

Hepatitis B virus infection and the risk of liver disease progression in type 2 diabetic patients with potential nonalcoholic fatty liver disease: a retrospective, observational, cohort study in the United Kingdom Clinical Practice Research Datalink

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Objective Assess the risk of progression to cirrhosis and hepatocellular carcinoma (HCC) due to hepatitis B virus (HBV)-infection in patients with nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM).

Methods Retrospective cohort study in the UK Clinical Practice Research Datalink with three cohorts: subjects with T2DM and HBV infection (T2DM+HBV cohort; $N=297$), with T2DM without HBV-infection (T2DM cohort; $N=261\,865$), and with HBV-infection without T2DM (HBV cohort; $N=3630$). Primary analyses were performed on the three cohorts and secondary analyses on subcohorts including patients with NAFLD diagnosis code ($N=6599$). Case/outcome definitions were formulated with International Classification of Diseases/Read codes/laboratory results and classified using validated algorithms. Adjusted incidence rate ratios (IRR) were estimated with a Poisson regression model.

Results When comparing the T2DM+HBV and T2DM cohorts, adjusted IRRs were 14.06 (95% confidence interval: 4.47–44.19) for cirrhosis and 2.83 (1.06–7.55) for HCC. When comparing the T2DM+HBV and HBV cohorts, adjusted IRRs were 0.68 (0.21–2.27) for cirrhosis and 1.39 (0.46–4.20) for HCC. No cirrhosis cases were identified in T2DM+NAFLD+HBV patients; IRs were 16.92/10 000 person-years (12.97–21.69) and 85.24/10 000 person-years (10.32–307.91) in the T2DM+NAFLD and NAFLD+HBV cohorts.

Conclusion HBV-infection increased significantly the risk for cirrhosis among T2DM patients, however, not beyond the expected incremental risk among infected non-T2DM subjects. Our approach to evaluate the role of T2DM/NAFLD and HBV-infection in liver disease progression could be applied to other settings with higher HBV prevalence. *Eur J Gastroenterol Hepatol* 32: 101–109

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in adults. Although a general consensus is yet to be reached, recent European practice guidelines subclassify NAFLD into two pathologically different conditions: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), with different fibrosis progression rates for each (around

14 and seven years per stage of fibrosis, for NAFL and NASH, respectively) [1,2]. NASH can present as a variety of manifestations with a wide range of severity, including liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC) [1]. The global prevalence of NAFLD is estimated at approximately 25% [3], but varies by region, with higher estimates ($\geq 30\%$) in the United States, Australia and parts of Europe [2]. However, NAFLD prevalence is believed to be underestimated due to the lack of consistent diagnosis techniques and practice standards to assess it. A considerable increase, in particular for NASH, has been observed over the past decades [2,3].

NAFLD prevalence differs by age group, gender and race/ethnicity, with higher values in older persons and males, and lower values in individuals of African descent [2]. The disease is especially highly associated with metabolic conditions, such as type 2 diabetes mellitus (T2DM), obesity, hypertension, dyslipidaemia or the combination of these conditions (classified as the metabolic syndrome) [1,2,4]. NAFLD and NASH prevalence can reach up to 70% in patients with T2DM [5]. Moreover, the presence of both NAFLD and T2DM increases the risk of developing T2DM complications and a higher risk of progression toward severe liver outcomes including cirrhosis, HCC and death [6,7].

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Hepatitis B virus (HBV) infection is an important cause of acute and chronic hepatitis, which leads to death from cirrhosis or liver cancer in about 15 to 25% of people with chronic HBV [8]. A global prevalence of HBV infection in the general population of 3.5% was estimated in 2015, and approximately, 257 million people are living with chronic HBV infection [9]. Although an association between HBV infection and the risk for NAFLD has been hypothesized [10,11], limited evidence exists on the role of HBV infection in the progression of liver disease in patients with T2DM, who have a high likelihood of concurrent NAFLD. A study in 1466 patients with chronic HBV infection showed that the risk of liver fibrosis progression can be increased by concurrent metabolic syndrome [12]; however, large cohort studies are lacking.

