and procedure data, and liver biopsy results. Electronic data used in this analysis were available retrospectively to January 1997 from the Detroit and Portland sites, to January 1998 from the Hawaii site, and to January 2001 from the Danville site.<sup>2,3</sup>

Patients meeting laboratory and diagnosis criteria for chronic hepatitis C were included in the cohort and were eligible for the survey, if they were known to be alive at the time of the survey (2011-2012). The CHeCS survey was designed to collect data on patient demo-

graphics, reported hepatitis risk factors, comorbidities, physical and mental functioning, use of alcohol and other psychoactive substances, treatment for alcohol and drug abuse, and on chronic hepatitis treatment history.

**Cohort Selection.** Algorithms for inclusion in the chronic hepatitis cohorts were developed and applied to the EHR data of patients aged 18 years or older from all sites with any healthcare utilization between January 1, 2006 and December 31, 2010.<sup>2,3</sup> Complete observation time for each patient was determined to be time from first evidence of hepatitis infection in the EHR including retrospective data prior to January 1, 2006, until either the last health system encounter or December 31, 2010. Patients were included in the hepatitis cohorts based on fulfillment of a combination of laboratory-based and ICD-9-based criteria discussed elsewhere.<sup>2,3</sup> Trained medical abstractors reviewed the EHRs to collect liver biopsy results, outside system laboratory reports, and detailed antiviral therapy data on all patients receiving treatment during 2001-2010. Electronic medical charts flagged by abstractors as missing evidence of chronic HCV infection were reviewed under the supervision of a hepatitis clinician using clinician-developed criteria. Cases for which chronic HCV infection had been ruled out were excluded from the study cohort.

**Survey Data Collection.** Altogether, we examined the records of 2,143,369 patients age  $\geq 18$  years in the four participating health systems that had one or more services provided between January 1, 2006 and December 31, 2010. Of these patients, 12,259 patients met the hepatitis C cohort inclusion criteria.<sup>2,3</sup> Median time under observation for patients in the HCV cohort was 4.3 years (range 0-18 years), for a total of 90,566 person-years of observation. Across all sites approximately three-quarters of the chronic hepatitis C patients were born between 1945 through 1964.<sup>2,3</sup> The payer status of patients varied by site, with the percentage of patients using only public insurance (Medicaid or Medicare only) ranging from 2.3% in Portland to 50.4% in Danville and the percentage of uninsured ranging from 3.9% in Danville to 10.0% in Detroit.

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Of the 12,259 patients who met the hepatitis C cohort inclusion criteria, 7,756 were known to be alive and not institutionalized and surveyed by mail and telephone during 2011-2012. Up to eight survey attempts were initiated in order to complete an interview with each patient. A small incentive was offered at each site to encourage survey response. Patients who were found to be deceased, incarcerated, in long-term care institutions, or who had invalid addresses or disconnected telephone numbers were excluded from the denominator. The survey was conducted in English only.

**Quality of Life Measures.** For the current study we included two quality of life measures—the PHQ-8 scale<sup>16,17</sup> and the SF-8 scale.<sup>18,19</sup> The PHQ-8 scale assesses current depression and has been clinically validated in population health research.<sup>16,17</sup> A PHQ-8 score of  $\geq 10$  has high sensitivity and specificity for both the presence of major depression and for the presence of any depressive disorders and was the clinical cutpoint used to define current depression.<sup>16</sup>

The SF-8 scale evolved from the Medical Outcome Study program, which originally included the Short-Form-36 (SF-36) instrument,<sup>20-22</sup> now widely used in clinical research.<sup>23,24</sup> The SF-8 is based on items related to physical and mental health status and has only eight items,<sup>24</sup> but these measures have the same metric as the SF-36 scale, whereby the average population mean for the SF-8 is designed to be 50, with a standard deviation of 10 for the U.S. population.<sup>24</sup> We used the current study population's 25th percentile as the cutoff score norm for the present study (i.e., means of 35.6 and 38.7, respectively, for physical and mental health). These score means for physical and mental health status are consistent with the 25th percentile norms for patients with advanced cancer or severe liver disease.<sup>23</sup> The SF scale results are typically reported in terms population benchmarks or norms.<sup>20-24</sup>

**Other Study Measures.** Other survey data included demographic information (age, race/ethnicity, marital status, education level, employment status, country of birth) and self-reported psychoactive substance use (cigarette smoking, history of heavy alcohol use, history of alcohol or drug abuse treatment, and history of injection of illicit drugs). The survey also collected data on current alcohol dependence using the AUDIT-C scale,<sup>25,26</sup> exposure to recent psychological stressors,<sup>13,27</sup> and level of social support.<sup>13,28</sup> In addition, the survey contained HCV-specific questions, including questions related to having visited a liver or hepatitis specialist, being prescribed hepatitis drugs, having stopped or changed hepatitis medication in the past 12 months, and use of hepatitis medications in the past

