BMJ Open

Chronic Hepatitis B Infection in Diabetic Patients: Friend or Foe? - A Nationwide Population-Based Nested Case-Control Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016179
Article Type:	Research
Date Submitted by the Author:	30-Jan-2017
Complete List of Authors:	Kuo, Chin-Sung; Taipei Veterans General Hospital, Division of Endocrinology and Metabolism Chen, Yung-Tai; Taipei City Hospital Heping Fuyou Branch, Department of Medicine Hsu, Chien-Yi; Taipei Medical University Hospital, Division of Cardiology, Department of Medicine Chang, Chun-Chin; Taipei Veterans General Hospital, Division of Cardiology, Department of Medicine Chou, Ruey-Hsing; Taipei Veterans General Hospital, Division of Cardiology, Department of Medicine Li, Szu-Yuan; Taipei Veterans General Hospital, Divisions of Nephrology Kuo, Shu-Chen; National Health Research Institutes, National Institute of Infectious Diseases and Vaccinology Huang, Po-Hsun; Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, ; Chen, Jaw-Wen; Taipei Veterans General Hospital, Department of Medical Research Lin, Shing-Jong; Taipei Veterans general Hospital, Division of Cardiology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Diabetes and endocrinology, Gastroenterology and hepatology
Keywords:	Myocardial infarction < CARDIOLOGY, Stroke < NEUROLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, Hepatology < INTERNAL MEDICINE

Chronic Hepatitis B Infection in Diabetic Patients: Friend or Foe? - A Nationwide Population-Based Nested Case-Control Study

Chin-Sung Kuo M.D.[1,9‡]; Yung-Tai Chen M.D.[6,9‡]; Chien-Yi Hsu M.D.[7,9,12,14]; Chun-Chin Chang M.D.[2,9]; Ruey-Hsing Chou M.D.[2,9]; Szu-Yuan Li M.D.[3,9]; Shu-Chen Kuo M.D.[4,11]; *Po-Hsun Huang M.D. Ph.D.[2,7,9]; Jaw-Wen Chen M.D. [2,5,7,8]; *Shing-Jong Lin M.D. Ph.D.[2,5,7,9,13]

[1]Division of Endocrinology and Metabolism; [2]Division of Cardiology; [3]Division of Nephrology; [4]Division of Infectious Diseases, Department of Medicine; [5]Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan; [6]Department of Medicine, Taipei City Hospital Heping Fuyou Branch, Taipei, Taiwan; [7]Cardiovascular Research Center; [8]Institute of Pharmacology; [9]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan; [10]Department of Medicine, Yuli branch, Taipei Veterans General Hospital, Hualien, Taiwan; [11]National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Miaoli County, Taiwan; [12]Department of Internal Medicine, School of Medicine, [13]Taipei Medical University, Taipei, Taiwan; [14]Division of Cardiology and Cardiovascular Research Center, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan.

Running title: Chronic Hepatitis B Infection in Diabetic Patients

‡These authors contributed equally and share the first authorship

***Address correspondence to:**

Dr. Po-Hsun Huang and Dr. Shing-Jong Lin

Division of Cardiology, Department of Medicine,

Taipei Veterans General Hospital

No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan (R.O.C.)

Tel: 886-2-2871-2121 ext. 7511

Fax: 886-2-2875-7735.

E-mail: huangbsvgh@gmail.com and sjlin@vghtpe.gov.tw

Electronic word counts: 2783

Table number: 2

Figure number: 3

Supplementary table number: 3

ABSTRACT

Objects: The association between hepatitis B virus (HBV) infection and cardiovascular disease remains uncertain. No previous study has explored long-term hard endpoints (i.e., myocardial infarction, ischemic stroke) and all-cause mortality in diabetic patients with chronic HBV infection.

Design: We conducted a nationwide longitudinal cohort study using Taiwan's National Health Insurance Research Database to identify propensity score–matched diabetic patients with and without HBV infection during 2000–2012. Chronic HBV infection was identified based on ≥3 outpatient clinic visits or one hospital admission with a diagnosis of HBV infection. Primary outcomes were major adverse cardiovascular events (MACE, including myocardial infarction and ischemic stroke), heart failure, and all-cause mortality.

Participants: The study included 40,162 diabetic patients with chronic HBV infection (HBV cohort) and 40,162 propensity score–matched diabetic patients without HBV infection (control cohort).

Results: During the median follow-up period of 5.3 ± 3.4 years, the HBV cohort had significantly lower risks of myocardial infarction (adjusted hazard ratio [aHR] = 0.49; 95% confidence interval [CI], 0.42–0.56), ischemic stroke (aHR = 0.61; 95% CI, 0.56–0.67), heart failure (aHR = 0.50; 95% CI, 0.43–0.59), and all-cause mortality (aHR =

0.72; 95% CI, 0.70–0.75) compared with the control cohort. The impact of HBV infection on the sequential risk of MACE was greater in patients with fewer diabetic complications.

Conclusions: Chronic HBV infection was associated with decreased risk of MACE and heart failure in diabetic patients. Further research is necessary to investigate the underlying mechanism of these findings.

Key Words: atherosclerosis, diabetes, hepatitis B virus, ischemic stroke, myocardial infarction

Strengths and limitations of this study

- An unselected nationwide population with the most extensive sample of diabetic patients with chronic HBV infection available, minimizing the possibility of referral bias
- This study is the largest-scale, diabetic HBV cohort study to date.
- No previous study has explored long-term hard endpoints (i.e., myocardial infarction, ischemic stroke) and all-cause mortality in diabetic patients with chronic HBV infection.
- Values of liver function tests and glycated hemoglobin were not available in the nationwide dataset.
- Some personal information, including body mass index and smoking status, was not available in the administrative dataset

INTRODUCTION

The global incidence of diabetes mellitus is increasing, and the number of diabetic patients is expected to reach 366 million by 2030 (1). Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality among individuals with diabetes, and the largest contributor to the direct and indirect economic costs of diabetes (2). Diabetes and commonly coexisting conditions (e.g., hypertension and dyslipidemia) are well-known risk factors for cardiovascular complications (3). Diabetes is also the leading cause of chronic kidney disease (CKD) and end-stage renal disease (4). Convincing evidence has shown that an interrelationship between chronic inflammation and metabolic abnormalities in diabetes leads to endothelial dysfunction and vascular complications (5).

Hepatitis B virus (HBV) infection has a high prevalence and is a major public health problem in Taiwan and other countries worldwide (6,7). Chronic HBV infection may cause chronic hepatitis, cirrhosis, hepatic decompensation, or hepatocellular carcinoma (HCC) (8). Chronic HBV infection is an inflammation condition. Other disease with chronic low grade inflammation have been shown to increase the risk of major cardiovascular events (MACE) (9). Nevertheless, chronic HBV infection has been reported to be inversely associated with metabolic syndrome in an analysis using the Third National Health and Nutrition Examination Survey (NHANES III) in the US (10) as

well as in a population-base study in Taiwan (11). The association between HBV infection and MACE, however, remains uncertain. Previous cross-sectional studies of this association have produced conflicting results (12–14). One Korean cohort study postulated that hepatitis B surface antigen (HBsAg) seropositivity was associated with decreased risks of ischemic stroke and myocardial infarction, as well as an increased risk of hemorrhagic stroke (15). A population-based prospective study conducted in Taiwan showed that HBsAg seropositivity was not associated with enhanced cardiovascular mortality during a 17-year follow-up period (16). There is no study to date has examined the relationship between chronic HBV infection and MACE or all-cause mortality in diabetic patients.

Accordingly, we conducted a nationwide longitudinal cohort study to investigate the relationship between chronic HBV infection and MACE, as well as all-cause mortality, in diabetic patients in Taiwan, which is one of the most hyperendemic areas for HBV infection in the world (17). To our knowledge, this study is the largest diabetic HBV cohort study.

METHODS

Data Sources

Data were extracted from the Taiwan National Health Insurance Research Database

(NHIRD), which contains anonymized secondary data that are available for research purposes. Taiwan's National Health Insurance (NHI) program, launched in 1995, currently covers 99% of the population of 23 million people. The database comprises all registry and claims data from the NHI system, ranging from demographic data to detailed orders for ambulatory and inpatient care. Taiwan's NHI Bureau is responsible for auditing medical payments through a comprehensive review of medical records, examination reports, and results of imaging studies. If a physician fails to meet the standards for clinical practice, Taiwan's NHI reserves the right to reject payment and may impose substantial financial penalties. Disease diagnoses are coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The diagnostic accuracy for major diseases of codes registered in the NHIRD has been validated thoroughly (18-21). In the present study, we used the Longitudinal Cohort of Diabetes Patients dataset, sourced directly from the NHIRD. This dataset includes all available medical registry data from a random sample of 120,000 patients with diagnoses of diabetes mellitus each year since 1999. The study was exempt from full review by the Institutional Review Board of Taipei City Hospital (TCHIRB-1030603-W), because the dataset comprised de-identified secondary data.

Study Design

This nationwide, population-based, observational, retrospective cohort study was conducted to determine the association between chronic HBV infection and sequential MACE in diabetic patients. Two cohorts were enrolled in the study: the HBV cohort and a matched control cohort. The HBV cohort consisted of patients diagnosed with chronic HBV infection, defined based on three of more outpatient clinic visits with ICD-9 codes 070.2, 070.3, and/or V02.61, or admission with a diagnosis of chronic HBV infection between 1 January 2000 and 31 December 2012 (22). The index date was defined as the first day of chronic HBV infection diagnosis. Patients with the following characteristics were excluded: age < 20 years, diagnosis with hepatitis C infection, fewer than three outpatient clinic visits for HBV infection, history of myocardial infarction, and history of cerebrovascular disease. The control cohort comprised all patients with no diagnosis of HBV infection in the Longitudinal Cohort of Diabetes Patients dataset. The exclusion criteria for the HBV cohort were also applied to the control cohort. Index dates for subjects in the control cohort were assigned randomly and corresponded to those of patients in the HBV cohort.

We used 1:1 propensity score matching and calculated propensity scores for the likelihood of diagnosis of chronic HBV infection using baseline covariates and multivariate logistic regression analysis (Supplemental Table A1). We matched one control patient with each patient in the HBV cohort with a similar propensity score based

on nearest-neighbor matching without replacement, using calipers of a width equal to 0.1 standard deviation of the logit of the propensity score.

Primary Outcome Measurement

The primary outcomes were hospitalization for myocardial infarction (ICD-9-CM code 410.x), ischemic stroke (ICD-9-CM codes 433.x, 434.x), or heart failure (ICD-9-CM code 428.x); and all-cause mortality. The MACE outcome was defined as a composite of myocardial infarction and ischemic stroke. Previous studies have validate the accuracy of myocardial infarction and ischemic stroke diagnoses in the NHIRD (21,23). We also chose the occurrence of HCC as a positive control outcome and hospitalization for appendicitis as a negative control outcome. To identify patients diagnosed with HCC, we used data from Taiwan's Catastrophic Illness Registry, which requires pathohistological confirmation of cancer diagnoses. Both cohorts were followed until death or the end of the study period (31 December 2013).

Baseline Characteristics

Data on baseline demographic characteristics, including age, sex, monthly income (in New Taiwan Dollars [NT$]: <NT$19,100, NT$19,100−$41,999, and ≥NT$42,000), level of urbanization, and Charlson Comorbidity Index score, were collected. Taiwan's

National Health Research Institute has defined four urbanization levels for Taiwan. The most urbanized areas are designated as level 1, and the least urbanized areas are designated as level 4. The Charlson Comorbidity Index score reflects overall systemic health, with each increase in number reflecting a stepwise increase in cumulative mortality (24). We also identified use of medications that could confound the relationship between chronic HBV infection and the primary outcomes.

Statistical Analysis

Descriptive statistics were used to characterize the baseline data from the study cohorts. Baseline characteristics of the two groups were compared using standardized mean differences. Propensity scores of the likelihood of diagnosis of chronic HBV infection were determined by multivariate logistic regression analysis, conditional on baseline covariates (Supplemental Table A1). The incidence rates of outcomes of interest in the two groups were calculated using Poisson distributions. The cumulative incidence or risk of outcomes was estimated using the Kaplan–Meier method, and differences between cohorts were evaluated with the log-rank test. Cox regression models with a conditional approach and stratification were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risks of outcomes (25). Cox regression with adjustment for significant differences in covariates between groups was used to

calculate adjusted HRs. Due to the high mortality rate of diabetic patients, competing-risk regression using Fine and Gray's model (26) was also performed. Finally, the likelihood ratio test was used to examine interactions between the occurrence of outcomes subsequent to chronic HBV infection and the following variables: age, sex, hypertension, coronary artery disease, CKD, dyslipidemia, use of insulin, and adapted Diabetes Complications Severity Index score. Subgroup analyses were also performed accordingly.

SQL Server 2012 (Microsoft Corporation, Redmond, WA, USA) was used for data linkage, processing, and sampling. Propensity scores were calculated with SAS version 9.3 (SAS Institute, Cary, NC, USA). All other statistical analyses were conducted using STATA statistical software (version 12.0; StataCorp, College Station, TX, USA). *P* values < 0.05 were considered to be statistically significant.

