



Risk behaviours associated with hepatitis C infection: application of a syndemic effects framework in NHANES

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ABSTRACT

Objectives: To apply syndemic theory to investigate the risk of hepatitis C virus (HCV) infection in the US population.

Methods: National representative data were from the National Health and Nutrition Examination Survey. We extracted and aggregated data on HCV antibody test, sociodemographic characteristics, alcohol and drug use, depression, sexual behaviour and sexually transmitted illnesses from 2005-2006 to 2011-2012. The study sample was restricted to men and women aged 20-59 years given the upper age limit of the risk factors used for the analysis.

Results: Overall, 11,593 people were included in the analysis (52.2% female). Higher prevalence of HCV, excessive alcohol consumption and drug use were found in men. Men also had higher odds of HCV in comparison to women among younger (20-39 years old) OR 1.37 (95%CI 1.36-1.37) and middle-aged adults (40-59 years old) OR 2.04 (95%CI 2.03-2.04). Among younger adults, non-Hispanic black and Hispanic people were found to have a lower likelihood of testing positive, OR 0.35 (95%CI 0.35-0.35) and OR 0.30 (95%CI 0.30-0.30), respectively. However, in the middle-aged adults non-Hispanic black people were found to have a higher likelihood of testing positive OR 1.45 (95%CI 1.45-1.46). Analysis showed that for each additional risk factor associated with HCV infection there is an additional increase in the risk OR 1.55 (95%CI 1.55-1.55).

Conclusions: For every additional risk factor for HCV a person is exposed to, the overall risk of HCV increases.

KEYWORDS

Hepatitis C Virus; Syndemic; Intravenous Drug Use; Risk; Disparity.

1. INTRODUCTION

Infections with the hepatitis C virus (HCV) are the most commonly reported blood borne infections in the United States [1], with an estimated national prevalence of 0.93% with great variability among different states [2]. Around half of people who develop a chronic HCV infection develop progressive liver cirrhosis and hepatocellular carcinoma. Reported mortality as a result of the HCV infection in 2016 was 4.45 per 100,000 in the US [3,4]. Risk factors associated with an HCV infection are linked to exposure to bodily fluids, mostly blood [5].

Due to societal changes and progress in biomedical research, there has been a significant shift in the HCV epidemic in the US. On one hand, the availability and effectiveness of direct-acting antivirals (DAA) has led to many people being cured of the HCV infection [6]. However, HCV mortality remains high [4], as HCV disproportionately affects people with psycho-social vulnerabilities such as mental illness, intravenous drug use and homelessness [7]. Also, among African American men and women, HCV prevalence is still disproportionately higher [8]. Moreover, the high prevalence level is maintained through rising levels of reported incidence [9], which is primarily associated with a rampant epidemic of illegal opioid use in the US and its consequences [10].

Intravenous drug use is the most common risk factor for HCV infection in the US, with more than 60% of all cases being linked to injecting drugs through sharing of needles and other paraphernalia [11]. Reports have also identified that most newly infected individuals are younger than 30, Caucasian, and residing in rural areas⁹. Further, there are reports of higher incidence of HCV in heavy alcohol drinkers in the absence of other risk factors, with studies also noting a correlation between viremia and reported alcohol consumption [12].

Although the transmission of HCV through unprotected sexual contact remains a controversial issue, studies report that around 15% of all US cases can be accounted for with sexual transmission, however, drug use is often a contributing factor in these cases as well [9,13]. Here co-infections with other sexually transmitted infections (STIs) play an important role in both heterosexual and homosexual partners. However, the risk of infection is higher among men who have sex with men,

where particular risk factors are more prevalent such as use of illicit drugs, HIV coinfection, and sexual practices that result in bleeding of the rectal mucosa [9,13].

In order to curb the rising incidence of HCV in the US it is not only important to identify the biological and structural key risk factors that are associated with contracting HCV but also to understand whether and how these risk factors cluster, and the synergistic effects they may have in increasing the risk of HCV. Here syndemic theory may provide the necessary theoretical framework that best suits the complex interactions of social and environmental factors that contribute to the excess disease burden in a population [14,15]. A syndemic is defined as “two or more afflictions, interacting synergistically, contributing to excess burden of disease in a population.” [16]. Syndemics encompass both disease epidemics and social factors that contribute to the proliferation of disease. Several studies thus far have used the syndemic theory to explain the risks associated with HCV in specific populations [17-19]. These studies have mostly focused on HCV coinfections with human immunodeficiency virus (HIV) and hepatitis B (HBV) virus. To our knowledge, there are no studies that used the syndemic framework to examine factors related to the contraction of HCV.

