scientific reports

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Association between resolved hepatitis B virus infection and depression in American adults : a cross-sectional study

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Hepatitis B virus (HBV) infection is a global health concern, and it can potentially affect mental health like depression. Resolved HBV infection, often perceived as a milder form of HBV infection, are often overlooked, and the association between it and depression remains unclear. This study aims to investigate the association between resolved HBV infection and depression. A cross-sectional analysis was conducted using the National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2018, including 20,655 adult Americans. Resolved HBV infection was defined as HBV surface antigen (HBsAg) negative and HBV core antibody (HBcAb) positive. Depression was assessed using the Patient Health Questionnaire-9 (PHQ-9) score. Propensity score matching (PSM) was performed to balance baseline characteristics. Algorithms such as inverse probability of treatment weighting (IPTW) were also applied. Among the participants, 1,551 (7.5%) were reported to have resolved HBV infection. Depression was reported by 1,796 participants (8.7%), with a higher prevalence among those with resolved HBV infection (10.6%) compared to those without HBV infection(8.5%). PSM and IPTW revealed a significantly positive association between resolved HBV infection and depression (PSM: OR = 1.40, 95%CI 1.09–1.79, $p = 0.008$; IPTW: OR = 1.48, 95%CI 1.26–1.74, $p < 0.001$). Subgroup and sensitivity analyses supported the robustness of the findings. The results suggest a complex relationship between resolved chronic viral infections and mental health. Based on this finding, it is advisable to conduct psychological monitoring and offer support to individuals who have achieved a functional cure for HBV. Further prospective studies are still needed to reveal the potential mechanism.

Keywords Resolved hepatitis B virus infection, Depression, Adults, NHANES

Globally, approximately 257 million individuals are chronically infected with the hepatitis B virus (HBV)[1,2]. Annually, nearly 1 million deaths result from complications of HBV infection[3,4]. It is estimated that in the United States alone, approximately 2.2 million people are infected with hepatitis B virus (HBV) annually[5]. However, individuals who have recovered from HBV infection, often perceived as having experienced a milder form of HBV infection, are often overlooked. It is not uncommon, and an estimated 9.87 million U.S. adults are affected[6].

Resolved HBV infection refers to individuals who have eliminated the virus from their bloodstream and achieved a non-infectious state, also known as individuals with HBV surface antigen (HBsAg) negative and HBV core antibody (HBcAb) positive detected[6,7]. Clearance of HBsAg is currently considered the optimal treatment outcome for HBV infection, marking a safe endpoint for acute or chronic HBV infection therapy, termed 'functional cure' or 'resolved HBV infection'[8]. However, studies indicate that covalentaly closed circular DNA, serving as a template for viral RNA transcription within long-lived liver cell nuclei, can persist indefinitely, acting as a reservoir for viral replication[9]. This persistent viral DNA can reactivate under specific conditions, potentially leading to a spectrum of complications and ongoing liver damage[10]. Consequently, risks persist for HBsAg seroreversion, HBV reactivation, cirrhosis, and hepatocellular carcinoma[10,11]. Moreover, other research indicates that compared to patients without chronic liver disease, mortality rates remain significantly elevated among individuals cured of HBV infection[12]. Therefore, individuals with resolved HBV infection also necessitate

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continued special medical monitoring and regular checkups to detect any signs of liver damage and viral reactivation[10,11,13].

Depression, which is clinically known as major depressive disorder or clinical depression, is one of the most common psychiatric conditions. Reported prevalence rates over a 12-month period and across a lifetime are 7.2 and 10.8% respectively[14]. It is also one of the leading causes of disease burden or death worldwide[15,16]. The World Health Organization forecasts that by 2030, it will ascend to the leading cause of disease burden worldwide[17,18]. Co-occurrence of depressive symptoms with HBV infection is not unusual[19]. Research from Vietnam indicates a 37.5% prevalence of depressive symptoms among chronic HBV infection patients[20], with reporting a 58.6% incidence of depression among them[21]. Moreover, chronic HBV infection significantly impacts overall psychological health-related quality of life (HRQL) and contributes to depression and anxiety[22].

Currently, the majority of researches focus on the relationship between current HBV infection and depression. However, there are limited studies delving into the connection between resolved HBV infection and depression. Further investigations into the association between resolved HBV infection and depression would enhance understanding of the psychological profiles of individuals with resolved HBV infection, and provide comprehensive insights for clinicians managing patients with resolved HBV infection and depression. Therefore, this cross-sectional study aims to investigate whether a significant correlation exists between resolved HBV infection and depression in adults derived from the National Health and Nutrition Examination Survey (NHANES).

