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RESEARCH ARTICLE

Association between chronic hepatitis B infection and metabolic syndrome

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Abstract

Purpose The association between chronic hepatitis B (CHB) infection and metabolic syndrome (MetS) remains inconclusive. This study was designed to determine the association between CHB infection and MetS among the US population with updated data and adjustments for a comprehensive set of risk factors.

Methods Adults aged 18 years or older who were clinically assessed for Hepatitis B and MetS from the National Health and Nutrition Examination Survey (NHANES) 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014 cycles were included in the study ($N = 53,392,666$). MetS was defined according to the NCEP/ATP III guideline. CHB was identified by the seropositivity of Hepatitis B surface antigen and core antibody in the absence of Hepatitis B surface antibody. Rao-Scott χ^2test and logistic regressions were employed in the analyses.

Results MetS was less prevalent among adults with CHB compared to adults without CHB (12.1% vs. 18.8%, $p = 0.073$). In adjusted analyses, adults with CHB were 48% less likely to have MetS compared to those without CHB (95% Confidence Interval [CI]: 0.29–0.94). Regarding individual component of MetS, CHB was inversely associated with high waist circumference (AOR = 0.32, 95% CI: 0.21–0.49) and hypoalphalipoproteinemia (AOR = 0.48, 95% CI: 0.25–0.91). No association between CHB and other metabolic components were found.

Conclusions CHB was inversely associated with MetS, high waist circumference, and hypoalphalipoproteinemia. No significant association was found between CHB and other MetS components.

Keywords Chronic hepatitis B infection · Metabolic syndrome · High waist circumference · Hypoalphalipoproteinemia · NHANES

Introduction

Metabolic syndrome (MetS), a constellation of several metabolic abnormalities, is a highly prevalent condition in all age groups in the United States (US). It affects approximately 35% of the adult population [1]. The prevalence of MetS is tightly associated with the epidemic of chronic diseases that can influence metabolic profiles. It is well known that individuals with diabetes or women with polycystic ovary syndrome are at increased risks for MetS. Recently, several studies found that some infectious diseases, such as hepatitis B, which can influence metabolic profiles, may also play a role in the development of MetS [2]. The relationship between hepatitis B, especially chronic hepatitis B (CHB), and MetS has drawn considerable attention from researchers [3].

The relationship between CHB and MetS has been explored in ten studies, nine of which focused on Asian populations [4–13]. The pooled estimates of a recent meta-analysis of 13 observational studies revealed that CHB was associated with reduced risk of MetS in East-Asian populations, in adults under 45 years old, and in males [14]. However, the data syntheses in the meta-analysis were subjected to remarkable heterogeneity due to the variations in study designs and adjustments for covariates in the included studies [14]. To better elucidate the association between CHB and MetS, several studies examined the presence of individual components of MetS among individuals with CHB. Two such components are central obesity and insulin resistance, which are thought to

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be the causes of MetS [15]. These components were examined in two Asian studies, though with limited and contrary findings [16, 17]. Other studies examined the association between CHB and dyslipidemia, another component of MetS. Dyslipidemia is characterized by abnormal concentrations of lipid biomarkers, such as total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C), in the plasma [18]. The relationship between CHB and dyslipidemia remained largely ambiguous due to inconsistent associations of CHB and individual lipid biomarker. Seven studies reported significantly lower levels of TC among individuals with CHB as compared to those without CHB [7, 9, 12, 19–22]. However, inconsistent findings were reported for TG and HDL-C levels [2, 4, 5, 7, 20, 23, 24].

The association between CHB and MetS remains inconclusive due to inconsistent findings from previous studies. It is worth pointing out that different risk factors of MetS were controlled for in the previously mentioned studies. Most of the studies adjusted for well-established factors such as sex, age, race/ethnicity, and alcohol consumption while examining the association. The alanine transaminase (ALT) level is an important factor in the treatment of CHB because elevated ALT levels (> 40 U/L for males/> 31 U/L for females) indicate the level of immune-mediated inflammation and liver damage [25]. Recent evidence also indicated that nonalcoholic fat liver diseases, which are usually indicated by elevated ALT levels, served as important risk factors of MetS [26]. Furthermore, studies have reported that elevated ALT levels were associated with higher risks of MetS [27, 28]. These evidences indicated ALT levels may play an important role in the association between CHB and MetS. Some other important factors such as diet quality [29, 30], family history of diabetes and/or heart diseases [31] were not controlled for in any study. The National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) has suggested dietary intervention to prevent MetS [32]. It is well established that diets rich in whole grain cereals, fruits, and vegetables with low animal-fat consumption, can effectively reduce MetS risk factors, like hypertension, hypercholesterolemia, and obesity [33]. On the other hand, studies examining the relationship between CHB and MetS in the US population remain scant. The only existing US study reported a reverse association between CHB and MetS using old data from the NHANES III cohort without adjusting for some of the risk factors discussed above. Examining the relationship between CHB and MetS can potentially help identify more biological risk factors for MetS. Therefore, the primary objective of our study was to evaluate the association between CHB and MetS as well as individual MetS components by controlling for comprehensive risk factors for MetS with updated nationally representative data (NHANES 2003–2014).