Therefore, we aimed to expand and add to the existing knowledge by using a syndemic framework to investigate the risk of HCV infection in a national representative sample of the US population.

2. METHODS

2.1. Study Population

The National Health and Nutrition Examination Survey (NHANES) uses nationally representative complex, stratified, multistage, probability clustered samples to evaluate the prevalence of health, nutrition, and potential lifestyle risk factors among the civilian non-institutionalized US population continuously in 2-year cycles. The participants were required to attend interviews at home and undertake a physical examination in a mobile examination centre (MEC). National Centre for Health Statistics Research Ethics Review Board (ERB) approved protocol #2011-17 and participants provided written informed consent. We extracted and aggregated data on HCV antibody test, sociodemographic characteristics, alcohol use, drug use, depression, sexual behaviours (multiple sex partners, condom use) and sexually transmitted infections (STIs) from cycle 2005-2006 to 2011-2012. We restricted our study sample to men and women aged 20 to 59 years because of the upper age limit of the multiple risk behaviours used in the present analyses.

2.2. Hepatitis C virus antibody test

The HCV antibody test was conducted during NHANES laboratory procedures. Participants' blood specimens were drawn by trained phlebotomists in the MEC and processed, stored, and shipped to the Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STI and TB Prevention, Centers for Disease Control and Prevention. The specimen was measured using direct solid-phase enzyme immunoassay with the anti-HCV screening ELISA [20]. Positive specimens were repeated in duplicate according to the same procedure. Repeatedly positive specimens are tested supplementally using the Chiron RIBA Processor System (Chiron Corporation, Inc.). Possible results on the HCV antibody test are "positive", "negative", and "indeterminate". We aggregated the results into a binary variable: HCV-positive vs. HCV-negative. We excluded indeterminate results due to the uncertain confirmation of infection.

2.3. Socio-demographic characteristics

We extracted data on age, gender (men, women), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic), annual household income (<\$25000, \$25000-<75000 and \geq \$75000) and level of education (less than high school, high school, and above high school).

2.4. Multiple risk behaviours

2.4.1. Binge drinking

Participants self-reported lifetime and current use of alcohol. Binge drinking was defined using the question "Was there ever a time or times in your life when you drank 5 or more drinks of any kind of alcoholic beverage almost every day?" with dichotomous responses of "Yes" and "No".

2.4.2. Drug use

Lifetime use of drugs (not prescribed by a doctor) was self-reported during the MEC interview. Participants were asked: "Have you ever, even once, 1) used marijuana or hashish? 2) used cocaine, crack cocaine, heroin, or methamphetamine? 3) used a needle to inject a drug?" with response options of "yes", "no", "refused", and "don't know". Three metrics on drug use were derived: marijuana or hashish, cocaine/heroin/methamphetamine, and illegal drug, with responses dichotomized to no drug use vs. at least one drug use.

2.4.3. Depressive symptoms

Depressive symptoms were assessed using the Patient Health Questionnaire (PHQ-9), a valid 9-item depression screener asking about the frequency of symptoms of depression over the past 2 weeks²¹. Each item was scored on a 0–3 scale. The total score of PHQ-9 ranged from 0 to 27. We categorized depressive symptoms by PHQ-9 score as four severity categories: “none or minimum” (0–4), “mild” (5–9), “moderate” (10–14), “moderately severe” (15–19), and “severe” (20–27). For the present analyses, participants who scored 10 or more were combined into one group as clinically relevant depression. Such diagnosis has shown a sensitivity of 88 % and a specificity of 88 % for major depression [21].

2.4.4. Sexual behaviours and STIs

The sexual behaviour questionnaire was completed by participants at the MEC. Information on lifetime and current sexual behaviour and history of STIs were collected. We derived number of sexual partners, condom use, and STIs. We summarized the total number of sexual partners (same or opposite sex) in the past year for each participant who reported having (performing or receiving) any type of sex. Due to the large inter-individual variation in the number of sexual partners, we used a dichotomized variable to indicate no (none) vs. any (≥ 1) sexual partners in the past year. Further, we categorized condom use in the past year into a binary variable: always (never had sex without condom) vs. not always (occasionally or always had sex without condom).

STIs including genital herpes, genital warts, gonorrhoea, chlamydia, and HPV (only for women) were determined by self-reports of doctor’s diagnosis. We summarized STIs as one binary variable: yes (doctor ever told had at least one of these STIs) vs. no (doctor never told had one of these STIs).