Methods

Data source

Executed by the National Center for Health Statistics (NCHS) under the aegis of the Centers for Disease Control and Prevention (CDC), NHANES constitutes a cross-sectional survey targeting the non-institutionalized civilian populace of the United States[23]. The survey entails physical examinations, interviews, and laboratory assessments conducted at mobile examination centers (MECs), following initial demographic, socioeconomic, and health-related interviews conducted in participants' residences. Sensitive topics were addressed privately within the MECs. Ethical approval was granted by the NCHS Ethics Review Board, with informed consent obtained from all participants. All methods were carried out in accordance with relevant guidelines and regulations. Full details on NHANES methodology and ethics are available on the CDC and NCHS websites (https://www.cdc.gov/nchs/nhanes/index.htm).

This study extracted data from adult participants (≥20 years) across 7 NHANES cycles (2005–2018). Exclusion criteria included pregnancy, HBsAg positivity, or missing data on relevant variables[24–26]. Ultimately, the analysis encompassed 20,655 participants.

HBV markers

In accordance with NHANES protocols, the assessment of HBV markers employed VITROS reagent kits and calibrators, executed on the VITROS ECi/ECiQ or VITROS 3600 Immunoassay System. Utilizing competitive immunoassay technology with horseradish peroxidase (HRP) as the label, antigen or antibody levels in the samples were quantified through chemiluminescent reactions indicative of HRP conjugate binding[27].

The VITROS HBsAg test results, expressed as signal-to-cutoff ratios (s/c), are classified as negative (< 1.00), positive (> 5.00), or reactive (≥ 1.00 and ≤ 5.00). Confirmatory testing with the VITROS Immunoassay Product HBsAg Confirmation Reagent Kit was required for reactive results to ascertain positivity. Results between ≥ 5.00 mIU/mL and < 12.0 mIU/mL were considered "Indeterminate". Initial VITROS HBcAb test results were deemed positive if the s/c was < 0.90, while results within 1.10 to 4.80 indicated negativity. For results ≥ 4.8, a retest following a 1:20 dilution was performed. Specimens with results between ≥ 0.90 and ≤ 1.10 underwent two additional confirmatory tests. No HBV infection was defined by negative results for both HBsAg and HBcAb, while resolved HBV infection was indicated by negative HBsAg and positive HBcAb results.

Depression

The Patient Health Questionnaire-9 (PHQ-9) was employed to identify depression during private interviews in MECs. The PHQ-9, a validated 9-item questionnaire[28], assesses depressive symptoms on a four-point scale (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day), yielding scores from 0 to 27. A score of 10 or higher, with a sensitivity and specificity of 88% for depression detection, was used to diagnose clinical depression[28–31].Using PHQ-9 (Patient Health Questionnaire-9), major depression was identified in MECs during private interview sessions. In the PHQ-9, nine items are scored on a four-point scale (0 = never; 3 = almost every day), with scores ranging from 0 to 27. Our study defined depression with scores ≥ 10 according to the previous paper[28,32–34].

Covariates

Several covariates were evaluated as potential factors associated with depression and HBV infection. These included age (continuous variable), educational attainment, race/ethnicity, gender, body mass index (BMI), marital status, alcohol consumption, smoking status, poverty income ratio (PIR), selective serotonin reuptake inhibitor (SSRI) use, reported medical comorbidities, and related blood laboratory tests. Race/ethnicity categories included Mexican American and other Hispanic, Non-Hispanic White, Non-Hispanic Black, and other races as defined by NHANES. Educational levels were dichotomized as "≤ high school" and "> high school". Marital status was categorized as: married or cohabitating; divorced, separated, or widowed; and never married. Income level was assessed by poverty-income ratio (PIR), which was calculated by dividing family (or individual) income by poverty guideline. A drinker was defined as someone consuming at least 12 drinks annually. Smoking status was classified into current, former, and never smokers, with "never smokers" having smoked fewer than

100 cigarettes, "former smokers" having smoked more than 100 cigarettes previously, and "current smokers" actively smoking at the time of the interview. BMI was calculated as weight (kg) divided by height squared (m^2). SSRI use was determined based on participant self-report. Comorbid conditions included diabetes, depression, heart disease (angina, myocardial infarction, chronic heart failure, coronary disease), pulmonary disease (emphysema, asthma, chronic bronchitis), hypertension, arthritis, and cancer. Comorbidities were ascertained through specific questions regarding medical diagnoses. Relevant laboratory tests used to predict liver function included measurements of albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total bilirubin, cholesterol, and triglycerides[35].