RESULTS

Patient Characteristics

The study cohort consisted of 40,162 diabetic patients with chronic HBV infection and 40,162 matched control subjects without HBV infection (Figure 1). The mean age was 52.7 (standard deviations, 11.6 [HBV] and 11.5 [control]) years, and 62.7% of subjects were male (Table 1). The prevalence of comorbidities, such as cardiovascular risk

factors, and concomitant medication use was similar in the HBV and control groups.

HBV Infection, Risk of Cardiovascular Disease, and All-Cause Mortality in Diabetic Patients

During the mean 5.3-year follow-up period, the incidence rates of all-cause mortality, myocardial infarction, ischemic stroke, and heart failure were 26.96, 1.38, 3.71, and 1.12 per 10^3 person-years, respectively, in the HBV cohort and 35.29, 2.76, 5.88, and 2.01 per 10^3 person-years, respectively, in the matched control cohort (Table 2). Compared with the matched control cohort, the HBV cohort had significantly reduced risks of all-cause mortality (adjusted HR = 0.72; 95% CI, 0.70–0.75; $p < 0.001$), myocardial infarction (aHR = 0.49; 95% CI, 0.42–0.56; $p < 0.001$), ischemic stroke (aHR = 0.61; 95% CI, 0.56–0.67; $p < 0.001$), MACE (aHR = 0.58; 95% CI, 0.53–0.62; $p < 0.001$), and heart failure (aHR = 0.50; 95% CI, 0.43–0.59; $p < 0.001$; Table 2). The cumulative incidence of all-cause mortality and MACE in both groups was illustrated in Figure 2. The HBV cohort had a significantly higher risk of HCC (aHR = 7.47; 95% CI, 6.53–8.56; $p < 0.001$) and a similar risk of hospitalization for appendicitis (aHR = 1.13; 95% CI, 0.93–1.38; $p = 0.227$). Competing risk analysis yielded consistent results (Table 2).

An interaction test for all-cause mortality showed significant correlations between

HBV infection and sex (p = 0.030), hypertension (p < 0.001), dyslipidemia (p < 0.001), use of insulin (p = 0.020), and adapted Diabetes Complications Severity Index score (p = 0.010; Supplemental Table A2). An interaction test for MACE showed significant correlations between HBV infection and sex (p = 0.002), hypertension (p = 0.005), coronary artery disease (p = 0.005), dyslipidemia (p = 0.003), use of insulin (p = 0.005), and adapted Diabetes Complications Severity Index score (p = 0.04; Supplemental Table A3). In Figure 3, we conducted multivariable stratified subgroup analyses. The effects of chronic HBV infection on all-cause mortality and MACE were greater in patients without hypertension and dyslipidemia compared with matched controls. The association between chronic HBV infection and all-cause mortality or sequential MACE was also greater in patients who were not using insulin. In stratified analyses, the effect of chronic HBV infection on the sequential risk of MACE was greater in patients with low adapted Diabetes Complications Severity Index scores (<2; Supplemental Tables 2 and 3).

CONCLUSIONS

To our knowledge, this propensity score–matched, nationwide, population-based study is the first to elucidate the correlation of chronic HBV infection with lower risks of MACE

and heart failure in diabetic patients. In addition, we found a significantly decreased risk of all-cause mortality in diabetic patients with chronic HBV infection during the mean 5.3-year follow-up period. The impact of HBV infection on the sequential risk of MACE was greater in patients with fewer diabetic complications.

HBV X protein (HBx), 1 of 4 open reading frames in the HBV genome, has been reported involving in regulating apoptosis, inflammation, and tumorigenesis (27,28). In addition, HBx also has been shown to cause hepatic steatosis through the transcriptional activation of sterol regulatory element-binding protein 1 (SREBP1) and peroxisome proliferator-activated receptor (PPARγ) transcripts (29), implying the involvement of HBV infection in regulation of lipid and glucose metabolism-related genes (10,29). Inverse association observed between metabolic syndrome and chronic HBV in the cross-sectional studies from NHANES III (10) and from Taiwan (11), supporting our findings. A recent systemic review article concluded that multiple, but not all, studies showed that patients with chronic HBV infection have lower risk of metabolic syndrome, non-alcoholic fatty liver disease and dyslipidemia (30). Their conclusions may provide part of the mechanism underlying the link between chronic HBV infection and MACE. A study of a non-diabetic Korean cohort showed that HBsAg seropositivity was associated with decreased risks of ischemic stroke and myocardial infarction (15). The Korean study found this association appeared to be secondary to HBV-associated

liver dysfunction (15). Other reported potential mechanisms linking chronic HBV infection to decreased risk of MACE include lower levels of clotting factors II and VII and fibrinogen among HBsAg-positive (*vs.* –negative) individuals, as found in blood donors in Gambia and London (31).

A cohort study from England and Wales showed no significantly increased risk of all-cause mortality in transfusion donors with HBV infection (32). The standardized mortality rate (SMR) for circulatory disease was significantly low in both males and females (32). Their results may support or not against our findings. Furthermore, we found that the risk of circulatory disease deaths in HBV cohort was significantly low in the Australian study (33), was comparable in the Taiwan study (16) and was significantly high in the study from China (34). The China study conducted in 1992-2002 with a very low cardiovascular mortality (20.6 in male, 16.4 in female per 100000 person-year) in their HBV cohort (34). The study in Taiwan showed that HBsAg seropositivity was not associated with atherosclerosis-related mortality risk in a general population (16). One possible explanation for this result is the lack of statistical power (HR = 0.84; 95% CI, 0.72–1.06) because of the examination of a relatively small sample (480 cases of death from atherosclerotic disease) (16). Both the Australian and British studies are in agreement with our findings about relationship between HBV and MACE (32,33).

Moreover, previous cohort studies reported an increased risk of all-cause mortality attributed mostly to excess liver-related deaths in a general population (16,33,34). A study from Australia reported that the risk of death was increased 1.4 times in subjects with HBV infection (33); another study from Taiwan reported a 1.7 times elevated risk (16) and a cohort study from China reported a three-fold increased risk (34). We are not aware of any study that has examined the relationship between all-cause mortality and chronic HBV infection in diabetic patients. We conducted this HBV study in population with very high risk for MACE. In our diabetic cohort, the incidence rate of MACE was high (498 vs. 839 per 100000 person-year) to provide sufficient endpoints (1098 vs. 1663 events). Our study demonstrated a reduced all-cause mortality risk in diabetic subjects with chronic HBV infection. This finding may be explained by the decreased MACE risk in our diabetic HBV cohort. Diabetes, which is considered to be a coronary artery disease equivalent, is an important risk factor for cardiovascular disease (35). Cardiovascular complication is the leading cause of mortality in diabetic patients (3). It is plausible to hypothesize that the impact of HBV infection on all-cause mortality would be greater in diabetic patients than in a general population.

This study has several strengths. First, it involved an unselected nationwide population with the most extensive sample of diabetic patients with chronic HBV infection available, minimizing the possibility of referral bias. Second, the diabetic

HBV cohort comprised 40,162 patients during the 12-year study period, providing adequate statistical power for the analysis of the risks of MACE, heart failure, and all-cause mortality in this population. To our knowledge, this study is the largest-scale, diabetic HBV cohort study to date. In addition, we compared study subjects with propensity score–matched control subjects, instead of conducting age- and sex-adjusted analysis in comparison with a general population.

Some limitations of our study should be noted. First, absolute values of liver function tests were not available in the nationwide dataset. An individual with chronic HBV infection may present as a “healthy” carrier with normal liver function or with chronic hepatitis. Second, the values of glycated hemoglobin, used widely as a glycemic control index, were not available in this dataset. Glycemic control may be a confounding factor for MACE. However, recent reports showed that blood glucose level reduction may have no beneficial effect or only modest effects on diabetic cardiovascular complications in high-risk populations (36,37). In addition, the emergence of MACE caused from poor glycemic control takes a long time (36). Third, some personal information, including body mass index and smoking status, was not available in the administrative dataset, preventing accurate assessment of the contributory and confounding effects of these factors. The effects of chronic HBV infection on MACE may be due to residual confounding. However, we performed a sensitivity analysis that

included positive and negative control outcomes to provide further support for our findings (38).

Despite the abovementioned limitations, we found chronic HBV infection associated with decreased risk of MACE, heart failure and all-cause mortality in diabetic patients. These findings may provide new insight into the pathogenesis of diabetes and future therapeutic strategies. However, further research is necessary to confirm our findings and to explore the underlying mechanism.

Funding: This study was supported in part by two research grants: MOST 104-2314-B-075-047 from the Ministry of Science and Technology of Taiwan and V105C-0207, V106C-045 from Taipei Veterans General Hospital. The aforementioned funding agencies had no influence on the study design, data collection or analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest: No potential conflicts of interest relevant to this article were reported.

Author contributions: Y.-T.C. is the guarantor of this work, as such, had full access to

all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: C.-S.K., P.-H.H., Y.-T.C. and S.-J.L. Acquisition of data: Y.-T.C., C.-Y.H. and C.-C.C. Analysis and interpretation of data: C.-S.K., Y.-T.C., and P.-H.H.. Drafting of the manuscript: C.-S.K., Y.-T.C., P.-H.H., C.-Y.H., and C.-C.C. Statistical analysis: P.-H.H. and Y.-T.C.. Administrative, technical, or material support: R.-H.C., S.-J.L., S.-C.K., J.-W.C. and S.-J.L.. Critical revision: Y.-T.C., P.-H.H. and S.-J.L.. Study supervision: P.-H.H. and S.-J.L.. The Corresponding Authors have the right to grant on behalf of all authors and do grant on behalf of all authors a worldwide license to the Publisher and its licensees in perpetuity.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27(5):1047–1053
2. Eckel RH, Kahn R, Robertson RM, Rizza RA. Preventing cardiovascular disease and diabetes: a call to action from the American Diabetes Association and the American Heart Association. Circulation 2006;113(25):2943–2946
3. Buse JB, Ginsberg HN, Bakris GL, et al.; American Heart Association; American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2007;30:162–172
4. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010. N Engl J Med 2013;368:1613–1624
5. Domingueti CP, Dusse LM, Carvalho MD, de Sousa LP, Gomes KB, Fernandes AP. Diabetes mellitus: the linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. J Diabetes Complications 2016;30(4):738–745
6. Kao JH, Chen DS. Global control of hepatitis B virus infection. Lancet Infect Dis

2002;2(7):395–403

7. Chen CL, Yang JY, Lin SF, Sun CA, Bai CH, You SL, Chen CJ, Kao JH, Chen PJ, Chen DS. Slow decline of hepatitis B burden in general population: results from a population-based survey and longitudinal follow-up study in Taiwan. J Hepatol 2015;63(2):354–363

8. Chen DS. From hepatitis to hepatoma: lessons from type B viral hepatitis. Science 1993;262(5132):369–370

9. Domingueti CP, Dusse LM, Carvalho MD, de Sousa LP, Gomes KB, Fernandes AP. Diabetes mellitus: the linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. J Diabetes Complications 2016;30(4):738–745

10. Jinjuvadia R, Liangpunsakul S. Association between metabolic syndrome and its individual components with viral hepatitis B. Am J Med Sci. 2014;347(1):23–27

11. Jan CF, Chen CJ, Chiu YH, Chen LS, Wu HM, Huang CC, Yen MF, Chen TH. A population-based study investigating the association between metabolic syndrome and hepatitis B/C infection (Keelung Community-based Integrated Screening study No. 10). Int J Obes (Lond). 2006;30(5):794–799.

12. Volzke H, Schwahn C, Wolff B, Mentel R, Robinson DM, Kleine V, Felix SB, John U. Hepatitis B and C virus infection and the risk of atherosclerosis in a general

population. Atherosclerosis 2004;174:99–103

13. Tong DY, Wang XH, Xu CF, Yang YZ, Xiong SD. Hepatitis B virus infection and coronary atherosclerosis: results from a population with relatively high prevalence of hepatitis B virus. World J Gastroenterol 2005;11:1292–1296

14. Ishizaka N, Ishizaka Y, Takahashi E, Toda EE, Hashimoto H, Ohno M, Nagai R, Yamakado M. Increased prevalence of carotid atherosclerosis in hepatitis B virus carriers. Circulation 2002;105:1028–1030

15. Sung J, Song YM, Choi YH, Ebrahim S, Davey SG. Hepatitis B virus seropositivity and the risk of stroke and myocardial infarction. Stroke 2007;38:1436–1441

16. Wang CH, Chen CJ, Lee MH, Yang HI, Hsiao CK. Chronic hepatitis B infection and risk of atherosclerosis-related mortality: a 17-year follow-up study based on 22,472 residents in Taiwan. Atherosclerosis 2010;211(2):624–629

17. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65–73

18. Chao TF, Liu CJ, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Tsao HM, Chen SA. Hyperuricemia and the risk of ischemic stroke in patients with atrial fibrillation: could it refine clinical risk stratification in AF? Int J Cardiol 2014;170:344–349

19. Chiu CC, Huang CC, Chan WL, Chung CM, Huang PH, Lin SJ, Chen JW, Leu HB. Increased risk of ischemic stroke in patients with systemic lupus erythematosus: a nationwide population-based study. Intern Med 2012;51:17–21

20. Lin CC, Lai MS, Syu CY, Chang SC, Tseng FY. Accuracy of diabetes diagnosis in health insurance claims data in Taiwan. J Formos Med Assoc 2005;104:157–163

21. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf 2011;20:236–242

22. Wu CY, Lin JT, Ho HJ, Su CW, Lee TY, Wang SY, Wu C, Wu JC. Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide cohort study. Gastroenterology 2014;147(1):143–151

23. Cheng CL, Lee CH, Chen PS, Li YH, Lin SJ, Yang YH. Validation of acute myocardial infarction cases in the national health insurance research database in Taiwan. J Epidemiol 2014;24:500–507

24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373–383

25. Austin PC. A critical appraisal of propensity-score matching in the medical literature

between 1996 and 2003. Stat Med 2008;27:2037–2049

26. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509

27. Kim CM, Koike K, Saito I, Miyamura T, Jay G. HBx gene of hepatitis B virus induces liver cancer in transgenic mice. Nature. 1991;23;351(6324):317–320

28. Yu DY, Moon HB, Son JK, et al. Incidence of hepatocellular carcinoma in transgenic mice expressing the hepatitis B virus X-protein. J Hepatol. 1999;31(1):123–132

29. Kim KH, Shin HJ, Kim K, et al. Hepatitis B virus X protein induces hepatic steatosis via transcriptional activation of SREBP1 and PPARgamma. Gastroenterology. 2007;132(5):1955–1967.