Materials and methods

Study design and data source

We used a cross-sectional design with pooled data from six continuous National Health and Nutrition Examination Survey (NHANES) cycles (2003–2004; 2005–2006; 2007–2008; 2009–2010; 2011–2012; 2013–2014). NHANES is a large, multistage, complex survey of the noninstitutionalized civilian US population who are two months of age and older conducted by the National Center for Health Statistics (NCHS) [34–36]. It collects information on demographic, socioeconomic, health-related information, and dietary pattern [37]. The dietary pattern is measured from two 24-h recalls of consumed foods and dietary supplements [38]. Also, NHANES obtained the physical examination and laboratory data from selected participants by highly trained medical professionals in the Mobile Examination Center (MEC) followed the household interview. NHANES was reviewed and approved by the NCHS ethics review board. Participants provided written informed consent before participation.

Compliance with ethical standards

The study did not involve any human subject and used publicly available data from the National Health and Nutrition Examination (NHANES), which was approved by the National Center for Health Statistics Institutional Review Board. The opinions expressed in this article are of the authors and do not reflect the views/opinions of any organization. The authors report no conflict of interest and this research has not been submitted in manuscript form anywhere else. Each author acknowledges she has participated in the work in a substantive way and is prepared to take full responsibility for the work.

Study sample

We included individuals who were aged 18 years or older at the time when NHANES data were collected. Individuals were excluded if they (1) had missing values in HBsAg serology; (2) had chronic hepatitis C (defined as HCV antibody seropositivity) (3) had diabetes mellitus (either self-reported or identified by the lab tests during the data collection time); or (4) were pregnant during the data collection period. The final study sample consisted of 34,958 adults; of whom 199 participants had CHB, and 34,759 participants did not have CHB.

Measures

Dependent variables The main dependent variable was the prevalence of MetS. We defined MetS basing on the modified NCEP-ATP III criteria [39, 40]. Individuals having MetS were

identified by the presence of at least three of the following conditions: (1) a high waist circumstance (≥35 in. in women, ≥ 40 in. in men); (2) a high triglyceride (TG) level (≥ 150 mg/dL); (3) hypoalphalipoproteinemia (a low HDL cholesterol level; ≤ 50 mg/dL in women, ≤ 40 mg/dL in men); (4) high blood pressure (systolic pressure ≥ 130 mmHg or diastolic pressure ≥ 85 mmHg, or being on medications to treat high blood pressure); and (5) high fasting blood sugar (≥ 100 mg/dL or being on medications to treat high blood sugar). Blood samples were drawn from the antecubital vein in the morning after fasting for at least 8 h. Samples were properly processed, immediately refrigerated at 2 °C to 8 °C and sent to a central laboratory. Serum triglyceride concentrations were measured enzymatically after hydrolyzation to glycerol (Roche Modular P chemistry analyzer, Roche, Indianapolis, IN, USA), and HDL cholesterol was measured after non-HDL fractions were complexed with a magnesium–dextran sulfate solution (Roche Modular P chemistry analyzer). Plasma glucose concentrations were measured using the hexokinase assay (Roche Modular P chemistry analyzer). LDL cholesterol concentrations were estimated from total cholesterol, HDL cholesterol, and triglycerides using the Friedewald formula. Trained health technicians collected the body measures data, including blood pressures and waist circumstance, in the MEC (Mobile Examination Center). Scheduled equipment calibration was performed by the health technicians and verified by supervisory staff. Systolic and diastolic blood pressures were measured up to three times for each measured participant. The average was used for participants who had more than one measurement to identify high blood pressure status. The details of NHANES laboratory and quality control methods are reported elsewhere [41, 42].

