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# Risk of diabetes in viral hepatitis B or C patients compared to that in noninfected individuals in Korea, 2002-2013: A population-based cohort study

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## Summary

While the association between hepatitis C virus (HCV) infection and diabetes has been established, the relationship between hepatitis B virus (HBV) infection and diabetes remains unclear. Therefore, we compared the association between diabetes development in HBV, HCV and co-infected (HBV/HCV) patients to that in noninfected participants using population-based cohort data. We used the National Health Insurance Service-National Sample Cohort, which consists of 514 791 randomly selected persons among those who underwent health check-ups from 2002 to 2003 aged 40-79 years. Adults found to have HBV or HCV infection from 2002 to 2003, without a prior history of diabetes, were selected as subjects. Competing risk regression models were used to estimate cumulative incidence and hazards ratios (HRs) of diabetes development. The cumulative incidences, incidence densities and HRs of diabetes were highest in the co-infected group, followed by those in the HCV-, HBV- and noninfected groups. The 12-year cumulative incidences were as follows: 42.0% in HBV/HCV-, 32.9% in HCV-, 23.9% in HBV- and 18.3% in the noninfected groups. The incidence density per 1000 person-years was 55.0, 51.5, 38.2 and 28.2 for the HBV/HCV-, HCV-, HBV- and noninfected groups, respectively. The adjusted HRs for diabetes were 1.90, 1.68 and 1.41 for the HBV/HCV-, HCV- and HBV-infected groups, respectively. Our findings suggest that both HCV and HBV infections are associated with the development of diabetes; therefore, prevention of, screening for, and treatment of both may reduce the risk of diabetes in these patients.

**KEYWORDS**
cohort, diabetes, hepatitis B virus, hepatitis C virus, incidence

## 1 | INTRODUCTION

Diabetes, one of the most prevalent noncommunicable diseases, affected 1 in 11 adults (415 million people) in 2015.[1] Hepatitis B virus (HBV) and hepatitis C virus (HCV) infectious are also global public health problems. It is estimated that approximately 2 billion people worldwide have evidence of past or present infection with HBV, and 248 million individuals are positive for the hepatitis B surface antigen (HBsAg).[2,3] It has been estimated that there were approximately 177.5 million HCV-infected adults in 2013.[4] Liver cancer is the sixth most common cancer and the third most common cause of death from cancer globally. Moreover, approximately 792 000 new cases of liver cancer were diagnosed in 2013.[5] Besides the known major risk factors for liver cancer, namely HBV and HCV infections, diabetes is

**Abbreviations:** HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; ICD, International Classification of Diseases; NHIS, National Health Insurance Services; NSC, National Sample Cohort.

The first two authors contributed equally to this study.

  

also a strong risk factor.[6,7] Moreover, several studies have reported a link between HBV and HCV infections and the development of diabetes. Beginning with a 1994 report by Allison et al,[8] there have been many studies regarding the association between HCV infection and diabetes.[9-16] However, while the relationship between HCV infection and the development of diabetes has been well established, the association between HBV infection and the development of diabetes remains unclear. Some studies have reported that HBV infection is strongly associated with diabetes,[17,18] whereas others have reported no such relationship.[10,19] The 2 most recent meta-analyses, released in 2015, both reported from China, also emphasized the uncertainties of HBV's effects on the development of diabetes.[20,21]

Although there have been some cross-sectional, case-control[7,22,23] and a few cohort studies[17,19] conducted, no study has yet assessed the relationship between HBV and HCV infections on the development of diabetes using competing risk analysis in a national population-based cohort. Therefore, the objective of this cohort study was, first, to estimate the incidence rates of diabetes development and, second, to analyse and compare the hazard ratios (HRs) of diabetes development in HBV-, HCV- and co-infected patients, as compared with the noninfected population in Korea, using competing risk analysis.

## 2 | MATERIALS AND METHODS

### 2.1 | Data source

This is a cohort study of individuals from the database of the National Sample Cohort (NSC) released by the National Health Insurance Service (NHIS). The cohort data used in this study included 514 791 persons, representing approximately 10% of the 5.15 million persons who had undergone health check-ups from among the total health check-up eligible Korean population aged between 40 and 79 years, from 2002 to 2003. Korea has achieved universal health insurance coverage, with more than 98% of the Korean population covered by the National Health Insurance. The NSC database contains the records of disease histories, medical institutions visited, medical treatments and routine biennial health examination results of the cohort from 2002 to 2013, with follow-up data collected for up to a maximum of 12 years. The NSC data also include mortality data through data linkage with Statistics Korea, available at: http://kostat.go.kr/portal/english/index.action.

### 2.2 | Study variables

This study defined patients who developed diabetes as persons with fasting glucose levels higher than 126 mg/dL according to their health check-up results and those who had been diagnosed with diabetes at medical institutions and received E11 code according to the International Classification of Diseases, tenth revision (ICD-10) system.