**Table 1. Profile of Hepatitis C Patients in the Chronic Hepatitis Cohort Study (N = 4,781)**

| Study Variable*                               | Total Sample<br>(N) Percent/Mean | (95% CI)    |
|---|----------------------------------|-------------|
| Male  | (2725) 57.0                      | (55.6-58.4) |
| Mean Age (in years)                           | (4781) 56.7                      | (56.2-57.2) |
| White Race                                    | (3395) 71.0                      | (69.7-72.3) |
| Married                                       | (2407) 50.4                      | (48.9-51.8) |
| College Graduate                              | (974) 20.4                       | (19.3-21.5) |
| Employed Full/Part-time/Occasionally          | (2181) 47.9                      | (46.5-49.4) |
| Private Insurance                             | (2922) 61.1                      | (59.7-62.5) |
| History of IDU                                | (2458) 51.4                      | (50.0-52.8) |
| Ever in Drug Abuse Treatment                  | (1557) 32.6                      | (31.3-33.9) |
| Ever in Alcohol Abuse Treatment               | (1479) 30.9                      | (29.6-32.3) |
| Current Alcohol Abuse/Dependence <sup>†</sup> | (839) 17.7                       | (16.6-18.8) |
| Ever Heavy Alcohol Use, 5+ Drinks/Day         | (1971) 41.2                      | (39.8-42.6) |
| Current Smoker                                | (1617) 33.9                      | (32.5-35.3) |
| Ever Treated for HCV                          | (2268) 47.4                      | (46.0-48.9) |
| Stopped HCV Meds Past 12 Months               | (711) 14.9                       | (13.9-15.9) |
| Currently on HCV Meds Past 4 Weeks            | (227) 4.7                        | (4.2-5.4)   |
| Liver Transplant                              | (285) 6.0                        | (5.3-6.7)   |
| SVR 12 Weeks                                  | (705) 14.8                       | (13.8-15.8) |
| HCV Genotype 1 <sup>‡</sup>                   | (2486) 84.2                      | (82.8-85.5) |
| Decompensated or ESLD                         | (258) 5.4                        | (4.8-6.1)   |
| High Charlson Score                           | (694) 14.5                       | (13.6-15.5) |
| PHQ-8 Depression Positive                     | (1409) 29.7                      | (28.4-31.0) |
| SF-8 Poor Physical Health                     | (1088) 24.6                      | (23.3-25.9) |

\*IDU, injection drug use; HCV, hepatitis C virus; SVR, sustained virologic response; ESLD, end stage liver disease; PHQ-8, Patient Health Questionnaire-8; SF-8, Short Form-8.

<sup>†</sup>Based on the AUDIT-C Scale.

<sup>‡</sup>Genotype based on n, 2,938, due to missing data.

4 weeks. Household income for survey respondents was geo-coded and based on recent U.S. Census data.<sup>29</sup> Patient data from the EHR also included gender, history of liver transplantation, the presence of decompensated or endstage liver disease, HCV genotype, use of pegylated interferon, use of ribavirin, and evidence of 12 or more week sustained viral response (SVR) following therapy. From the EHR, scores for the Charlson Comorbidity Index were also calculated.<sup>30-32</sup> Based on previous research, the Charlson Comorbidity Index was used to categorize patients into no score, low score, moderate score, or high score results.<sup>33</sup>

**Statistical Methods.** For population descriptive statistics, we used the exact binomial method to create 95% confidence intervals around study point estimates (Table 1). Logistic regression modeling was also used to assess individual risk factors associated with poor quality of life, including the presence of depression and/or poor physical or mental health status, controlling for other risk factors and confounders. The variables with  $P < 0.20$  in bivariate analyses were included as candidate measures in the initial multivariate models. Using forward stepwise selection, the final models retained only risk factors with  $P < 0.10$ . Statistical

analyses were conducted using Stata v. 13.1.<sup>34</sup> Because the PHQ-8 depression scale was highly correlated with SF-8 mental health component scale ( $r = 0.80$ ) and both these scales assess depression, the SF-8 mental health results are not presented in the current study, but are available upon request. All logistic regression models shown were adjusted for the four study sites.

**Ethical Conduct and Funding of Study.** The study was funded by donations from pharmaceutical companies to the CDC Foundation; granting corporations did not have access to CHeCS data and did not contribute to data analysis or writing of articles. The study protocol was reviewed by an Institutional Review Board and approved by the Office for Human Research Protections at each participating study site.

## Results

Overall, 4,781 surveys were completed, representing ~60% of those surveyed. Altogether, 156 of these 4,781 respondents (~3%) were hepatitis B virus (HBV) or human immunodeficiency virus (HIV) coinfecting. Comparison of survey respondents to nonrespondents indicated that survey respondents tended to be female, white, older, privately insured, and to have had HCV treatments ( $P < 0.001$ ). The survey respondents were mainly male (57%), a mean age of 56.7 years old, were mostly White (71%), and often married (50.4%) (Table 1). In addition, 20.4% were college graduates, 47.9% were employed full-time or part-time, 61.1% were privately insured, 51.4% had a history of injection drug use (IDU), and substantial proportions were current cigarette smokers (33.9%) (Table 1). While 7.2% reported drinking alcohol 4+ times per week, per AUDIT-C scale, 17.7% were classified as current alcohol abusers. Many (47.4%) had a history of treatment for HCV, and 14.8% had a 12-week SVR to treatment. A total of 29.7% of patients were depressed on the PHQ-8 scale and, by study design, 24.6% were classified as having poor physical health on the SF-8 scale (Table 1).

In bivariate analyses, current depression was strongly statistically associated with many demographic, social, and medical status variables (Table 2): with history of IDU; alcohol rehabilitation; drug abuse treatment; being a current smoker; and with not having private healthcare insurance. Depression was also associated with exposure to stressful life events in the past year, having lower social support in the past year, currently receiving HCV treatment, and higher scores on the Charlson Comorbidity Index. Finally, those achieving 12-week SVR from previous HCV therapy (i.e., cured) were significantly less likely to be depressed (Table 2).

