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Mortality in Adults with Chronic Hepatitis B Infection in the United States: A Population-Based Study

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Abstract

Background: Chronic hepatitis B infection is an important contributor to mortality in the United States, yet impact of available and effective oral antivirals on mortality among infected individuals is unknown.

Aim(s): To compare risks and predictors of mortality in a recent time period between those with chronic, prior and no hepatitis B infection.

Methods: This is a population-based cohort study of National Health and Nutrition Examination Surveys participants between 1999 and 2014 linked to National Death Index data. Adults aged 20 years or older with hepatitis B serologic testing were included. Outcomes of all-cause and liver-related mortality were evaluated using Cox regression.

Results: Of 39,206 participants, 192 (0.5%) had chronic and 2694 (6.9%) had prior hepatitis B infection. The all-cause age/sex-standardized mortality rates for chronic, prior and uninfected were 21.4, 15.1 and 11.8 per 1000 person-years, respectively. Liver-related mortality occurred at respective rates of 4.1, 0.3 and 0.1 per 1000 person-years. In multivariable analyses, those with chronic infection had 1.9-fold (95% CI 1.1–3.3) increased hazard of all-cause mortality and 13.3-fold (95% CI 3.9–45.5) increased hazard of liver-related mortality compared to uninfected.

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Authorship Statement

Norah Terrault is the guarantor of the article and all authors approved the final version of the manuscript. The authors made the following contributions:

Concept and design: Zhou, Dodge, Terrault.

Acquisition, analysis, or interpretation of data: Zhou, Poltavskiy, Grab, Dodge, Terrault.

Statistical analysis: Zhou, Grab, Dodge.

Drafting of the manuscript: Zhou.

Critical revision of the manuscript for important intellectual content: All authors.

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Statement of Interests

Authors' declaration of personal interests

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Predictors of all-cause mortality among chronic infection included heavy alcohol use (HR 18.3, 95% CI 3.3–100.6) and higher alanine aminotransferase (HR 1.02, 95% CI 1.00–1.03).

Conclusions: Mortality among adults living with chronic hepatitis B infection still exceeds that of uninfected despite availability of improved therapeutics. Identification of chronic infection, initiation of treatment among eligible, and modulation of co-factors for disease progression are needed to improve survival.

Keywords

chronic hepatitis B infection; mortality; viral hepatitis; hepatitis B virus; epidemiology

Introduction

Globally, viral hepatitis causes 1.3 million deaths per year, on par with other communicable diseases such as human immunodeficiency virus (HIV), malaria and tuberculosis[1]. Among those with chronic infection, the major driver of mortality is development of cirrhosis and hepatocellular carcinoma (HCC). Chronic hepatitis B virus (HBV) infection accounts for over 30% of cirrhosis and 50% of HCC cases worldwide[2]. While future estimates of HBV prevalence are expected to decline with broader uptake of vaccination, immigration from endemic regions has kept HBV prevalence in the US relatively constant over the past three decades[3]. Thus, an estimated 800,000 to 2.2 million individuals living in the US remain at risk for adverse liver-related outcomes and increased mortality[3, 4].

Mortality due to chronic HBV infection in the US has not been well characterized, particularly since the introduction in the mid-2000s of oral HBV antiviral therapies with minimal to no resistance (i.e. entecavir and tenofovir) with long-term use [5, 6]. Existing studies on HBV mortality relying on death certificate records reported no significant change in deaths attributable to HBV infection between 1999 and 2007, followed by a small temporal decline in deaths between 2007 and 2016[7, 8]. Death certificate studies, however, may be subject to under-reporting of HBV status, as well as ascertainment and misclassification biases[9, 10] and accurate capture of HBV-related mortality are crucial to inform policymakers on gaps in HBV care and prioritization of treatment.

The objective of this study was to evaluate mortality among a population-based cohort of adults with chronic HBV infection in the era of effective HBV therapies (1999–2014) by linking serologic evidence of HBV infection to death using the National Health and Nutrition Examination Surveys (NHANES)-Linked Mortality Dataset.