The risk factors for diabetes were classified into sociodemographic factors, lifestyle factors and physiological factors.

### 2.3 | Sociodemographic factors

Ages at the time of health check-up, sex and income levels were considered as sociodemographic factors. In terms of income levels, the values were categorized into percentiles from lowest to highest 0-20th, 21-40th, 41-60th, 61-80th and 81-100th levels, based on the costs imposed on health insurance premiums by the NHIS.[24] Even though the immigrant workers and multicultural families have been growing in Korea, the percentage is about 3.2% of the whole population in 2014, neither race nor ethnicity was considered a risk factor in this study.

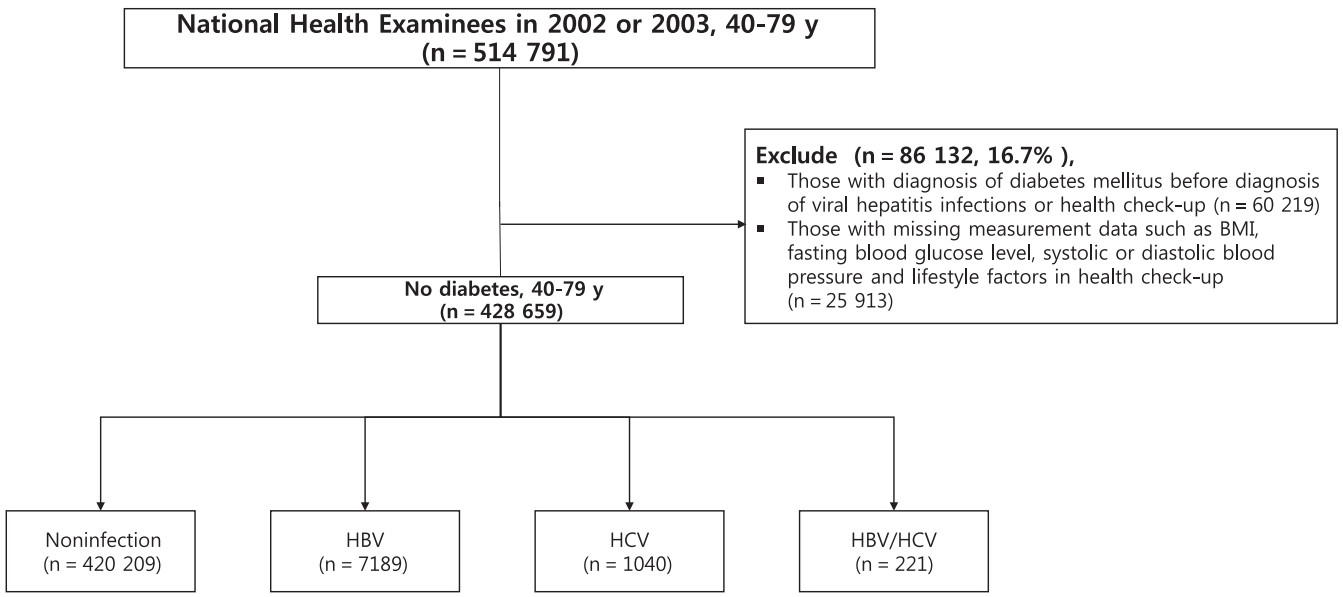


**FIGURE 1** Flow chart of study participant selection by viral hepatitis infection using National Health Examination Sample Data, South Korea