In multivariate logistic regression analysis, the strongest predictors of current depression ( $P < 0.001$ ) were current employment status, moderate or high stressful life events, and low or moderate social support (Table 2). However, having achieved an SVR from antiviral therapy was protective against being depressed (odds ratio [OR] = 0.72,  $P = 0.008$ ).

In bivariate analyses, poor physical health measured on the SF-8 scale was also significantly associated with a number of demographic and socioeconomic factors ( $P < 0.001$ ), including marital status, income, education, employment status, and health insurance status (Table 3). Poor physical health was also significantly associated with exposure to stressful life events, social support level, having seen a hepatologist, having a liver transplant, and Charlson Comorbidity score. Patients with decompensated or endstage liver disease more often had poor physical health, but patients who took antiviral drugs, either pegylated interferon or ribavirin in the past, more often reported better physical health. Finally, in the bivariate analyses, having achieved sustained virologic response from previous anti-HCV therapy was also associated with better physical health (Table 3).

In general, multivariate analysis confirmed the significant statistical associations seen in the bivariate analysis (Table 3); namely, non-White race was protective, having lower income was a risk factor, being employed was protective, and that having higher stressful life events and lower social support were risk factors for poor health. Additionally, not having private health insurance was associated with poor health and having received care from a hepatologist was protective against poor health (Table 3). However, in multivariate analyses, having achieved SVR from anti-HCV therapy was not associated with better physical health.

## Discussion

To our knowledge, this study represents one of the largest surveys of diagnosed chronic hepatitis C patients in the United States and provides insights into their mental and physical health and their comorbidities. As might be expected, both depression and physical health were positively associated with unemployment, higher stressful events, lower social support, and higher Charlson Comorbidity scores. Achieving SVR from therapy was protective against depression, and achieving SVR was associated with better physical health in bivariate analyses, but otherwise HCV treatment did not generally affect current mental or physical health status in multivariate analysis, once other covariates were