Statistical analyses

Descriptive analyses were conducted for all participants. Continuous data were summarized using means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on their distribution[35]. Categorical variables were expressed as percentages. The Chi-square test was used for categorical variables, and student's t test, one-way analysis of variance (ANOVA) or Kruskal-Wallis test were employed for continuous variables. Statistical significance was determined by comparing adjusted odds ratios (OR) with 1.0 and reporting 95% confidence intervals (CI). Besides, baseline imbalance in covariates may introduce confounding bias and potentially distort the observed association between exposure and outcome. To address this, we used logistic regression to estimate propensity scores for propensity score matching (PSM). A 1:1 nearest neighbor matching algorithm with a caliper width of 0.3 was applied without replacement. All measured baseline covariates were included in the propensity score model. The standardized mean difference (SMD) was calculated to evaluate matching quality, with an SMD threshold of <0.1 considered acceptable for minimal residual imbalance. Meanwhile, the inverse probability of treatment weighting (IPTW) can assign weights to observations to mimic randomization and ensure covariates distributions comparable. Therefore, using the estimated propensity scores as weights, we applied the inverse probability of treatment weighting (IPTW), pairwise algorithmic (PA), and overlap weight (OW) models to generate a weighted cohort.

In the subgroup analysis, multivariate logistic regression was utilized to assess the heterogeneity within subgroups. The regression models included the covariates utilized in the PSM algorithm for sample matching. Bonferroni correction was applied for multiple comparisons. Furthermore, a likelihood ratio test was carried out to assess the interaction between subgroups and resolved HBV infection. Multivariate logistic regression analyses were conducted to examine the independent associations after adjusting for all covariates listed in Table 1.

All analyses were conducted using R (http://www.R-project.org, The R Foundation) and Free Statistics software versions 1.9. A two-tailed p-value <0.05 was considered statistically significant.

Result

Study population

A total of 39,749 individuals aged > 20 years old from the NHANES cycles of 2005–2018 were initially included in this cross-sectional study. After excluding individuals with pregnancy ($n=708$), HBsAg positive($n=201$), missing data on HBsAg and HBcAb ($n=12,877$), depression($n=2521$) and covariates ($n=2787$), a final sample of 20,655 participants were included in the analysis. Following PSM, 1546 pairs were matched. The enrollment flowchart is presented in Fig. 1.

Baseline characteristics

Out of the 20,665 participants, 1551(7.5%) were found to have resolved HBV infection. After PSM, participant characteristics were well-balanced between the no HBV infection and resolved HBV infection groups. The mean age of the participants was 56.4 ± 15.6; the mean BMI was 27.9 ± 6.1 kg/m2 and the mean PIR was 2.2 ± 1.5. Detailed demographic characteristics of all participants and the matched cohort are presented in Table 1.

Association between resolved HBV and depression

Before PSM, participants with resolved HBV infection had a significantly higher risk of depression compared to those with no HBV infection (10.6% vs.8.5%, $p=0.001$). After PSM, similar findings were still observed (10.6% vs.7.8%, $p=0.008$, Table 2).

Before PSM, a positive association between resolved HBV infection and depression was observed(OR = 1.27, 95%CI 1.07–1.50, $p=0.006$). After PSM, a positive association was observed between resolved HBV infection and depression (OR = 1.40, 95%CI 1.09–1.79, $p=0.008$). Consistent results were obtained using weighting analysis with IPTW and OW (IPTW: OR = 1.48, 95% CI 1.26–1.74, $p<0.001$; OW: OR = 1.30, 95% CI 1.00-1.69, $p=0.048$). Nevertheless, the weighted calculation analysis using PA was (OR = 1.24, 95%CI 0.98–1.58, $p=0.078$), which is not statistic significantly (Fig. 2).

Sensitivity analyses

After adjusting for all covariates listed in Table 1, multivariate logistic regression analyses in the full-participant cohort yielded consistent findings. Resolved HBV infection demonstrated a positive association with depression (OR = 1.25, 95% CI 1.03–1.51, $p=0.021$). After adjusting for the propensity score, the results remained stable, although statistical significance in the PA model (Fig. 2).

The subgroup analyses demonstrated a positive association between resolved HBV infection and depression, irrespective of the subgroup being considered. No significant interactions were found in various subgroups, including age, gender, PIR, BMI, diabetes, hypertension and SSRI (all the p for interaction > 0.05), and the results were stable (Fig. 3). This is also true for subgroups of heart disease, cancer and various comorbidities (Supplementary Fig. 1).