**TABLE 1** Epidemiologic characteristics of study participants by viral hepatitis infection, South Korea

| Variables | Noninfection (n = 420 209) | | Hepatitis B virus (n = 7189) | | Hepatitis C virus (n = 1040) | | Hepatitis B virus / Hepatitis C virus (n = 221) | | *P* value[a] |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | |
| Age group (y) | | | | | | | | | |
| 40-49 | 196044 | 46.7 | 3698 | 51.4 | 373 | 35.9 | 80 | 36.2 | <.001 |
| 50-59 | 117820 | 28.0 | 2187 | 30.4 | 323 | 31.1 | 73 | 33.0 | |
| 60+ | 106345 | 25.3 | 1304 | 18.1 | 344 | 33.1 | 68 | 30.8 | |
| Sex | | | | | | | | | |
| Male | 225384 | 53.6 | 4309 | 59.9 | 597 | 57.4 | 142 | 64.3 | <.001 |
| Female | 194825 | 46.4 | 2880 | 40.1 | 443 | 42.6 | 79 | 35.7 | |
| Body Mass Index(kg/m$^2$) | | | | | | | | | |
| <18.5 | 10054 | 2.4 | 122 | 1.7 | 25 | 2.4 | 5 | 2.3 | <.001 |
| 18.5-22.9 | 153636 | 36.6 | 2466 | 34.3 | 309 | 29.7 | 83 | 37.6 | |
| 23.0-24.9 | 114680 | 27.3 | 1958 | 27.2 | 300 | 28.8 | 59 | 26.7 | |
| 25.0-29.9 | 130928 | 31.2 | 2477 | 34.5 | 376 | 36.2 | 70 | 31.7 | |
| ≥30.0 | 10911 | 2.6 | 166 | 2.3 | 30 | 2.9 | 4 | 1.8 | |
| Smoking | | | | | | | | | |
| Nonsmoker | 281035 | 66.9 | 4819 | 67.0 | 709 | 68.2 | 141 | 63.8 | <.001 |
| Former smoker | 37052 | 8.8 | 750 | 10.4 | 113 | 10.9 | 30 | 13.6 | |
| Current smoker | 102122 | 24.3 | 1620 | 22.5 | 218 | 21.0 | 50 | 22.6 | |
| Drinking alcohol | | | | | | | | | |
| Nondrinker | 234924 | 55.9 | 4129 | 57.4 | 633 | 60.9 | 123 | 55.7 | <.001 |
| 2-3 sessions/mo | 64971 | 15.5 | 992 | 13.8 | 112 | 10.8 | 32 | 14.5 | |
| 1-2 sessions/wk | 68510 | 16.3 | 1007 | 14.0 | 111 | 10.7 | 22 | 10.0 | |
| Heavy drinker[b] | 51804 | 12.3 | 1061 | 14.8 | 184 | 17.7 | 44 | 19.9 | |
| Exercise[c] | | | | | | | | | |
| No activity | 242863 | 57.8 | 3894 | 54.2 | 592 | 56.9 | 107 | 48.4 | <.001 |
| 1-2 counts/wk | 100450 | 23.9 | 1881 | 26.2 | 244 | 23.5 | 63 | 28.5 | |
| ≥3 counts/wk | 76896 | 18.3 | 1414 | 19.7 | 204 | 19.6 | 51 | 23.1 | |
| Hypertension | | | | | | | | | |
| Yes[d] | 112115 | 26.7 | 1459 | 20.3 | 262 | 25.2 | 38 | 17.2 | <.001 |
| No | 308094 | 73.3 | 5730 | 79.7 | 778 | 74.8 | 183 | 82.8 | |
| Income percentile[e] | | | | | | | | | |
| ≤20th | 66439 | 15.8 | 901 | 12.5 | 154 | 14.8 | 26 | 11.8 | <.001 |
| 21-40th | 58386 | 13.9 | 843 | 11.7 | 138 | 13.3 | 27 | 12.2 | |
| 41-60th | 66476 | 15.8 | 1060 | 14.7 | 158 | 15.2 | 42 | 19.0 | |
| 61-80th | 87176 | 20.7 | 1576 | 21.9 | 233 | 22.4 | 45 | 20.4 | |
| 81-100th | 141732 | 33.7 | 2809 | 39.1 | 357 | 34.3 | 81 | 36.7 | |
| Outcome | | | | | | | | | |
| Diabetes | 108638 | 25.9 | 2352 | 32.7 | 423 | 40.7 | 96 | 43.5 | <.001 |
| Death | 19548 | 4.6 | 495 | 6.9 | 76 | 7.3 | 16 | 7.2 | |
| Censored (no diabetes, no death) | 292023 | 69.5 | 4342 | 60.4 | 541 | 52.0 | 109 | 49.3 | |

(Continues)

**TABLE 1** (Continued)

| Variables | Noninfection (n = 420 209) n | % | Hepatitis B virus (n = 7189) n | % | Hepatitis C virus (n = 1040) n | % | Hepatitis B virus / Hepatitis C virus (n = 221) n | % | *P* value[a] |
|---|---|---|---|---|---|---|---|---|---|
| Follow-up years | | | | | | | | | |
| Average | 9.2 | | 8.6 | | 7.9 | | 7.9 | | |
| Median(Q1, Q3) | 10.5 (8.6, 11.2) | | 10.5 (5.7, 11.4) | | 10.2 (4.2, 11.2) | | 10.2 (3.9, 11.6) | | |

[a]*P* values were obtained using chi-square test.
[b]Heavy drinker refers to subject who answered in the question on drinking as "drink almost every day" or those diagnosed with alcoholic liver disease (ICD10th: K70) between 2002 and 2003.
[c]Question: How many times do you exercise per week to the extent that you sweat?
[d]Hypertension is defined as one of these following criteria, (i) systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg, (ii) diagnosed essential(primary) hypertension, hypertensive heart disease, hypertensive renal disease, hypertensive heart and renal diseases(ICD10th: I10-I13) between 2002 and 2003.
[e]It is classified as deciles through health insurance premium information that is imposed on each household unit.

