BMJ Open

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

Chin-Sung Kuo,[1,2,3] Yung-Tai Chen,[2,4] Chien-Yi Hsu,[2,3,5,6] Chun-Chin Chang,[2,3,7] Ruey-Hsing Chou,[2,3,7] Szu-Yuan Li,[2,3,8] Shu-Chen Kuo,[9,10] Po-Hsun Huang,[2,3,7,11] Jaw-Wen Chen,[3,7,12,13] Shing-Jong Lin[2,3,5,7,12,14]

To cite: Kuo C-S, Chen Y-T, Hsu C-Y, *et al*. The impact of chronic hepatitis B infection on major adverse cardiovascular events and all-cause mortality in patients with diabetes: a nationwide population-based study from Taiwan. *BMJ Open* 2017;**7**:e016179. doi:10.1136/bmjopen-2017-016179

► Prepublication history and additional material for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-016179).

C-SK and Y-TC contributed equally.
P-HH and S-JL contributed equally.

Received 30 January 2017
Revised 13 June 2017
Accepted 5 July 2017

For numbered affiliations see end of article.

Correspondence to
Prof. Po-Hsun Huang; huangbsvgh@gmail.com and Prof. Shing-Jong Lin; sjlin@vghtpe.gov.tw

ABSTRACT

Objectives The association between hepatitis B virus (HBV) infection and cardiovascular disease remains uncertain. This study explored long-term hard endpoints (ie, myocardial infarction and ischaemic 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 ischaemic 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 HR (aHR)=0.49; 95% CI 0.42 to 0.56), ischaemic stroke (aHR=0.61; 95% CI 0.56 to 0.67), heart failure (aHR=0.50; 95% CI 0.43 to 0.59) and all-cause mortality (aHR=0.72; 95% CI 0.70 to 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 patients with diabetes. Further research is needed to investigate the mechanism underlying these findings.

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 (ie, myocardial infarction and ischaemic 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 patients with diabetes 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 (eg, 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 USA, 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 ischaemic 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 patients with diabetes .

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 patients with diabetes 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 this 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 patients with diabetes. 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 (online supplementary 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 SD of the logit of the propensity score.

Primary outcome measures

The primary outcomes were hospitalisation for myocardial infarction (ICD-9-CM code 410.x), ischaemic 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 ischaemic stroke. Previous studies have validated the accuracy of myocardial infarction and ischaemic 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–NT$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 (online supplementary 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 HRs and 95% CIs for the risks of outcomes.[25] Cox regression with adjustment for significant differences in covariates between groups was used to calculate adjusted HRs (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, Washington, USA) was used for data linkage, processing and sampling. Propensity scores were calculated with SAS V.9.3 (SAS Institute, Cary, NC, USA). All other statistical analyses were conducted using STATA statistical software (V.12.0; StataCorp, College Station, Texas, 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 (SD, 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 patients with diabetes

During the mean 5.3-year follow-up period, the incidence rates of all-cause mortality, myocardial infarction, ischaemic stroke and heart failure were 26.96, 1.38, 3.71 and

