

Online Only Supplemental Material

Table of Contents

Methods	2
Other Measures and study definitions.....	2
Linked Mortality.....	4
Results	5
Online-only Supplemental Figure 1. Trends in the Prevalence of Chronic Hepatitis C and Anti-Hepatitis C in the US Adult Population (NHANES 1999-2012)	5
Online-only Supplemental Table 1. Prevalence of Chronic Hepatitis C and Anti-Hepatitis C in the US Adult Population (NHANES 1999-2012)	6
Online-only Supplemental Table 2. Adjusted a prevalence estimates (95% CIs) of selected risk factors for Hepatitis C Infection in the US Adult Population (NHANES 1999-2012) by Chronic Hepatitis C Status	7
Online-only Supplemental Table 3. Adjusted ^a prevalence estimates (95% CIs) and odds ratios (95% CIs) of health-care related utilization and quality of life in the US Adult Population (NHANES 1999-2012) by Chronic Hepatitis C Virus Status.....	8
Online-only Supplemental Table 4. Characteristics of the population by Anti-HCV and HCV-RNA Status.....	9
Online-only Supplemental Table 5. Mortality rates (95% CI), median survival, and adjusted hazard ratios (95%CI) for all-cause mortality by chronic hepatitis C (CHC), diabetes, obesity and chronic kidney disease (CKD) status in the U.S. Adult Population (NHANES III 1988-1994 and NHANES 1999-2012) (follow-up to December 31, 2011).....	10
References.....	11

Methods

Other Measures and study definitions

NHANES participants answered standard questionnaires to obtain data on: sex, age, race/ethnicity (categorized as recommended by the CDC/NCHS as non-Hispanic white, non-Hispanic black, Mexican-American, or other (including Multi-Racial or other Hispanic), education, income, smoking, alcohol consumption, past blood transfusion, hospital utilization in the last 12 months, health insurance, access to care, and medical history. Health related quality of life (HRQOL) and disability were assessed using the CDC's Core HRQOL Module.(1) Information about sexual behavior and injection drug use was collected only in participants aged 20-59 years per NHANES protocol.

Standardized measurements of height, weight, waist circumference, and systolic and diastolic blood pressure were measured at the MEC. Body mass index (BMI) was calculated dividing weight in kilograms by height in meters squared.

Standard laboratory methods were used for the following serum biochemistries: albumin, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total cholesterol, high density lipoprotein cholesterol (HDL), creatinine and fasting triglycerides. Fasting low density lipoprotein cholesterol (LDL) was calculated using the Friedewald equation. Other laboratory tests included: fasting plasma glucose, complete blood count, and urinary albumin and creatinine from a random spot urine sample.

Serum specimens were tested for Hepatitis B surface antigen (HBsAg) (AUSZYME, Abbot Laboratories) and antibody to Hepatitis B core antigen (anti-HBc) (ORTHO HBc ELISA). Positive HBsAg were repeat-tested in duplicate. Specimens positive in either of the repeat tests were considered positive.

HIV-1/HIV-2 antibody status was assessed using the Synthetic Peptide Enzyme Immunoassay (EIA) (Genetic Systems HIV-1/HIV-2 Peptide EIA). Reactive specimens were retested in duplicate. Positive tests were then tested using the Cambridge Biotech HIV-1 Western Blot Kit (Calypste Biomedical Corporation, Rockville, MD).

We defined diabetes as a self-reported physician diagnosis or fasting plasma glucose ≥ 126 mg/dL. Hypertension was defined as a self-reported physician diagnosis or mean blood pressure $\geq 140/90$ mmHg. History of cardiovascular disease was defined as history of physician diagnosis of coronary heart disease, heart attack or stroke. History of cancer was defined as history of physician diagnosis of cancer.

Estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease-Epidemiology 2009 Equation based on age, sex, race, and serum creatinine.⁽²⁾ Albuminuria was defined as ≥ 30 mg/g. Reduced kidney function was defined as eGFR < 60 mL/min/1.73m². Any chronic kidney disease was defined as eGFR < 90 mL/min/1.73m² or albuminuria ≥ 30 mg/g, representing CKD stage 1 or greater based on a modified CKD classification established by the National Kidney Foundation Disease Outcomes Quality Initiative.⁽³⁾

Hypo-lipidemia traits were defined as the lowest sex-specific quartile of each lipid parameter⁽⁴⁾: Total cholesterol < 177 mg/dL for men and < 180 mg/dL for women; fasting LDL-cholesterol: < 100 mg/dL for men and < 96 for women; HDL- cholesterol: < 38 mg/dL for men and < 46 mg/dL for women; fasting triglycerides: < 90 mg/dL for men and < 79 mg/dL for women. Anemia was defined as hemoglobin < 12 g/dl among women and < 13.5 among men.

We examined the following liver related measures: awareness of liver disease (yes/no) was based on the answer to the following question: "Has a doctor or other health professional ever told you that you had any kind of liver condition? And categorized as yes or no. Elevated liver enzymes were defined by the upper limit of normal of the NHANES laboratory values (ALT: > 41 U/L among males, and > 31