### 2.4 | Lifestyle factors

The lifestyle risk factors assessed included smoking, drinking and physical activity. Smoking status was categorized into nonsmoker, former smoker and current smoker. Physical activity, defined as exercising to the extent that the individual sweats, was divided into none, once- or twice-per-week, and 3 or more times-per-week. The questionnaire for drinking was separated into nondrinker, 2-3 drinking sessions-per-month, 1-2 drinking sessions-per-week and heavy drinkers, which included those who had 3-4 drinking sessions-per-week, those who drank every day or those who were diagnosed with alcoholic liver disease (ICD-10: K70) before the date of the health check-up between 2002 and 2003.

### 2.5 | Physiological factors

Body mass index (BMI) and hypertension were included as physiological factors. BMIs were categorized as <18.5 kg/m$^2$ (underweight), 18.5-22.9 kg/m$^2$ (normal), 23-24.9 kg/m$^2$ (overweight), 25-29.9 kg/m$^2$ (obese) and ≥30 kg/m$^2$ (extremely obese), according to the suggested categorizations for Asian adults made by the International Association for the Study of Obesity in 2000.[25] Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or persons diagnosed with essential (primary) hypertension, hypertensive heart disease, hypertensive renal disease, or hypertensive heart and renal disease (ICD-10: I10-I13), based on the criteria of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[26]

### 2.6 | Case definitions and study population

We divided the study population into 4 groups according to their viral hepatitis infection status between 2002 and 2003: HBV infection (ICD-10: B16, B16.1, B16.2, B16.9, B17.0, B18.0 or B18.1), HCV infection (ICD-10: B17.1 or B18.2), co-infection (HBV/HCV) and noninfection. The study population for the noninfected group included persons who had claims data from 2002 to 2003 without HBV or HCV infection during the entire follow-up period of 2002 to 2013. The subjects excluded were (i) those who had been treated for diabetes or those with fasting glucose levels of 126 mg/dL or greater until the diagnosis of viral hepatitis from the entire cohort between 2002 and 2003 and/or (ii) those with missing measurement (BMI, fasting blood, systolic or diastolic blood and lifestyle factors) data at health check-ups (Figure 1).

### 2.7 | Statistical analyses

The Fine and Gray competing risk regression model[27] was used to estimate cumulative incidence and hazard ratios for each group studied (noninfection and HBV-, HCV- and HBV/HCV- infections), with adjustments made for death. Survival time (time to event) was defined in relation to the outcome, such as diabetes, death or the end of the study date, 31 December 2013. Statistical significance was defined as *P*-value less than 0.05, and all statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

### 2.8 | Ethical considerations

This study was exempt from approval by an institutional review board, because the subjects could not be identified, either directly or through identifiers linked to them (NCC2014-0085, NCC2017-0034). The NHIS-NSC database is available upon request. For more details, please see http://nhiss.nhis. or.kr/bd/ab/bdaba021eng.do.[28]

## 3 | RESULTS

### 3.1 | General and clinical characteristics

Of the total study population of 514 791 persons, the final number of subjects included in this study was 428 659. Approximately 16.7% of the total study population was excluded. The excluded persons

**TABLE 2** Incidence density of the development of diabetes by viral hepatitis infection, South Korea

| Variables | No./1000 person-years | | | |
|---|---|---|---|---|
| | Noninfection | Hepatitis B virus | Hepatitis C virus | Hepatitis B virus / Hepatitis C virus |
| Incidence of diabetes | | | | |
| Per 1000 person-years | 28.2 | 38.2 | 51.5 | 55.0 |
| Cumulative incidence of 12 y (%)[a] | (18.3) | (23.9) | (32.9) | (42.0) |
| Age group (y) | | | | |
| 40-49 | 20.6 | 29.4 | 39.5 | 41.6 |
| 50-59 | 31.5 | 44.5 | 50.3 | 62.5 |
| 60+ | 40.9 | 58.3 | 69.1 | 65.6 |
| Sex | | | | |
| Male | 30.9 | 41.9 | 53.6 | 50.5 |
| Female | 25.2 | 33.1 | 48.8 | 63.3 |
| Body Mass Index(kg/m$^2$) | | | | |
| <23.0 | 21.3 | 29.2 | 41.9 | 44.1 |
| 23.0-24.9 | 27.4 | 38.9 | 46.0 | 67.0 |
| ≥25.0 | 37.4 | 47.3 | 64.8 | 60.1 |
| Smoking | | | | |
| Nonsmoker | 26.7 | 35.3 | 49.9 | 65.4 |
| Former smoker | 29.8 | 41.1 | 64.5 | 42.3 |
| Current smoker | 32.0 | 46.3 | 50.5 | 36.1 |
| Drinking alcohol | | | | |
| Nondrinker | 27.2 | 35.2 | 50.3 | 59.9 |
| 2-3 sessions/mo | 25.6 | 37.2 | 44.5 | 32.5 |
| 1-2 sessions/wk | 28.6 | 42.7 | 51.2 | 69.2 |
| Heavy drinker[b] | 36.0 | 47.7 | 61.2 | 54.9 |
| Exercise[c] | | | | |
| No activity | 28.5 | 39.0 | 51.0 | 65.3 |
| 1-2 counts/wk | 27.2 | 36.1 | 48.3 | 39.4 |
| ≥3 counts/wk | 28.7 | 39.0 | 56.8 | 54.8 |
| Hypertension | | | | |
| Yes[d] | 42.3 | 57.0 | 68.2 | 88.4 |
| No | 23.7 | 34.2 | 46.8 | 49.4 |
| Income percentile[e] | | | | |
| ≤20th | 31.8 | 42.4 | 59.3 | 54.2 |
| 21-40th | 30.1 | 44.9 | 61.4 | 52.1 |
| 41-60th | 29.6 | 41.8 | 64.6 | 70.0 |
| 61-80th | 28.5 | 37.9 | 41.6 | 54.1 |
| 81-100th | 25.0 | 34.0 | 46.4 | 49.5 |