Key independent variable The key variable of interest was CHB status measured as a binary variable (YES/NO). CHB was identified by the presence of Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (anti-HBc) without the presence of Hepatitis B surface antibody (anti-HBs), which was detected by the AUSZYME Monoclonal test from 2003 to 2006 and the VITROS HBsAg assay using an immunometric technique from 2007 to 2014, respectively [43].

Other explanatory variables We included other explanatory variables according to the constructs and elements in the models of social determinants of health [44, 45]. The MetS may be associated with (1) individual physical makeup, including age, sex, and race/ethnicity; (2) socioeconomic status that is commonly conceptualized as the social standing or class of an individual, including income and education; (3) access to healthcare; (4) health behaviors, including alcohol consumption, smoking status, physical activity; and diet quality; and (5) biological risk factors, including family history of cardiovascular diseases (CVDs) and diabetes mellites (DM) and ALT levels. The access to care was indicated by two categorical variables, including health insurance and the type of place most often go for healthcare. We measured participants' annual household income level by the poverty status variable in NHANES, which was defined as poor (< 100%), near poor (100% - 200%), middle income (200% - 400%), and high income (≥400%) of the federal poverty line. We defined no/limited access to care as having no place or emergency department for usual care. Physical activity was indicated by the number of days having at least 1 h of physical activity in the past 30 days. Alcohol consumption was calculated by multiplying the average number of alcohol drinks per day with the number of days of drinking in the past 12 months. The diet quality was measured using the Healthy Eating Index (HEI), a diet quality index (0–100) that measures conformance with federal dietary guidance [46, 47]. Due to the modification of survey designs, we measured diet quality with HEI-2015 for individuals from NHANES 2005–2014 and HEI-2010 for those from NHANES 2003–2004. We further categorized individuals into two groups: "Good" for those scored above "50″, and "Poor" for those scored at "50″ or below.

Statistical analyses

We used Chi-square tests to examine the group differences between individuals with and without CHB. Multivariable Logistic regressions were used to examine the association between CHB and MetS, adjusting for individual physical makeup, socioeconomic status, access to care, health behaviors, and biological risk factors. Odds ratios (ORs) were calculated with 95% confidence intervals (CIs) from multivariate logistic regression analyses were reported to demonstrate the observed associations. We also performed subgroup analyses to assess the association between CHB and individual MetS component. All analyses were conducted using appropriate sample weights to represent national estimates. A p value less than 0.05 was considered as statistically significant. We performed all the data management and analyses with SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Description of study sample

The study sample consisted of 34,959 adults from 2003 to 2014. Approximately 0.4% of adults had Chronic Hepatitis B (CHB). Adults with and without CHB were similar in most characteristics except for race/ethnicity, poverty level, access to care, alcohol consumption, family history of CVD/DM, and ALT levels (Table 1). We found higher percentages of African Americans (27.6% vs. 69.6%, $p < 0.001$) and individuals with elevated ALT levels (28.7% vs. 12.3%, $p < 0.001$) among

Table 1 Sample description by presence/absence of Chronic Hepatitis B (CHB), using National Health and Nutrition Survey (NHANES) 2003–2014 data and Rao-Scott X2 test analyses