Materials and Methods

National Health and Nutrition Examination Survey

NHANES is a cross-sectional, stratified, multistage probability survey of a representative non-institutionalized civilian US population. Previously completed in 6-year cycles, the continuous NHANES has sampled every 2 years since 1999. NHANES samples in four-stages: 1) selection of primary sampling units (PSUs) typically individual counties; 2)

selection of segments within each county; 3) selection of households within segments; and 4) selection of individuals within each household.

Cohort Selection

The study cohort included all NHANES participants for survey years 1999 to 2014 aged 20 years or older with available hepatitis B serologies. Laboratory testing included immunoassays for qualitative detection of hepatitis B core antibody (anti-HBc, total) and hepatitis B surface antigen (HBsAg) (Ortho CD VITROS Anti-HBc and HBsAg test; Ortho Clinical Diagnostics, Raritan, NJ). Only participants with a positive anti-HBc test had HBsAg testing performed[11]. Participants were classified into 3 groups: (1) no HBV infection if negative anti-HBc test, (2) prior HBV if positive anti-HBc test but negative HBsAg test, and (3) chronic HBV infection if positive tests for both anti-HBc and HBsAg.

Covariate Definitions

The following covariate definitions were used in this study:

> Cohort years: 1999–2006 and 2007–2014.

> Poverty index: calculated by dividing family income by the poverty guidelines. A poverty index below 1 was considered below the poverty line.

> Ever smoking: defined as reporting at least 100 cigarettes used over lifetime.

> Alcohol use: none, low (>0-<4 drinks/day in men and >0-<2 drinks/day in women) and heavy (≥4 drinks/day in men and ≥2 drinks/day in women). Due to 19% missing data, participants who responded “Yes” to “Have you had more than 12 drinks over your lifetime?” but failed to report amount or frequency of use were imputed as low alcohol use.

> Hypertension: average systolic or diastolic blood pressures ≥140 mm Hg or ≥90 mm Hg or self-reported history of oral antihypertensive medication use.

> Diabetes: hemoglobin A1c ≥6.5% or self-reported history of oral hypoglycemics or insulin use.

> Hyperlipidemia: cholesterol >200 mg/dL, low-density lipoprotein ≥130 mg/dL, HDL <40 mg/dL for men and <50 mg/dL for women, or self-reported history of oral cholesterol medication use[12].

> Obesity: body mass index (BMI) ≥30 kg/m^2. Since we were unable to determine Asian race, the lower recommended cut-off of ≥25 could not be applied.

> HBV treatment: yes, if HBV therapy identified by generic drug name as one of participant’s prescription medications.

Mortality Outcome Assessment

Primary outcome of this study was all-cause mortality and secondary outcome was liver-related mortality. We determined mortality status using the NHANES Linked Mortality File,

in which NHANES 1999–2014 participants were matched through a probabilistic matching algorithm with multiple identifiers to the US National Death Index (NDI)[13]. Participant follow-up continued from enrollment into NHANES until death. Participants not matched with a death record were considered alive and censored at the end of follow-up (December 31, 2015). Participants with incomplete identifiers necessary for the probabilistic matching algorithm (N=48) were excluded from the mortality analysis[13]. To evaluate liver-related mortality, we obtained restricted access to cause-specific mortality data; data were accessed through the Research Data Center. We utilized the Underlying Causes of Death (113) Recode variable and defined liver-related mortality as death from viral hepatitis (B15-B19), malignant neoplasms of liver and intrahepatic bile ducts (C22), and chronic liver disease and cirrhosis (K70, K73-K74).

Statistical Analysis

All analyses accounted for weighting (due to differential probability of selection through oversampling, nonresponse and adjustment to independent population controls) and complex survey design of NHANES. Weights were given by NHANES for each 2-year cycle and combined to create 4-, 8- and 16-year weights to be applied at appropriate steps in analysis as recommended by NHANES statistical guidelines[14]. Variance estimation was performed using Taylor Series Linearization.