This retrospective study aimed at assessing whether there is an increased risk of progression to cirrhosis and HCC due to HBV infection in patients with T2DM (possibly with NAFLD) and in patients with NAFLD.

Methods and analysis

Study design and population

This retrospective, observational, cohort study used electronic health records of the population registered in the UK Clinical Practice Research Datalink (CPRD) [13] between 1 January 2000 and 31 December 2015. Hospital Episode Statistics (HES)-linkage eligible cohorts were employed, because liver disease and the related complications are more likely to be diagnosed in a hospital setting, and T2DM is primarily managed by general practitioners.

Patients aged at least 18 years of both sexes, who were eligible for linkage with HES Admitted Patient Care were included in the study, in one of three primary cohorts: subjects with T2DM and HBV infection (T2DM+HBV cohort), subjects with T2DM and without HBV-infection (T2DM cohort), and subjects with HBV-infection and without T2DM (HBV cohort).

The study's main focus was to assess the risk of liver disease progression in NAFLD patients with HBV infection. However, because NAFLD is often underdiagnosed, the main objective of the study was first assessed in patients with T2DM, in whom a high prevalence of NAFLD has been reported [14,15]. Additionally, secondary analyses were performed on subcohorts including subjects with recorded NAFLD diagnosis.

Three subcohorts including subjects with NAFLD were also defined based on the presence of the three conditions: T2DM+NAFLD+HBV, T2DM+NAFLD (without HBV infection) and NAFLD+HBV (without T2DM). Subjects with hepatic disease comorbidities including alcoholism-related disease, history of liver cancer and other chronic liver diseases including history of infectious hepatitis were excluded from the primary analyses. Type I diabetes patients were excluded. The complete list of inclusion and exclusion criteria is presented in Supplementary File S1, Supplemental digital content 1, <http://links.lww.com/EJGH/A453>.

Subjects were allocated to the cohorts and cases identified based on the definitions used in the study for conditions and outcomes (Table 1), using International Classification of Diseases (ICD)-10 codes and Read codes

(Supplementary File S2, Supplemental digital content 2, <http://links.lww.com/EJGH/A454>). Patients diagnosed with diabetes mellitus were further classified according to type based on an algorithm adapted from that proposed by Taylor *et al.* [16]. An additional algorithm was used to classify HBV infection as chronic or nonchronic, based on HBV diagnostic test results (see Supplementary File S3, Supplemental digital content 3, <http://links.lww.com/EJGH/A455>, for a detailed description of the algorithms).

Ethics

The study protocol was approved by the Independent Scientific Advisory Committee for the UK Medicines and Healthcare products Regulatory Agency Database Research (protocol 16_296R). The study was conducted in accordance with all applicable regulatory requirements, with the Guidelines for Good Pharmacoepidemiology Practices and all applicable participants' privacy requirements.

Study objectives

The primary objective was to compare the incidence rate of developing cirrhosis by calculating incidence rate ratios (IRRs) between the T2DM+HBV cohort and the T2DM and HBV cohorts.

Secondary objectives were to evaluate the time-to-event (TTE) from inclusion in the cohort to cirrhosis in the T2DM+HBV cohort compared to the T2DM and HBV cohorts, and to estimate IRRs and TTEs for cirrhosis in the T2DM+NAFLD+HBV versus the T2DM+NAFLD and NAFLD+HBV cohorts. In exploratory objectives, the IRRs and TTEs for HCC were also assessed in the T2DM+HBV cohort versus the T2DM and HBV cohorts.

One of the objectives of the study, to evaluate the risk of HBV infection on developing liver fibrosis in patients with T2DM and/or NAFLD, could not be assessed due to the small number of liver fibrosis cases captured.