Variable	CHB ($N = 199$)			Non-CHB ($N = 34,760$)			p value
	N	Wt. N	Wt. Col%	N	Wt. N	Wt. Col%	
Age							0.821
18–29 years	35	180,259	19.9	7643	53,212,407	21.5	
30–39 years	36	187,474	20.7	6287	47,046,670	19.0	
40–49 years	44	168,433	18.6	6115	49,832,200	20.2	
50–64 years	58	260,644	28.8	7632	59,128,901	23.9	
65 years or older	26	107,540	11.9	7083	37,981,198	15.4	
Sex							0.052
Female	84	380,834	42.1	17,769	127,858,838	51.7	
Male	115	523,515	57.9	16,991	119,342,538	48.3	
Race/ethnicity							< 0.001 ***
White	24	249,556	27.6	16,017	172,151,387	69.6	
African American	60	212,682	23.5	7068	25,438,334	10.3	
Hispanic/Latino	13	48,675	5.4	8184	33,183,985	13.4	
Other	102	393,437	43.5	3491	16,427,670	6.6	
Education level [a]							0.351
Less than high school	52	179,242	20.6	7907	38,623,136	15.9	
High school or equivalent	48	221,854	25.5	7616	54,972,483	22.7	
More than high school	94	468,831	53.9	17,925	148,975,318	61.4	
Poverty level							0.041 *
Poor/near poor	93	347,977	38.5	15,215	80,071,830	32.4	
Middle/High income	78	455,027	50.3	16,966	152,220,514	61.6	
NR	28	101,346	11.2	2579	14,909,033	6.0	
Insurance status							0.140
Yes	142	670,849	74.2	26,319	198,541,057	80.5	
No	57	233,500	25.8	8370	48,239,058	19.5	
Access to care							0.017 **
Yes	50	249,887	27.6	6860	43,731,449	17.7	
No/Limited	97	420,743	46.5	20,418	149,914,477	60.6	
NR	52	233,719	25.8	7482	53,555,450	21.7	
Alcohol consumption							0.012 *
None/mild	66	244,237	27.0	8432	50,277,222	20.3	
Moderate	61	312,312	34.5	11,411	94,002,438	38.0	
Heavy	28	125,372	13.9	8099	62,551,020	25.3	
NR	44	222,428	24.6	6818	40,370,696	16.3	
Smoking status							0.548
Current smoker	32	151,610	16.8	7246	52,286,769	21.5	
Former smoker	41	236,763	26.2	7632	56,404,925	23.1	
Never smoker	126	515,976	57.1	18,833	135,012,546	55.4	
Physical activity							0.406
Vigorous/moderate	14	109,609	12.1	4811	39,783,946	16.1	
No exercise	16	83,885	9.3	2621	17,287,483	7.0	
NR	169	710,855	78.6	27,328	190,129,947	76.9	
Diet quality							0.624
Good	98	437,713	48.4	17,514	125,897,885	50.9	
Poor	85	401,342	44.4	15,076	108,651,857	44.0	
NR	16	65,295	7.2	2170	12,651,634	5.1	
Co-existing conditions							0.710
Yes	61	314,470	34.8	12,898	90,144,187	36.5	
No	138	589,879	65.2	21,862	157,057,189	63.5	
Family history of CVD/DM							0.016 *
Yes	49	228,785	25.3	14,531	103,443,085	41.8	
No	140	577,209	63.8	18,042	133,565,810	54.0	
ALT levels [a]							< 0.001 ***
Elevated	51	259,364	28.8	4133	30,438,942	12.4	
Normal	146	639,782	71.2	30,299	214,524,362	87.6	

Based on individuals with ages 18 years and above who were alive during the observation year. Adults who had missing values for Hepatitis B Surface Antigen serology, who had hepatitis C or diabetes myelitis, and those who were pregnant during the survey period were excluded from the analyses. Poor/near poor: family annual income ≤200% Federal Poverty Line (FPL); Mid/High income: > 200% FPL; Having Access to care was defined as having (not Emergency room) places to go for usual care. Good diet quality was defined as Healthy Eating Index (2010 and 2015) scored 50 or higher; ALT: alanine aminotransferase; elevated ALT levels were defined as ALT ≥40 U/L among males or ≥ 31 U/L among females

NR, not reported in the data; *Wt.*, Weighted. Col%: Column %

[a] Missing values were omitted due to small cell size ($n < 11$) for the variable

* $p < 0.05$; ** $0.05 < p < 0.01$; *** $p < 0.001$

adults with CHB as compared to those without CHB. Similarly, more adults in the CHB group had limited or no access to care as compared to those in the non-CHB group (37.7% vs. 22.5%, p < 0.001). On the other hand, adults with CHB consisted of lower percentages of individuals with family history of diabetes (23.8% vs. 36.1%, $p = 0.037$) and heavy drinkers (18.4% vs. 30.2%, $p = 0.018$) than those without CHB.

CHB and MetS

We found 18.8% of the study sample having MetS, with a lower proportion among adults with CHB as compared to those without CHB (12.1% vs. 18.8%, $p = 0.073$). To adjust for the differences in potential risk factors between the two groups, we assessed the association between CHB and MetS with six models. Table 2 shows the unadjusted and adjusted logistic regression analyses of having MetS. CHB was significantly associated with the likelihood of having MetS only in the fully adjusted model (Model 6). After adjusting for all the variables mentioned above, we found that adults with CHB were 48% less likely to have MetS as compared to those without CHB (Adjusted Odds Ratio [AOR] = 0.52, 95% CI: 0.29–0.94, $p = 0.031$). The association was not significant in models that controlled for individual physical made-up, socioeconomic status, access to care, and health behaviors. Further, we identified that CHB became significantly associated with MetS only when we controlled for ALT levels in the model. Adults with elevated ALT levels had more than twice the odds of having MetS (AOR = 2.22, 95%CI: 1.99–2.48). Other factors that significantly associated with having MetS included older age, poor diet quality, having a family history of CVD/DM, and the presence of other co-existing medical conditions (Table 3).