Population characteristics collected at NHANES enrollment examination were estimated as weighted means and percentages with standard errors (SE) and HBV status (no, prior, or chronic infection). Hypothesis testing was performed using t-test for continuous variables and chi-square test for proportions. All-cause and liver-related mortality rates (per 1000 person-years), standardized to age and sex distribution of US population, were calculated by HBV status and cohort years using the direct method of standardization. Both age- and sex-standardization was performed using the 2000 US census population as the standard. Linear trend over time by 4-year intervals was examined using linear contrasts.

We performed left-truncated Cox proportional hazards regression to estimate the hazard ratios (HRs) and 95% CIs for risk of all-cause and liver-related mortality in chronic and prior HBV infection compared to no infection. Left-truncation better controls for age, the principal confounder of a mortality outcome, than does time-on-study. Characteristics with a univariate pvalue <0.1, known associations with HBV-related mortality (race, foreign-born, and alanine aminotransferase [ALT]), or of interest for the study (HBV status and cohort years) were evaluated in multivariable modeling. Backward elimination ($p<0.05$) was used to select the adjusted multivariable models, retaining covariates related to HBV mortality or of interest to the study, regardless of statistical significance. Predictors of all-cause mortality among chronic HBV were also similarly examined. We tested for interaction between HBV status and cohort years (1999–2006 and 2007–2014) to examine change in hazard over time. Data were analyzed using SAS-SUDAAN and STATA v14.0. All tests were 2-sided and $p<0.05$ was considered statistically significant.

Results

Overall Characteristics of US Adults between 1999–2014 by HBV Status

A total of 39,206 NHANES participants met inclusion criteria, of which 2694 (6.9%) had prior HBV infection and 192 (0.5%) had chronic infection (Figure 1). In the prior HBV infection group (positive HBV core antibody test), 77% were also positive for HBV surface antibody. Demographic characteristics stratified by HBV status are reported in Table 1. Within the chronic HBV group, mean age was 47 years, 58% were male, and 44% identified "other" as race/ethnicity which included Asian race; 31% of those with prior infection and 10% with no infection identified "other" as race. The majority with chronic HBV (50%) were foreign-born; foreign-born comprised 41% with prior infection and 15% with no infection. Other than proportion with diabetes (13%), those with chronic infection had slightly lower prevalence of metabolic co-morbidities, such as hypertension (28%), hyperlipidemia (62%), and obesity (18%), compared to the other two groups. Mean ALT was highest among chronically infected (40 U/L) and lowest among uninfected (26 U/L). Eleven (5.7%) of 192 with chronic infection reported current antiviral therapy for HBV, including lamivudine, adefovir, emtricitabine-tenofovir, entecavir and tenofovir alone. Past antiviral therapy was not captured.

Complete mortality follow-up data were available for 39,158 out of 39,206 participants (99.9%) and nearly all participants with chronic HBV (191/192, 99.5%). The mean duration of follow-up for all participants was 7.9 ± 4.5 years. Overall, there were 5042 deaths over 309,348 person-years of follow-up.

Changes in Characteristics of Adults with Chronic HBV Over Time

Of a total 192 chronically infected participants, 72 (38%) entered NHANES between 1999–2006 and 120 (62%) between 2007–2014 (Supplemental Table 1). A greater proportion were "Other race" in the latter time period (40% vs 47%). Proportion foreign-born also increased from 41% to 57%. Reporting of ever smoking (at least 100 cigarettes) increased from 49% to 60% while no alcohol use increased from 22% to 29%. Mean BMI and waist circumference increased slightly, but the proportion categorized as obese remained similar (under 20%). Mean ALT was higher between 1999–2006 compared to 2007–2014 with values of 47 vs 36 U/L, respectively. Only mean platelet count was significantly different between cohort years with decrease from 248 to 215 cells/uL (p=0.004).

Of 29 total deaths among chronic HBV between 1999–2014, the majority of deaths were attributed to other causes (n=16; 57%), followed by heart disease (n=6; 21%) and malignant neoplasms (n=5; 18%) (results for two categories were suppressed due to low number of persons). Among decedents, 55% were men and the median age at death was 66 years (IQR 57–81).