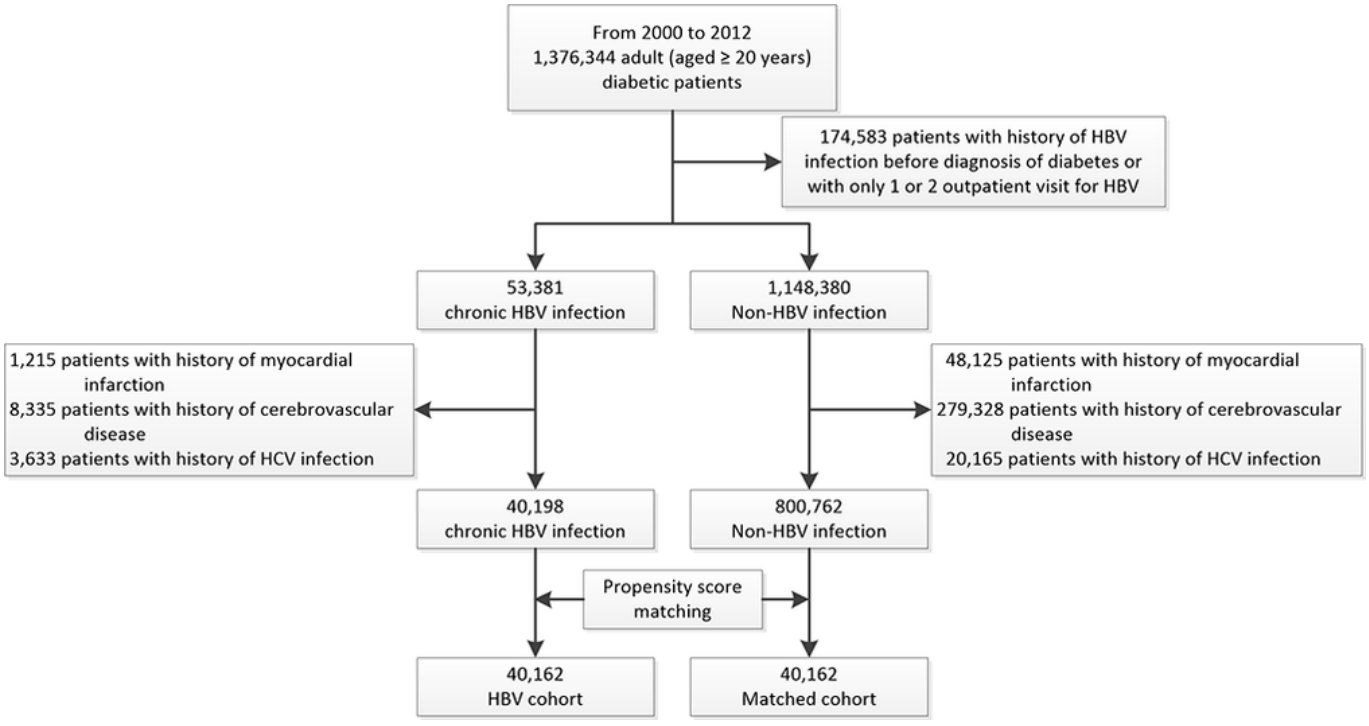

Figure 1 Flow diagram of cohort selection. The study cohort consisted of 40 162 diabetic patients with chronic HBV infection and 40 162 matched control subjects without HBV infection. HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 1 Baseline characteristics of patients with diabetes

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	8787 (21.9)	8510 (21.2)	0.017
<19 100	6859 (17.1)	6342 (15.8)	0.035
19 100–41 999	18 910 (47.1)	19 343 (48.2)	−0.022
≥42 000	5606 (14.0)	5967 (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	1593 (4.0)	1498 (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	3752 (9.3)	3774 (9.4)	−0.002
11–15	975 (2.4)	1049 (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	3885 (9.7)	3950 (9.8)	−0.005
Beta blocker	3256 (8.1)	3337 (8.3)	−0.007
Calcium channel blocker	3887 (9.7)	3866 (9.6)	0.002
Diuretic	2701 (6.7)	2507 (6.2)	0.020
Anti-diabetic drug use			
Acarbose	823 (2.0)	886 (2.2)	−0.011
Sulfonylurea	7374 (18.4)	7795 (19.4)	−0.027
Insulin	865 (2.2)	831 (2.1)	0.006
Metformin	6921 (17.2)	7235 (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	2097 (5.2)	2073 (5.2)	0.003
NSAID	8662 (21.6)	8728 (21.7)	−0.004
Proton pump inhibitor	1836 (4.6)	1436 (3.6)	0.050
Steroid	2005 (5.0)	1942 (4.8)	0.007
Antidepressant	1117 (2.8)	1137 (2.8)	−0.003
Statin	1701 (4.2)	1718 (4.3)	−0.002
Comorbidities			
Coronary artery disease	9694 (24.1)	9731 (24.2)	−0.002
Hypertension	19 839 (49.4)	19 859 (49.4)	−0.001
Heart failure	2002 (5.0)	1791 (4.5)	0.025

Continued

Table 1 Continued

Characteristic	Propensity score-matched		
	HBV cohort	Control cohort	Standardised difference*
Peripheral vascular disease	1369 (3.4)	1543 (3.8)	−0.023
Chronic kidney disease	5929 (14.8)	5916 (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	2588 (6.4)	2547 (6.3)	0.004
Cancer	6835 (17.0)	6546 (16.3)	0.019
Autoimmune disease	1543 (3.8)	1559 (3.9)	−0.002
Dialysis	386 (1.0)	345 (0.9)	0.011
Physical limitation	1592 (4.0)	1606 (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 seven 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 and 2 = severe abnormality).
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HBV, hepatitis B virus; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug.