2.4.5. Cumulative score

Finally, to account for the syndemic effect of multiple risk behaviours, we generated a cumulative score for the above six behaviours (binge drinking, drug use, depressive symptoms, multiple sexual partners, non-use of condoms, and STIs) into one continuous variable (0-6).

2.5. Statistical Analysis

Survey analysis procedures were used to account for the sample weights, stratification, and clustering of the complex sampling design to ensure nationally representative estimates. Descriptive

characteristics were analysed separately in men and women due to the documented gender difference in HCV prevalence [22]. We summarized weighted proportions for categorical variables by gender.

Multivariable models were carried out to test the association between cumulative risk behaviour score and testing positive for HCV. Given the established age differences in a number of the included risk behaviours, we carried out the weighted regression on the entire sample (20-59 years), and separately on subgroups of younger (20-39 years) and middle-aged adults (40-59 years). All models were corrected for rare events of HCV by using firthlogit program to reduce bias of logistic regression [23]. Multivariable models were adjusted for age, gender, race/ethnicity, household income and education. All statistical significance was set at $p < 0.05$. All statistical analyses were performed using STATA version 14.0 (STATA Corp., Texas, USA).

3. RESULTS

Table 1 shows the frequencies and weighted proportions of participants according to characteristics by gender. There were 5,546 men and 6,047 women aged 20 to 59 years in the four NHANES cycles with data on HCV antibody test and multiple risk behaviours. Overall, 2.6% men and 1.7% women tested positive for HCV. The prevalence of STIs was higher among women (13%) than men (6.4%). In addition, the prevalence of moderate to severe depressive symptoms was higher among women (11%) than that among men (6.2%). However, more men than women reported lifetime binge drinking (23% vs 10%) and drug use (68% vs 57%).

Table 1. Characteristics of adults aged 20-59 years from the NHANES (2005-2012), by gender

		Male	Female
	N	5546(100)	6047(100)
Age group			
20-39	n (%)	2790(50)	3176(48)
40-59	n (%)	2756(50)	2871(52)
Race			
Non-Hispanic White	n (%)	2699(73)	2824(72)
Non-Hispanic Black	n (%)	1219(11)	1438(13)
Hispanic	n (%)	1628(16)	1785(15)
Education			
<High School	n (%)	1444(18)	1398(15)
High School	n (%)	1414(25)	1256(20)
>High School	n (%)	2686(57)	3393(65)
Annual household income			
<25000	n (%)	1503(18)	1916(22)
\$25,000-75,000	n (%)	2451(42)	2574(42)

>75000	n (%)	1592(40)	1557(36)
Hepatitis C-positive	n (%)	164(2.6)	100(1.7)
Binge drinking	n (%)	1207(23)	463(10)
Drug use	n (%)	3227(68)	2690(57)
Marijuana or hashish	n (%)	3220(68)	2686(57)
Cocaine/heroin/methamphetamine	n (%)	1318(27)	802(17)
Inject illegal drug	n (%)	158(3.3)	89(1.6)
Depression	n (%)	424(6.2)	784(11)
Multiple (≥ 2) sex partners	n (%)	598(18)	412(12)
Condom use			
Always	n (%)	939(21)	1003(20)
Sexually transmitted disease	n (%)	289(6.4)	598(13)
Genital herpes	n (%)	106(2.3)	304(6.9)
Genital warts	n (%)	161(3.9)	295(6.7)
Gonorrhea	n (%)	25(0.3)	20(0.3)
Chlamydia	n (%)	40(0.6)	61(0.9)

Table 2 summarizes multivariable logistic regression results of the association between cumulative risk behaviour score and the odds of testing positive for HCV stratified by age groups, for male and female respectively. For men, each increasing risk behavior was associated with elevated odds of testing positive for HCV among both younger (OR= 1.53, 95% CI: 1.53 to 1.54) and middle-aged (OR= 1.46, 95% CI: 1.46, 95% CI: 1.45 to 1.46) groups. Also, the results were consistent among younger (OR= 1.28, 95% CI: 1.27 to 1.28) and middle-aged (OR= 1.75, 95% CI: 1.75 to 1.75) women. In addition, striking disparity patterns among participants testing positive for HCV were observed according to socio-demographic characteristics. For instance, among younger adults, Non-Hispanic Whites were more likely to test positive for HCV compared with Non-Hispanic Blacks (male: OR=0.20, 95% CI: 0.20 to 0.20; female: OR=0.54, 95% CI: 0.53 to 0.54) and Hispanics (male: OR=0.32, 95% CI: 0.31 to 0.32; female: OR=0.33, 95% CI: 0.33 to 0.33). However, among middle-aged adults, Non-Hispanic Blacks have the higher chance of testing positive for HCV for both male (OR=1.12, 95% CI: 1.12 to 1.13) and female (OR=2.09, 95% CI: 2.09 to 2.10). Finally, higher annual household income was associated with lower odds of testing positive for HCV among all subgroups (all *P* value for trend <.001). Similarly, odds of testing positive for HCV declined as education level increased (all *P* value for trend <.001).