**Table 2. PHQ-8 Depression Results by Key Study Variables (N = 4,742-4,451)**

| Study Variable*                  | No Depression (N)<br>Percent | Depression (N)<br>Percent | Depression: Bivariate<br>OR (95% CI) | Depression: Multivariate <sup>†</sup><br>OR (95% CI) |
|----------------------------------|------------------------------|---------------------------|--------------------------------------|--|
| Gender                           |                              |                           |                                      |  |
| Female                           | (1354) 66.4                  | (684) 33.6                | 1.00                                 | 1.00   |
| Male                             | (1979) 73.2                  | (725) 26.8                | 0.73 (0.64-0.82) <sup>¶</sup>        | 0.70 (0.59-0.82) <sup>¶</sup>                        |
| Age                              |                              |                           |                                      |  |
| 20-44                            | (303) 61.0                   | (194) 39.0                | 2.41 (1.86-3.12) <sup>¶</sup>        | 2.27 (1.55-3.31) <sup>¶</sup>                        |
| 45-54                            | (689) 64.0                   | (388) 36.0                | 2.12 (1.69-2.65) <sup>¶</sup>        | 2.61 (1.91-3.56) <sup>¶</sup>                        |
| 55-64                            | (1809) 72.5                  | (686) 27.5                | 1.43 (1.16-1.75) <sup>§</sup>        | 2.02 (1.53-2.67) <sup>¶</sup>                        |
| 65+                              | (530) 79.0                   | (141) 21.0                | 1.00                                 | 1.00   |
| Race                             |                              |                           |                                      |  |
| White                            | (2331) 69.0                  | (1047) 31.0               | 1.00                                 | 1.00   |
| Black                            | (694) 73.4                   | (251) 26.6                | 0.81 (0.69-0.95) <sup>§</sup>        | 0.60 (0.47-0.76) <sup>¶</sup>                        |
| Asian/PI                         | (176) 78.9                   | (47) 21.1                 | 0.60 (0.43-0.83) <sup>§</sup>        | 0.75 (0.48-1.17)                                     |
| Other/Unknown                    | (132) 67.3                   | (64) 32.7                 | 1.08 (0.79-1.47)                     | 0.83 (0.57-1.21)                                     |
| Hispanic                         |                              |                           |                                      |  |
| No                               | (3182) 70.3                  | (1342) 29.7               | 1.00                                 | —  |
| Yes                              | (151) 69.3                   | (67) 30.7                 | 1.05 (0.78-1.41)                     | —  |
| Born in USA                      |                              |                           |                                      |  |
| No                               | (254) 76.7                   | (77) 23.3                 | 1.00                                 | —  |
| Yes                              | (3079) 69.8                  | (1332) 30.2               | 1.43(1.10-1.86) <sup>§</sup>         | —  |
| Married                          |                              |                           |                                      |  |
| No                               | (1516) 64.5                  | (833) 35.5                | 1.00                                 | —  |
| Yes                              | (1817) 75.9                  | (576) 24.1                | 0.58 (0.51-0.65) <sup>¶</sup>        | —  |
| Income                           |                              |                           |                                      |  |
| Less than \$30K                  | (565) 64.4                   | (312) 35.6                | 1.79 (1.49-2.14) <sup>¶</sup>        | —  |
| \$30-49K                         | (1536) 68.2                  | (717) 31.8                | 1.51(1.31-1.75) <sup>¶</sup>         | —  |
| \$50K or more                    | (1185) 76.4                  | (366) 23.6                | 1.00                                 | —  |
| Education                        |                              |                           |                                      |  |
| Less than HS                     | (303) 58.3                   | (217) 41.7                | 2.79 (2.21-3.52) <sup>¶</sup>        | 1.81 (1.36-2.41) <sup>¶</sup>                        |
| HS/GED                           | (794) 65.5                   | (419) 34.5                | 2.06 (1.69-2.50) <sup>¶</sup>        | 1.57 (1.25-1.98) <sup>¶</sup>                        |
| Some College                     | (1140) 73.5                  | (412) 26.5                | 1.41 (1.16-1.71) <sup>¶</sup>        | 1.19 (0.95-1.49)                                     |
| College Grad or higher           | (775) 79.6                   | (199) 20.4                | 1.00                                 | 1.00   |
| Employment                       |                              |                           |                                      |  |
| Full-time/part-time/occasionally | (1787) 82.2                  | (388) 17.8                | 0.33 (0.29-0.38) <sup>¶</sup>        | 0.36 (0.30-0.44) <sup>¶</sup>                        |
| Unemployed/retired/disabled      | (1419) 60.3                  | (934) 39.7                | 1.00                                 | 1.00   |
| Health Insurance                 |                              |                           |                                      |  |
| Private                          | (2213) 76.2                  | (690) 23.8                | 1.00                                 | 1.00   |
| Medicaid                         | (225) 47.2                   | (252) 52.8                | 3.59 (2.94-4.38) <sup>¶</sup>        | 1.57 (1.19-2.06) <sup>§</sup>                        |
| Medicare                         | (790) 67.1                   | (387) 32.9                | 1.57 (1.35-1.82) <sup>¶</sup>        | 1.17 (0.93-1.47)                                     |
| None reported                    | (105) 56.8                   | (80) 43.2                 | 2.44 (1.81-3.31) <sup>¶</sup>        | 1.47 (1.00-2.17) <sup>‡</sup>                        |
| History of IDU                   |                              |                           |                                      |  |
| No                               | (1673) 72.9                  | (622) 27.1                | 1.00                                 | —  |
| Yes                              | (1660) 67.8                  | (787) 32.2                | 1.28 (1.23-1.45) <sup>¶</sup>        | —  |
| Ever Alcohol Treatment           |                              |                           |                                      |  |
| No                               | (2397) 73.2                  | (878) 26.8                | 1.00                                 | —  |
| Yes                              | (936) 63.8                   | (531) 36.2                | 1.55 (1.36-1.77) <sup>¶</sup>        | —  |
| Ever Drug Treatment              |                              |                           |                                      |  |
| No                               | (2378) 74.5                  | (815) 25.5                | 1.00                                 | 1.00   |
| Yes                              | (955) 61.7                   | (594) 38.3                | 1.82 (1.59-2.07) <sup>¶</sup>        | 1.51 (1.27-1.80) <sup>¶</sup>                        |
| Current Smoker                   |                              |                           |                                      |  |
| No                               | (2371) 75.6                  | (764) 24.4                | 1.00                                 | 1.00   |
| Yes                              | (962) 59.9                   | (645) 40.1                | 2.08 (1.83-2.37) <sup>¶</sup>        | 1.26 (1.06-1.50) <sup>‡</sup>                        |
| Current Alcohol Abuse/Depend.    |                              |                           |                                      |  |
| No                               | (2764) 71.2                  | (1119) 28.8               | 1.00                                 | —  |
| Yes                              | (555) 66.5                   | (280) 33.5                | 1.25 (1.06-1.46) <sup>§</sup>        | —  |
| Life Stressors - past year       |                              |                           |                                      |  |
| Low                              | (2101) 77.6                  | (608) 22.4                | 1.00                                 | 1.00   |
| Moderate                         | (872) 66.6                   | (438) 33.4                | 1.74 (1.50-2.01) <sup>¶</sup>        | 1.48 (1.24-1.77) <sup>¶</sup>                        |
| High                             | (360) 49.8                   | (363) 50.2                | 3.48 (2.94-4.14) <sup>¶</sup>        | 2.44 (1.96-3.03) <sup>¶</sup>                        |
| Social Support - past year       |                              |                           |                                      |  |
| Low                              | (600) 55.4                   | (483) 44.6                | 3.34 (2.82-3.96) <sup>¶</sup>        | 2.78 (2.27-3.40) <sup>¶</sup>                        |
| Moderate                         | (1124) 68.3                  | (521) 31.7                | 1.92 (1.64-2.25) <sup>¶</sup>        | 1.68 (1.39-2.02) <sup>¶</sup>                        |
| High                             | (1403) 80.6                  | (338) 19.4                | 1.00                                 | 1.00   |