30. Jarcuska P, Drazilova S, Fedacko J, Pella D, Janicko M. Association between hepatitis B and metabolic syndrome: Current state of the art. World J Gastroenterol. 2016;22(1):155–164

31. Meade TW, Stirling Y, Thompson SG, Ajdukiewicz A, Barbara JA, Chalmers DM. Carriers of hepatitis B surface antigen: possible association between low levels of clotting factors and protection against ischaemic heart disease. Thromb Res 1987;45(5):709–713

32. Crook PD, Jones ME, Hall AJ. Mortality of hepatitis B surface antigen-positive

blood donors in England and Wales. Int J Epidemiol 2003;32:118–124

33. Amin J, Law MG, Bartlett M, Kaldor JM, Dore GJ. Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study. Lancet 2006;368(9539):938–945

34. Chen G, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Chronic hepatitis B virus infection and mortality from non-liver causes: results from the Haimen City cohort study. Int J Epidemiol 2005;34:132–137

35. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234

36. Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, McCarren M, Duckworth WC, Emanuele NV; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;372(23):2197–2206

37. ACCORD Study Group Writing Committee. 9-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. Diabetes Care 2016;39(5):701–708

38. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology 2010;21(3):383–

388

FIGURE LEGENDS

Figure 1. Study patient selection flow diagram. The study cohort consisted of 40,162 diabetic patients with chronic HBV infection and 40,162 matched control subjects without HBV infection.

Figure 2. The cumulative incidence of all-cause mortality (A) and major adverse cardiovascular events (B) among diabetic patients with chronic HBV infection and matched control subjects without HBV infection.

Figure 3. Multivariable stratified subgroup analyses. The effects of chronic HBV infection on all-cause mortality (A) and major adverse cardiovascular events (B).

Table 1–Baseline characteristics of diabetic patients

Characteristic	Propensity Score–Matched		
	HBV cohort	Control cohort	Standardized difference*
Patients (*n*)	40,162	40,162	
Mean age (SD), years	52.7 (11.6)	52.7 (11.5)	0.002
Sex (male)	25,173 (62.7)	25,173 (62.7)	0.000
Monthly income, NT$			
Dependent	8,787 (21.9)	8,510 (21.2)	0.017
<19,100	6,859 (17.1)	6,342 (15.8)	0.035
19,100–41,999	18,910 (47.1)	19,343 (48.2)	-0.022
≥42,000	5,606 (14.0)	5,967 (14.9)	-0.026
Urbanization level			
1 (urban area)	14,845 (37.0)	15,501 (38.6)	-0.034
2	23,400 (58.3)	22,828 (56.8)	0.029
3	1,593 (4.0)	1,498 (3.7)	0.012
4 (rural area)	324 (0.8)	335 (0.8)	-0.003
Outpatient visits to metabolism and endocrinology professionals in the past year			
0–5	35,055 (87.3)	34,947 (87.0)	0.008
6–10	3,752 (9.3)	3,774 (9.4)	-0.002
11–15	975 (2.4)	1,049 (2.6)	-0.012
>15	380 (0.9)	382 (1.0)	-0.003
Charlson Comorbidity Index score, median (IQR)	6 (5–8)	6 (4–8)	0.035
Adapted Diabetes Complications Severity Index score, median (IQR)†	0 (0–1)	0 (0–1)	-0.001
Median (IQR) duration of diabetes mellitus, months	38 (12–74)	39 (16–73)	-0.024
Anti-hypertensive drug use			
Alpha blocker	420 (1.0)	362 (0.9)	0.015
ACE inhibitor or ARB	3,885 (9.7)	3,950 (9.8)	-0.005
Beta blocker	3,256 (8.1)	3,337 (8.3)	-0.007
Calcium channel blocker	3,887 (9.7)	3,866 (9.6)	0.002
Diuretic	2,701 (6.7)	2,507 (6.2)	0.020

Anti-diabetic drug use			
Acarbose	823 (2.0)	886 (2.2)	-0.011
Sulfonylurea	7,374 (18.4)	7,795 (19.4)	-0.027
Insulin	865 (2.2)	831 (2.1)	0.006
Metformin	6,921 (17.2)	7,235 (18.0)	-0.021
Thiazolidinedione	689 (1.7)	707 (1.8)	-0.003
Dipeptidyl peptidase-4 inhibitor	398 (1.0)	458 (1.1)	-0.015
Other concomitant medications			
Antiplatelet agent	2,097 (5.2)	2,073 (5.2)	0.003
NSAID	8,662 (21.6)	8,728 (21.7)	-0.004
Proton pump inhibitor	1,836 (4.6)	1,436 (3.6)	0.050
Steroid	2,005 (5.0)	1,942 (4.8)	0.007
Antidepressant	1,117 (2.8)	1,137 (2.8)	-0.003
Statin	1,701 (4.2)	1,718 (4.3)	-0.002
Comorbidities			
Coronary artery disease	9,694 (24.1)	9,731 (24.2)	-0.002
Hypertension	19,839 (49.4)	19,859 (49.4)	-0.001
Heart failure	2,002 (5.0)	1,791 (4.5)	0.025
Peripheral vascular disease	1,369 (3.4)	1,543 (3.8)	-0.023
Chronic kidney disease	5,929 (14.8)	5,916 (14.7)	0.001
Atrial fibrillation	472 (1.2)	399 (1.0)	0.018
Dyslipidemia	22,827 (56.8)	23,813 (59.3)	-0.050
Valvular heart disease	2,588 (6.4)	2,547 (6.3)	0.004
Cancer	6,835 (17.0)	6,546 (16.3)	0.019
Autoimmune disease	1,543 (3.8)	1,559 (3.9)	-0.002
Dialysis	386 (1.0)	345 (0.9)	0.011
Physical limitation	1,592 (4.0)	1,606 (4.0)	-0.002
Propensity score, mean (SD)	0.08 (0.06)	0.08 (0.06)	0.000

Data are presented as *n* (%) except where otherwise indicated.

*Imbalance defined as absolute value > 0.014.

†A 13-point scale with 7 complication categories: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic. Each complication is given a numeric score ranging from 0 to 2 (0 = no abnormality, 1 = some abnormality, 2 = severe abnormality).

Abbreviations: IQR, interquartile range; ARB, angiotensin II receptor blocker; NSAID, non-steroidal anti-inflammatory drug.

Table 2–Incidence and risks of all-cause mortality, myocardial infarction, stroke, hospitalization for heart failure, and cancer after propensity score matching

	HBV cohort			Control cohort (reference)			Crude		Adjusted		Competing risk	
	No. of events	Person-years	Incidence rate*	No. of events	Person-years	Incidence rate*	Hazard ratio (95% CI)	*p* value	Hazard ratio† (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
All-cause mortality	6,027	223,588	26.96	7,140	202,307	35.29	0.78 (0.76–0.81)	<0.001	0.72 (0.70–0.75)	<0.001		
MACE‡	1,098	220,605	4.98	1,663	198,131	8.39	0.59 (0.55–0.64)	<0.001	0.58 (0.53–0.62)	<0.001	0.62 (0.57–0.66)	<0.001
Myocardial infarction	308	222,847	1.38	554	201,078	2.76	0.50 (0.43–0.57)	<0.001	0.49 (0.42–0.56)	<0.001	0.52 (0.45–0.60)	<0.001
Ischemic stroke	822	221,298	3.71	1,171	199,259	5.88	0.63 (0.57–0.69)	<0.001	0.61 (0.56–0.67)	<0.001	0.66 (0.60–0.72)	<0.001
Heart failure	249	223,050	1.12	405	201,494	2.01	0.55 (0.47–0.65)	<0.001	0.50 (0.43–0.59)	<0.001	0.58 (0.49–0.68)	<0.001
HCC	1,590	220,573	7.21	153	202,145	0.76	9.58 (8.12–11.31)	<0.001	9.34 (7.91–11.03)	<0.001	10.06 (8.52–11.87)	<0.001
Acute appendicitis	222	222,682	1.00	179	201,644	0.89	1.13 (0.93–1.37)	0.233	1.13 (0.93–1.38)	0.227	1.18 (0.97–1.43)	0.102

*Per 10^3 person-years.

†Adjusted for monthly income, urbanization level, Charlson Comorbidity Index score, dipeptidyl peptidase-4 inhibitor use, metformin use, sulfonylurea use, alpha blocker use, dyslipidemia, atrial fibrillation, peripheral vascular disease, and heart failure.

‡Myocardial infarction and ischemic stroke.

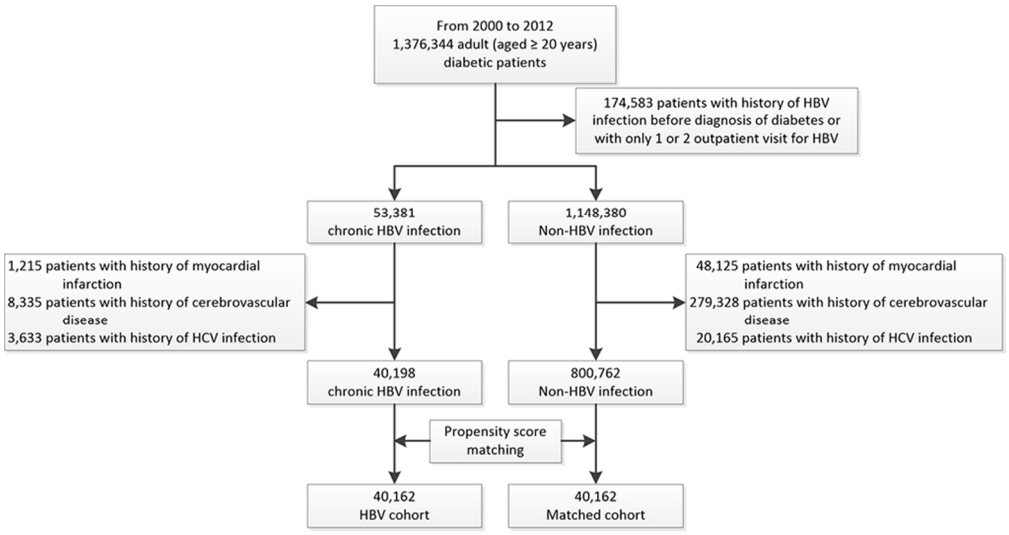
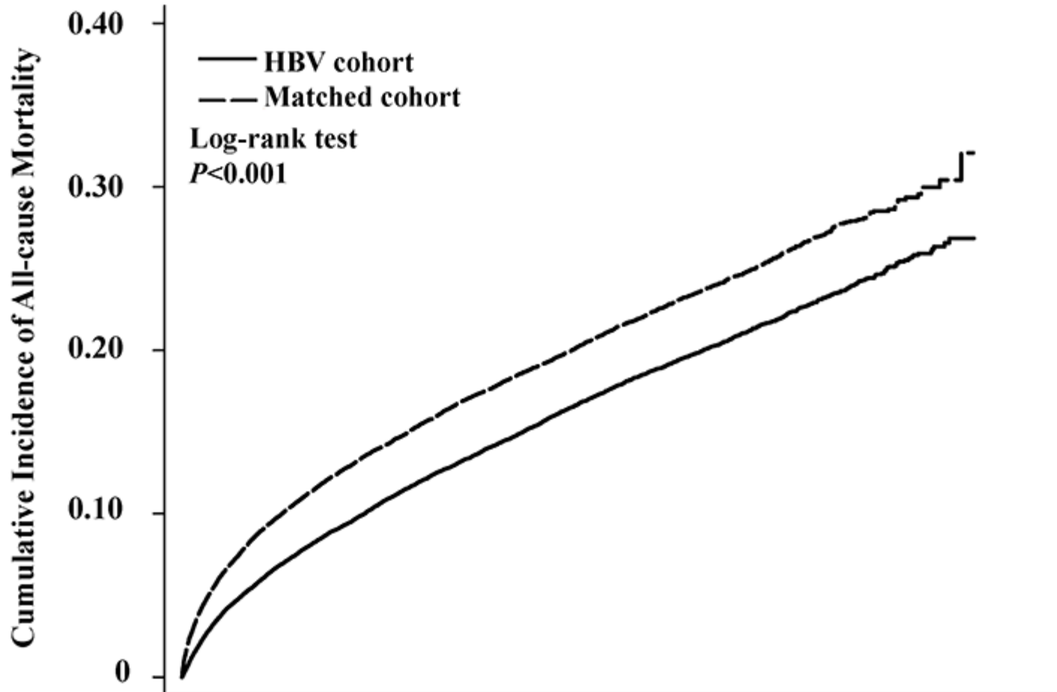


Figure 1. Study patient selection flow diagram. The study cohort consisted of 40,162 diabetic patients with chronic HBV infection and 40,162 matched control subjects without HBV infection.