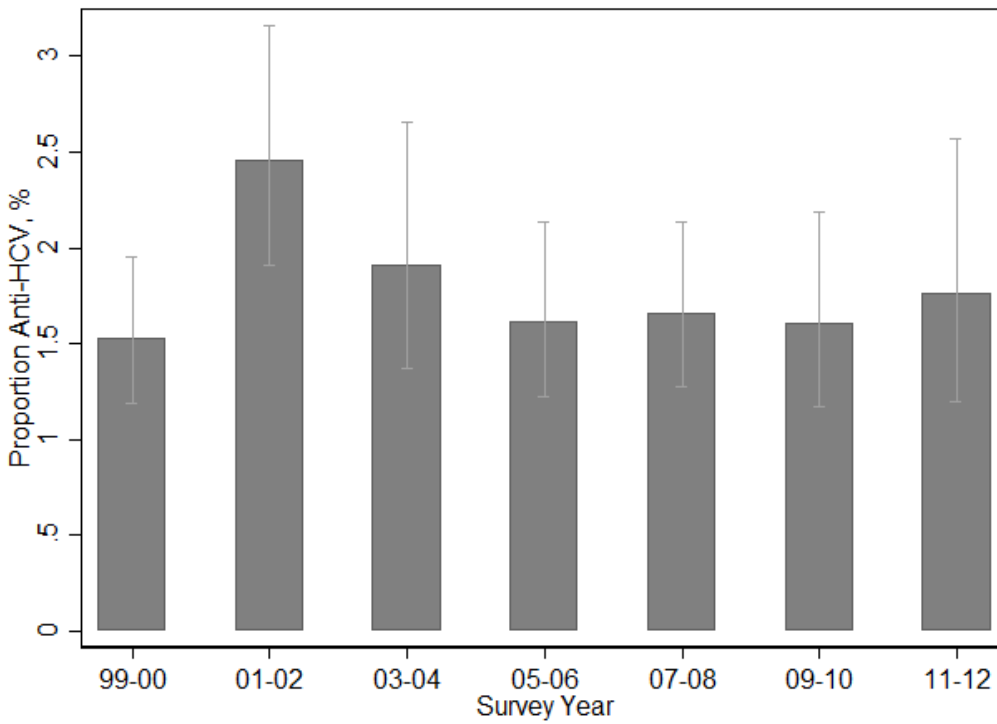
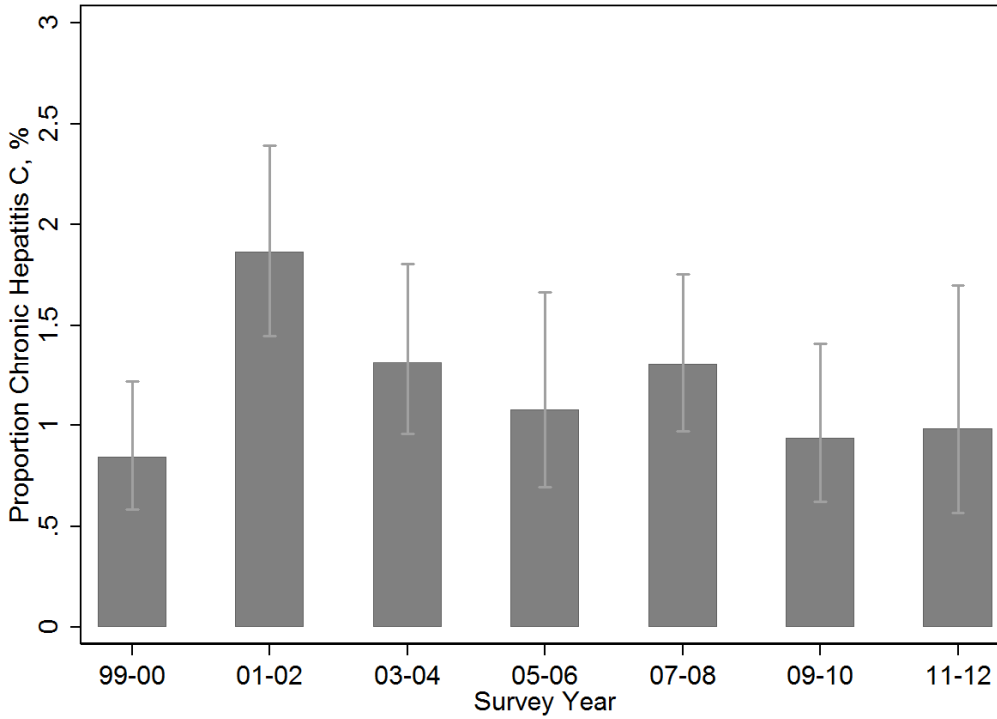
U/L among females; AST: >37 U/L among males, and >31 U/L among females; GGT: >49 U/L among males, and >32 U/L among females). We used the following noninvasive indices of liver fibrosis: aspartate aminotransferase-to-platelet ratio index (APRI) and Fibrosis-4 (FIB-4). We calculated APRI as $([AST/upper\ limit\ of\ normal] / Platelet\ count\ [109/L]) \times 100$, and categorized as elevated using 2 previously described cut-offs for fibrosis (0.5 and 1.5).(5) FIB-4 was calculated as: $(age\ [years] \times AST[U/L] / (PLT[109/L] \times ALT[U/L])^{1/2}$. Elevated FIB-4 was defined as FIB-4 > 1.30.(6) Low albumin was defined as albumin <3.5 mg/dL. Low platelet count was defined as platelets <100,000 X 10³ cells/μL.

Linked Mortality

To determine the vital status and cause of death, the National Center for Health Statistics linked NHANES participants aged 20 years and older who participated in the NHANES III and in NHANES 1999-2010 surveys to the National Death Index. Presently, follow-up extends from the date of the NHANES examination through the date of death or December 31, 2011. Cause of death was determined from the underlying cause of death listed on the death certificate and coded according to the International Classification of Disease, Tenth Revision (ICD-10).

Results

Online-only Supplemental Figure 1. Trends in the Prevalence of Chronic Hepatitis C and Anti-Hepatitis C in the US Adult Population (NHANES 1999-2012)



Online-only Supplemental Table 1. Prevalence of Chronic Hepatitis C and Anti-Hepatitis C in the US Adult Population (NHANES 1999-2012)