Variables	Unmatched participants				Propensity score matched participants			
	Total ($n=20665$)	No HBV infection ($n=19104$)	Resolved HBV Infection ($n=1551$)	SMD	Total ($n=3092$)	No HBV infection ($n=1546$)	Resolved HBV infection ($n=1546$)	SMD
Gender, female, n (%)	10,256 (49.7)	9590 (50.2)	666 (42.9)	0.146	1356 (43.9)	690 (44.6)	666 (43.1)	0.031
Age	49.4 (17.6)	48.83 (17.71)	56.70 (14.40)	0.488	56.4 (15.6)	56.18 (16.83)	56.63 (14.37)	0.029
Race/Ethnicity, n (%)				0.902				0.056
Mexican American	3090 (15.0)	2981 (15.6)	109 (7.0)		212 (6.9)	103 (6.7)	109 (7.1)	
Other Hispanic	1775 (8.6)	1589 (8.3)	186 (12.0)		388 (12.5)	202 (13.1)	186 (12.0)	
Non-Hispanic White	9829 (47.6)	9536 (49.9)	293 (18.9)		565 (18.3)	272 (17.6)	293 (19.0)	
Non-Hispanic Black	4245 (20.6)	3672 (19.2)	573 (36.9)		1171 (37.9)	598 (38.7)	573 (37.1)	
Other race	1716 (8.3)	1326 (6.9)	390 (25.1)		756 (24.5)	371 (24.0)	385 (24.9)	
Education Level, > high school, n (%)	10,871 (52.6)	10,170 (53.2)	701 (45.2)	0.161	1423 (46.0)	723 (46.8)	700 (45.3)	0.03
Marital status, n (%)				0.18				0.022
Married or living with partner	12,411 (60.1)	11,538 (60.4)	873 (56.3)		1723 (55.7)	853 (55.2)	870 (56.3)	
Divorced, separated, or widowed	4610 (22.3)	4156 (21.8)	454 (29.3)		916 (29.6)	464 (30.0)	452 (29.2)	
Never married	3634 (17.6)	3410 (17.8)	224 (14.4)		453 (14.7)	229 (14.8)	224 (14.5)	
PIR, Mean (SD)	2.6 (1.6)	2.59 (1.64)	2.24 (1.56)	0.221	2.2 ± 1.5	2.22 (1.53)	2.24 (1.56)	0.011
Drinking, n (%)	15,020 (72.7)	13,989 (73.2)	1031 (66.5)	0.148	2078 (67.2)	1048 (67.8)	1030 (66.6)	0.025
Smoking status, n (%)				0.107				0.03
Never	11,061 (53.6)	10,307 (54.0)	754 (48.6)		1479 (47.8)	728 (47.1)	751 (48.6)	
Former	5139 (24.9)	4715 (24.7)	424 (27.3)		857 (27.7)	434 (28.1)	423 (27.4)	
Current	4455 (21.6)	4082 (21.4)	373 (24.0)		756 (24.5)	384 (24.8)	372 (24.1)	
BMI (kg/m2), Mean (SD)	29.1(6.8)	29.14 (6.88)	28.02 (6.16)	0.172	27.9 (6.10)	27.81 (6.01)	28.03 (6.16)	0.036
Diabetes, n (%)	2440 (11.8)	2185 (11.4)	255 (16.4)	0.145	486 (15.7)	234 (15.1)	252 (16.3)	0.032
Hypertension, n (%)	7352 (35.6)	6673 (34.9)	679 (43.8)	0.182	1318 (42.6)	643 (41.6)	675 (43.7)	0.042
Heart disease, n (%)	1649 (8.0)	1503 (7.9)	146 (9.4)	0.055	286 (9.2)	140 (9.1)	146 (9.4)	0.013
Pulmonary disease, n (%)	3742 (18.1)	3470 (18.2)	272 (17.5)	0.016	516 (16.7)	244 (15.8)	272 (17.6)	0.049
Cancer, n (%)	1933 (9.4)	1805 (9.4)	128 (8.3)	0.042	249 (8.1)	121 (7.8)	128 (8.3)	0.017
Stroke, n (%)	710 (3.4)	637 (3.3)	73 (4.7)	0.07	161 (5.2)	88 (5.7)	73 (4.7)	0.044
Arthritis, n (%)	5590 (27.1)	5136 (26.9)	454 (29.3)	0.053	885 (28.6)	432 (27.9)	453 (29.3)	0.03
SSRI use, n (%)	1398 (6.8)	1313 (6.9)	85 (5.5)	0.058	166 (5.4)	81 (5.2)	85 (5.5)	0.011
Albumin (g/L), Mean (SD)	42.5 (3.3)	42.51 (3.25)	42.06 (3.51)	0.132	42.0 (3.4)	42.04 (3.34)	42.06 (3.51)	0.006
ALT (U/L), Median (IQR)	21.0 (16.0, 28.0)	25.51 (21.09)	27.37 (22.26)	0.086	21.0 (16.0, 29.0)	25.84 (21.68)	27.39 (22.28)	0.07
AST (U/L), Median (IQR)	23.0 (20.0, 28.0)	25.81 (15.60)	29.41 (27.92)	0.159	24.0 (20.0, 29.0)	28.12 (21.91)	29.43 (27.97)	0.052
ALP (U/L), Median (IQR)	65.0 (54.0, 80.0)	68.86 (24.10)	70.11 (26.97)	0.049	66.0 (54.0, 81.0)	70.20 (24.61)	70.09 (26.99)	0.004
GGT (U/L), Median (IQR)	20.0 (14.0, 31.0)	28.99 (41.43)	37.00 (57.14)	0.16	21.5 (15.0, 33.0)	36.14 (79.84)	37.03 (57.22)	0.013
Cholesterol (mmol/L), Mean (SD)	5.0 (1.1)	5.03 (1.08)	4.98 (1.09)	0.045	5.0 (1.1)	4.96 (1.07)	4.98 (1.09)	0.021
Total bilirubin (umol/L), Median (IQR)	12.0 (8.6, 13.7)	12.38 (5.42)	11.67 (5.09)	0.136	10.3 (8.6, 13.7)	11.66 (4.45)	11.69 (5.07)	0.006
Triglycerides (mmol/L), Median (IQR)	1.4 (0.9, 2.1)	1.75 (1.52)	1.75 (1.27)	0.005	1.3 (0.9, 2.1)	1.71 (1.39)	1.74 (1.27)	0.028