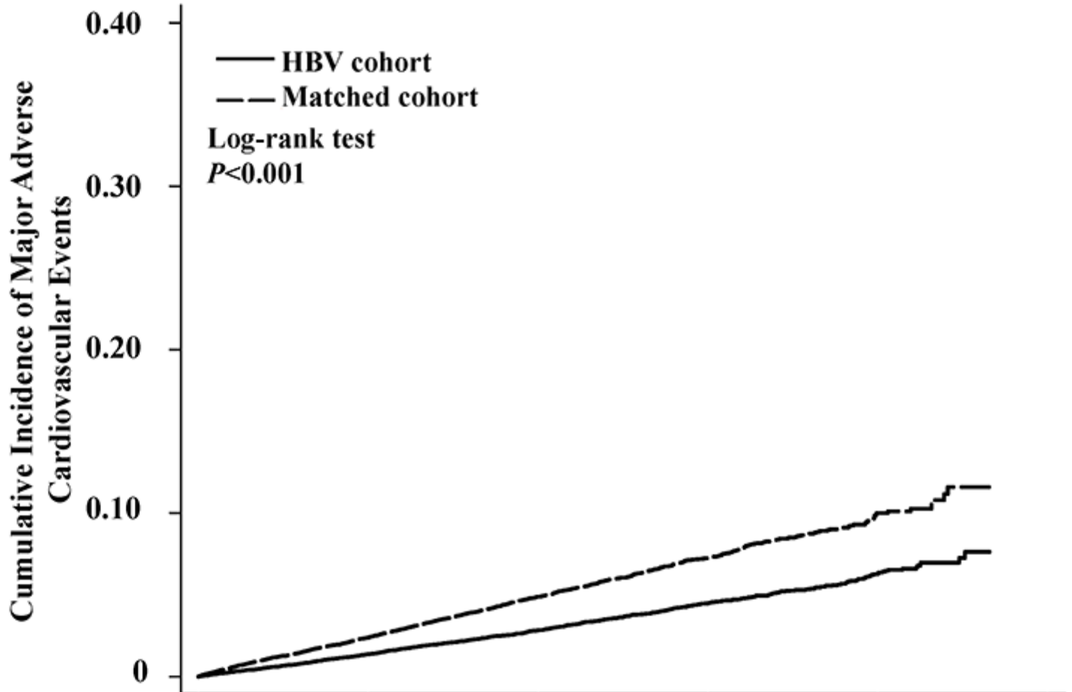
86x45mm (300 x 300 DPI)

A



No. of patients at risk					
HBV cohort	40,162	28,673	17,029	7,548	2,052
Matched cohort	40,162	26,903	15,020	5,654	1,145

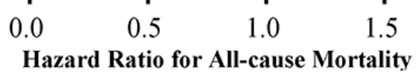
B



No. of patients at risk					
HBV cohort	40,162	28,364	16,693	7,320	1,958
Matched cohort	40,162	26,454	14,497	5,373	1,048

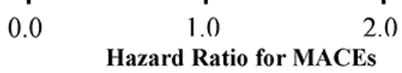
A

	HR (95% CI)	$P_{Interaction}$
Sex		
Male	0.79 (0.75-0.82)	0.030
Female	0.71 (0.67-0.77)	
Age		
20–65 years	0.75 (0.72-0.78)	0.165
>65 years	0.77 (0.72-0.82)	
Hypertension		
Yes	0.87 (0.83-0.91)	<0.001
No	0.67 (0.64-0.70)	
Coronary artery disease		
Yes	0.79 (0.74-0.84)	0.345
No	0.76 (0.73-0.79)	
Chronic Kidney disease		
Yes	0.82 (0.76-0.89)	0.114
No	0.75 (0.73-0.78)	
Dyslipidemia		
Yes	0.94 (0.89-0.99)	<0.001
No	0.63 (0.60-0.66)	
Use of insulin		
Yes	0.93 (0.79-1.10)	0.020
No	0.76 (0.73-0.79)	
Adapted Diabetes Complications Severity Index score		
0–1	0.75 (0.72-0.78)	0.010
≥2	0.83 (0.77-0.88)	



B

	HR (95% CI)	$P_{Interaction}$
Sex		
Male	0.53 (0.48-0.58)	0.002
Female	0.69 (0.60-0.79)	
Age		
20–65 years	0.58 (0.53-0.64)	0.799
>65 years	0.58 (0.50-0.66)	
Hypertension		
Yes	0.62 (0.56-0.68)	0.005
No	0.49 (0.43-0.56)	
Coronary artery disease		
Yes	0.67 (0.59-0.77)	0.005
No	0.53 (0.49-0.59)	
Chronic Kidney disease		
Yes	0.64 (0.54-0.76)	0.158
No	0.56 (0.51-0.61)	
Dyslipidemia		
Yes	0.64 (0.58-0.71)	0.003
No	0.50 (0.45-0.56)	
Use of insulin		
Yes	1.14 (0.73-1.78)	0.005
No	0.56 (0.52-0.61)	
Adapted Diabetes Complications Severity Index score		
0–1	0.55 (0.50-0.60)	0.044
≥2	0.64 (0.56-0.74)	



Supplemental Table A1–Propensity score model results of probability of diagnosis of HBV infection

Parameter	Estimate	Odds Ratio	95% CI Lower	95% CI Upper	*p* value
Age, per year	-0.0411	0.96	0.959	0.961	<0.0001
Male	0.4718	1.603	1.568	1.638	<0.0001
Year of index date					
2000		1			
2001	-0.1146	0.892	0.822	0.967	0.0055
2002	-0.2589	0.772	0.714	0.835	<0.0001
2003	-0.4023	0.669	0.619	0.723	<0.0001
2004	-0.4794	0.619	0.575	0.667	<0.0001
2005	-0.5758	0.562	0.523	0.605	<0.0001
2006	-0.6641	0.515	0.479	0.553	<0.0001
2007	-0.7626	0.466	0.434	0.501	<0.0001
2008	-0.8804	0.415	0.386	0.446	<0.0001
2009	-0.9874	0.373	0.347	0.401	<0.0001
2010	-1.0996	0.333	0.31	0.358	<0.0001
2011	-1.2988	0.273	0.254	0.293	<0.0001
2012	-1.3871	0.25	0.232	0.269	<0.0001
Month of index date					
January		1			
February	-0.0141	0.986	0.933	1.042	0.6135
March	-0.0354	0.965	0.916	1.016	0.18
April	-0.0224	0.978	0.929	1.03	0.3935
May	-0.044	0.957	0.909	1.007	0.0913
June	-0.0566	0.945	0.897	0.995	0.0315
July	-0.0694	0.933	0.887	0.982	0.0074
August	-0.0812	0.922	0.876	0.97	0.0017
September	-0.1023	0.903	0.858	0.95	<0.0001
October	-0.0938	0.91	0.865	0.958	0.0003
November	-0.116	0.891	0.846	0.937	<0.0001
December	-0.1214	0.886	0.842	0.932	<0.0001
Monthly income, NT$					
Dependent		1			
<19,100	-0.1658	0.847	0.819	0.876	<0.0001
19,100–41,999	0.1102	1.116	1.087	1.147	<0.0001
≥42,000	0.2833	1.328	1.279	1.377	<0.0001

Urbanization level					
1 (urban area)		1			
2	-0.0904	0.914	0.894	0.934	<0.0001
3	-0.1119	0.894	0.847	0.944	<0.0001
4 (rural area)	-0.0171	0.983	0.877	1.103	0.7708
Outpatient visits to metabolism and endocrinology professionals in the past year					
0					
1–5	0.158	1.171	1.13	1.214	<0.0001
6–10	-0.1084	0.897	0.84	0.959	0.0014
>10	-0.0625	0.939	0.845	1.044	0.2474
Charlson Comorbidity Index score[a]	0.1398	1.15	1.143	1.157	<0.0001
Adapted Diabetes Complications Severity Index score[b]	-0.073	0.93	0.917	0.942	<0.0001
Duration of diabetes, months	0.0028	1.003	1.003	1.003	<0.0001
Anti-diabetic drugs					
Acarbose	0.0507	1.052	0.977	1.133	0.18
Sulfonylurea	0.1154	1.122	1.084	1.162	<0.0001
Insulin	0.2091	1.233	1.145	1.327	<0.0001
Metformin	0.151	1.163	1.122	1.206	<0.0001
Thiazolidinedione	-0.3096	0.734	0.677	0.795	<0.0001
Dipeptidyl peptidase-4 inhibitor	0.0812	1.085	0.976	1.205	0.1308
Anti-hypertensive drugs					
Alpha blocker	-0.081	0.922	0.833	1.02	0.1164
Beta blocker	0.032	1.032	0.991	1.076	0.1247
Calcium channel blocker	-0.0569	0.945	0.908	0.982	0.0044
Diuretic	0.3296	1.39	1.33	1.454	<0.0001
ACE inhibitor/ARB	-0.0856	0.918	0.882	0.955	<0.0001
Other concomitant medications					
Antiplatelet	-0.185	0.831	0.791	0.873	<0.0001
Steroid	-0.1578	0.854	0.814	0.896	<0.0001
Antidepressant	0.0542	1.056	0.991	1.125	0.0936
Statin	-0.4718	0.624	0.592	0.658	<0.0001
PPI	1.1059	3.022	2.864	3.189	<0.0001
NSAID	0.0767	1.08	1.053	1.108	<0.0001
Comorbidities					
Hypertension	-0.1764	0.838	0.818	0.859	<0.0001
Coronary artery disease	0.0571	1.059	1.028	1.09	0.0002
Heart failure	-0.3525	0.703	0.666	0.741	<0.0001

Peptic ulcer disease	0.1731	1.189	1.162	1.217	<0.0001
Chronic kidney disease	0.0234	1.024	0.993	1.055	0.1335
Atrial fibrillation	-0.1366	0.872	0.792	0.961	0.0057
Dyslipidemia	0.103	1.108	1.084	1.133	<0.0001
Valvular heart disease	0.0353	1.036	0.992	1.082	0.1102
Cancer	0.1052	1.111	1.07	1.153	<0.0001
Autoimmune disease	0.0809	1.084	1.028	1.144	0.0031
Physical limitation	0.0747	1.078	1.021	1.137	0.0063

[a] Used to determine overall systemic health; each increase reflects a stepwise increase in cumulative mortality.

[b] A 13-point scale with 7 complication categories: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic. Each complication is given a numeric score ranging from 0 to 2 (0 = no abnormality, 1 = some abnormality, 2 = severe abnormality).

Abbreviations: ARB, angiotensin II receptor blocker; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Supplemental Table A2–Subgroup analysis of risk of mortality among diabetic patients with HBV infection and matched control cohort

Characteristic	Adjusted[a] Hazard ratio (95% CI)	*p* value	Interaction *p* value
Sex			
Male	0.785 (0.754–0.817)	<0.001	0.030
Female	0.714 (0.667–0.765)	<0.001	
Age			
20–65 years	0.749 (0.719–0.781)	<0.001	0.165
>65 years	0.770 (0.724–0.819)	<0.001	
Hypertension			
Yes	0.870 (0.831–0.912)	<0.001	<0.001
No	0.668 (0.635–0.703)	<0.001	
Coronary artery disease			
Yes	0.786 (0.735–0.840)	<0.001	0.345
No	0.759 (0.729–0.790)	<0.001	
Chronic kidney disease			
Yes	0.818 (0.757–0.886)	<0.001	0.114
No	0.754 (0.726–0.784)	<0.001	
Dyslipidemia			
Yes	0.936 (0.887–0.986)	0.014	<0.001
No	0.630 (0.602–0.659)	<0.001	
Use of insulin			
Yes	0.932 (0.792–1.096)	0.395	0.020
No	0.759 (0.733–0.786)	<0.001	
Adapted Diabetes Complications Severity Index score			
0–1	0.749 (0.719–0.780)	<0.001	0.010
≥2	0.826 (0.774–0.881)	<0.001	

[a] Adjusted for monthly income, urbanization level, Charlson Comorbidity Index score, dipeptidyl peptidase-4 inhibitor use, metformin use, sulfonylurea use, alpha blocker use, dyslipidemia, atrial fibrillation, peripheral vascular disease, and heart failure.