	Anti-HCV Positive		Chronic Hepatitis C	
	% (SE)	N (95% CI) in millions	% (SE)	N (95% CI) in millions
Overall	1.8 (0.10)	4.0 (3.54-4.44)	1.2 (0.08)	2.6 (2.30-3.03)
Age group				
20-<30	0.3 (0.13)	0.1 (0.07-0.31)	0.2 (0.08)	0.1 (0.04-0.19)
30-<40	1.3 (0.21)	0.5 (0.38-0.71)	0.7 (0.13)	0.3 (0.21-0.41)
40-<50	3.6 (0.30)	1.6 (1.32-1.84)	2.4 (0.23)	1.0 (0.84-1.24)
50-<60	2.9 (0.27)	1.2 (1.00-1.45)	2.1 (0.23)	0.9 (0.70-1.07)
≥60	0.8 (0.10)	0.5 (0.36-0.57)	0.6 (0.09)	0.3 (0.25-0.45)
Race				
Non-Hispanic White	1.7 (0.13)	2.6 (2.21-2.98)	1.1 (0.10)	1.6 (1.36-1.98)
Non-Hispanic Black	3.3 (0.25)	0.9 (0.73-0.99)	2.6 (0.25)	0.7 (0.56-0.81)
Mexican-American	1.4 (0.20)	0.4 (0.33-0.57)	0.9 (0.18)	0.3 (0.18-0.41)
Other	1.3 (0.21)	-	0.8 (0.16)	-
Gender				
Female	1.3 (0.12)	1.5 (1.20-1.75)	0.8 (0.08)	0.9 (0.71-1.08)
Male	2.5 (0.16)	2.5 (2.20-2.89)	1.7 (0.14)	1.8 (1.49-2.10)
Family income ^a				
≥2 times poverty threshold	1.2 (0.12)	-	0.7 (0.09)	-
1-1.9 times poverty threshold	2.6 (0.22)	-	1.8 (0.22)	-
Below poverty threshold	3.7 (0.29)	-	2.6 (0.24)	-
Education level				
More than high school	1.3 (0.17)	-	0.8 (0.09)	-
High school diploma or equivalent	3.0 (0.41)	-	1.6 (0.19)	-
Less than high school	2.5 (0.32)	-	1.8 (0.18)	-

Prevalence presented as weighted percentage (standard error).

N= Prevalence estimate x population subgroup from 2010 Census data

SOURCE: U.S. Census Bureau, Current Population Survey, Annual Social and Economic Supplement, 2010.

^a Categorized based on poverty income ratio: ratio of family income/poverty threshold

Online-only Supplemental Table 2. Adjusted a prevalence estimates (95% CIs) of selected risk factors for Hepatitis C Infection in the US Adult Population (NHANES 1999-2012) by Chronic Hepatitis C Status

	Chronic Hepatitis C	No Chronic Hepatitis C	p-value
Anti-HBc positivity, %	34.3 (28.5- 40.1)	4.8 (4.4- 5.2)	<0.001
HBsAg positivity, %	0.7 (0.0- 1.4)	0.3 (0.3- 0.4)	0.193
HIV positive ^b , %	1.2 (0.1- 2.4)	0.4 (0.3- 0.5)	0.018
Injection drug use ^c , %	52.4 (45.3- 59.4)	2.2 (1.8- 2.5)	<0.001
Blood transfusion, %	24.5 (19.3- 29.7)	11.2 (10.8- 11.7)	<0.001
History of Sexual contact with men among men (MSM) ^c , %	12.9 (2.3- 23.4)	5.8 (4.5- 7.0)	0.072
Smoking status, %			<0.001
Never	16.1 (11.3- 20.9)	52.8 (51.7- 54.0)	
Former	21.8 (17.1- 26.6)	24.9 (24.1- 25.8)	
Current	62.0 (56.8- 67.3)	22.2 (21.4- 23.1)	
Drinking Status, %			<0.001
Never	3.0 (0.6-5.3)	10.9 (10.1-11.6)	
Low consumption	19.1 (14.4-23.8)	39.3 (38.1-40.5)	
High consumption	61.5 (56.2-66.8)	40.7 (39.5-41.8)	
Former	16.4 (12.0-20.8)	9.2 (8.4-10.0)	

^a Adjusted for age, sex, and race/ethnicity. ^b Among 18-49 years old individuals. ^c Among 20-59 years old individuals.