Table 2. Continued

| Study Variable*                     | No Depression (N)<br>Percent | Depression (N)<br>Percent | Depression: Bivariate<br>OR (95% CI) | Depression: Multivariate†<br>OR (95% CI) |
|-------------------------------------|------------------------------|---------------------------|--------------------------------------|--|
| HCV Treatment Naive                 |                              |                           |                                      |  |
| No                                  | (1613) 71.5                  | (643) 28.5                | 1.00                                 | —  |
| Yes                                 | (1720) 69.2                  | (766) 30.8                | 1.12(0.99-1.27)                      | —  |
| Currently on HCV meds past 4 wks    |                              |                           |                                      |  |
| No                                  | (3190) 70.6                  | (1326) 29.4               | 1.00                                 | 1.00                                     |
| Yes                                 | (143) 63.3                   | (83) 36.7                 | 1.40 (1.06-1.84)‡                    | 1.58 (1.11-2.25)‡                        |
| Stopped HCV meds past 12 mos.       |                              |                           |                                      |  |
| No                                  | (2834) 70.2                  | (1201) 29.8               | 1.00                                 | 1.00                                     |
| Yes                                 | (499) 70.6                   | (208) 29.4                | 0.98 (0.83-1.17)                     | 0.82 (0.65-1.04)                         |
| Ever Visited Hepatologist           |                              |                           |                                      |  |
| No                                  | (574) 68.9                   | (259) 31.1                | 1.00                                 | —  |
| Yes                                 | (2759) 70.6                  | (1150) 29.4               | 0.92 (0.79-1.09)                     | —  |
| Ever Liver Transplant               |                              |                           |                                      |  |
| No                                  | (3137) 70.4                  | (1322) 29.6               | 1.00                                 | —  |
| Yes                                 | (196) 69.3                   | (87) 30.7                 | 1.05 (0.81-1.37)                     | —  |
| Charlson Score                      |                              |                           |                                      |  |
| No Disease Score                    | (1922) 73.3                  | (699) 26.7                | 1.00                                 | 1.00                                     |
| Low Score                           | (700) 68.0                   | (330) 32.0                | 1.30 (1.11-1.52)§                    | 1.30 (1.06-1.58)‡                        |
| Moderate Score                      | (286) 70.4                   | (120) 29.6                | 1.15 (0.92-1.45)                     | 1.25 (0.94-1.67)                         |
| High Score                          | (425) 62.0                   | (260) 38.0                | 1.68 (1.41-2.01)¶                    | 1.58 (1.24-2.00)¶                        |
| Decompensated or ESLD               |                              |                           |                                      |  |
| No                                  | (3164) 70.5                  | (1321) 29.5               | 1.00                                 | —  |
| Yes                                 | (169) 65.8                   | (88) 34.2                 | 1.24 (0.96-1.63)                     | —  |
| Ever used Ribavirin                 |                              |                           |                                      |  |
| No                                  | (1853) 69.2                  | (825) 30.8                | 1.00                                 | —  |
| Yes                                 | (1480) 71.7                  | (584) 28.3                | 0.89 (0.78-1.01)                     | —  |
| Ever used Pegylated interferon-alfa |                              |                           |                                      |  |
| No                                  | (1999) 69.6                  | (873) 30.4                | 1.00                                 | 1.00                                     |
| Yes                                 | (1334) 71.3                  | (536) 28.7                | 0.92 (0.81-1.05)                     | 1.21 (1.01-1.45)‡                        |
| Sustained 12 week Viral Response    |                              |                           |                                      |  |
| No                                  | (2786) 68.9                  | (1255) 31.1               | 1.00                                 | 1.00                                     |
| Yes                                 | (547) 78.0                   | (154) 22.0                | 0.63 (0.52-0.76)¶                    | 0.72 (0.56-0.92)§                        |

\*IDU, injection drug use; HCV, hepatitis C virus; SVR, sustained virologic response; ESLD, end stage liver disease; PHQ-8, Patient Health Questionnaire-8; Current alcohol abuse/dependence based on the AUDIT-C Scale; Depression defined as present for PHQ-8 score  $\geq 10$ .

†In multivariate analyses, forward stepwise regression used, with  $P < 0.10$  for inclusion,  $P < 0.10$  exclusion, with only variables  $P < 0.20$  included from bivariate analyses. Study site (KPNW, KPHI, HFHS,GHS) was forced entered at first step for multivariate analyses, otherwise only the variables shown in the multivariate column were included in the final model.

‡ $P < 0.05$

§ $P < 0.01$

¶ $P < 0.001$ .

controlled. A notable exception was that those currently reporting “any” HCV medication had a tendency to be depressed (Table 2, OR = 1.58,  $P = 0.011$ ), but this did not appear to be associated with taking interferon medications, since the latter was not associated with depression ( $\chi^2 = 0.018$ ,  $P = 0.84$ ). However, the latter association is likely confounded by the time lag between EHR data collection and survey self-report. Nevertheless, in total, these data reflect wide comorbidities in those with chronic hepatitis C. This survey also provides some data not previously reported for a large HCV-infected population, such as the high current rates of cigarette smoking and current alcohol abuse among these patients. Such substance use, especially as they affect disease progression and outcomes, need to be

incorporated in analyses of HCV patients’ morbidity and mortality.