Table 1. Baseline characteristics of participants before and after propensity score matching. PIR, poverty income ratio; BMI, body mass index; SSRI, selective serotonin reuptake inhibitor use; HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase.

Discussion

In this cross-sectional analysis of American adults, we utilized data from the NHANES database and employed a propensity score matched design. Our findings indicate that resolved HBV infection is associated with an elevated risk of depression. Subgroup analyses consistently supported these results. These results remained robust across different adjustment models (IPTW: OR = 1.48, 95% CI 1.26–1.74, $p < 0.001$; OW: OR = 1.30, 95% CI 1.00-1.69, $p = 0.048$) and exclusion criteria applied to the participants. In comparison, the PA was not statistically significant(PA: OR = 1.24, 95% CI 0.98–1.58, $p = 0.078$), which may be that the small sample size caused some instability of the results. To our knowledge, this is the inaugural study specifically investigating the correlation between resolved HBV infection and subsequent depressive symptoms.

The global burden of HBV infection is considerable[1,36–39]. While extensive researches have explored the association between HBV infection and its comorbidities[40–45], few studies have delved into the relationship between resolved HBV infection and its potentially related diseases. Previous studies indicated that patients with resolved hepatitis B infection still experience HBV infection related comorbidities such as diabetes[46], decreased bone density[47] and exhibit a significantly higher mortality rate[12], compared to individuals without chronic liver