[a]All-cause mortality was the competing risk.

[b]Heavy drinker refers to subjects who answered in the question on drinking as "drink almost every day" or those diagnosed with alcoholic liver disease (ICD10th: K70) between 2002 and 2003.

[c]Question: How many times do you exercise per week to the extent that you sweat?

[d]Hypertension is defined as one of these following criteria, (i) systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg, (ii) diagnosed essential(primary) hypertension, hypertensive heart disease, hypertensive renal disease, hypertensive heart and renal diseases(ICD10th: I10-I13) between 2002 and 2003.

[e]It is classified as deciles through health insurance premium information that is imposed on each household unit.

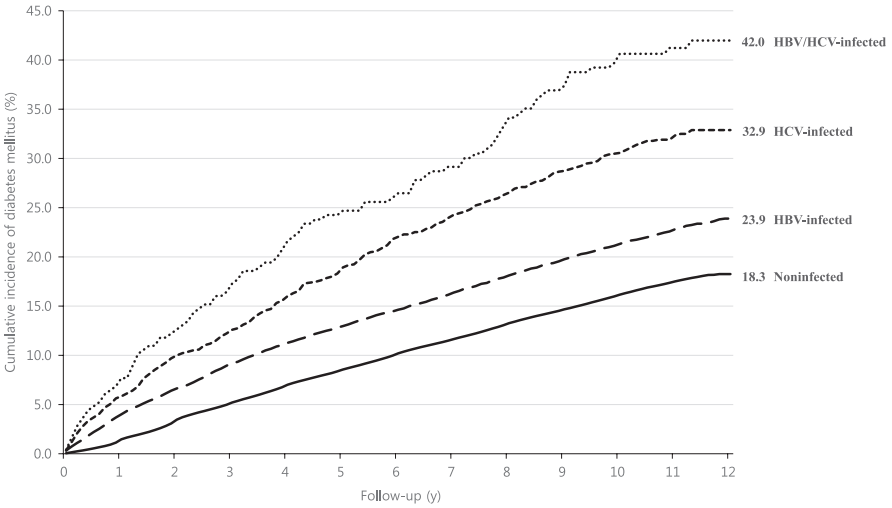


**FIGURE 2** Cumulative incidence of diabetes by viral hepatitis infection using Fine and Gray model, South Korea

included those who had a history of diabetes before their first health check-ups between 2002 and 2003 and those who were diagnosed or had a history of diabetes before being diagnosed with HBV or HCV infection (Figure 1). A large proportion of noninfected subjects and those in the HBV-infected group were in their 40s or 50s, while ages of the subjects in the HCV- and HBV/HCV-infected groups tended to be evenly spread out among age groups. The gender distribution was similar in all groups, except that the number of males in the HBV/HCV-infected group was 1.8 times greater than the number of females in that group. In terms of drinking habits, the noninfected group had the lowest percentage (12.3%) of heavy drinkers, whereas the HBV/HCV-infected group had the highest percentage (19.9%). The number of subjects with hypertension was greatest in the noninfected group, at 26.7%, and the lowest was in the HBV/HCV-infected group, at 17.2%. During the study period, the number of subjects who died before developing diabetes was 19 548 (4.6%) in the noninfected, 495 (6.9%) in the HBV-infected, 76 (7.3%) in the HCV-infected and 16 (7.2%) in the HBV/HCV-infected groups (Table 1).