Supplemental Table A3–Subgroup analysis of risk of MACE among diabetic patients with HBV infection and matched control cohort

Characteristic	Adjusted[a] Hazard ratio (95% CI)	*p* value	Interaction *p* value
Sex			
Male	0.526 (0.480–0.576)	<0.001	0.002
Female	0.686 (0.596–0.789)	<0.001	
Age			
20–65 years	0.579 (0.528–0.636)	<0.001	0.799
>65 years	0.575 (0.502–0.659)	<0.001	
Hypertension			
Yes	0.619 (0.563–0.680)	<0.001	0.005
No	0.493 (0.431–0.564)	<0.001	
Coronary artery disease			
Yes	0.670 (0.585–0.766)	<0.001	0.005
No	0.533 (0.486–0.585)	<0.001	
Chronic kidney disease			
Yes	0.638 (0.536–0.760)	<0.001	0.158
No	0.558 (0.512–0.607)	<0.001	
Dyslipidemia			
Yes	0.638 (0.576–0.707)	<0.001	0.003
No	0.501 (0.447–0.562)	<0.001	
Use of insulin			
Yes	1.143 (0.734–1.781)	0.555	0.005
No	0.560 (0.518–0.605)	<0.001	
Adapted Diabetes Complications Severity Index score			
0–1	0.545 (0.497–0.598)	<0.001	0.044
≥2	0.640 (0.557–0.735)	<0.001	

[a] Adjusted for monthly income, urbanization level, Charlson Comorbidity Index score, dipeptidyl peptidase-4 inhibitor use, metformin use, sulfonylurea use, alpha blocker use, dyslipidemia, atrial fibrillation, peripheral vascular disease, and heart failure.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 7
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 8
Methods			
Study design	4	Present key elements of study design early in the paper	Page 10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 9 and 10
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Page 10
		(*b*) For matched studies, give matching criteria and the number of controls per case	Page 10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Page 8*
Bias	9	Describe any efforts to address potential sources of bias	Page 11, 12, 13
Study size	10	Explain how the study size was arrived at	Page 10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 11, 12, 13
		(*b*) Describe any methods used to examine subgroups and interactions	Page 12, 13
		(*c*) Explain how missing data were addressed	Page 12, 13
		(*d*) If applicable, explain how matching of cases and controls was addressed	Page 12, 13
		(*e*) Describe any sensitivity analyses	Page 12, 13
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 13
		(b) Give reasons for non-participation at each stage	Page 13
		(c) Consider use of a flow diagram	Page 13, Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 13, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Hard endpoint, no missing data
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Page 14, 15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 14, 15
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 14, Table 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 14, 15
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 15,16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 20
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 18
Other information			Page 19,20
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The impact of chronic hepatitis B infection on major adverse cardiovascular events and all-cause mortality in diabetic patients: a nationwide population-based study from Taiwan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016179.R1
Article Type:	Research
Date Submitted by the Author:	13-Jun-2017
Complete List of Authors:	Kuo, Chin-Sung; Taipei Veterans General Hospital, Division of Endocrinology and Metabolism Chen, Yung-Tai; Taipei City Hospital Heping Fuyou Branch, Department of Medicine Hsu, Chien-Yi; Taipei Medical University Hospital, Division of Cardiology, Department of Medicine Chang, Chun-Chin; Taipei Veterans General Hospital, Division of Cardiology, Department of Medicine Chou, Ruey-Hsing; Taipei Veterans General Hospital, Division of Cardiology, Department of Medicine Li, Szu-Yuan; Taipei Veterans General Hospital, Divisions of Nephrology Kuo, Shu-Chen; National Health Research Institutes, National Institute of Infectious Diseases and Vaccinology Huang, Po-Hsun; Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, ; Chen, Jaw-Wen; Taipei Veterans General Hospital, Department of Medical Research Lin, Shing-Jong; Taipei Veterans general Hospital, Division of Cardiology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Diabetes and endocrinology, Gastroenterology and hepatology
Keywords:	Myocardial infarction < CARDIOLOGY, Stroke < NEUROLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, Hepatology < INTERNAL MEDICINE

The impact of chronic hepatitis B infection on major adverse cardiovascular events and all-cause mortality in diabetic patients: a nationwide population-based study from Taiwan

Chin-Sung Kuo M.D.[1,9‡]; Yung-Tai Chen M.D.[6,9‡]; Chien-Yi Hsu M.D.[7,9,12,14]; Chun-Chin Chang M.D.[2,9]; Ruey-Hsing Chou M.D.[2,9]; Szu-Yuan Li M.D.[3,9]; Shu-Chen Kuo M.D.[4,11]; *Po-Hsun Huang M.D. Ph.D.[2,7,9]; Jaw-Wen Chen M.D. [2,5,7,8]; *Shing-Jong Lin M.D. Ph.D.[2,5,7,9,13]

[1]Division of Endocrinology and Metabolism; [2]Division of Cardiology; [3]Division of Nephrology; [4]Division of Infectious Diseases, Department of Medicine; [5]Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan; [6]Department of Medicine, Taipei City Hospital Heping Fuyou Branch, Taipei, Taiwan; [7]Cardiovascular Research Center; [8]Institute of Pharmacology; [9]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan; [10]Department of Medicine, Yuli branch, Taipei Veterans General Hospital, Hualien, Taiwan; [11]National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Miaoli County, Taiwan; [12]Department of Internal Medicine, School of Medicine, [13]Taipei Medical University, Taipei, Taiwan; [14]Division of Cardiology and Cardiovascular Research Center,

Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan.

Running title: Chronic hepatitis B infection in diabetic patients

‡These authors contributed equally and share the first authorship

***Address correspondence to:**

Dr. Po-Hsun Huang and Dr. Shing-Jong Lin

Division of Cardiology, Department of Medicine,

Taipei Veterans General Hospital

No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan (R.O.C.)

Tel: 886-2-2871-2121 ext. 7511

Fax: 886-2-2875-7735.

E-mail: huangbsvgh@gmail.com and sjlin@vghtpe.gov.tw

Word counts: 3128

Number of tables: 2

Number of figures: 3

Number of supplementary tables: 3

ABSTRACT

Objectives The association between hepatitis B virus (HBV) infection and cardiovascular disease remains uncertain. This study explored long-term hard endpoints (i.e., myocardial infarction, ischemic stroke) and all-cause mortality in diabetic patients with chronic HBV infection in Taiwan from 2000 to 2013.

Design This study was retrospective, longitudinal and propensity score–matched.

Setting Nationwide claims data for the period 2000–2013 were retrieved from Taiwan's National Health Insurance Research Database.

Participants The study included 40,162 diabetic patients with chronic HBV infection (HBV cohort) and 40,162 propensity score–matched diabetic patients without HBV infection (control cohort). Chronic HBV infection was identified based on three or more outpatient clinic visits or one hospital admission with a diagnosis of HBV infection.

Main outcome measures Primary outcomes were major adverse cardiovascular events (MACE, including myocardial infarction and ischemic stroke), heart failure, and all-cause mortality.

Results During the median follow-up period of 5.3 ± 3.4 years, the HBV cohort had significantly lower risks of myocardial infarction (adjusted hazard ratio [aHR] = 0.49; 95% confidence interval [CI], 0.42–0.56), ischemic stroke (aHR = 0.61; 95% CI, 0.56–0.67), heart failure (aHR = 0.50; 95% CI, 0.43–0.59), and all-cause mortality (aHR =

0.72; 95% CI, 0.70–0.75) compared with the control cohort. The impact of HBV infection on the sequential risk of MACE was greater in patients with fewer diabetic complications.

Conclusions Chronic HBV infection was associated with decreased risk of MACE, heart failure and all-cause mortality in diabetic patients. Further research is needed to investigate the mechanism underlying these findings.

Key words: atherosclerosis, diabetes, hepatitis B virus, ischemic stroke, myocardial infarction

Strengths and limitations of this study

- An unselected nationwide population with the most extensive sample of diabetic patients with chronic HBV infection available was examined, minimising the possibility of referral bias
- This study is the largest-scale examination of a diabetic HBV cohort to date.
- No previous study has explored long-term hard endpoints (i.e. myocardial infarction, ischemic stroke) and all-cause mortality in diabetic patients with chronic HBV infection.
- Liver function test results and glycated haemoglobin values were not available in the nationwide dataset.
- Some personal information, including body mass index and smoking status, was not available in the administrative dataset.

INTRODUCTION

The global incidence of diabetes mellitus is increasing, and the number of diabetic patients is expected to reach 366 million by 2030.[1] Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality among individuals with diabetes, and the largest contributor to the direct and indirect economic costs of diabetes.[2] Diabetes and commonly co-existing conditions (e.g. hypertension and dyslipidaemia) are well-known risk factors for cardiovascular complications.[3] Diabetes is also the leading cause of chronic kidney disease (CKD) and end-stage renal disease.[4] Convincing evidence has shown that an inter-relationship between chronic inflammation and metabolic abnormalities in diabetes leads to endothelial dysfunction and vascular complications.[5]

Hepatitis B virus (HBV) infection has a high prevalence and is a major public health problem in Taiwan and other countries worldwide.[6,7] Chronic HBV infection may cause chronic hepatitis, cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).[8] Chronic HBV infection is an inflammatory condition. Other diseases with chronic low-grade inflammation have been shown to increase the risk of major adverse cardiovascular events (MACE).[9] Nevertheless, chronic HBV infection has been reported to be associated inversely with metabolic syndrome in the United States, based on the Third National Health and Nutrition Examination Survey (NHANES III),[10] as well as in a

population-based study in Taiwan.[11] The association between HBV infection and MACE, however, remains uncertain. Previous cross-sectional studies of this association have produced conflicting results.[12–14] A Korean cohort study postulated that hepatitis B surface antigen (HBsAg) seropositivity was associated with decreased risks of ischemic stroke and myocardial infarction, as well as an increased risk of haemorrhagic stroke.[15] A population-based prospective study conducted in Taiwan showed that HBsAg seropositivity was not associated with enhanced cardiovascular mortality during a 17-year follow-up period.[16] No study to date has examined the relationship between chronic HBV infection and MACE or all-cause mortality in diabetic patients.

Accordingly, we conducted a nationwide longitudinal cohort study to investigate the relationship between chronic HBV infection and MACE, as well as all-cause mortality, in diabetic patients in Taiwan, which is one of the most hyperendemic areas for HBV infection in the world.[17] To our knowledge, this study is the largest-scale examination of a diabetic HBV cohort.

METHODS

Data sources

Data were extracted from the Taiwan National Health Insurance Research Database (NHIRD), which contains anonymised secondary data that are available for research

purposes. Taiwan's National Health Insurance (NHI) programme, launched in 1995, currently covers 99% of the population of 23 million people. The database comprises all registry and claims data from the NHI system, ranging from demographic data to detailed orders for ambulatory and inpatient care. Taiwan's NHI Bureau is responsible for auditing medical payments through a comprehensive review of medical records, examination reports, and results of imaging studies. If a physician fails to meet the standards for clinical practice, Taiwan's NHI reserves the right to reject payment and may impose substantial financial penalties. Disease diagnoses are coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The diagnostic accuracy for major diseases of codes registered in the NHIRD has been validated thoroughly.[18-21] In the present study, we used the Longitudinal Cohort of Diabetes Patients dataset, sourced directly from the NHIRD. This dataset includes all available medical registry data from a random sample of 120,000 patients diagnosed with diabetes mellitus for each year since 1999. The study was exempted from full review by the Institutional Review Board of Taipei City Hospital (TCHIRB-1030603-W) because the dataset comprised de-identified secondary data.

Study Design

This nationwide, population-based, observational, retrospective cohort study was

conducted to determine the association between chronic HBV infection and sequential MACE in diabetic patients. Two cohorts were enrolled in the study: the HBV cohort and a matched control cohort. The HBV cohort consisted of patients diagnosed with chronic HBV infection, defined based on three or more outpatient clinic visits with ICD-9-CM codes 070.2, 070.3, and/or V02.61, or admission with a diagnosis of chronic HBV infection between 1 January 2000 and 31 December 2012.[22] The index date was defined as the first day of chronic HBV infection diagnosis. Patients with the following characteristics were excluded: age < 20 years, diagnosis with hepatitis C infection, fewer than three outpatient clinic visits for HBV infection, history of myocardial infarction, and history of cerebrovascular disease. The control cohort comprised all patients with no diagnosis of HBV infection in the Longitudinal Cohort of Diabetes Patients dataset. The exclusion criteria for the HBV cohort were also applied to the control cohort. Index dates for subjects in the control cohort were assigned randomly and corresponded to those of patients in the HBV cohort.

We used 1:1 propensity score matching and calculated propensity scores for the likelihood of diagnosis of chronic HBV infection using baseline covariates and multivariate logistic regression analysis (Supplemental Table A1). We matched one control patient with each patient in the HBV cohort with a similar propensity score based on nearest-neighbour matching without replacement, using callipers of a width equal to

0.1 standard deviation of the logit of the propensity score.

Primary outcome measures

The primary outcomes were hospitalisation for myocardial infarction (ICD-9-CM code 410.x), ischemic stroke (ICD-9-CM codes 433.x, 434.x), or heart failure (ICD-9-CM code 428.x); and all-cause mortality. The MACE outcome was defined as a composite of myocardial infarction and ischemic stroke. Previous studies have validated the accuracy of myocardial infarction and ischemic stroke diagnoses in the NHIRD.[21,23] We also chose the occurrence of HCC as a positive control outcome and hospitalisation for appendicitis as a negative control outcome. To identify patients diagnosed with HCC, we used data from Taiwan's Catastrophic Illness Registry, which requires pathohistological confirmation of cancer diagnoses. Both cohorts were followed until death or the end of the study period (31 December 2013).