Table 2. Weighted Logistic Regression Models of Hepatitis C-positive Among Adults, Adjusted for socio-demographic characteristics, NHANES 2005-2012

	Odds Ratio, 95 % CI			
	Male		Female	
	20-39 years	40-59 years	20-39 years	40-59 years
Cumulative risk behaviours	1.53 (1.53 to 1.54)	1.46 (1.45 to 1.46)	1.28 (1.27 to 1.28)	1.75 (1.75 to 1.75)
Age	1.21 (1.21 to 1.21)	1.03 (1.03 to 1.03)	1.34 (1.34 to 1.34)	0.99 (0.99 to 0.99)
Race/ethnicity				
Non-Hispanic White	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Non-Hispanic Black	0.20 (0.20 to 0.20)	1.12 (1.12 to 1.13)	0.54 (0.53 to 0.54)	2.09 (2.09 to 2.10)
Hispanic	0.32 (0.31 to 0.32)	0.71 (0.71 to 0.72)	0.33 (0.33 to 0.33)	0.67 (0.67 to 0.68)
Annual household income				
<\$25,000	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
\$25,000-<\$75,000	0.57 (0.56 to 0.57)	0.86 (0.86 to 0.86)	0.50 (0.50 to 0.50)	0.42 (0.42 to 0.42)
≥\$75,000	0.19 (0.19 to 0.19)	0.25 (0.25 to 0.25)	0.03 (0.03 to 0.03)	0.29 (0.29 to 0.29)
<i>P</i> value for trend	<.001	<.001	<.001	<.001
Education				
<High school	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
High school	0.37 (0.37 to 0.37)	0.64 (0.64 to 0.64)	0.76 (0.76 to 0.77)	0.59 (0.59 to 0.59)
>High school	0.17 (0.17 to 0.17)	0.53 (0.53 to 0.54)	0.41 (0.41 to 0.42)	0.59 (0.59 to 0.59)
<i>P</i> value for trend	<.001	<.001	<.001	<.001

Table 3 shows the associations between risk behaviours and a positive HCV status. All the risk factors; binge drinking, drug use, depression, multiple sex partners, not always using a condom and previously being diagnosed with an STI were found significantly associated with the odds of being tested positive for HCV. For younger men (20-39 years old) binge drinking was associated with the highest odds of testing HCV positive, while for older man (40-59 years old) highest odds were associated with drug use. Same was observed in women of both age groups. Interestingly, having multiple sexual partners was found to reduce the chance of being tested positive for HCV in the older male group. Not always using a condom was associated with a higher chance of being HCV positive in men but with lower changes in women. Furthermore, having a previous diagnosis of an STI was associated with lower odds of being tested positive for HCV in men but higher odds in women.

Table 3. Association Between Risk Behaviors and Hepatitis C-positive Among Adults, Adjusted for Socio-demographic and Lifestyle Factors, NHANES 2005-2012^a

	Odds Ratio, 95 % CI			
	Male		Female	
	20-39 years	40-59 years	20-39 years	40-59 years
Bing Drinking	4.08 (4.06 to 4.10)	3.15 (3.15 to 3.16)	- ^b	5.89 (5.87 to 5.90)
Drug use	2.32 (2.31 to 2.34)	4.06 (4.05 to 4.07)	4.25 (4.22 to 4.28)	6.08 (6.06 to 6.10)
Depression	1.87 (1.86 to 1.89)	2.00 (1.99 to 2.00)	3.86 (3.84 to 3.88)	1.80 (1.80 to 1.81))
Multiple (≥ 2) sex partners	2.09 (2.07 to 2.10)	0.77 (0.77 to 0.78)	1.29 (1.28 to 1.30)	1.83 (1.83 to 1.84)
Not always condom use	2.03 (2.01 to 2.05)	1.14 (1.14 to 1.15)	0.26 (0.26 to 0.26)	0.54 (0.54 to 0.54)
Sexually transmitted disease	- ^b	0.66 (0.66 to 0.67)	- ^b	1.72 (1.72 to 1.73)

^a For each risk behavior, the logistic regression model was adjusted for age, race, household income, and education level.