### 3.2 | The risk of developing diabetes over 12 years

Among the 428 659 total subjects, 111 509 (26%) developed diabetes, and their average age at diagnosis was 59.6 years. By group, the number of subjects who developed diabetes was 108 638 (25.9%) of the noninfected, 2352 (32.7%) of the HBV-infected, 423 (40.7%) of the HCV-infected and 96 (43.4%) of the HBV/HCV-infected ($P < .001$). The average age of diabetes development for each group was as follows, in increasing order: 57 years for the HBV-infected, 59.2 years for the HBV/HCV-infected, 59.7 years for the noninfected and 60 years for the HCV-infected groups.

The incidence density of diabetes per 1000 person-years was, by group, 28.2 for the noninfected, 38.2 for the HBV-infected, 51.5 for the HCV-infected and 55.0 for the HBV/HCV-infected groups. The 12-year cumulative incidence showed the same order of incidence density: 18.3 for the noninfected, 23.9 for the HBV-infected, 32.9 for the HCV-infected and 42.0 for the HBV/HCV-infected groups (Table 2, Figure 2).

Advanced age, male sex, obesity and hypertension increased HRs for diabetes in all 4 groups. Smoking and drinking increased the HRs for diabetes in the noninfected and HBV-infected groups. However, the amount of exercise did not show any effect on the development of diabetes in all 4 groups (Table 3).

The HRs for diabetes, in the final model (model 8) adjusted for age, sex, BMI, smoking, exercise, drinking, hypertension and income, were 1.41 (95% confidence interval [CI]: 1.35-1.47), 1.68 (95% CI: 1.52-1.86) and 1.90 (95% CI: 1.53-2.35) for the HBV-, HCV- and HBV/HCV-infected groups, respectively, with statistically significant differences (Table 4).

## 4 | DISCUSSION

The present study sought to evaluate the relationship between hepatitis infection and the development of diabetes and especially to establish an association between HBV and diabetes, using a national, population-based cohort.

The 12-year cumulative incidence rates, as well as the HRs for diabetes development, were highest in the HBV/HCV-infected group, followed by the HCV-, HBV- and noninfected groups. Therefore, the present study demonstrated that there is an association between HBV and HCV infection and the development of diabetes in the Korean adult population. This result is supported by previous studies. Recently, it was reported by Hong et al[17] that HBV infection with the risk of incident diabetes. However, the study participants were those who underwent routine health check-ups at specific hospitals in Korea, so it is hard to generalize their findings to the nationwide population. Also, it was reported that the HR for diabetes, determined by comparing HBsAg(+) to HBsAg(-) individuals, was 1.23 (95% CI: 1.08-0.41) in the Korean population.[17] A community-based longitudinal study in Taiwan reported that HCV-infected patients had a higher cumulative incidence of diabetes than did patients without HCV infection; the 7-year cumulative incidence for HCV-seropositive patients was 14.3%, while it was 8.6% for seronegative patients.[10] This is consistent with the present study, in which the cumulative incidence

**TABLE 3** Hazard ratio for the development of diabetes by viral hepatitis infection using univariate competing risk analysis[a], South Korea