Online-only Supplemental Table 3. Adjusted^a prevalence estimates (95% CIs) and odds ratios (95% CIs) of health-care related utilization and quality of life in the US Adult Population (NHANES 1999-2012) by Chronic Hepatitis C Virus Status

	Chronic Hepatitis C	No Chronic Hepatitis C	Odds Ratio (95% CI)
Any hospitalization in the last 12 months, %	13.5 (9.0- 18.0)	10.8 (10.3- 11.2)	1.3 (0.9-1.9)
Hospitalizations in the past 12 months ^b , %			
0	81.8 (76.8- 86.8)	87.7 (87.2- 88.2)	1 (<i>reference</i>)
1	12.7 (8.1- 17.4)	9.5 (9.0- 9.9)	1.5 (1.0-2.2)
>1	5.5 (3.0- 8.0)	2.9 (2.6- 3.1)	2.1 (1.3-3.4)
Health insurance ^c , %	64.1 (58.4- 69.8)	81.5 (80.5- 82.4)	0.3 (0.3-0.5)
Age <65 years old	60.2 (53.7- 66.7)	77.9 (76.8- 79.0)	0.4 (0.3-0.5)
Age ≥65 years old	99.8 (99.5- 100.0)	98.5 (98.3- 98.8)	8.5 (1.1-63.9)
Routine place to go for healthcare ^d , %			
Yes	78.3 (73.8- 82.9)	84.9 (84.1- 85.7)	1 (<i>reference</i>)
There is no place	20.9 (16.4- 25.5)	14.4 (13.7- 15.1)	1.7 (1.2-2.3)
There is more than one place	0.7 (0.3- 1.2)	0.7 (0.6- 0.9)	1.1 (0.6-2.3)
Poor physical health ^e , %			
0-10 days	77.2 (71.0- 83.4)	89.1 (88.5- 89.7)	1 (<i>reference</i>)
>10 days	22.8 (16.6- 29.0)	10.9 (10.3- 11.5)	2.5 (1.7-3.5)
Poor mental health ^f , %			
0-10 days	73.3 (66.9- 79.6)	88.1 (87.5- 88.7)	1 (<i>reference</i>)
>10 days	26.7 (20.4- 33.1)	11.9 (11.3- 12.5)	2.7 (2.0-3.8)

^a Adjusted for age, sex, and race/ethnicity. ^b Self-reported. ^c Health insurance (yes, no) was categorized based on the response to the following question: Are you covered by health insurance or some other kind of health care plan? (Include health insurance obtained through employment, or purchased directly as well as government programs like medicare or Medicaid that provide medical care or help pay medical bills). ^d Access to care was categorized based on response to the questions: Is there a place that you usually go when you are sick or need advice about your health (yes, no, there is more than one place). ^e Thinking about your physical health, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good?. ^f Thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?

Online-only Supplemental Table 4. Characteristics of the population by Anti-HCV and HCV-RNA Status