Baseline Characteristics

Data on baseline demographic characteristics, including age, sex, monthly income (in New Taiwan Dollars [NT$]: <NT$19,100, NT$19,100−$41,999, and ≥NT$42,000), level of urbanisation, and Charlson Comorbidity Index score, were collected. Taiwan's National Health Research Institute has defined four urbanisation levels for Taiwan. The

most urbanised areas are designated as level 1, and the least urbanised areas are designated as level 4. The Charlson Comorbidity Index score reflects overall systemic health, with each increase in number reflecting a stepwise increase in cumulative mortality.[24] We also identified use of medications that could confound the relationship between chronic HBV infection and the primary outcomes.

Statistical analysis

Descriptive statistics were used to characterise the baseline data from the study cohorts. Baseline characteristics of the two groups were compared using standardised mean differences. Propensity scores of the likelihood of diagnosis of chronic HBV infection were determined by multivariate logistic regression analysis, conditional on baseline covariates (Supplemental Table A1). The incidence rates of outcomes of interest in the two groups were calculated using Poisson distributions. The cumulative incidence or risk of outcomes was estimated using the Kaplan–Meier method, and differences between cohorts were evaluated with the log-rank test. Cox regression models with a conditional approach and stratification were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risks of outcomes.[25] Cox regression with adjustment for significant differences in covariates between groups was used to calculate adjusted hazard ratios (aHRs). Finally, the likelihood ratio test was used to

examine interactions between the occurrence of outcomes subsequent to chronic HBV infection and the following variables: age, sex, hypertension, coronary artery disease, CKD, dyslipidaemia, use of insulin, and adapted Diabetes Complications Severity Index score. Subgroup analyses were also performed accordingly.

The SQL Server 2012 (Microsoft Corporation, Redmond, WA, USA) was used for data linkage, processing, and sampling. Propensity scores were calculated with SAS version 9.3 (SAS Institute, Cary, NC, USA). All other statistical analyses were conducted using STATA statistical software (version 12.0; StataCorp, College Station, TX, USA). *P* values < 0.05 were considered to be statistically significant.

RESULTS

Patient characteristics

The study cohort consisted of 40,162 diabetic patients with chronic HBV infection and 40,162 matched control subjects without HBV infection (Figure 1). The mean age was 52.7 (standard deviations, 11.6 [HBV] and 11.5 [control]) years, and 62.7% of subjects were male (Table 1). The prevalence of comorbidities, such as cardiovascular risk factors, and concomitant medication use was similar in the HBV and control groups.

HBV infection, risk of cardiovascular disease, and all-cause mortality in diabetic

patients

During the mean 5.3-year follow-up period, the incidence rates of all-cause mortality, myocardial infarction, ischemic stroke, and heart failure were 26.96, 1.38, 3.71, and 1.12 per 10^3 person-years, respectively, in the HBV cohort and 35.29, 2.76, 5.88, and 2.01 per 10^3 person-years, respectively, in the matched control cohort (Table 2). Compared with the matched control cohort, the HBV cohort had significantly reduced risks of all-cause mortality (aHR = 0.72; 95% CI, 0.70–0.75; $p < 0.001$), myocardial infarction (aHR = 0.49; 95% CI, 0.42–0.56; $p < 0.001$), ischemic stroke (aHR = 0.61; 95% CI, 0.56–0.67; $p < 0.001$), MACE (aHR = 0.58; 95% CI, 0.53–0.62; $p < 0.001$), and heart failure (aHR = 0.50; 95% CI, 0.43–0.59; $p < 0.001$; Table 2). The cumulative incidences of all-cause mortality and MACE in both groups are illustrated in Figure 2. The HBV cohort had a significantly higher risk of HCC (aHR = 7.47; 95% CI, 6.53–8.56; $p < 0.001$) and a similar risk of hospitalisation for appendicitis (aHR = 1.13; 95% CI, 0.93–1.38; $p = 0.227$).

An interaction test for all-cause mortality showed significant correlations between HBV infection and sex ($p = 0.030$), hypertension ($p < 0.001$), dyslipidaemia ($p < 0.001$), use of insulin ($p = 0.020$), and adapted Diabetes Complications Severity Index score ($p = 0.010$; Supplemental Table A2). An interaction test for MACE showed significant correlations between HBV infection and sex ($p = 0.002$), hypertension ($p = 0.005$),

coronary artery disease (p = 0.005), dyslipidaemia (p = 0.003), use of insulin (p = 0.005), and adapted Diabetes Complications Severity Index score (p = 0.04; Supplemental Table A3). Figure 3 shows the results of multivariable stratified subgroup analyses. The effects of chronic HBV infection on all-cause mortality and MACE were greater in patients without hypertension and dyslipidaemia than in matched controls. The association between chronic HBV infection and all-cause mortality or sequential MACE was also greater in patients who were not using insulin. In stratified analyses, the effect of chronic HBV infection on the sequential risk of MACE was greater in patients with low (<2) adapted Diabetes Complications Severity Index scores (Supplemental Tables A2 and A3).

DISCUSSION

To our knowledge, this propensity score–matched, nationwide, population-based study is the first to elucidate the correlation of chronic HBV infection with lower risks of MACE and heart failure in diabetic patients. In addition, we found a significantly decreased risk of all-cause mortality in diabetic patients with chronic HBV infection during the mean 5.3-year follow-up period. The impact of HBV infection on the sequential risk of MACE was greater in patients with fewer diabetic complications.

This study has several strengths. First, it involved an unselected nationwide population with the most extensive sample of diabetic patients with chronic HBV infection available, minimising the possibility of referral bias. Second, the diabetic HBV cohort comprised 40,162 patients during the 12-year study period, providing adequate statistical power for analysis of the risks of MACE, heart failure, and all-cause mortality (all hard endpoints) in this population. To our knowledge, this study is the largest-scale examination of a diabetic HBV cohort to date. In addition, we compared study subjects with propensity score–matched control subjects, instead of conducting age- and sex-adjusted analyses in comparison with a general population. Competing risks are the rule in clinical epidemiological studies.[26] Use of the Kaplan–Meier method may lead to overestimation of the event (MACE) risk in the presence of the competing risk (death).[26] However, we found reduced risks of MACE and all-cause mortality in the diabetic HBV cohort. These results would remain robust in the presence of competing risks. Furthermore, the risks of all-cause mortality and MACE in our study were comparable with the previously published data.[27,28]

Some limitations of our study should be noted. First, absolute values from liver function tests were not available in the nationwide dataset. An individual with chronic HBV infection may present as a 'healthy' carrier with normal liver function or with chronic hepatitis. Second, data on glycated haemoglobin concentration, used widely as

a glycaemic control index, were not available in this dataset. Glycaemic control may be a confounding factor for MACE. However, recent reports have suggested that reduction of the blood glucose level has no beneficial effect or only modest effects on diabetic cardiovascular complications in high-risk populations.[29,30] In addition, the emergence of MACE caused by poor glycaemic control is a lengthy process.[29] Third, some personal information, including body mass index and smoking status, was not available in the administrative dataset, preventing accurate assessment of the contributory and confounding effects of these factors. The effects of chronic HBV infection on MACE may be due to residual confounding. However, we performed a sensitivity analysis that included positive and negative control outcomes to provide further support for our findings.[31] Fourth, this observational study provided clinically relevant risk estimates without speculating on causation.

Cross-sectional studies conducted as part of the NHANES III[10] and in Taiwan[11] have documented an inverse association between metabolic syndrome and chronic HBV, supporting our findings. A recent systemic review revealed that many, but not all, relevant studies have shown that patients with chronic HBV infection have lower risks of metabolic syndrome, non-alcoholic fatty liver disease, and dyslipidaemia.[32] A study of a non-diabetic Korean cohort showed that HBsAg seropositivity was associated with decreased risks of ischemic stroke and myocardial infarction, secondary to

HBV-associated liver dysfunction.[15] Other reported mechanisms potentially linking chronic HBV infection to a decreased risk of MACE include lower levels of clotting factors II and VII and fibrinogen among HBsAg-positive (*vs.* -negative) individuals, as found in blood donors in Gambia and London.[33]

A cohort study from England and Wales showed no significantly increased risk of all-cause mortality in transfusion donors with HBV infection compared with donors without HBV infection.[34] In that study, the standardised mortality rate for circulatory disease was significantly lower in both males and females with hepatitis B.[34] These results may support our findings. Furthermore, the risk of circulatory disease–related death in our HBV cohort was significantly lower than in an Australian study,[35] comparable to that reported in another Taiwanese study,[16] and significantly higher than that found in a study conducted in China.[36] The Chinese study examined the period 1992–2002 and the HBV cohort had very low cardiovascular mortality rates (20.6 and 16.4 per 100,000 person-years in males and females, respectively).[36] The study conducted in Taiwan showed that HBsAg seropositivity was not associated with atherosclerosis-related mortality risk in a general population.[16] One possible explanation for this result is the lack of statistical power (HR = 0.84; 95% CI, 0.72–1.06) due to the small sample (480 cases of death from atherosclerotic disease) .[16] Results of Australian and British studies are in agreement with our findings regarding the

relationship between HBV and MACE .[34 35]

Moreover, previous cohort studies have shown that the increased risk of all-cause mortality can be attributed mostly to excesses of liver-related deaths in general population s.[16 35 36] In the Australian study, the risk of death was increased 1.4 times in subjects with HBV infection;[35] this risk was increased 1.7 times in Taiwan[16] and three-fold in China.[36] We are not aware of any study that has examined the relationship between all-cause mortality and chronic HBV infection in diabetic patients. We conducted this HBV study in a population with a very high risk of MACE. In our diabetic cohort, the incidence rate of MACE was high (498 vs. 839 per 100000 person-years) to provide sufficient endpoints (1098 vs. 1663 events). Our study demonstrated a reduced all-cause mortality risk in diabetic subjects with chronic HBV infection. This finding may be explained by the decreased MACE risk in our diabetic HBV cohort. Diabetes, which is considered to be a coronary artery disease equivalent, is an important risk factor for cardiovascular disease.[37] Cardiovascular complication is the leading cause of mortality in diabetic patients.[3] Thus, the impact of HBV infection on all-cause mortality could plausibly be hypothesised to be greater in diabetic patients than in the general population.

CONCLUSION

In this nationwide, longitudinal, propensity score–matched analysis, chronic HBV infection was associated with decreased risks of MACE, heart failure and all-cause mortality in diabetic patients. These findings may provide new insight into the pathogenesis of diabetes and future therapeutic strategies. However, further research is need to confirm our findings and to explore the underlying mechanism.

Contributors: YTC, the guarantor of this work, had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the analysis. Study concept and design: CSK, PHH, YTC and SJL. Acquisition of data: YTC, CYH and CCC. Analysis and interpretation of data: CSK, YTC and PHH. Drafting of the manuscript: CSK, YTC, PHH, CYH and CCC. Statistical analysis: PHH and YTC. Administrative, technical, and/or material support: RHC, SJL, SCK, JWC and SJL. Critical revision: YTC, PHH and SJL. Study supervision: PHH and SJL. The Corresponding Authors have the right to grant on behalf of all authors and do grant on behalf of all authors a worldwide license to the Publisher and its licensees in perpetuity.

Funding: This study was supported in part by research grants from the Ministry of Science and Technology of Taiwan (MOST 104-2314-B-075-047) and from Taipei

Veterans General Hospital (V105C-0207, V106C-045). These funding agencies had no influence on the study design, data collection or analysis, decision to publish, or preparation of the manuscript.

Competing Interest: The authors report no potential conflicts of interest relevant to this article.

Ethics approval: Institutional Review Board of Taipei City Hospital.

Data sharing statement: The authors have obtained nationwide claims data for the period 2000–2013 from the Taiwan National Health Insurance Research Database (NHIRD). NHIRD does not permit external sharing of any of the data elements. No additional data are available.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27(5):1047–1053
2. Eckel RH, Kahn R, Robertson RM, Rizza RA. Preventing cardiovascular disease and diabetes: a call to action from the American Diabetes Association and the American Heart Association. Circulation 2006;113(25):2943–2946
3. Buse JB, Ginsberg HN, Bakris GL, et al.; American Heart Association; American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2007;30:162–172
4. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010. N Engl J Med 2013;368:1613–1624
5. Domingueti CP, Dusse LM, Carvalho MD, de Sousa LP, Gomes KB, Fernandes AP. Diabetes mellitus: the linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. J Diabetes Complications 2016;30(4):738–745
6. Kao JH, Chen DS. Global control of hepatitis B virus infection. Lancet Infect Dis

2002;2(7):395–403

7. Chen CL, Yang JY, Lin SF, Sun CA, Bai CH, You SL, Chen CJ, Kao JH, Chen PJ, Chen DS. Slow decline of hepatitis B burden in general population: results from a population-based survey and longitudinal follow-up study in Taiwan. J Hepatol 2015;63(2):354–363

8. Chen DS. From hepatitis to hepatoma: lessons from type B viral hepatitis. Science 1993;262(5132):369–370

9. Domingueti CP, Dusse LM, Carvalho MD, de Sousa LP, Gomes KB, Fernandes AP. Diabetes mellitus: the linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. J Diabetes Complications 2016;30(4):738–745

10. Jinjuvadia R, Liangpunsakul S. Association between metabolic syndrome and its individual components with viral hepatitis B. Am J Med Sci. 2014;347(1):23–27

11. Jan CF, Chen CJ, Chiu YH, Chen LS, Wu HM, Huang CC, Yen MF, Chen TH. A population-based study investigating the association between metabolic syndrome and hepatitis B/C infection (Keelung Community-based Integrated Screening study No. 10). Int J Obes (Lond). 2006;30(5):794–799.