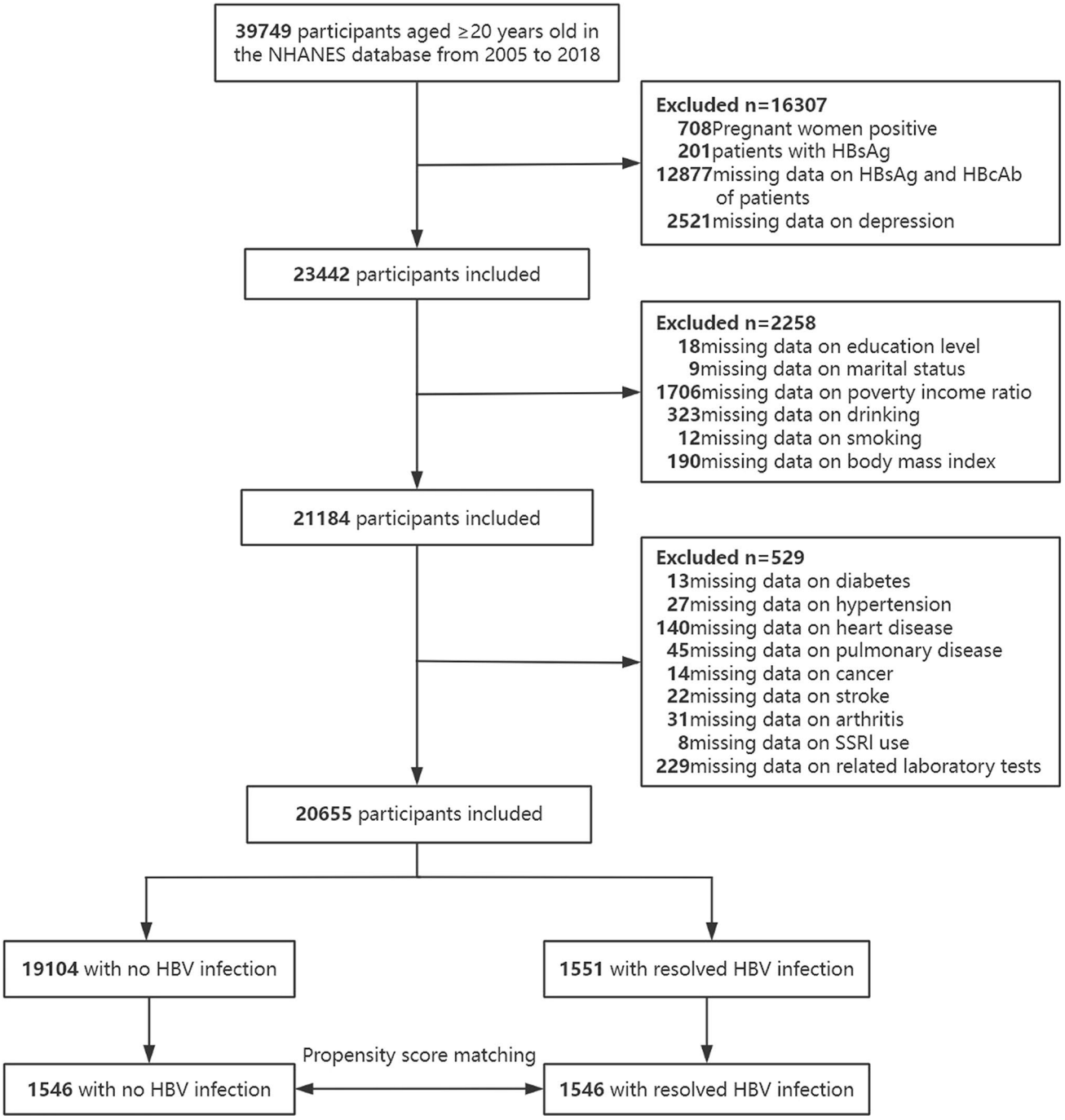

Fig. 1. Flow diagram of the sample selection from the National Health and Nutrition Examination Survey (NHANES) 2005–2018. HBV, hepatitis B virus; SSRI, selective serotonin reuptake inhibitor use.

Variables	Unmatched participants				Propensity score matched participants			
	Total ($n=20665$)	No HBV infection ($n=19104$)	Resolved HBV infection ($n=1551$)	*P*-value	Total ($n=3092$)	No HBV infection ($n=1546$)	Resolved HBV infection ($n=1546$)	*P*-value
Depression, (%)				0.006				0.008
No	18,859 (91.3)	17,472 (91.5)	1387 (89.4)		2807 (90.8)	1425 (92.2)	1382 (89.4)	
Yes	1796 (8.7)	1632 (8.5)	164 (10.6)		285 (9.2)	121 (7.8)	164 (10.6)	

Table 2. Depression status before and after propensity score matching. HBV, hepatitis B virus.

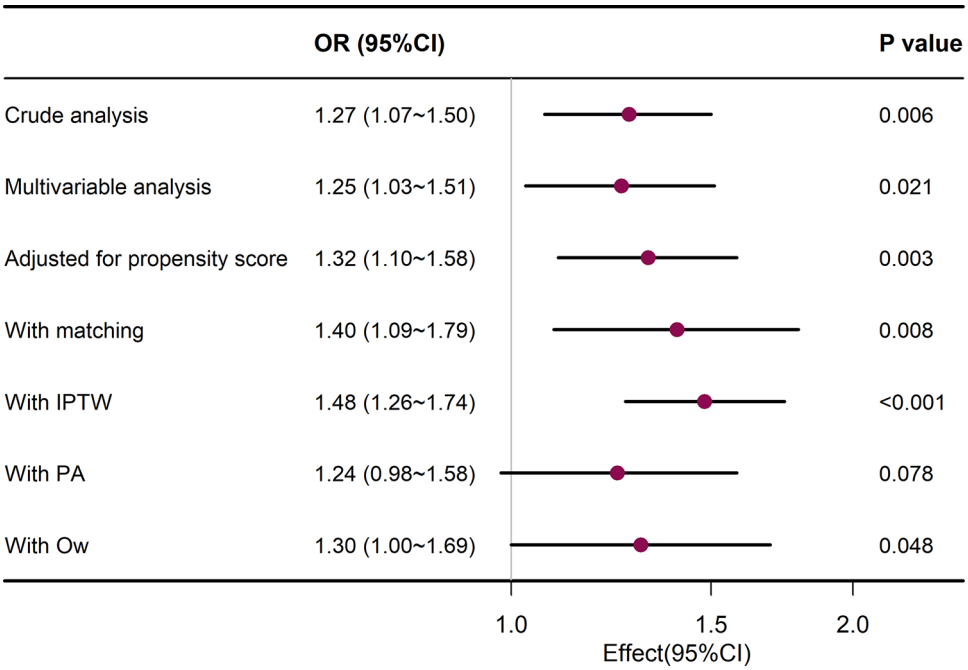

Fig. 2. Forest plot showing the association between resolved HBV infection and depression using different statistical models. IPTW, inverse probability of treatment weighting; PA, pairwise algorithmic; Ow, overlap weight; OR, odds ratios; CI, confidence intervals.