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 to 0.75; p<0.001), myocardial infarction (aHR=0.49; 95% CI 0.42 to 0.56; p<0.001), ischaemic stroke (aHR=0.61; 95% CI 0.56 to 0.67; p<0.001), MACE (aHR=0.58; 95% CI 0.53 to 0.62; p<0.001) and heart failure (aHR=0.50; 95% CI 0.43 to 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 to 8.56; p<0.001) and a similar risk of hospitalisation for appendicitis (aHR=1.13; 95% CI 0.93 to 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 (online supplementary 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 (online supplementary 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 (online supplementary table 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 patients with diabetes. 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-adjusted 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

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*	HR (95% CI)	p Value	HR† (95% CI)	p value
All-cause mortality	6027	223 588	26.96	7140	202 307	35.29	0.78 (0.76 to 0.81)	<0.001	0.72 (0.70 to 0.75)	<0.001
MACE‡	1098	220 605	4.98	1663	198 131	8.39	0.59 (0.55 to 0.64)	<0.001	0.58 (0.53 to 0.62)	<0.001
Myocardial infarction	308	222 847	1.38	554	201 078	2.76	0.50 (0.43 to 0.57)	<0.001	0.49 (0.42 to 0.56)	<0.001
Ischaemic stroke	822	221 298	3.71	1171	199 259	5.88	0.63 (0.57 to 0.69)	<0.001	0.61 (0.56 to 0.67)	<0.001
Heart failure	249	223 050	1.12	405	201 494	2.01	0.55 (0.47 to 0.65)	<0.001	0.50 (0.43 to 0.59)	<0.001
HCC	1590	220 573	7.21	153	202 145	0.76	9.58 (8.12 to 11.31)	<0.001	9.34 (7.91 to 11.03)	<0.001
Acute appendicitis	222	222 682	1.00	179	201 644	0.89	1.13 (0.93 to 1.37)	0.233	1.13 (0.93 to 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 ischaemic stroke.
HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MACE, major adverse cardiovascular event.

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 ischaemic 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

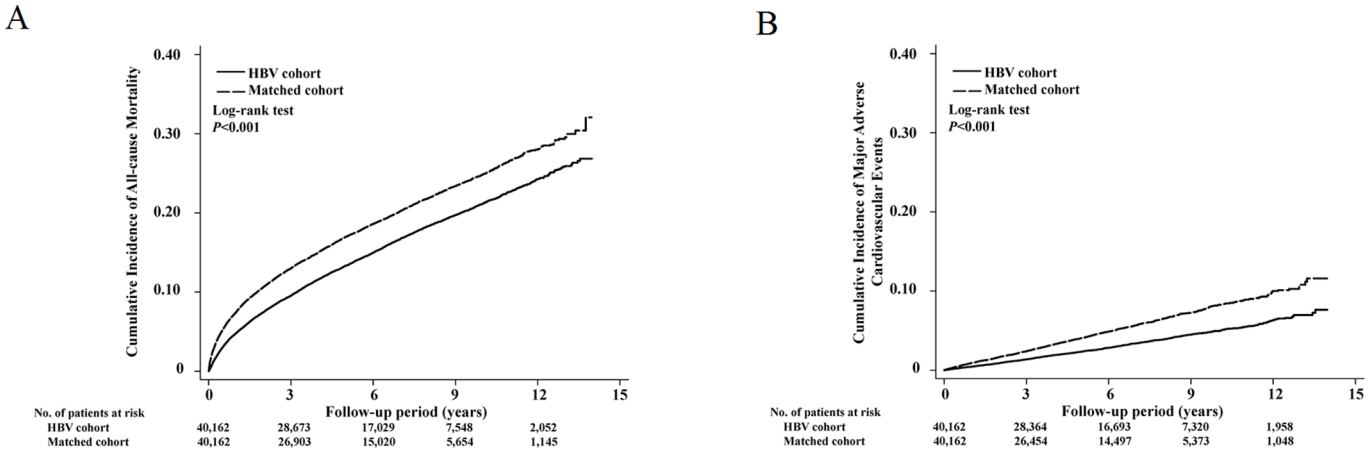

Figure 2 The cumulative incidence of all-cause mortality (A) and major adverse cardiovascular events (B) among diabetic patients with chronic HBV infection and matched control subjects without HBV infection. HBV, hepatitis B virus.

atherosclerosis-related mortality risk in the general population.[16] One possible explanation for this result is the lack of statistical power (HR=0.84; 95% CI 0.72 to 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 the general populations.[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 threefold in China.[36] We are not aware of any study that has examined the relationship between all-cause mortality and chronic HBV infection in patients with diabetes. 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 100 000 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 patients with diabetes.[3] Thus, the impact of HBV infection on all-cause mortality could plausibly be hypothesised to be greater in patients with diabetes 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 patients with diabetes. These findings may provide new insight into the pathogenesis of diabetes and future therapeutic strategies. However, further research is needed to confirm our findings and to explore the underlying mechanism.