| | Hazard ratio (95% Confidence Interval) | | | |
|---|---|---|---|---|
| Variables | Noninfection | Hepatitis B virus | Hepatitis C virus | Hepatitis B virus / Hepatitis C virus |
| Age group (y) | | | | |
| 40-49 | 1 | 1.41 (1.33-1.50) | 1.89 (1.59-2.26) | 2.02 (1.39-2.95) |
| 50-59 | 1.51 (1.49-1.53) | 2.07 (1.92-2.22) | 2.38 (1.99-2.84) | 3.00 (2.15-4.18) |
| 60+ | 1.84 (1.82-1.87) | 2.55 (2.34-2.78) | 3.04 (2.59-3.58) | 2.84 (1.96-4.12) |
| Sex | | | | |
| Female | 1 | 1.31 (1.22-1.40) | 1.92 (1.65-2.24) | 2.55 (1.85-3.53) |
| Male | 1.21 (1.19-1.22) | 1.61 (1.52-1.69) | 2.03 (1.78-2.30) | 1.92 (1.47-2.51) |
| Body Mass Index(kg/m$^2$) | | | | |
| <23.0 | 1 | 1.36 (1.26-1.47) | 1.93 (1.60-2.32) | 2.06 (1.46-2.90) |
| 23.0-24.9 | 1.30 (1.28-1.33) | 1.80 (1.66-1.95) | 2.16 (1.78-2.63) | 3.16 (2.20-4.54) |
| ≥25.0 | 1.78 (1.75-1.80) | 2.23 (2.09-2.37) | 2.98 (2.58-3.45) | 2.78 (1.92-4.03) |
| Smoking | | | | |
| Nonsmoker | 1 | 1.31 (1.24-1.38) | 1.84 (1.63-2.07) | 2.49 (1.94-3.18) |
| Former smoker | 1.11 (1.09-1.14) | 1.50 (1.32-1.70) | 2.29 (1.71-3.05) | 1.53 (0.86-2.74) |
| Current smoker | 1.18 (1.17-1.20) | 1.68 (1.54-1.82) | 1.83 (1.48-2.27) | 1.25 (0.75-2.10) |
| Drinking alcohol | | | | |
| Nondrinker | 1 | 1.28 (1.21-1.35) | 1.81(1.60-2.06) | 2.22 (1.69-2.93) |
| 2-3 sessions/mo | 0.95 (0.94-0.97) | 1.37 (1.22-1.53) | 1.67 (1.24-2.26) | 1.22 (0.67-2.23) |
| 1-2 sessions/wk | 1.06 (1.04-1.08) | 1.56 (1.41-1.74) | 1.89 (1.39-2.56) | 2.36 (1.33-4.22) |
| Heavy drinker[b] | 1.30 (1.28-1.32) | 1.68 (1.52-1.86) | 2.10 (1.67-2.63) | 1.86 (1.16-3.01) |
| Exercise[c] | | | | |
| No activity | 1 | 1.35 (1.27-1.43) | 1.75 (1.53-1.99) | 2.28 (1.73-3.01) |
| 1-2 counts/wk | 0.97 (0.95-0.98) | 1.27 (1.17-1.38) | 1.68 (1.36-2.06) | 1.38 (0.88-2.16) |
| ≥3 counts/wk | 1.02 (1.00-1.03) | 1.37 (1.25-1.50) | 1.99 (1.60-2.46) | 1.88 (1.23-2.89) |
| Hypertension[d] | | | | |
| No | 1 | 1.43 (1.36-1.50) | 1.95 (1.74-2.19) | 2.07 (1.63-2.62) |
| Yes | 1.74 (1.72-1.76) | 2.29 (2.11-2.49) | 2.67 (2.21-3.23) | 3.44 (2.25-5.27) |
| Income percentile[e] | | | | |
| ≤20th | 1 | 1.30 (1.16-1.46) | 1.86 (1.45-2.38) | 1.64 (0.90-3.00) |
| 21-40th | 0.95 (0.93-0.97) | 1.39 (1.24-1.55) | 1.85 (1.44-2.37) | 1.69 (0.97-2.95) |
| 41-60th | 0.94 (0.92-0.96) | 1.30 (1.17-1.44) | 1.98 (1.55-2.52) | 2.19 (1.44-3.33) |
| 61-80th | 0.91 (0.89-0.93) | 1.19 (1.09-1.31) | 1.31 (1.04-1.65) | 1.69 (1.06-2.71) |
| 81-100th | 0.80 (0.79-0.82) | 1.08 (1.01-1.16) | 1.46 (1.23-1.73) | 1.55 (1.08-2.25) |

[a]All-cause mortality was the competing risk.
[b]Heavy drinker refers to subjects who answered in the question on drinking as "drink almost every day" or those diagnosed with alcoholic liver disease (ICD10th: K70) between 2002 and 2003.
[c]Question: How many times do you exercise per week to the extent that you sweat?
[d]Hypertension is defined as one of these following criteria, (i) systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg, (ii) diagnosed essential(primary) hypertension, hypertensive heart disease, hypertensive renal disease, hypertensive heart and renal diseases(ICD10th: I10-I13) between 2002 and 2003.
[e]It is classified as deciles through health insurance premium information that is imposed on each household unit.

rate of 12 years was 32.9% in the HCV-infected group and 18.3% in the noninfected group.

However, in terms of the association between HBV infection and the development of diabetes, our results were in contrast with those reported in several previous studies. A Taiwanese study reported that, in subjects aged ≥40 years, the 7-year cumulative incidence rate of diabetes was 7.5% for HBsAg+ patients and 8.6% for seronegative individuals; moreover, no significant difference

**TABLE 4** Hazard ratio for the development of diabetes by viral hepatitis infections using multivariate competing risk analysis[a], South Korea

| | Hazard ratio (95% Confidence Interval) | | | |
|---|---|---|---|---|
| Model | Noninfection | Hepatitis B virus | Hepatitis C virus | Hepatitis B virus / Hepatitis C virus |
| Model 1: Nonadjusted | 1 | 1.34 (1.25-1.39) | 1.79 (1.62-1.97) | 1.92 (1.56-2.36) |
| Model 2: Age and sex adjusted | 1 | 1.38 (1.32-1.44) | 1.67 (1.51-1.85) | 1.77 (1.44-2.19) |
| Model 3: Model 2 + body mass index adjusted | 1 | 1.36 (1.30-1.42) | 1.63 (1.48-1.80) | 1.78 (1.44-2.21) |
| Model 4: Model 3 + smoking adjusted | 1 | 1.37 (1.31-1.43) | 1.65 (1.49-1.82) | 1.79 (1.45-2.22) |
| Model 5: Model 4 + exercise adjusted | 1 | 1.37 (1.32-1.43) | 1.65 (1.49-1.82) | 1.80 (1.45-2.23) |
| Model 6: Model 5 + drinking adjusted | 1 | 1.37 (1.31-1.43) | 1.64 (1.48-1.81) | 1.78 (1.43-2.21) |
| Model 7: Model 6 + hypertension adjusted | 1 | 1.40 (1.35-1.46) | 1.68 (1.52-1.85) | 1.89 (1.53-2.34) |
| Model 8: Model 7 + income adjusted | 1 | 1.41 (1.35-1.47) | 1.68 (1.52-1.86) | 1.90 (1.53-2.35) |