Similar to what has been previously reported for HIV disease,<sup>35,36</sup> it was anticipated that quality of life status of patients with chronic HCV infection would be associated with sociodemographic factors, treatment history, and disease progression status.<sup>5-7,37</sup> Our assumption was that better understanding of the psychosocial impact of this disease, knowledge of patients’ psychosocial responses to treatment, and the use of psychological interventions would likely result in better patient outcomes over time.<sup>38-41</sup> Our study of depression and physical health in these patients was guided, in part, by a “psychosocial-stressor” model used in previous investigations.<sup>10,11</sup> This model suggests that

**Table 3. SF-8 Physical Health Results by Key Study Variables (N = 4,427-4,183)**

| Study Variable*                  | Not Poor Health (N)<br>Percent | Poor Health (N)<br>Percent | Poor Health: Bivariate<br>OR (95% CI) | Poor Health: Multivariate <sup>†</sup><br>OR (95% CI) |
|----------------------------------|--------------------------------|----------------------------|---------------------------------------|---|
| Gender                           |                                |                            |                                       |   |
| Female                           | (1390) 73.7                    | (495) 26.3                 | 1.00                                  | 1.00  |
| Male                             | (1949) 76.7                    | (593) 23.3                 | 0.85 (0.74-0.98) <sup>‡</sup>         | 0.81 (0.68-0.97) <sup>‡</sup>                         |
| Age                              |                                |                            |                                       |   |
| 20-44                            | (390) 82.8                     | (81) 17.2                  | 0.63 (0.47-0.85) <sup>§</sup>         | 1.01 (0.67-1.54)                                      |
| 45-54                            | (755) 74.8                     | (255) 25.2                 | 1.02 (0.81-1.29)                      | 2.09 (1.53-2.85) <sup>¶</sup>                         |
| 55-64                            | (1719) 74.3                    | (596) 25.7                 | 1.05 (0.86-1.29)                      | 2.12 (1.61-2.79) <sup>¶</sup>                         |
| 65+                              | (473) 75.2                     | (156) 24.8                 | 1.00                                  | 1.00  |
| Race                             |                                |                            |                                       |   |
| White                            | (2375) 75.0                    | (791) 25.0                 | 1.00                                  | 1.00  |
| Black                            | (661) 75.0                     | (220) 25.0                 | 0.99 (0.84-1.19)                      | 0.61 (0.49-0.83) <sup>§</sup>                         |
| Asian/PI                         | (176) 85.0                     | (31) 15.0                  | 0.53 (0.36-0.78) <sup>§</sup>         | 0.56 (0.33-0.93) <sup>‡</sup>                         |
| Other/Unknown                    | (127) 73.4                     | (46) 26.6                  | 1.09 (0.77-1.54)                      | 0.95 (0.63-1.45)                                      |
| Hispanic                         |                                |                            |                                       |   |
| No                               | (3190) 75.5                    | (1033) 24.5                | 1.00                                  | —   |
| Yes                              | (149) 73.0                     | (55) 27.0                  | 1.14 (0.83-1.57)                      | —   |
| Born in USA                      |                                |                            |                                       |   |
| No                               | (248) 80.0                     | (62) 20.0                  | 1.00                                  | —   |
| Yes                              | (3091) 75.1                    | (1026) 24.9                | 1.33 (0.99-1.77)                      | —   |
| Married                          |                                |                            |                                       |   |
| No                               | (1576) 72.5                    | (598) 27.5                 | 1.00                                  | —   |
| Yes                              | (1763) 78.3                    | (490) 21.7                 | 0.73 (0.64-0.84) <sup>¶</sup>         | —   |
| Income                           |                                |                            |                                       |   |
| Less than \$30K                  | (558) 70.4                     | (235) 29.6                 | 1.80 (1.47-2.20) <sup>¶</sup>         | 1.32 (1.01-1.74) <sup>‡</sup>                         |
| \$30-49K                         | (1545) 73.2                    | (567) 26.8                 | 1.57 (1.34-1.85) <sup>¶</sup>         | 1.27 (1.04-1.57) <sup>‡</sup>                         |
| \$50K or more                    | (1189) 81.0                    | (278) 19.0                 | 1.00                                  | 1.00  |
| Education                        |                                |                            |                                       |   |
| Less than HS                     | (304) 64.7                     | (166) 35.3                 | 2.27 (1.77-2.91) <sup>¶</sup>         | 1.54 (1.13-2.08) <sup>§</sup>                         |
| HS/GED                           | (858) 74.2                     | (298) 25.8                 | 1.44 (1.17-1.78) <sup>§</sup>         | 1.17 (0.91-1.50)                                      |
| Some College                     | (1142) 77.7                    | (327) 22.3                 | 1.19 (0.97-1.46)                      | 1.02 (0.80-1.29)                                      |
| College Grad or higher           | (743) 80.6                     | (179) 19.4                 | 1.00                                  | 1.00  |
| Employment                       |                                |                            |                                       |   |
| Full-time/part-time/occasionally | (1858) 89.5                    | (218) 10.5                 | 0.20 (0.17-0.24) <sup>¶</sup>         | 0.25 (0.20-0.31) <sup>¶</sup>                         |
| Unemployed/retired/disabled      | (1367) 63.2                    | (797) 36.8                 | 1.00                                  | 1.00  |
| Health Insurance                 |                                |                            |                                       |   |
| Private                          | (2239) 82.2                    | (484) 17.8                 | 1.00                                  | 1.00  |
| Medicaid                         | (282) 65.1                     | (151) 34.9                 | 2.48 (1.99-3.09) <sup>¶</sup>         | 1.56 (1.15-2.09) <sup>§</sup>                         |
| Medicare                         | (699) 63.7                     | (398) 36.3                 | 2.63 (2.25-3.08) <sup>¶</sup>         | 1.48 (1.17-1.86) <sup>§</sup>                         |
| None reported                    | (119) 68.4                     | (55) 31.6                  | 2.14 (1.53-2.99) <sup>¶</sup>         | 1.72 (1.13-2.62) <sup>‡</sup>                         |
| History of IDU                   |                                |                            |                                       |   |
| No                               | (1549) 72.2                    | (596) 27.8                 | 1.00                                  | 1.00  |
| Yes                              | (1790) 78.4                    | (492) 21.6                 | 0.71 (0.62-0.82) <sup>¶</sup>         | 0.63 (0.51-0.76) <sup>¶</sup>                         |
| Ever Alcohol treatment           |                                |                            |                                       |   |
| No                               | (2308) 75.5                    | (748) 24.5                 | 1.00                                  | —   |
| Yes                              | (1031) 75.2                    | (340) 24.8                 | 1.02 (0.88-1.18)                      | —   |
| Ever Drug treatment              |                                |                            |                                       |   |
| No                               | (2266) 75.5                    | (736) 24.5                 | 1.00                                  | 1.00  |
| Yes                              | (1073) 75.3                    | (352) 24.7                 | 1.01 (0.87-1.17)                      | 1.20 (0.97-1.48)                                      |
| Current Smoker                   |                                |                            |                                       |   |
| No                               | (2268) 77.2                    | (670) 22.8                 | 1.00                                  | —   |
| Yes                              | (1071) 71.9                    | (418) 28.1                 | 1.32 (1.15-1.52) <sup>¶</sup>         | —   |
| Current Alcohol Abuse/Depend.    |                                |                            |                                       |   |
| No                               | (2718) 75.1                    | (901) 24.9                 | 1.00                                  | —   |
| Yes                              | (607) 77.1                     | (180) 22.9                 | 0.90 (0.75-1.07)                      | —   |
| Life Stressors – past year       |                                |                            |                                       |   |
| Low                              | (2013) 79.0                    | (534) 21.0                 | 1.00                                  | 1.00  |
| Moderate                         | (903) 74.1                     | (316) 25.9                 | 1.32 (1.12-1.55) <sup>§</sup>         | 1.22 (1.00-1.48) <sup>‡</sup>                         |
| High                             | (423) 64.0                     | (238) 36.0                 | 2.12 (1.76-2.55) <sup>¶</sup>         | 1.64 (1.30-2.08) <sup>¶</sup>                         |
| Social Support – past year       |                                |                            |                                       |   |
| Low                              | (684) 68.5                     | (315) 31.5                 | 1.85 (1.55-2.22) <sup>¶</sup>         | 1.40 (1.12-1.75) <sup>§</sup>                         |
| Moderate                         | (1150) 74.6                    | (391) 25.4                 | 1.37 (1.16-1.62) <sup>¶</sup>         | 1.26 (1.03-1.54) <sup>‡</sup>                         |
| High                             | (1316) 80.1                    | (327) 19.9                 | 1.00                                  | 1.00  |