CHB and individual MetS components

Almost three quarters (74.3%) of the study sample had at least one MetS component. Table 4 presents the bivariate associations between CHB and individual MetS components in the study sample. Regardless of CHB status, high WC was the most prevalent MetS component, followed by high fasting glucose (38.6%) and hypoalphalipoproteinemia (28.3%). We found significantly fewer individuals with high WC (29.3% vs. 51.2%, $p < 0.001$) and low HDL-C (18.2% vs. 28.3%, $p = 0.043$) among adults with CHB as compared to those without CHB. The distribution of the other three components of MetS was similar between the two groups. In the adjusted analyses (Table 3), the association between CHB and high WC/hypoalphalipoproteinemia remained significant. Adults with CHB were 68% (AOR = 0.32, 95%CI: 0.21–0.49) and 52% (AOR = 0.48, 95%CI: 0.25–0.91) less likely to have high WC and hypoalphalipoproteinemia, respectively. We found that being female, having poor diet quality, family history of CVD/DM, other medical conditions, and elevated ALT levels were significantly associated with high WC as well as hypoalphalipoproteinemia. Furthermore, adults who were older (vs. 18–29 years old), African American (vs. White), former smokers (vs. never smokers), and those having access to care (vs. no/limited access) were more likely to have high WC. Similarly, adults who were 50 years or older or current smokers were more likely to have hypoalphalipoproteinemia.

Table 2 Unadjusted and adjusted Logistic regression analyses of the presence of Metabolic Syndrome among adults with and without Chronic Hepatitis B (CHB), using National Health and Nutrition Survey 2003–2014 data

Variable	OR	95% CI	p value
Model 0: Unadjusted Model			
CHB	0.60	[0.33, 1.07]	0.082
Non-CHB	Reference group		
Model 1: Adjust for individual physical makeup [a].			
CHB	0.60	[0.34, 1.06]	0.080
Model 2: Adjust for individual physical makeup [a], socioeconomic status [b].			
CHB	0.61	[0.34, 1.09]	0.092
Model 3: Adjust for individual physical makeup [a], socioeconomic status [b], access to care [c].			
CHB	0.61	[0.34, 1.08]	0.091
Model 4: Adjust for individual physical makeup [a], socioeconomic status [b], access to care [c], health behaviors [d].			
CHB	0.61	[0.34, 1.08]	0.090
Model 5: Adjust for individual physical makeup [a], socioeconomic status [b], access to care [c], health behaviors [d], and elevated alanine transaminase (ALT) levels.			
CHB	0.51	[0.28, 0.93]	0.030 *
Model 6: Adjust for individual physical makeup [a], socioeconomic status [b], access to care [c], health behaviors [d], and biological risk factors [e].			
CHB	0.52	[0.29, 0.94]	0.031 *

Based on individuals with ages 18 years and above who were alive during the observation year. Adults who had missing values for Hepatitis B Surface Antigen serology, who had hepatitis C or diabetes myelitis, and those who were pregnant during the survey period were excluded from the analyses

OR, odds ratio obtained from the logistic regression analyses; *95% CI*, 95% Wald confidence interval obtained from the logistic regression analyses

[a] Individual physical makeup includes age, sex, race/ethnicity

[b] Socioeconomic status includes family income-to-poverty ratio and education

[c] Access to care is defined as having non-Emergency department healthcare settings for usual care and having insurance coverage

[d] Health behaviors include smoking status, alcohol consumption, physical activity, and diet quality

[e] Biological risk factors include co-existing medical conditions, family history of CVD/DM, and ALT levels

* $p < 0.05$

Discussion

We systematically examined the association between chronic hepatitis B (CHB) and metabolic syndrome (MetS) with a

Table 3 Selected results from adjusted Logistic regression analyses of the presence of Metabolic Syndrome and metabolic components among adults with and without Chronic Hepatitis B (CHB), using National Health and Nutrition Survey 2003–2014 data