Age- and Sex-Standardized Mortality Rates

Age- and sex-adjusted all-cause mortality rate for the entire cohort over the 16-year period was 12.1 per 1000 person-years (Supplemental Table 2). The overall mortality rate was 11.8 per 1000 person-years among uninfected, 15.1 per 1000 person-years among prior infected,

and 21.4 per 1000 person-years among chronically infected. There was a significant trend towards decreasing all-cause mortality rates among all groups when mortality rates were examined in 4-year intervals (p-value for linear trend=0.01 for chronic infection, p=0.02 for prior infection and p<0.001 for no infection) (Figure 2). Overall age- and sex-adjusted liver-related mortality rates were highest among those with chronic infection, estimated at 4.1 per 1000 person-years (95% CI 1.9–10.0). Estimated liver-related mortality in those with prior infection was lower at 0.3 per 1000 person-years (95% CI 0.1–0.6) and lowest in those without infection at 0.1 per 1000 person-years (95% CI 0.1–0.2). Notably no liver-related deaths occurred in participants with chronic infection recruited between 2007–2014.

Risk of All-Cause and Liver-Related Mortality by HBV Status

In Cox regression analysis using no infection as the comparator group, the crude HR for all-cause mortality was 1.3 (95% CI 1.1–1.4; p=0.001) in the prior infection group and 1.9 (95% CI 1.1–3.3; p=0.02) in the chronic infection group (Table 2). In multivariate analysis, the HR was 1.1 (95% CI 1.0–1.3; p=0.2) in the prior infection group and 1.9 (95% CI 1.1–3.3; p=0.03) in the chronic infection group. There was no interaction between chronic infection and cohort years (p=0.62) suggesting the association between mortality and chronic infection did not differ statistically over the two time periods (1999–2006 vs 2007–2014).

While liver-related mortality was 2.5-fold higher in prior infection compared to no infection in crude analysis (95% CI 1.4–4.5), the adjusted HR of 1.7 was not statistically significant in multivariable analysis (95% CI 0.9–3.3). Among participants with chronic infection, the adjusted analysis showed a 13.3-fold higher likelihood of dying from a liver-related cause than those with no infection (95% CI 3.9–45.5).

Predictors of Mortality among Adults with Chronic HBV

Factors associated with all-cause mortality among chronically infected adults in univariate analysis included foreign-born, smoking, alcohol use, hypertension, and ALT level (p<0.1). HBV treatment was not associated with mortality (p=0.36). The only independent predictors of all-cause mortality among chronically infected adults were heavy alcohol use (HR 18.3, 95% CI 3.3–100.6) and elevated ALT (HR 1.02 per 10-unit increase, 95% CI 1.00–1.03) (see Table 3).

Discussion

Using population-based survey data, we demonstrate that mortality in the United States among chronically infected adults with HBV exceeded that of uninfected by two-fold over the past two decades. Deaths related to cirrhosis and HCC are postulated drivers of this difference, with chronically infected persons incurring a 13-fold increased risk of liver-related mortality over the same time period. While there was a numeric trend towards decreased overall mortality among chronic HBV-infected for the 1999–2014 time period, we did not detect a statistical difference, which may be attributed to lack of power from low HBV prevalence in the NHANES cohort or reflect insufficient penetrance of antiviral therapy among those with chronic HBV infection.

To date, population-based studies using national death certificate data have provided estimates of US death rates attributable to HBV, reported at 0.85 per 100,000 persons in 2007 and 0.67 per 100,000 in 2016 (annual percent change −2.1%)[8, 15]. However, population-based data on mortality risk among individuals with chronic HBV are lacking. The Chronic Hepatitis Cohort Study (CHeCS), recruited at four healthcare centers between 2006–2013, corroborates our study findings as they observed a similar 1.9-fold increased risk of all-cause mortality and 16-fold increased risk of liver-related mortality compared to the general US population[10]. A striking 81% did not have hepatitis B infection reported on their death certificates, emphasizing the limitations of death certificate analyses[10].