[a]All-cause mortality was the competing risk.

was found between HBsAg+ alone and seronegative participants.[10] These results conflict with the current results, which demonstrated a higher 12-year cumulative incidence of 23.9% and a higher incidence density of 38.2 per 1000 person-years in the HBV-infected group than the 18.3% and 28.2 per 1000 person-years reported for the noninfected group. The differences between the present study and the Taiwanese study may be due to different definitions of hepatitis infection. While we used the ICD-10 coding system, Wang et al used serological tests to define hepatitis B. Because we did not use serological markers and nucleic acid testing, the positive association between HBV and diabetes shown in the present study might have shown a different result from the study by Wang et al. Another difference was that the Taiwanese study did not consider competing risks.

One mechanism that may underlie the association between HCV infection and risk of diabetes is that HCV can replicate in extrahepatic sites, thus damaging insulin-producing β-cells in the pancreas and resulting in diabetes.[14] A recent study used the HCV core gene transgenic mouse model to determine that either HCV, per se, or the host's inflammatory response to HCV infection contributed to the development of insulin resistance and a subsequent long-term risk of diabetes.[29] As hepatic tumour necrosis factor-α (TNF-α), which affects insulin signalling, was elevated in this animal model as well as in HCV-infected patients, the authors evaluated the role of TNF-α and found that TNF-α inhibited insulin-stimulated insulin receptor substrate-1 tyrosine phosphorylation.[16,29]

In contrast, there have been limited suggestions offered for potential mechanisms linking HBV infection to the onset of diabetes. As HBV infection is well prevented in many developed countries through active HBV immunization programs, a reason for the inconclusive and conflicting results regarding the association between HBV and diabetes may be due to the low rate of chronic HBV infection. Nevertheless, the alleged mechanisms of insulin resistance are yet to be discovered, and direct pancreatic islet β-cell damage, caused by an autoimmune process via molecular mimicry or by dysregulation of autoimmune functions, may play a role in the development of diabetes in HBV-infected patients.[14,30]

The present study has several strengths. First, the study design was that of a population-based cohort study with a long-term follow-up of 12 years, from 2002 to 2013. Another strength of this study was the large sample size of more than half of a million subjects, representing 10% of the adult health check-up population aged between 40 and 79 years in Korea, which allows the findings of this study to be generalized to the Korean adult population. Moreover, previous cohort studies were community-based, rather than national population-based. In addition, we considered other known risk factors for diabetes and adjusted for the effect of death during the follow-up period using competing risk analysis.

A limitation of our study is that HBV or HCV carriers' viral infection statuses may have changed due to either the natural course of the disease or specific treatment, and these changes could have biased the study results. Another limitation is that the exact dates of HCV and HBV infection and the development of diabetes could not be confirmed, because these are chronic illnesses and may have only been reported when the patients visited hospitals. Similarly, concern about reverse causality could be raised. As diabetes is a chronic disease, without the subjects' entire medical history long before 2002, there is a limitation to clearly say that they did not have diabetes before they were diagnosed with viral hepatitis. However, to minimize this possibility, we prescreened the subjects between 2002 and 2003. Additionally, there could be a possible bias concerning diabetes screening intensification in HBV- and HCV-infected subjects as compared to noninfected subjects, because patients with the infection might have visited hospitals more frequently compared to those without the infection. However, as the health insurance system in Korea covers 98% of the Korean population[31] and access to the healthcare system is easy and affordable, the possibility of this bias is low. Another limitation of this study could be the fact that only ICD-10 codes were used to define the study subjects. We did not have any data on serological markers or nucleic acid testing for HBV infection. This limitation could have affected the outcome and caused a stronger association between HBV and diabetes.

In conclusion, the present study demonstrated that both HCV and HBV infections are associated with the development of diabetes;

therefore, prevention of, screening for, and treatment of both will reduce the risk of diabetes in these patients. Moreover, these findings are important because HBV and HCV infections, as well as diabetes, are important independent risk factors for HCC.

## CONFLICT OF INTEREST

None.

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