	Anti-HCV negative	Anti-HCV Positive HCV RNA Negative	Anti-HCV Positive HCV RNA Positive	P value
%	98.4%	0.4%	1.1%	
Age, Mean (SD)	48.4 (18.2)	47.8 (10.9)	50.0 (10.7)	0.01
% Men	47.9	53.9	66.6	<0.001
Race				<0.001
% Non-Hispanic White	70.6	78	64.1	
% Non-Hispanic Black	10.4	9.6	23.0	
% Mexican American	7.9	5.6	5.8	
% Other	11.1	6.9	7.2	
Income (PIR)				<0.001
≥2	65.9	46.7	39.6	
1-1.9	20.6	30.7	30.0	
<1	13.9	22.7	30.5	
Education				<0.001
Less than High School	19.0	23.1	28.6	
High School Diploma	24.2	33.5	31.7	
More than High School	56.8	43.4	39.7	
Smoking				<0.001
Never	53.0	14.8	15.4	
Former	24.9	27.4	21.6	
Current	22.1	57.8	63.0	
Alcohol				<0.001
Never	10.9	7.1	2.8	
Former	9.1	20.2	17.3	
Low consumption	39.3	22.2	20.9	
High consumption	40.7	50.4	59.0	
BMI >30 kg/m ²	33.2	27.0	23.3	0.002
Hypertension (Diagnosed)	29.0	29.9	38.1	0.008
Diabetes (Diagnosed)	7.8	5.9	8.6	0.71
Albuminuria >30 mg/g , %	8.1	10.5	10.1	0.40
eGFR<60 mL/min/1.73m ² , %	6.8	2.1	5.2	0.07
APRI >1.5	0.3	0.7	15.0	<0.001
FIB-4 >1.3	0.1	0	0.7	0.02

Online-only Supplemental Table 5. Mortality rates (95% CI), median survival, and adjusted hazard ratios (95%CI) for all-cause mortality by chronic hepatitis C (CHC), diabetes, obesity and chronic kidney disease (CKD) status in the U.S. Adult Population (NHANES III 1988-1994 and NHANES 1999-2012) (follow-up to December 31, 2011)

Subgroup	Adjusted ^a mortality rate per 1,000 person-years (95%CI)	Median survival for a 45 year old individual (years)	Adjusted HR (95% CI)	
			Model 1 ^b	Model 2 ^c
Diabetes				
No diabetes, No CHC	5.1 (4.4, 5.5)	84.8	1 [Reference]	1 [Reference]
Diabetes, No CHC	8.6 (7.7, 9.5)	75.8	1.90 (1.72, 2.11)	1.88 (1.69, 2.09)
No Diabetes, CHC	13.7 (9.2, 18.1)	71.5	2.94 (2.08, 4.14)	2.45 (1.75, 3.42)
Diabetes, CHC	24.2 (9.3, 39.1)	62.3	6.41 (3.26, 12.60)	4.96 (2.50, 9.81)
Obesity				
No Obesity, No CHC	5.1 (4.6, 5.5)	84.3	1 [Reference]	1 [Reference]
Obesity, No CHC	5.7 (5.2, 2.3)	83.7	1.19 (1.09, 1.30)	1.24 (1.13, 1.35)
Obesity, CHC	13.6 (9.6, 17.5)	73.1	3.03 (2.20, 4.17)	2.42 (1.80, 3.27)
Obesity, CHC	15.8 (3.8, 27.7)	71.5	3.29 (1.58, 6.85)	3.24 (1.54, 6.81)
CKD				
No CKD, No CHC	4.9 (4.4, 5.3)	86.5	1 [Reference]	1 [Reference]
Any CKD, No CHC	8.1 (7.3, 8.9)	75.0	1.91 (1.77, 2.06)	1.87 (1.73, 2.00)
No CKD, CHC	12.8 (8.4, 17.3)	73.2	2.93 (2.06, 4.18)	2.41 (1.67, 3.47)
Any CKD, CHC	20.5 (11.0, 30.03)	64.7	5.06 (3.02, 8.48)	4.39 (2.80, 6.88)

^a Adjusted for age, age², sex, race, estimated using Poisson regression and margins command

^b Model 1: Adjusted for age, sex, race, education

^c Model 2: Further adjusted for alcohol, smoking

References

1. CDC. CDC HRQOL-14 "healthy Days Measure".
2. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-12.
3. National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39(2 Suppl 1):S1-266.
4. Lao XQ, Thompson A, McHutchison JG, McCarthy JJ. Sex and age differences in lipid response to chronic infection with the hepatitis C virus in the United States National Health and Nutrition Examination Surveys. *J Viral Hepat.* 2011;18(8):571-9.
5. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology.* 2011;53(3):726-36.
6. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology.* 2006;43(6):1317-25.