There are many potential explanations for the persistent excess mortality over a time period in which improved HBV therapeutics have become increasingly available, with lamuvidine approved in 1998, entecavir in 2005 and tenofovir in 2008. Barriers to effective delivery of care along each step of the HBV care cascade, from insufficient screening and awareness to low provision or uptake of treatment in eligible patients, may be contributing. Across various clinical settings in the US, up to 40–60% of treatment-eligible patients are not on treatment[16, 17]. The low percentage currently on therapy in our cohort (6%) suggests uptake as an issue, although based on ALT alone only an additional 8% would be definitively eligible without additional clinical information. Diminished access to care, including drug availability and cost concerns, among at-risk populations such as immigrants, incarcerated and injection drug users is one possible obstacle[18]. The complexity of confirming treatment eligibility for chronic HBV and need for lifelong monitoring and therapy, in comparison to the more straightforward regimens for hepatitis C virus, may also contribute to inadequate uptake[19]. Furthermore, while HBV treatment improves outcomes, it does not completely ameliorate risk of HCC, particularly among those with a long duration of infection or pre-existing cirrhosis[20]. In one US study of which liver disease etiology was not considered, a decline in HCC (2.7% decrease per year) as cause of death among Asians in the same time period of our study was observed[21], potentially reflecting improved screening practices or HBV treatment uptake/response. Thus, the impact of antiviral therapy on all-cause mortality among HBV-infected may be anticipated in future NHANES cohorts.

We found heavy alcohol use and higher ALT to be independent predictors of all-cause mortality among those with chronic HBV infection. While we acknowledge that use of simple imputation for missing alcohol use responses in our study may have biased alcohol risk estimates toward the null hypothesis, the mortality HR for the high alcohol use group remained statistically significant despite this. Alcohol use as an independent predictor of death among chronic HBV patients has been demonstrated in studies from Europe and Asia[22–24]. The combination of HBV and alcohol not unexpectedly leads to more rapid progression to cirrhosis than HBV alone and increased carcinogenesis, manifested by an up to 8-fold higher risk of HCC[24–26]. Furthermore, the overall rising rates of and mortality from alcohol-related liver disease and non-alcoholic fatty liver disease (NAFLD) in US, including among HBV-infected, may negate some of the mortality benefits from HBV therapy[21, 27]. Screening and counseling on the dangers of concurrent alcohol use need to be prioritized among those with existing liver injury due to HBV, including those without active disease or on treatment.

Serum ALT is an important marker of hepatic inflammation and a key parameter in clinical decision making on HBV treatment initiation[28]. Encouragingly, the mean ALT among HBV-infected was lower in the later time period (36 U/L in 2007–2014) compared to the earlier time period (47 U/L in 1999–2006) and may indirectly suggest increased uptake of treatment. However, the ALT level may also reflect a secondary cause of liver disease such as NAFLD. Assessment and counseling for NAFLD risk factors should be incorporated into routine management of chronic HBV patients. Furthermore, the positive association between ALT level and mortality in this study is consistent with other observational studies, the largest of which (REVEAL-B study) demonstrated that ALT independently predicted development of cirrhosis and HCC[29]. We described in a previous study that less than half of NHANES participants with an elevated ALT and chronic HBV infection were aware of their disease[30]. For improvement in HBV-related mortality to be realized, evidence-based strategies to promote screening for HBV among individuals with elevated liver tests in the primary care setting should be implemented, followed by linkage to specialty care for treatment initiation[31].

While the major strengths of this study are decreased selection bias from a population-based sample and robust linkage between serologic data and vital status, several limitations are present. First, mortality among chronic HBV and prior HBV-infected are likely underestimated by the exclusion of incarcerated and homeless populations in NHANES sampling. The low prevalence of chronic infection in the US resulted in a small number of infected patients despite the large number of total patients sampled, thus limiting the precision of our results. Absence of available viral and host characteristics, including HBV DNA, hepatitis B e-antigen status and cirrhosis, did not allow further risk stratification among those with chronic infection. While we had limited data on receipt of HBV therapy, we were unable to demonstrate or make direct conclusions on the impact of these therapies given small percentage (6%) on therapy. The addition of an HBV-specific questionnaire to NHANES (including self-reported treatment) starting in the 2013–2014 cycle will facilitate assessment of treatment influence in future studies. Due to long latency between disease onset and adverse outcomes, an even longer period of follow-up may be required to appreciate the full impact of current HBV treatments on a population level[32]. Notably these results may not be generalizable to other countries or regions outside of the US, however, despite small sample size with chronic infection, we do believe our results to be nationally representative of our racially diverse population with HBV.