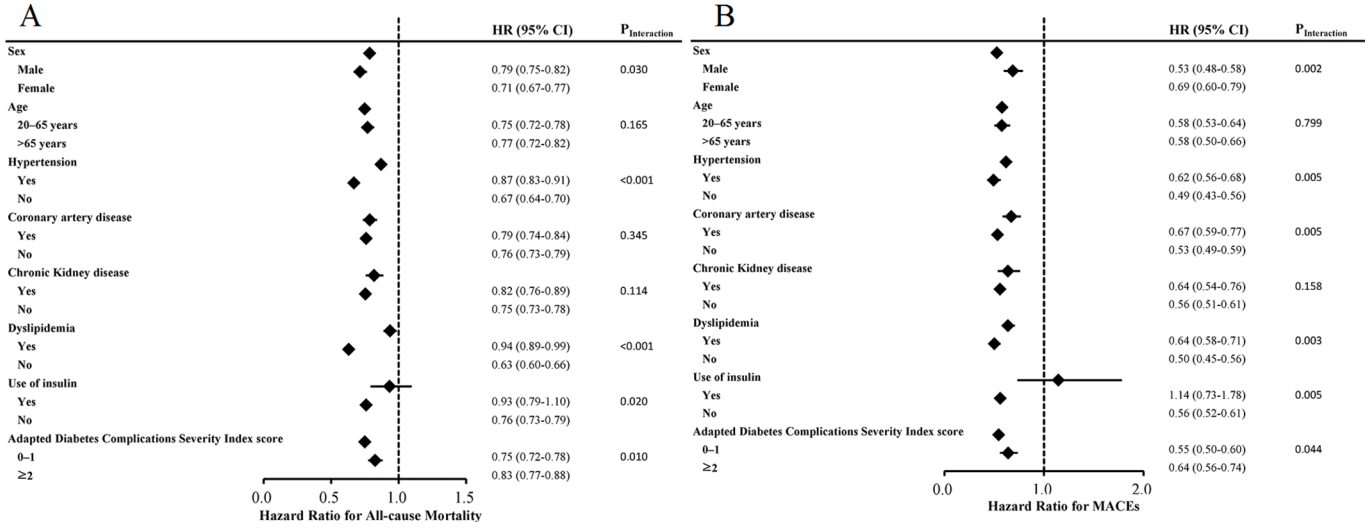

Figure 3 Results of multivariable stratified subgroup analyses, showing the effects of chronic HBV infection on all-cause mortality (A) and major adverse cardiovascular events (B). HBV, hepatitis B virus; MACE, major adverse cardiovascular events.

Author affiliations
[1]Division of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[2]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan
[3]Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan
[4]Department of Medicine, Taipei City Hospital Heping Fuyou, Taipei, Taiwan
[5]Department of Internal Medicine, School of Medicine, Taipei Medical University, Taipei, Taiwan
[6]Division of Cardiology and Cardiovascular Research Center, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan
[7]Division of Cardiology, Department of medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[8]Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[9]Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[10]National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Zhunan, Taiwan
[11]Department of Critical Care Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[12]Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan
[13]Institute of Pharmacology, National Yang-Ming University, Taipei, Taiwan
[14]Healthcare and Management Center, Taipei Veterans General Hospital, Taipei, Taiwan

Contributors Y-TC, 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: C-SK, P-HH, Y-TC and S-JL. Acquisition of data: Y-TC, C-YH and C-CC. Analysis and interpretation of data: C-SK, Y-TC and P-HH. Drafting of the manuscript: C-SK, Y-TC, P-HH, C-YH and C-CC. Statistical analysis: P-HH and Y-TC. Administrative, technical and/or material support: R-HC, S-JL, S-CK, J-WC and S-JL. Critical revision: Y-TC, P-HH and S-JL. Study supervision: P-HH and S-JL. 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, MOST 106-2633-B-009-001), from the Ministry of Health and Welfare (MOHW106-TDU-B-211-113001) and from Taipei Veterans General Hospital (V105C-207, 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 interests None declared.

Patient consent Because the dataset comprised de-identified secondary data.

Ethics approval Institutional Review Board of Taipei City Hospital (TCHIRB-1030603-W)

Provenance and peer review Not commissioned; externally peer reviewed.

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.

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