12. Volzke H, Schwahn C, Wolff B, Mentel R, Robinson DM, Kleine V, Felix SB, John U. Hepatitis B and C virus infection and the risk of atherosclerosis in a general

population. Atherosclerosis 2004;174:99–103

13. Tong DY, Wang XH, Xu CF, Yang YZ, Xiong SD. Hepatitis B virus infection and coronary atherosclerosis: results from a population with relatively high prevalence of hepatitis B virus. World J Gastroenterol 2005;11:1292–1296

14. Ishizaka N, Ishizaka Y, Takahashi E, Toda EE, Hashimoto H, Ohno M, Nagai R, Yamakado M. Increased prevalence of carotid atherosclerosis in hepatitis B virus carriers. Circulation 2002;105:1028–1030

15. Sung J, Song YM, Choi YH, Ebrahim S, Davey SG. Hepatitis B virus seropositivity and the risk of stroke and myocardial infarction. Stroke 2007;38:1436–1441

16. Wang CH, Chen CJ, Lee MH, Yang HI, Hsiao CK. Chronic hepatitis B infection and risk of atherosclerosis-related mortality: a 17-year follow-up study based on 22,472 residents in Taiwan. Atherosclerosis 2010;211(2):624–629

17. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65–73

18. Chao TF, Liu CJ, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Tsao HM, Chen SA. Hyperuricemia and the risk of ischemic stroke in patients with atrial fibrillation: could it refine clinical risk stratification in AF? Int J Cardiol 2014;170:344–349

19. Chiu CC, Huang CC, Chan WL, Chung CM, Huang PH, Lin SJ, Chen JW, Leu HB. Increased risk of ischemic stroke in patients with systemic lupus erythematosus: a nationwide population-based study. Intern Med 2012;51:17–21

20. Lin CC, Lai MS, Syu CY, Chang SC, Tseng FY. Accuracy of diabetes diagnosis in health insurance claims data in Taiwan. J Formos Med Assoc 2005;104:157–163

21. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf 2011;20:236–242

22. Wu CY, Lin JT, Ho HJ, Su CW, Lee TY, Wang SY, Wu C, Wu JC. Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide cohort study. Gastroenterology 2014;147(1):143–151

23. Cheng CL, Lee CH, Chen PS, Li YH, Lin SJ, Yang YH. Validation of acute myocardial infarction cases in the national health insurance research database in Taiwan. J Epidemiol 2014;24:500–507

24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373–383

25. Austin PC. A critical appraisal of propensity-score matching in the medical literature

between 1996 and 2003. Stat Med 2008;27:2037–2049

26. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology. 2015;62:292-302.

27. Tseng CH. Factors Associated with Cancer- and Non-Cancer-Related Deaths among Taiwanese Patients with Diabetes after 17 Years of Follow-Up. PLoS One. 2016;11(12):e0147916.

28. Hsieh HM, Lin TH, Lee IC, Huang CJ, Shin SJ, Chiu HC. The association between participation in a pay-for-performance program and macrovascular complications in patients with type 2 diabetes in Taiwan: A nationwide population-based cohort study. Prev Med. 2016;85:53-9.

29. Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, McCarren M, Duckworth WC, Emanuele NV; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;372(23):2197–2206

30. ACCORD Study Group Writing Committee. 9-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. Diabetes Care 2016;39(5):701–708

31. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting

confounding and bias in observational studies. Epidemiology 2010;21(3):383–388

32. Jarcuska P, Drazilova S, Fedacko J, Pella D, Janicko M. Association between hepatitis B and metabolic syndrome: Current state of the art. World J Gastroenterol. 2016;22(1):155–164

33. Meade TW, Stirling Y, Thompson SG, Ajdukiewicz A, Barbara JA, Chalmers DM. Carriers of hepatitis B surface antigen: possible association between low levels of clotting factors and protection against ischaemic heart disease. Thromb Res 1987;45(5):709–713

34. Crook PD, Jones ME, Hall AJ. Mortality of hepatitis B surface antigen-positive blood donors in England and Wales. Int J Epidemiol 2003;32:118–124

35. Amin J, Law MG, Bartlett M, Kaldor JM, Dore GJ. Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study. Lancet 2006;368(9539):938–945

36. Chen G, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Chronic hepatitis B virus infection and mortality from non-liver causes: results from the Haimen City cohort study. Int J Epidemiol 2005;34:132–137

37. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and

without prior myocardial infarction. N Engl J Med 1998;339:229–234

FIGURE LEGENDS

Figure 1 Flow diagram of cohort selection. The study cohort consisted of 40,162 diabetic patients with chronic HBV infection and 40,162 matched control subjects without HBV infection.

Figure 2 The cumulative incidence of all-cause mortality (A) and major adverse cardiovascular events (B) among diabetic patients with chronic HBV infection and matched control subjects without HBV infection.

Figure 3 Results of multivariable stratified subgroup analyses, showing the effects of chronic HBV infection on all-cause mortality (A) and major adverse cardiovascular events (B).

Table 1 Baseline characteristics of diabetic patients

Characteristic	Propensity score–matched		
	HBV cohort	Control cohort	Standardised difference*
Patients (*n*)	40,162	40,162	
Mean age (SD), years	52.7 (11.6)	52.7 (11.5)	0.002
Sex (male)	25,173 (62.7)	25,173 (62.7)	0.000
Monthly income, NT$			
Dependent	8,787 (21.9)	8,510 (21.2)	0.017
<19,100	6,859 (17.1)	6,342 (15.8)	0.035
19,100–41,999	18,910 (47.1)	19,343 (48.2)	-0.022
≥42,000	5,606 (14.0)	5,967 (14.9)	-0.026
Urbanisation level			
1 (urban)	14,845 (37.0)	15,501 (38.6)	-0.034
2	23,400 (58.3)	22,828 (56.8)	0.029
3	1,593 (4.0)	1,498 (3.7)	0.012
4 (rural)	324 (0.8)	335 (0.8)	-0.003
Outpatient visits to metabolism and endocrinology professionals in the past year			
0–5	35,055 (87.3)	34,947 (87.0)	0.008
6–10	3,752 (9.3)	3,774 (9.4)	-0.002
11–15	975 (2.4)	1,049 (2.6)	-0.012
>15	380 (0.9)	382 (1.0)	-0.003
Charlson Comorbidity Index score, median (IQR)	6 (5–8)	6 (4–8)	0.035
Adapted Diabetes Complications Severity Index score, median (IQR)†	0 (0–1)	0 (0–1)	-0.001
Median (IQR) duration of diabetes mellitus, months	38 (12–74)	39 (16–73)	-0.024
Anti-hypertensive drug use			
Alpha blocker	420 (1.0)	362 (0.9)	0.015
ACE inhibitor or ARB	3,885 (9.7)	3,950 (9.8)	-0.005
Beta blocker	3,256 (8.1)	3,337 (8.3)	-0.007
Calcium channel blocker	3,887 (9.7)	3,866 (9.6)	0.002
Diuretic	2,701 (6.7)	2,507 (6.2)	0.020

Anti-diabetic drug use			
Acarbose	823 (2.0)	886 (2.2)	-0.011
Sulfonylurea	7,374 (18.4)	7,795 (19.4)	-0.027
Insulin	865 (2.2)	831 (2.1)	0.006
Metformin	6,921 (17.2)	7,235 (18.0)	-0.021
Thiazolidinedione	689 (1.7)	707 (1.8)	-0.003
Dipeptidyl peptidase-4 inhibitor	398 (1.0)	458 (1.1)	-0.015
Other concomitant medications			
Antiplatelet agent	2,097 (5.2)	2,073 (5.2)	0.003
NSAID	8,662 (21.6)	8,728 (21.7)	-0.004
Proton pump inhibitor	1,836 (4.6)	1,436 (3.6)	0.050
Steroid	2,005 (5.0)	1,942 (4.8)	0.007
Antidepressant	1,117 (2.8)	1,137 (2.8)	-0.003
Statin	1,701 (4.2)	1,718 (4.3)	-0.002
Comorbidities			
Coronary artery disease	9,694 (24.1)	9,731 (24.2)	-0.002
Hypertension	19,839 (49.4)	19,859 (49.4)	-0.001
Heart failure	2,002 (5.0)	1,791 (4.5)	0.025
Peripheral vascular disease	1,369 (3.4)	1,543 (3.8)	-0.023
Chronic kidney disease	5,929 (14.8)	5,916 (14.7)	0.001
Atrial fibrillation	472 (1.2)	399 (1.0)	0.018
Dyslipidaemia	22,827 (56.8)	23,813 (59.3)	-0.050
Valvular heart disease	2,588 (6.4)	2,547 (6.3)	0.004
Cancer	6,835 (17.0)	6,546 (16.3)	0.019
Autoimmune disease	1,543 (3.8)	1,559 (3.9)	-0.002
Dialysis	386 (1.0)	345 (0.9)	0.011
Physical limitation	1,592 (4.0)	1,606 (4.0)	-0.002
Propensity score, mean (SD)	0.08 (0.06)	0.08 (0.06)	0.000

Data are presented as *n* (%) except where otherwise indicated.

*Imbalance defined as absolute value > 0.014.

†A 13-point scale with 7 complication categories: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic. Each complication is given a numeric score ranging from 0 to 2 (0 = no abnormality, 1 = some abnormality, 2 = severe abnormality).

Abbreviations: HBV, hepatitis B virus; SD, standard deviation; IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; NSAID, non-steroidal anti-inflammatory drug.

Table 2 Incidence and risks of all-cause mortality, myocardial infarction, stroke, hospitalisation for heart failure, and cancer after propensity score matching

	HBV cohort			Control cohort (reference)			Crude		Adjusted	
	No. of events	Person-years	Incidence rate*	No. of events	Person-years	Incidence rate*	Hazard ratio (95% CI)	*p* value	Hazard ratio† (95% CI)	*p* value
All-cause mortality	6,027	223,588	26.96	7,140	202,307	35.29	0.78 (0.76–0.81)	<0.001	0.72 (0.70–0.75)	<0.001
MACE‡	1,098	220,605	4.98	1,663	198,131	8.39	0.59 (0.55–0.64)	<0.001	0.58 (0.53–0.62)	<0.001
Myocardial infarction	308	222,847	1.38	554	201,078	2.76	0.50 (0.43–0.57)	<0.001	0.49 (0.42–0.56)	<0.001
Ischemic stroke	822	221,298	3.71	1,171	199,259	5.88	0.63 (0.57–0.69)	<0.001	0.61 (0.56–0.67)	<0.001
Heart failure	249	223,050	1.12	405	201,494	2.01	0.55 (0.47–0.65)	<0.001	0.50 (0.43–0.59)	<0.001
HCC	1,590	220,573	7.21	153	202,145	0.76	9.58 (8.12–11.31)	<0.001	9.34 (7.91–11.03)	<0.001
Acute appendicitis	222	222,682	1.00	179	201,644	0.89	1.13 (0.93–1.37)	0.233	1.13 (0.93–1.38)	0.227

*Per 10^3 person-years.

†Adjusted for monthly income, urbanisation level, Charlson Comorbidity Index score, dipeptidyl peptidase-4 inhibitor use, metformin use, sulfonylurea use, alpha blocker use, dyslipidaemia, atrial fibrillation, peripheral vascular disease, and heart failure.

‡Myocardial infarction and ischemic stroke.

Abbreviations: HBV, hepatitis B virus; MACE, major adverse cardiovascular event; HCC, hepatocellular carcinoma.

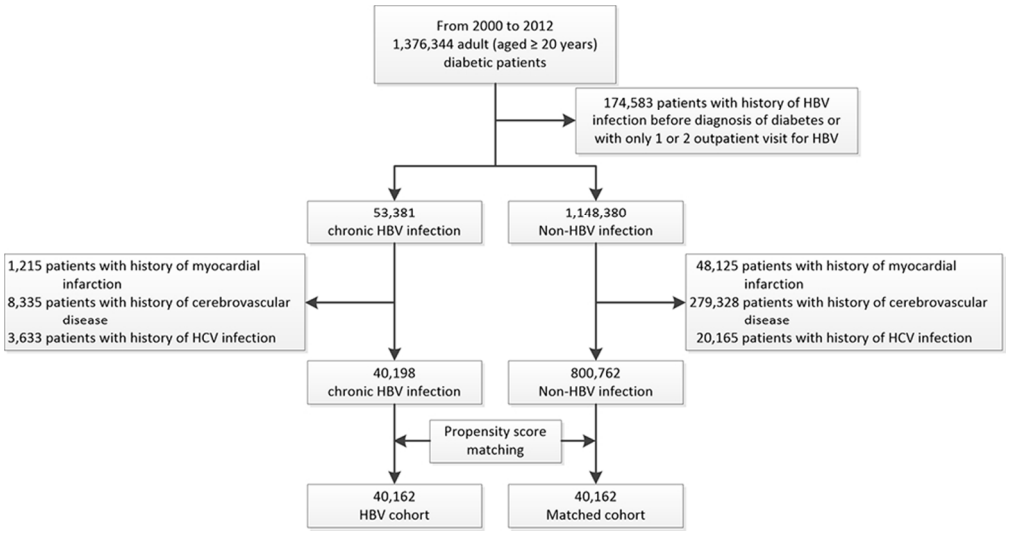


Figure 1 Flow diagram of cohort selection. The study cohort consisted of 40,162 diabetic patients with chronic HBV infection and 40,162 matched control subjects without HBV infection.