Variable	Metabolic syndrome [a]			High WC [b]			Hypoalphalipoproteinemia [c]		
	AOR	95% CI	p value	AOR	95% CI	p value	AOR	95% CI	p value
CHB									
Yes vs. No	0.52	[0.29, 0.94]	0.031 *	0.32	[0.21, 0.49]	< 0.001 ***	0.48	[0.25, 0.91]	0.024 *
Sex									
Female vs Male	0.91	[0.83, 1.01]	0.065	2.38	[2.21, 2.57]	< 0.001 ***	1.17	[1.07, 1.27]	< 0.001 ***
Age									
30–39 vs. 18–29	1.94	[1.62, 2.32]	< 0.001 ***	1.65	[1.45, 1.88]	< 0.001 ***	0.96	[0.84, 1.11]	0.611
40–49 vs. 18–29	3.04	[2.60, 3.56]	< 0.001 ***	2.11	[1.88, 2.38]	< 0.001 ***	0.92	[0.81, 1.05]	0.206
50+ vs. 18–29	4.29	[3.62, 5.09]	< 0.001 ***	2.95	[2.58, 3.37]	< 0.001 ***	0.66	[0.58, 0.76]	< 0.001 ***
Race/ethnicity									
African American vs. White	0.83	[0.74, 0.93]	0.002 **	1.24	[1.13, 1.37]	< 0.001 ***	0.73	[0.66, 0.80]	< 0.001 ***
Hispanic/other race vs. White	0.82	[0.72, 0.92]	< 0.001 ***	0.80	[0.71, 0.90]	< 0.001 ***	1.07	[0.97, 1.17]	0.187
Education									
More than high school vs. less than high school	0.79	[0.70, 0.90]	< 0.001 ***	0.91	[0.84, 1.00]	0.042	0.85	[0.75, 0.96]	0.010 **
Marital status									
Widowed/Divorced/Separated vs. married	0.84	[0.84, 1.08]	0.446	1.00	[0.88, 1.13]	0.959	0.88	[0.80, 0.96]	0.005 **
Never married vs. married	0.94	[0.82, 1.08]	0.375	0.87	[0.80, 0.94]	< 0.001 ***	0.81	[0.73, 0.90]	< 0.001 ***
Income									
Middle/High income vs. low income	0.85	[0.78, 0.94]	0.001 **	0.85	[0.76, 0.94]	0.001 **	0.79	[0.72, 0.86]	< 0.001 ***
Access to care									
Yes vs. limited/no	1.10	[0.94, 1.30]	0.242	1.19	[1.07, 1.32]	< 0.001 ***	0.97	[0.88, 1.08]	0.603
Alcohol consumption									
Moderate vs. mild/none	0.69	[0.61, 0.77]	< 0.001 ***	0.74	[0.66, 0.83]	< 0.001 ***	0.63	[0.57, 0.70]	< 0.001 ***
Heavy vs. mild/none	0.74	[0.65, 0.84]	< 0.001 ***	0.92	[0.82, 1.03]	0.161	0.54	[0.48, 0.60]	< 0.001 ***
Smoking status									
Current smoker vs Never smoker	1.05	[0.94, 1.19]	0.381	0.75	[0.69, 0.82]	< 0.001 ***	1.41	[1.27, 1.57]	< 0.001 ***
Former smoker vs Never smoker	1.09	[0.98, 1.20]	0.102	1.22	[1.09, 1.36]	< 0.001 ***	0.88	[0.79, 1.00]	0.039 *
Physical activity									
Vigorous/moderate vs None	0.86	[0.73, 1.03]	0.092	0.76	[0.68, 0.86]	< 0.001 ***	0.85	[0.74, 0.99]	0.030 *
Diet quality									
Poor vs. good	1.36	[1.23, 1.49]	< 0.001 ***	1.42	[1.32, 1.53]	< 0.001 ***	1.50	[1.37, 1.64]	< 0.001 ***
Family history of CVD/DM									
Yes vs. No	1.42	[1.31, 1.55]	< 0.001 ***	1.45	[1.33, 1.59]	< 0.001 ***	1.30	[1.20, 1.42]	< 0.001 ***
Co-existing medical conditions									
Yes vs. No	1.28	[1.18, 1.38]	< 0.001 ***	1.29	[1.21, 1.37]	< 0.001 ***	1.12	[1.03, 1.21]	0.005 **
Elevated ALT									
Yes vs. No	2.22	[1.99, 2.48]	< 0.001 ***	2.31	[2.02, 2.64]	< 0.001 ***	2.00	[1.81, 2.21]	< 0.001 ***

Based on individuals with ages 18 years and above who were alive during the observation year. Adults who had missing values for Hepatitis B Surface Antigen serology, who had hepatitis C or diabetes myelitis, and those who were pregnant during the survey period were excluded from the analyses. Only significant variables are presented. AOR: adjusted odds ratio from regression analyses; 95% CI: 95% confidence interval for OR from regression analyses