In summary, the presence of HBV infection in chronically infected adults living in the US continues to contribute to excess mortality, both all-cause and liver-related, despite availability of highly effective antiviral therapy that can reduce these risks. With elimination of viral hepatitis a growing global reality, concurrent with developing a HBV functional cure, greater efforts are needed by policy makers and key stakeholders to expand treatment access and delivery across the broader HBV-infected US population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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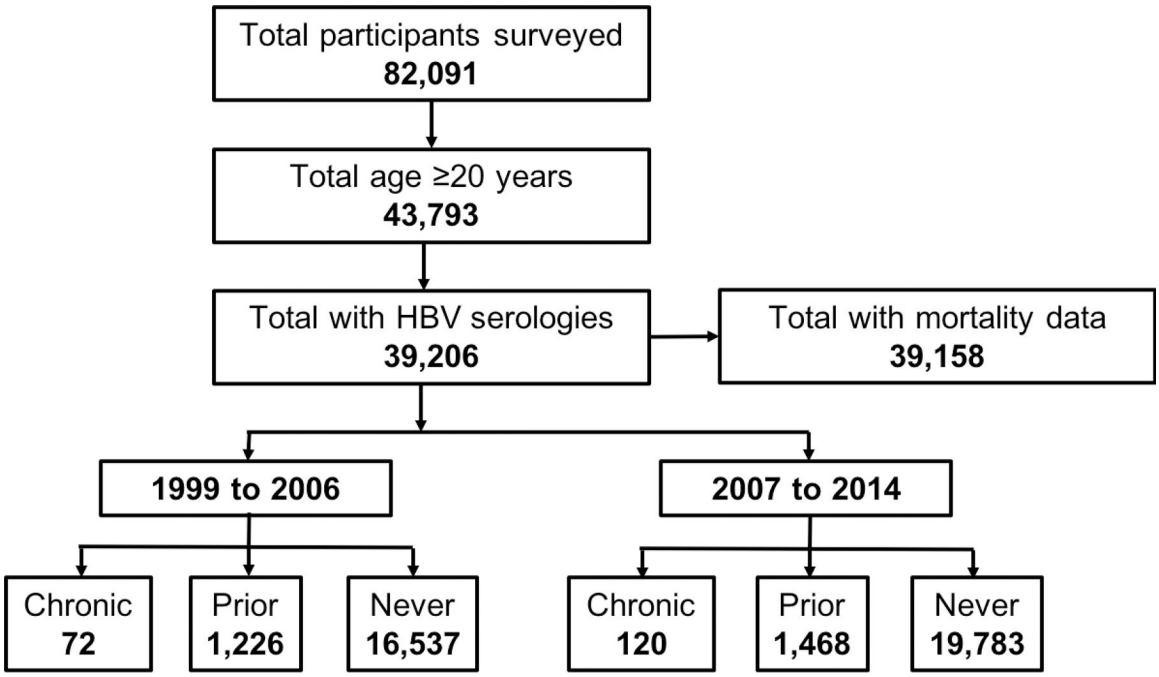
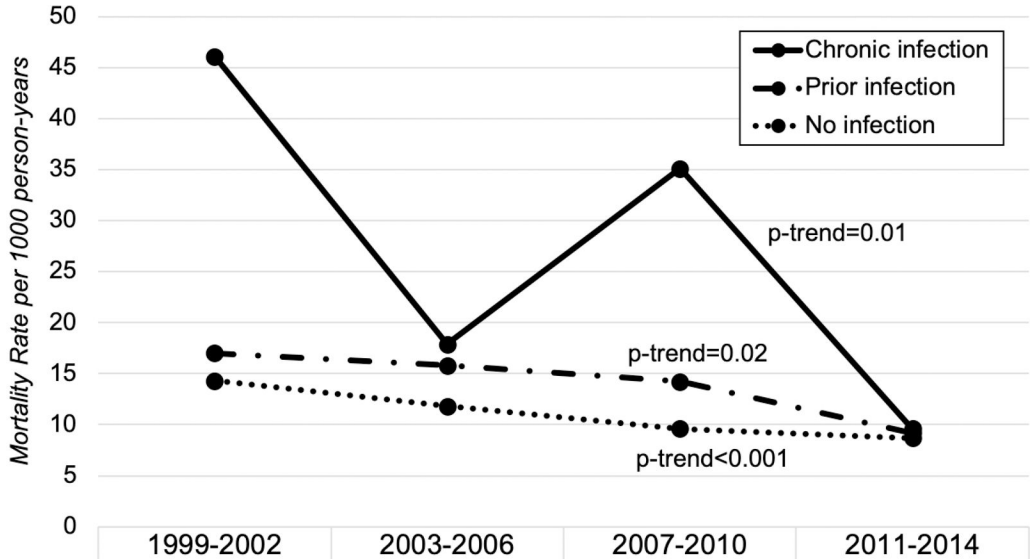