disease. Analyzing data from the NHANES database, our research found that the resolved HBV infection was positively associated with an increased risk of depression, (OR = 1.40, 95%CI 1.09 to 1.79, $p = 0.008$), which advances our understanding of the long-term effects of resolved hepatitis B infection. There have been many researches show that HBV infection may increase the risk of the depression[11,21,48–56]. However, limited research has focused on non-cirrhotic HBV infection, which can help elucidate the direct effects of HBV infection itself on depression, excluding the influence of cirrhosis, a recognized high-risk factor for depression[48,49]. Evidence indicates that even chronic HBV infection patients without cirrhosis experience considerable levels of depression, detrimentally affecting their overall health-related quality of life[57]. Our study participants consisted of participants with resolved HBV infection, a milder form of HBV infection, aligning with prior researches suggesting that even short-term presence of HBV may lead to depressive symptoms.

Current therapeutic modalities inadequately eliminate HBV from the body[58]. The insidious nature of this disease may impact patients' psychological well-being through socio-psychological pathways[20,59,60], even following attainment of clinical cure standards (HBsAg negativity). Patients with HBV infection commonly contend with depression and anxiety primarily due to feelings of isolation, despair, potential social stigma, susceptibility to social exclusion and fear of disease complications[61], all contributing to diminished health-related quality of life (particularly social engagement). Additionally, lingering guilt over past HBV infection, concerns about disease recurrence, and misconceptions regarding HBV transmission may heighten psychological stress in recovered HBV patients[58,62], thereby predisposing them to depression.

The precise mechanistic link between resolved HBV infection and depression remains incompletely understood. One plausible explanation involves heightened inflammatory mediators in chronic liver disease, including IL-6, IL-17 A, TNF-α, etc., directly involving in the pathophysiological process of depression[63,64]. These cytokines stimulate the hypothalamic-pituitary-adrenal (HPA) axis and trigger cortisol release, which correlates strongly with psychotic depression[65,66]. Furthermore, inflammatory cytokines can disrupt synaptic plasticity and neuronal activity, altering synaptic transmission in the brain and precipitating emotional dysregulation that predisposes individuals to depression[67,68]. Additionally, interferon (IFN), commonly employed in HBV infection treatment, may induce depression by reducing synaptic concentrations of serotonin[62,69]. Other potential mechanisms that have been suggested including insulin resistance[70] and alterations in the gut microbiota[71], which can indirectly affect mental health[72].

This study is subject to several inherent limitations. Firstly, due to its cross-sectional nature, it cannot establish a causal relationship between resolved HBV infection and depression. A long-term prospective cohort study containing a large population is required to substantiate such causality. Secondly, as a retrospective analysis, this study may be susceptible to residual confounding, necessitating adjustment for various potential confounders. Although we conducted stratified and sensitivity analyses to mitigate bias[67], unmeasured confounding may still exist. Thirdly, the presence of occult HBV infection (OBI) cannot be definitively ruled out. OBI is characterized by detectable HBV DNA in the liver despite the absence of serum HBsAg, with or without detectable HBV DNA in the blood[73]. However, assessing HBV DNA levels in the liver in large-scale epidemiological studies poses challenges, and data on HBV DNA levels in both liver and blood are lacking in NHANES[47]. Finally, NHANES

Subgroup	Total	Event (%)	OR (95%CI)	P for interaction
Gender				**0.285**
Male	880	72 (8.2)	1.63 (1.08~2.49)	
Female	666	92 (13.8)	1.22 (0.85~1.76)	
Age				**0.440**
<60	816	91 (11.2)	1.10 (0.75~1.60)	
>=60	730	73 (10.0)	1.33 (0.89~2.01)	
PIR				**0.143**
<1.3	583	104 (17.8)	1.68 (1.17~2.43)	
1.3-3.5	587	47 (8.0)	1.03 (0.64~1.66)	
>=3.5	376	13 (3.5)	1.03 (0.41~2.57)	
BMI				**0.493**
<25	522	45 (8.6)	1.24 (0.75~2.05)	
25-30	559	51 (9.1)	1.23 (0.75~2.02)	
>=30	465	68 (14.6)	2.04 (1.26~3.30)	
SSRI				**0.504**
No	1461	136 (9.3)	1.42 (1.06~1.90)	
Yes	85	28 (32.9)	1.59 (0.65~3.85)	
Diabetes				**0.179**
No	1294	135 (10.4)	1.52 (1.13~2.06)	
Yes	252	29 (11.5)	0.98 (0.50~1.91)	
Hypertension				**0.429**
No	871	73 (8.4)	1.25 (0.85~1.84)	
Yes	675	91 (13.5)	1.51 (1.01~2.24)	