[a] The regression on the presence of metabolic syndrome was performed among adults who had data for metabolic syndrome (N = 34,958)

[b] High WC represents high waist circumstance (≥ 35 in. for females or ≥ 40 in. males); the regression analysis was done among adults who had data for WC measurements ($N = 34,766$)

[c] Hypoalphalipoproteinemia represents low high-density-lipid cholesterol level (< 50 mg/dL for females or < 40 mg/dL for males); the regression analysis was done among adults who had data for HDL-C lab values ($N = 36,172$)

* $p < 0.05$; ** $0.05 < p < 0.01$; *** $p < 0.001$

nationally representative sample of adults. Our results indicated that adults with CHB were significantly less likely to have co-existing MetS as compared to those without CHB after adjusting for the alanine transaminase (ALT) levels and other factors. However, the association was not significant in unadjusted analysis and adjusted analyses where ALT levels were not controlled for. Unlike the previous US study analyzing the NHANES III data [9], we did not observe any significant difference in MetS prevalence between adults with and those without CHB. This might be due to the exclusion of adults with diabetes in our study as diabetes has been found associated with hepatitis B infection as well as MetS [48, 49]. However, our result regarding the adjusted association between CHB and MetS after controlling for other risk factors of MetS was in line with that of the previous US study [9]. Our results from the adjusted analyses also indicated that ALT levels played an important role in the observed association between CHB and MetS. We found that adults with elevated

Table 4 Prevalence of Metabolic Components by the Presence/Absence of Chronic Hepatitis B (CHB), using National Health and Nutrition Survey (NHANES) 2003–2014 data and Rao-Scott X2 test analyses

Metabolic components	CHB			Non-CHB			p value
	N	Wt. N	Wt. Col%	N	Wt. N	Wt. Col%	
High waist circumstance [a]	186	856,899		33,272	238,076,564		<0.001 ***
Yes	50	250,957	29.3	16,992	121,895,147	51.2	
No	136	605,942	70.7	16,280	116,181,417	48.8	
Hypoalphalipoproteinemia [b]	197	899,146		34,635	246,390,679		0.043 *
Yes	35	163,800	18.2	10,057	69,701,965	28.3	
No	162	735,345	81.8	24,578	176,688,713	71.7	
High triglyceride [c]	98	479,368		16,401	116,267,612		0.438
Yes	19	91,455	19.1	3909	28,601,213	24.6	
No	79	387,913	80.9	12,492	87,666,398	75.4	
High blood pressure [d]	189	877,316		33,373	238,272,601		0.284
Yes	49	196,049	22.3	10,078	64,712,477	27.2	
No	140	681,268	77.7	23,295	173,560,125	72.8	
High fasting blood sugar [e]	99	488,279		16,434	116,451,667		0.812
Yes	44	194,915	39.9	6580	44,960,756	38.6	
No	55	293,364	60.1	9854	71,490,912	61.4	

Based on individuals with ages 18 years and above who were alive during the observation year. Adults who had missing values for Hepatitis B Surface Antigen serology, who had hepatitis C or diabetes myelitis, and those who were pregnant during the survey period were excluded from the analyses

Wt., Weighted; *Col%*, Column %

[a] High waist circumstance was defined as a waist measurement of 35 in. or more for females or 40 in. or more for males

[b] Hypoalphalipoproteinemia was defined indicates as having a high-density-lipid cholesterol level less than 50 mg/dL for females and less than 40 mg/dL for males

[c] High Triglyceride was defined as having a triglyceride level of 150 mg/dL or higher

[d] High blood pressure was defined as having a high blood pressure of 130/85 mmHg or higher or being to treat high blood pressure

[e] High fasting blood sugar was defined as having fasting blood sugar level of 100 mg/dL or higher or being on medicine to treat high blood sugar