Figure 1.

NHANES Cohort Selection

Abbr: HBV=hepatitis B virus; anti-HBc=hepatitis B core antibody; HBsAg=hepatitis B surface antigen

"Chronic" infection defined as anti-HBc+/HBsAg+; "Prior" infection defined as anti-HBc+/HBsAg-; "Never" infection defined as anti-HBc-/HBsAg-



	1999-2002	2003-2006	2007-2010	2011-2014
Chronic infection	46.1	17.9	35.1	9.6
Prior infection	17	15.8	14.2	9.2
No infection	14.3	11.8	9.6	8.7

Figure 2.

Trend in All-Cause Mortality Rates by Chronic Hepatitis B Status in 4-year Intervals (1999–2014)

All-cause age- and sex-standardized mortality rates for chronic infection (solid), prior infection (solid/dot) and no infection (dotted) presented per 1000 person-years by 4-year intervals between 1999 and 2014. P-value given for linear trend.

Table 1.

Baseline Characteristics Among Adults Aged 20–85 Years by Hepatitis B Status

Characteristics	No infection N=36,320	Prior infection N=2694	Chronic infection N=192
Age, years	46.2 ± 0.1	47.4 ± 0.2	47.2 ± 0.5
Male, %	47.9 ± 0.2	53.4 ± 1.6	58.2 ± 3.9
Race, %			
Mexican	8.0 ± 0.6	4.0 ± 0.6	2.5 ± 1.3
White	72.3 ± 1.1	38.5 ± 1.8	27.0 ± 4.0
Black	9.7 ± 0.6	26.5 ± 1.5	26.7 ± 3.9
Other[b]	10.0 ± 0.6	31.0 ± 1.9	43.8 ± 4.3
Foreign-born, %	14.5 ± 0.7	40.6 ± 2.0	50.2 ± 5.3
Married, %	64.5 ± 0.5	56.8 ± 1.6	55.8 ± 5.6
Poverty Index >1, %	13.9 ± 0.5	21.6 ± 1.2	19.8 ± 3.9
Education, %			
<HS	17.5 ± 0.5	27.1 ± 1.3	24.1 ± 3.7
HS or eq	23.8 ± 0.5	24.0 ± 1.4	24.2 ± 3.8
>HS (college)	58.7 ± 0.8	48.9 ± 1.7	51.7 ± 4.6
Ever smoker, %	53.2 ± 0.6	48.9 ± 1.6	54.4 ± 4.2
Alcohol use, %			
None	22.6 ± 0.7	25.4 ± 1.3	26.2 ± 4.1
Low	75.3 ± 0.7	72.0 ± 1.3	72.3 ± 4.4
Heavy[c]	2.1 ± 0.1	2.6 ± 0.4	1.5 ± 1.5[a]
BMI, kg/m^2	28.5 ± 0.1	27.3 ± 0.2	26.8 ± 0.9
Waist circumference, cm	97.7 ± 0.2	94.8 ± 0.5	93.0 ± 1.6
Diabetes, %	9.0 ± 0.2	11.0 ± 0.6	13.4 ± 3.2
Hypertension, %	29.7 ± 0.3	29.6 ± 1.0	27.6 ± 4.1
Hyperlipidemia[d], %	68.9 ± 0.4	68.4 ±1.4	61.7 ± 4.0
Obesity, %	34.0 ± 0.4	27.2 ± 1.4	17.8 ± 3.9
ALT, U/L	25.6 ± 0.1	28.2 ± 0.5	40.2 ± 6.0
AST, U/L	25.2 ± 0.1	28.2 ± 0.6	36.1 ± 4.6
ALP, U/L	68.6 ± 0.3	69.9 ± 0.7	70.3 ± 2.4
Total bilirubin, mg/dL	0.7 ± 0.004	0.7 ± 0.01	0.8 ± 0.03
Platelet count, cells/uL	257.8 ± 0.7	251.0 ± 2.0	230.3 ± 5.9
Albumin, g/dL	4.3 ± 0.004	4.3 ± 0.01	4.3 ± 0.04
Creatinine, mg/dL	0.88 ± 0.002	0.88 ± 0.01	0.89 ± 0.03
HCV-infected, %	0.7 ± 0.06	7.4 ± 0.7	2.9 ± 1.4[a]