Table 3. Continued

| Study Variable*                     | Not Poor Health (N)<br>Percent | Poor Health (N)<br>Percent | Poor Health: Bivariate<br>OR (95% CI) | Poor Health: Multivariate†<br>OR (95% CI) |
|-------------------------------------|--------------------------------|----------------------------|---------------------------------------|---|
| HCV Treatment Naive                 |                                |                            |                                       |   |
| No                                  | (1611) 76.4                    | (498) 23.6                 | 1.00                                  | —   |
| Yes                                 | (1728) 74.5                    | (590) 25.5                 | 1.11 (0.96-1.27)                      | —   |
| Currently on HCV meds past 4 wks    |                                |                            |                                       |   |
| No                                  | (3195) 75.7                    | (1024) 24.3                | 1.00                                  | —   |
| Yes                                 | (144) 69.2                     | (64) 30.8                  | 1.39 (1.02-1.88)‡                     | —   |
| Stopped HCV meds - past 12 mos.     |                                |                            |                                       |   |
| No                                  | (2856) 75.8                    | (912) 24.2                 | 1.00                                  | —   |
| Yes                                 | (483) 73.3                     | (176) 26.7                 | 1.14 (0.95-1.38)                      | —   |
| Ever Visited Hepatologist           |                                |                            |                                       |   |
| No                                  | (545) 70.4                     | (229) 29.6                 | 1.00                                  | 1.00                                      |
| Yes                                 | (2794) 76.5                    | (859) 23.5                 | 0.73 (0.62-0.87)¶                     | 0.82 (0.66-1.02)                          |
| Ever Liver Transplant               |                                |                            |                                       |   |
| No                                  | (3158) 75.9                    | (1001) 24.1                | 1.00                                  | —   |
| Yes                                 | (181) 67.5                     | (87) 32.5                  | 1.52 (1.16-1.98)§                     | —   |
| Charlson Score                      |                                |                            |                                       |   |
| No Disease Score                    | (2005) 81.8                    | (445) 18.2                 | 1.00                                  | 1.00                                      |
| Low Score                           | (682) 71.6                     | (270) 28.4                 | 1.78 (1.50-2.12)¶                     | 1.64 (1.32-2.03)¶                         |
| Moderate Score                      | (269) 70.1                     | (115) 29.9                 | 1.93 (1.51-2.45)¶                     | 1.65 (1.23-2.22)§                         |
| High Score                          | (383) 59.8                     | (258) 40.2                 | 3.04 (2.51-3.66)¶                     | 2.12 (1.67-2.74)¶                         |
| Decompensated or ESLD               |                                |                            |                                       |   |
| No                                  | (3174) 75.9                    | (1007) 24.1                | 1.00                                  | —   |
| Yes                                 | (165) 67.1                     | (81) 32.9                  | 1.55 (1.18-2.04)§                     | —   |
| Ever used Ribavirin                 |                                |                            |                                       |   |
| No                                  | (1849) 74.0                    | (649) 26.0                 | 1.00                                  | —   |
| Yes                                 | (1490) 77.2                    | (439) 22.8                 | 0.84 (0.73-0.97)‡                     | —   |
| Ever used Pegylated interferon-alfa |                                |                            |                                       |   |
| No                                  | (1971) 73.7                    | (705) 26.3                 | 1.00                                  | —   |
| Yes                                 | (1368) 78.1                    | (383) 21.9                 | 0.78 (0.68-0.90)§                     | —   |
| Sustained 12 week Viral Response    |                                |                            |                                       |   |
| No                                  | (2812) 74.5                    | (964) 25.5                 | 1.00                                  | —   |
| Yes                                 | (527) 81.0                     | (124) 19.0                 | 0.69 (0.56-0.85)¶                     | —   |