* $p < 0.05$; ** $0.05 < p < 0.01$; *** $p < 0.001$

ALT levels were more likely to have MetS as compared to those with normal levels. This finding is consistent with reports from two previous studies that examined the associations between various liver markers and the development of MetS [27, 28]. Furthermore, a recent published longitudinal study among 777 adults with CHB reported that MetS was independently associated with higher ALT levels over time [50]. It is suggested that MetS might contribute to the elevated ALT levels and greater disease severity of CHB. Although mechanistic studies are needed to understand the underlying mechanisms between ALT levels and MetS among adults with CHB, screening for MetS and the potential influence of MetS on ALT were suggested to be considered in the treatment decisions for CHB. One interesting finding of this study was that the association between CHB and MetS became significant when ALT was controlled for in the analysis. A possible explanation for this finding could be that CHB patients with normal ALT levels might be more mindful in their health and have healthier lifestyles as compared to CHB patients with elevated ALT levels and adults without CHB. A recent community-based study reported a possible medication effect from awareness of HBV infection in the associations between HBV infection and MetS status: adults who were unaware of HBV infection had a higher risk of MetS, central obesity, hyperglycemia, and insulin resistance than those who were aware of the infection [51]. CHB patients with normal ALT levels might be more likely to be those who were aware of their HBV infection and overall health status than those with elevated ALT levels. Future prospective primary studies are needed to test this hypothesis and further explore the underlying mechanism of the observed association between CHB and MetS.

When looking at the association between CHB and individual component of MetS, we observed that individuals with CHB were less likely to have high waist circumference and hypoalphalipoproteinemia. The significantly inverse association between CHB and hypoalphalipoproteinemia has been reported by several previous studies [2, 9, 19]. However, no clear mechanism has been identified to explain the lipid profile in the serum of people with CHB. Studies with hepatocytes and murine models indicated that HBV infection profoundly modifies the metabolism of infected hepatocytes [52–54]. It was suggested that the increased chronic inflammatory cytokines along with CHB might play a role in the observed association [55]. A recently published meta-

analysis of 13 observational studies reported that CHB was associated with hypoalphalipoproteinemia among adults younger than 45 years [14]. Due to the limited sample size of adults with CHB, we did not perform subgroup analysis by age. However, we found similar age compositions between adults with and without CHB in our study sample. A study by researchers from the CDC reported declining prevalence of hypoalphalipoproteinemia by aging [56]. It is possible that the difference in the prevalence of hypoalphalipoproteinemia between the two groups (CHB vs. non-CHB) diminishes as the overall prevalence reduces.

Both our study and the previous US study found adults with CHB were less likely to have visceral obesity (high waist circumference) as compared to those without CHB [9]. Although the meta-analysis concluded that the association between CHB and visceral obesity was not significant based on pooled results of nine studies, it must be noted that none of the nine studies had adjusted for diet quality in their studies [14]. Poor diet quality has been known as the risk factor for obesity and other metabolic disorders [29, 30]. We found that poor diet quality was associated the presence of MetS and all the metabolic components. The associations might be distorted if this important factor is ignored. Visceral obesity is the most prevalent metabolic abnormalities in our study. We speculated that visceral obesity might play a leading role in the development of MetS through increased oxidative stress in accumulated fat [57]. Therefore, lifestyle interventions such as promoting healthy diet pattern may be the key component in combating obesity and metabolic disorders in the US. Although the abovementioned meta-analysis reported that CHB was associated with reduced risk of elevated blood pressure, hypoalphalipoproteinemia, increased fasting glucose, and increased TG in some subgroups, publication bias was detected for studies that have investigated these relationships [14].

The interpretation of our study results should be in view of its strengths and limitations. We utilized data from a nationally representative survey and adjusted for a comprehensive list of factors that may affect the development of MetS. The rigorous study methods and complex sampling design employed in the survey allows the generalization of our study results to the US population. Secondly, we comprehensively evaluated the association between CHB and MetS by adjusting extensive confounders. However, our study is not free of limitations. First, the study employed a cross-sectional design did not allow us to examine the temporal relationship between CHB and MetS. Therefore, no causal relationship can be inferred form the results of our study. Second, we conducted analyses based on the participants who had relevant laboratory test results available. There might be misclassification among participants whose laboratory results were missing. However, same results were obtained from sensitivity analyses where only participants who had all the relevant laboratory tests were included. Third, a relatively low prevalence of Hepatitis B infection was found in the US, resulting relatively high (> 30%) relative standard errors of some estimates of our study. The observed effect size of the association between CHB and MetS might have been overestimated. However, the significant associations found in our study were robust even with small sample size identified.

In this US population-based study, we identified a significant inverse association between chronic hepatitis B (CHB) infection and metabolic syndrome (MetS). Also, CHB infection was found inversely associated with high waist circumference and hypoalphalipoproteinemia. This study emphasizes the role of alanine aminotransaminase levels and lifestyle factors in the paradoxical association between CHB and MetS. Well-designed prospective observational studies and pathophysiological studies are needed to ascertain the causality and explore the possible biological mechanisms involved in the observed association between CHB and MetS, visceral obesity, as well as other MetS components.

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Compliance with ethical standards

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