Data are presented as mean or % ± SE

BMI = body mass index; ALT = alanine aminotransferase; AST = aspartate aminotransferase, ALP = alkaline phosphatase; GGT = gamma glutamyl-transferase; HCV = hepatitis C virus

[a]Does not meet the standard of statistical reliability and precision (relative SE≥30%)

[b] Includes non-Mexican Hispanics, Aleut, Eskimo, American Indian, and Asian or Pacific islander.

[c] Defined as >4 drinks/day in men and >2 drinks/day in women.

[d] Based on non-fasting values

Table 2.

Crude and Adjusted Risk of All-Cause and Liver-Related Mortality by Hepatitis B Status

	Hazard Ratio for All-Cause Mortality				Hazard Ratio for Liver-Related Mortality			
HBV status	**Crude**	**95% CI**	**Adjusted†**	**95% CI**	**Crude**	**95% CI**	**Adjusted‡**	**95% CI**
No infection	Ref		Ref		Ref		Ref	
Prior infection	1.3	1.1–1.4	1.1	0.95–1.3	2.5	1.4–4.5	1.7	0.9–3.3
Chronic infection	1.9	1.1–3.3	1.9	1.1–3.3	17.0	6.1–47.6	13.3	3.9–45.5

†Adjusted for age, sex, race/ethnicity, cohort years, foreign-born, marital status, poverty, education, smoking, alcohol use, diabetes, hypertension, hyperlipidemia, waist circumference, and alanine aminotransferase

‡Adjusted for age, race/ethnicity, cohort years, foreign-born, smoking, alcohol use, hyperlipidemia, waist circumference, and alanine aminotransferase

Table 3.

Multivariable Predictors of All-Cause Mortality among Adults with Chronic Hepatitis B (n=191)

Variables	Hazard Ratio	95% CI	p-value
Sex			
Male	1.0		
Female	0.8	0.2–2.9	0.75
Cohort 8-yr			
1999–2006	1.0		
2007–2014	1.4	0.5–3.9	0.56
Race / Ethnicity			
NH White	1.0		
NH Black	1.8	0.6–5.8	0.33
Mexican	2.8	0.6–14.2	0.21
Other	0.9	0.2–5.6	0.95
Foreign Born			
US	1.0		
Foreign	0.6	0.3–1.4	0.22
Alcohol use			
No	1.0		
Low[†]	1.1	0.4–3.3	0.86
Heavy	18.3	3.3–100.6	**<0.001**
ALT (U/L)[‡]			
Per 10 unit increase	1.02	1.00–1.03	**0.01**

[†]Missing alcohol use data imputed as low (n=24)

[‡]Missing for ALT value (n=2)