86x45mm (300 x 300 DPI)

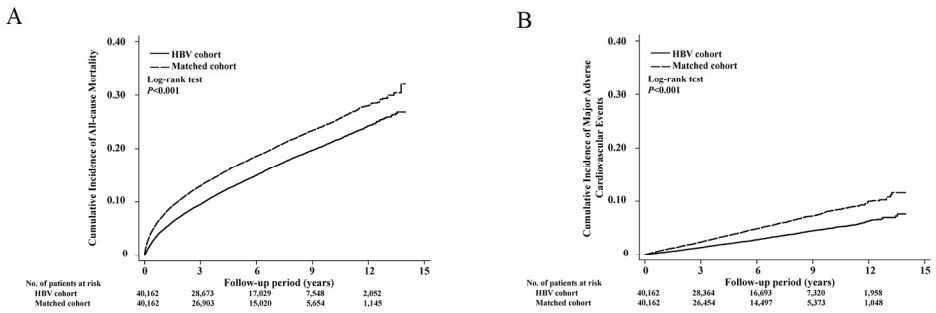


Figure 2 The cumulative incidence of all-cause mortality (A) and major adverse cardiovascular events (B) among diabetic patients with chronic HBV infection and matched control subjects without HBV infection.

172x60mm (300 x 300 DPI)

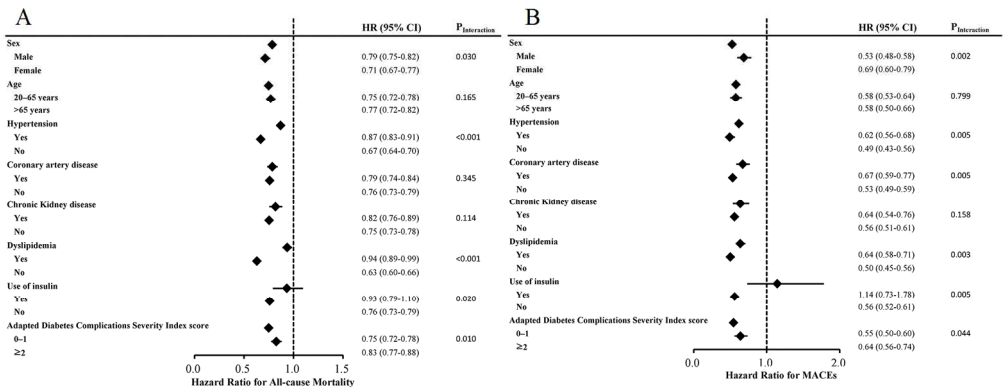


Figure 3 Results of multivariable stratified subgroup analyses, showing the effects of chronic HBV infection on all-cause mortality (A) and major adverse cardiovascular events (B).

172x67mm (300 x 300 DPI)

Supplemental Table A1 Propensity score model results for the probability of diagnosis of HBV infection

			95% CI		
Parameter	**Estimate**	**Odds ratio**	**Lower**	**Upper**	***p* value**
Age, per year	-0.0411	0.96	0.959	0.961	<0.0001
Male sex	0.4718	1.603	1.568	1.638	<0.0001
Year of index date					
2000		1			
2001	-0.1146	0.892	0.822	0.967	0.0055
2002	-0.2589	0.772	0.714	0.835	<0.0001
2003	-0.4023	0.669	0.619	0.723	<0.0001
2004	-0.4794	0.619	0.575	0.667	<0.0001
2005	-0.5758	0.562	0.523	0.605	<0.0001
2006	-0.6641	0.515	0.479	0.553	<0.0001
2007	-0.7626	0.466	0.434	0.501	<0.0001
2008	-0.8804	0.415	0.386	0.446	<0.0001
2009	-0.9874	0.373	0.347	0.401	<0.0001
2010	-1.0996	0.333	0.31	0.358	<0.0001
2011	-1.2988	0.273	0.254	0.293	<0.0001
2012	-1.3871	0.25	0.232	0.269	<0.0001
Month of index date					
January		1			
February	-0.0141	0.986	0.933	1.042	0.6135
March	-0.0354	0.965	0.916	1.016	0.18
April	-0.0224	0.978	0.929	1.03	0.3935
May	-0.044	0.957	0.909	1.007	0.0913
June	-0.0566	0.945	0.897	0.995	0.0315
July	-0.0694	0.933	0.887	0.982	0.0074
August	-0.0812	0.922	0.876	0.97	0.0017
September	-0.1023	0.903	0.858	0.95	<0.0001
October	-0.0938	0.91	0.865	0.958	0.0003
November	-0.116	0.891	0.846	0.937	<0.0001
December	-0.1214	0.886	0.842	0.932	<0.0001
Monthly income, NT$					
Dependent		1			
<19,100	-0.1658	0.847	0.819	0.876	<0.0001
19,100–41,999	0.1102	1.116	1.087	1.147	<0.0001
≥42,000	0.2833	1.328	1.279	1.377	<0.0001

Urbanisation level					
1 (urban)		1			
2	-0.0904	0.914	0.894	0.934	<0.0001
3	-0.1119	0.894	0.847	0.944	<0.0001
4 (rural)	-0.0171	0.983	0.877	1.103	0.7708
Outpatient visits to metabolism and endocrinology professionals in the past year					
0					
1–5	0.158	1.171	1.13	1.214	<0.0001
6–10	-0.1084	0.897	0.84	0.959	0.0014
>10	-0.0625	0.939	0.845	1.044	0.2474
Charlson Comorbidity Index score[a]	0.1398	1.15	1.143	1.157	<0.0001
Adapted Diabetes Complications Severity Index score[b]	-0.073	0.93	0.917	0.942	<0.0001
Duration of diabetes, months	0.0028	1.003	1.003	1.003	<0.0001
Anti-diabetic drugs					
Acarbose	0.0507	1.052	0.977	1.133	0.18
Sulfonylurea	0.1154	1.122	1.084	1.162	<0.0001
Insulin	0.2091	1.233	1.145	1.327	<0.0001
Metformin	0.151	1.163	1.122	1.206	<0.0001
Thiazolidinedione	-0.3096	0.734	0.677	0.795	<0.0001
Dipeptidyl peptidase-4 inhibitor	0.0812	1.085	0.976	1.205	0.1308
Anti-hypertensive drugs					
Alpha blocker	-0.081	0.922	0.833	1.02	0.1164
Beta blocker	0.032	1.032	0.991	1.076	0.1247
Calcium channel blocker	-0.0569	0.945	0.908	0.982	0.0044
Diuretic	0.3296	1.39	1.33	1.454	<0.0001
ACE inhibitor/ARB	-0.0856	0.918	0.882	0.955	<0.0001
Other concomitant medications					
Antiplatelet	-0.185	0.831	0.791	0.873	<0.0001
Steroid	-0.1578	0.854	0.814	0.896	<0.0001
Antidepressant	0.0542	1.056	0.991	1.125	0.0936
Statin	-0.4718	0.624	0.592	0.658	<0.0001
PPI	1.1059	3.022	2.864	3.189	<0.0001
NSAID	0.0767	1.08	1.053	1.108	<0.0001
Comorbidities					
Hypertension	-0.1764	0.838	0.818	0.859	<0.0001
Coronary artery disease	0.0571	1.059	1.028	1.09	0.0002
Heart failure	-0.3525	0.703	0.666	0.741	<0.0001

Peptic ulcer disease	0.1731	1.189	1.162	1.217	<0.0001
Chronic kidney disease	0.0234	1.024	0.993	1.055	0.1335
Atrial fibrillation	-0.1366	0.872	0.792	0.961	0.0057
Dyslipidaemia	0.103	1.108	1.084	1.133	<0.0001
Valvular heart disease	0.0353	1.036	0.992	1.082	0.1102
Cancer	0.1052	1.111	1.07	1.153	<0.0001
Autoimmune disease	0.0809	1.084	1.028	1.144	0.0031
Physical limitation	0.0747	1.078	1.021	1.137	0.0063

[a] Used to determine overall systemic health; each increase reflects a stepwise increase in cumulative mortality.

[b] A 13-point scale with 7 complication categories: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic.
Each complication is given a numeric score ranging from 0 to 2 (0 = no abnormality, 1 = some abnormality, 2 = severe abnormality).

Abbreviations: CI, confidence interval; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug.

Supplemental Table A2 Results of subgroup analyses of mortality risk among diabetic patients with HBV infection and matched control subjects

Characteristic	Adjusted[a]		
	Hazard ratio (95% CI)	*p* value	Interaction *p* value
Sex			
Male	0.785 (0.754–0.817)	<0.001	0.030
Female	0.714 (0.667–0.765)	<0.001	
Age			
20–65 years	0.749 (0.719–0.781)	<0.001	0.165
>65 years	0.770 (0.724–0.819)	<0.001	
Hypertension			
Yes	0.870 (0.831–0.912)	<0.001	<0.001
No	0.668 (0.635–0.703)	<0.001	
Coronary artery disease			
Yes	0.786 (0.735–0.840)	<0.001	0.345
No	0.759 (0.729–0.790)	<0.001	
Chronic kidney disease			
Yes	0.818 (0.757–0.886)	<0.001	0.114
No	0.754 (0.726–0.784)	<0.001	
Dyslipidaemia			
Yes	0.936 (0.887–0.986)	0.014	<0.001
No	0.630 (0.602–0.659)	<0.001	
Use of insulin			
Yes	0.932 (0.792–1.096)	0.395	0.020
No	0.759 (0.733–0.786)	<0.001	
Adapted Diabetes Complications Severity Index score			
0–1	0.749 (0.719–0.780)	<0.001	0.010
≥2	0.826 (0.774–0.881)	<0.001	

[a]Adjusted for monthly income, urbanisation level, Charlson Comorbidity Index score, dipeptidyl peptidase-4 inhibitor use, metformin use, sulfonylurea use, alpha blocker use, dyslipidaemia, atrial fibrillation, peripheral vascular disease, and heart failure.

Supplemental Table A3 Results of subgroup analysis of risk of MACE among diabetic patients with HBV infection and matched control subjects

Characteristic	Adjusted[a] Hazard ratio (95% CI)	*p* value	Interaction *p* value
Sex			
Male	0.526 (0.480–0.576)	<0.001	0.002
Female	0.686 (0.596–0.789)	<0.001	
Age			
20–65 years	0.579 (0.528–0.636)	<0.001	0.799
>65 years	0.575 (0.502–0.659)	<0.001	
Hypertension			
Yes	0.619 (0.563–0.680)	<0.001	0.005
No	0.493 (0.431–0.564)	<0.001	
Coronary artery disease			
Yes	0.670 (0.585–0.766)	<0.001	0.005
No	0.533 (0.486–0.585)	<0.001	
Chronic kidney disease			
Yes	0.638 (0.536–0.760)	<0.001	0.158
No	0.558 (0.512–0.607)	<0.001	
Dyslipidaemia			
Yes	0.638 (0.576–0.707)	<0.001	0.003
No	0.501 (0.447–0.562)	<0.001	
Use of insulin			
Yes	1.143 (0.734–1.781)	0.555	0.005
No	0.560 (0.518–0.605)	<0.001	
Adapted Diabetes Complications Severity Index score			
0–1	0.545 (0.497–0.598)	<0.001	0.044
≥2	0.640 (0.557–0.735)	<0.001	

[a]Adjusted for monthly income, urbanisation level, Charlson Comorbidity Index score, dipeptidyl peptidase-4 inhibitor use, metformin use, sulfonylurea use, alpha blocker use, dyslipidaemia, atrial fibrillation, peripheral vascular disease, and heart failure.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 7
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 8
Methods			
Study design	4	Present key elements of study design early in the paper	Page 9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 8,9, 10
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Page 10
		(*b*) For matched studies, give matching criteria and the number of controls per case	Page 10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Page 8*
Bias	9	Describe any efforts to address potential sources of bias	Page 11, 12, 13
Study size	10	Explain how the study size was arrived at	Page 9,10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 11, 12, 13
		(*b*) Describe any methods used to examine subgroups and interactions	Page 12, 13
		(*c*) Explain how missing data were addressed	Page 12, 13
		(*d*) If applicable, explain how matching of cases and controls was addressed	Page 12, 13
		(*e*) Describe any sensitivity analyses	Page 12, 13
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 13
		(b) Give reasons for non-participation at each stage	Page 13
		(c) Consider use of a flow diagram	Page 13, Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 13, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Hard endpoint, no missing data
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Page 14, 15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 14, 15
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 14, Table 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 14, 15
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 15,16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 16,17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 17,18,19
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 16,17 and 20
Other information			Page 10,21
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.