^b No estimate was calculated due to no case among patients exposed to the risk behaviors

4. DISCUSSION

The present study of a representative sample of US adults found that men were at higher risk of contracting HCV in comparison with women, with the risk being higher among middle-aged adults (40-59 years) as opposed to younger adults (20-39 years). Disparities between age groups were observed across various racial and ethnic groups. Among younger adults, non-Hispanic black and Hispanic younger adults had a 70% and 65% lower odds respectively of testing HCV positive, compared with their non-Hispanic white counterparts. However, this was not true for the middle-aged group, where non-Hispanic black people had a 55% higher odds of testing positive for HCV. Not surprisingly, both higher household incomes and higher education levels were associated with a lesser likelihood of being tested positive for HCV. Most importantly, we observed an increase in odds of being tested positive for HCV with each contributing risk factor in both younger and older adults.

Perhaps the most interesting result from this nationally representative US analysis is in using the syndemic framework, which showed that with each additional risk factor a person is exposed to there is an increase in the risk of testing positive for HCV. Our findings suggest that potentially removing one risk factor could significantly reduce the risk of contracting HCV. These results highlight a clear need for multifaceted public health interventions that take into consideration behavioural, biological and structural (cultural, economic and social) factors in order to have long-lasting effects [14,19,24,25]. These are important from the point of improving the community resilience where there are known social and health disparities. Furthermore, we found that depression and addiction issues such as binge drinking and drug use were found to be associated with higher odds of being tested

positive for HCV (table 3). The confluence of these variables is well known, as depression is a known comorbidity in people with alcohol and drug addiction and HCV. However, they often present major obstacles for appropriate treatment of HCV [26,27].

Interestingly, having multiple sexual partners was associated with higher chances of testing positive for HCV in all groups but men between ages 40 and 59, where it was associated with lower odds. Inconsistent condom use was found to increase the odds of being tested HCV positive in men but with lower odds in women. Although we found no literature to support this claim, inconsistent condom use was found to be associated with drug and alcohol use which are known risk factors for HCV. The result may be furthermore explained by more women having monogamous partners, which is also a known factor for less condom use [28]. There was also a discrepancy in having a diagnosed STD, which was found to bring lower odds for men but higher for women. Potentially this may be due to men having more overt symptoms of STD and thusly using more protection than women.

The present study supports the previous US findings that men are at increased risk of contracting HCV [29]. This may be owing to a higher prevalence of known risk factors among men, such as intravenous drug use [30], which was also seen in our study population (table 1). Furthermore, the disparities seen between age groups are supported by epidemiological surveys that reported the highest prevalence of HCV in the 1945-1965 birth cohort mostly due to the inability to test or treat the infection combined with the high rise of the incidence in 1980s [31].

Ethnic and racial disparities were also found, with Hispanic and non-Hispanic black younger adults having lower odds of testing HCV positive in comparison with non-Hispanic white. This is supported by newer reports that report young Caucasian adults residing in rural areas are at most risk [9]. This is probably mitigated by lower accessibility of health care in rural areas where de-industrialization, underemployment and poverty are more common [31]. Furthermore, these factors are associated with the prevalence of the opioid misuse epidemic and limited preventive measures, such as access to needle exchange programs which still remain low in many states and if present are often very dispersed [2]. HCV testing and treatment have been found to be cost-effective and are considered the cornerstone of stopping the high incidence rates [32,33]. Therefore, questions of access to such medical services remains an issue and could further explain our results where non-Hispanic black adults aged 40-59 were found to have higher chances of testing positive for HCV given the known issues of accessing appropriate health care of this population [34]. All the above mentioned structural issues are further highlighted by our results, where socio-economic status was found to have an effect on the likelihood of testing HCV positive. Both an increase in household income and educational status were associated with a reduction in odds of testing positive.

Strengths of this study include the use of the syndemic framework to explain the interactions of various factors and their associations with HCV positive status. Limitations include the cross-sectional study design that prevents causal relationships, and the study population. While NHANES is a nationally represented US survey that has been used to determine the prevalence rate of HCV in the US, it does not include institutionalized people, such as those incarcerated or those experiencing homelessness. Both of these groups have been known to have higher prevalence of HCV. Therefore, the results of our study cannot be generalized to the whole US population.

In conclusion, the results of the first nationally representative analysis of US adults show that with increased exposure to different HCV risk factors there is increased risk of contracting HCV. Multifaceted community based public health interventions are urgently needed reduce the incidence of HCV in the US.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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