\*IDU, injection drug use; HCV, hepatitis C virus; SVR, sustained virologic response; ESLD, end stage liver disease; SF-8, Short Form-8; Current alcohol abuse/dependence based on the AUDIT-C Scale; Low SF-8 Physical Health Score defined as the lowest quartile.

†In multivariate analyses, forward stepwise regression used, with  $P < 0.10$  for inclusion,  $P < 0.10$  exclusion, with only variables  $P < 0.20$  included from bivariate analyses. Study site (KPNW, KPHI, HFHS,GHS) was forced entered at first step for multivariate analyses, otherwise only the variables shown in the multivariate column were included in the final model.

‡ $P < 0.05$

§ $P < 0.01$

¶ $P < 0.001$ .

exposure to psychosocial stressors and/or the availability of psychosocial resources, including socioeconomic resources, are important and can significantly impact health outcomes.<sup>12-15</sup>

As was seen, 29.7% of HCV patients met criteria for current depression on the PHQ-8 scale and 24.6% are classified as having poor current physical health on the SF-8 scale. By comparison, in general population surveys, only about 9% have current depression using the PHQ-8 with a cutpoint  $\geq 10$ .<sup>16</sup> Similar findings are true for the SF-8 scale: The 25th percentile cutpoint used to define poor physical health in the current study population (i.e., T-score  $\leq 35.55$ ) is typically the population percentile score reported for advanced cancer patients and those with severe liver

disease.<sup>23</sup> The survey respondents studied mirrored the population of diagnosed HCV patients both in and out of care<sup>2</sup>: about half (51.4%) acknowledged previous IDU and about half are not currently employed (52.1%). It is also noteworthy that almost half of survey respondents had a history of HCV treatment (47.4%), 14.9% had stopped HCV treatments in the past 12 months, and 14.8% had experienced a 12-week SVR at some point, which is indicative of an HCV cure. Conversely, for those who did not generally achieve SVR, 5% have decompensated or endstage liver disease, and 6% have had a liver transplant.

Both having chronic HCV infection and initiating interferon-based therapy are known to be associated with depression.<sup>5,37</sup> Further, patients' functional health



status and work productivity have been recently reported to be more adversely affected by pegylated interferon treatments than interferon-free treatments.<sup>6,42</sup> However, achieving SVR was associated with improved emotional well-being—at least the absence of depression—in these patients. Conversely, there appeared to be little physical or mental health benefit for those who did not achieve SVR, for whatever reason, after starting antiviral therapy.

This study has some limitations. First, this study was mostly based on self-reported survey data and, thus, is subject to response biases. However, interview remains the only practical way to assess many of the elements examined in this survey of thousands of HCV patients, such as feelings of depression, stressful life events, social support, or substance misuse. Second, the survey response rate was only about 60%, after patients who were deceased, incarcerated, in long-term care institutions, or who had invalid addresses or disconnected telephone numbers were excluded from the study.<sup>4</sup> Still, those responding did not differ from the overall CHeCS cohort in demographic characteristics.<sup>2</sup> However, as noted, females, older persons, Whites, those with a history of HCV treatments, and those with private insurance were more likely to complete the survey. This response bias may have affected our study results. In addition, the majority of those with a history of HCV treatment (~70%), were more likely to have compensated cirrhosis versus being noncirrhotic. Third, the survey was conducted in English only, which likely excluded some minority ethnic groups. Fourth, this study was cross-sectional and, therefore, causal inference is limited. For example, the finding reported for SVR and depression may be due to the fact that those with lower levels of depression may be more likely to adhere to treatment and, thus, achieve SVR. Fifth, we included 156 patients (~3%) who were HBV or HIV coinfecting in our study and this may have biased our results, although we found little evidence of this in our analyses. Finally, the external validity of this study may be limited due to the fact that the research was restricted to four study sites in the U.S., although these were large and geographically and demographically diverse sites representing well over 2 million U.S. adults.

In conclusion, the impact of many behavioral, psychosocial, and treatment factors on functional mental and physical health status in chronic HCV patients is complex. We expect that even with the advent of interferon-free all-oral HCV treatments, psychosocial and socioeconomic factors will continue to be an important consideration in assessing patient outcomes, risks, and costs.<sup>41,43,44</sup>

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