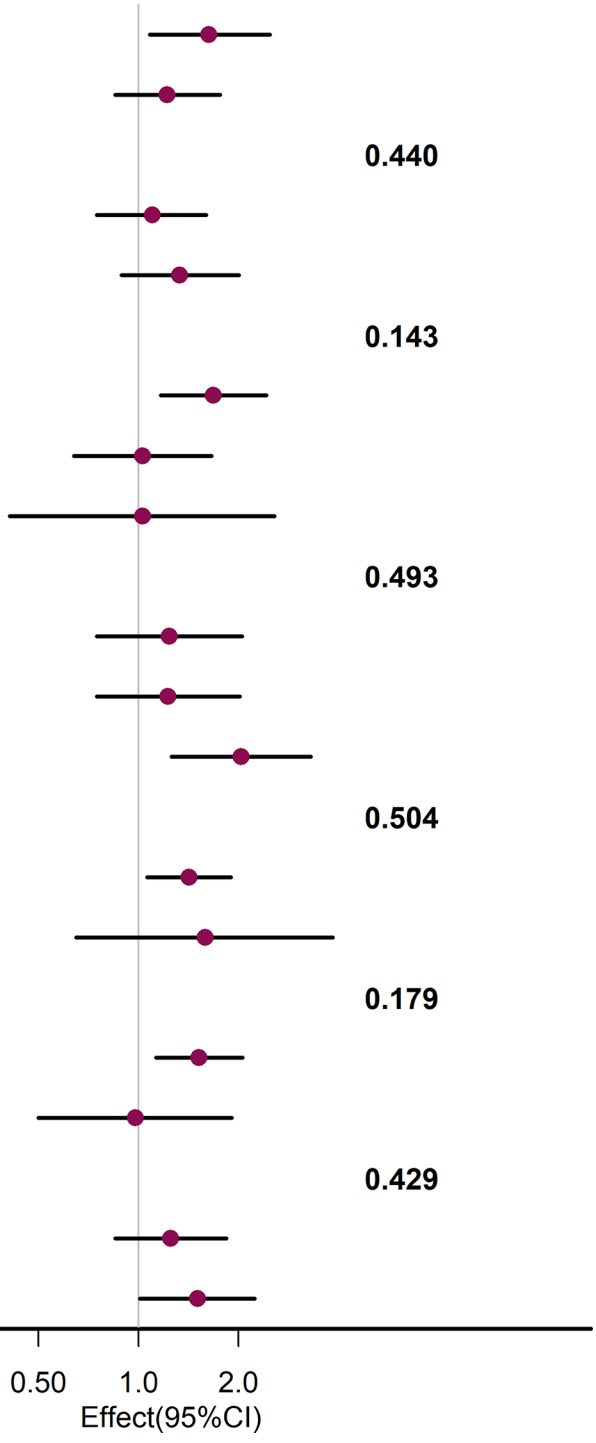

Fig. 3. Association between resolved HBV infection and depression in different stratifications. PIR, poverty income ratio; BMI, body mass index; SSRI, selective serotonin reuptake inhibitor use; HBV, hepatitis B virus; OR, odds ratios; CI, confidence intervals.

can only represent the American population, additional researches are required to determine whether the current findings can be extrapolated to other populations based on this study of American adults.

In conclusion, the results suggest a complex relationship between resolved chronic viral infections and mental health. Based on this finding, it is advisable to conduct psychological monitoring and offer support to individuals who have achieved a functional cure for HBV. Further longitudinal studies are warranted to elucidate the causal mechanisms and to develop targeted interventions for this population.

Data availability

Publicly available and de-identified data used in this analysis can be found in the CDC National Center for Health Statistics NHANES database at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Received: 8 September 2024; Accepted: 23 April 2025
Published online: 08 May 2025

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Acknowledgements

We are grateful to Dr. Jie Liu for their contribution to the comments regarding the manuscript.

Author contributions

All authors have made substantial contributions to the following: (1) conceptualization and design of the study (Zihan Qin，Yizhuo Liu), or obtain, analysis and interpretation of data (Zihan Qin, Yizhuo Liu, Yifei Liu), (2) drafting of the article (Zihan Qin, Yizhuo Liu, Yifei Liu, Kun Zhang, Anqi yang, Ruoyi Zhang) or revising it critically for important intellectual content (all authors), (3) final approval of the version to be submitted (all authors).

Funding

None.

Declarations

Competing interests
The authors declare no competing interests.

Informed consent
All individuals provided written consent.

Institutional review board statement
Institutional Research Ethics Review Board of the CDC approved the protocol for the NHANES survey. The protocol was approved by the NCHS Ethics Review Board with informed consent from all participants.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-99864-2.

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