Table 1. Definitions used in the study

Condition/outcome	Definition
Diabetes (any type)	At least one diagnostic code related with diabetes, or At least two prescriptions of antidiabetic drugs or diabetes monitoring devices, or At least one abnormal test result: Fasting blood glucose ≥ 7.0 mmol/L Random glucose test ≥ 11.1 mmol/L Glucose tolerance test 'Abnormal' Glycosylated hemoglobin (HbA1C) $\geq 7.0\%$
HBV infection	Any recorded HBV Read code with Diagnosis = 'Confirmatory', or Any ICD-10 code, or HBV test result 'present'
NAFLD	Diagnostic code for NAFLD
Cirrhosis, HCC	Diagnostic code for cirrhosis or HCC, and Not being caused by other factors than NAFLD and HBV-infection, by exclusion of the following etiologies: alcoholic liver disease, autoimmune liver disease, any viral hepatitis other than HBV, liver transplantation, hemochromatosis, liver failure

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HES, Hospital Episode Statistics; ICD, International Classification of Disease; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

Statistical analysis

Sample size and power

An initial exploratory assessment using the CPRD-GOLD January 2017 feasibility count was performed. Based on the incremental counts, a sample size of 395 persons (1598 person-years) was projected for the T2DM+HBV cohort. The number of incident cirrhosis cases predicted was 669 for the combined T2DM+HBV and T2DM cohorts (projected $N=226\,067$) and 50 for the combined T2DM+HBV and HBV cohorts (projected $N=7544$). The smallest IRRs which can be detected in an unadjusted analysis with 80% power at a two-sided α level of 5% were estimated to be 6.43 and 3.57 for the comparison of the T2DM+HBV cohort with cohorts T2DM and HBV, respectively.

Assessed outcomes

The incidence rate of cirrhosis was expressed as the number of cases per 10 000 person-years with exact 95% confidence interval (CI) and was calculated as the total number of incident cirrhosis cases identified during the study period divided by the total person-time contributing to each cohort. The total person-time was computed as the sum of the date of the end of follow-up minus the date of inclusion in cohort + 1 day for each subject in the cohort. Moreover, because only incident events were considered, the follow-up was ended at the earliest occurrence of the event (if this occurred before the end of follow-up), and any subject with an event with missing date or dated before inclusion in the cohort was excluded from the analyses.

The unadjusted IRRs comparing the T2DM+HBV cohort to the T2DM and HBV cohorts (primary analysis) and the T2DM+NAFLD+HBV cohort to the T2DM+NAFLD and NAFLD +HBV cohorts (secondary analysis) were calculated with exact 95% CIs, overall for the entire cohort, by calendar year and by patient characteristics (age group, sex, ethnicity, BMI, alcohol consumption, smoking status, absence/presence of dyslipidaemia and HBV vaccination status).

The adjusted IRRs were estimated based on a Poisson regression model for the number of incident cases, including cohort as the main covariate, logarithm of person-time as an offset and covariates (calendar year and patient characteristics) [17]. However, covariates with more than 50% of missing data were left out of the regression model. The analysis was further stratified by status (new-onset during follow-up versus prevalent at cohort inclusion date), allowing for more comparable subcohorts.

Furthermore, a between-group comparison of the TTE from inclusion in the cohort to the outcome was performed, using a Cox proportional hazards regression model to estimate crude hazard ratios. Subjects with selected liver diseases documented prior to cohort inclusion date or during their entire medical record were excluded (Supplementary File S1, Supplemental digital content 1, <http://links.lww.com/EJGH/A453>). In sensitivity analyses, these exclusion criteria were removed or modified to evaluate their impact on the primary analyses. These analyses, as well as additional sensitivity analyses performed, are summarized in Supplementary File S4, Supplemental digital content 4, <http://links.lww.com/EJGH/A456>.

For 100 patients with cirrhosis, a clinical profile review of the diagnoses, referrals, prescriptions, laboratory tests and vaccinations was performed independently by two reviewers to estimate the positive predictive value of the NAFLD-related cirrhosis classification algorithm and the inter-reviewer agreement. The case definitions were to be refined for a positive predictive value less than 90%.

In order to maintain confidentiality and individual data anonymization, the results of the planned statistical analyses are reported only if at least five cases were observed for a given cohort, subcohort or strata.

Results

Demographics

From the total of 16 918 695 people identified in CPRD, 265 972 patients were included in one of the three primary study cohorts (Fig. 1). The T2DM cohort, including 261 865 subjects, was considerably larger than the other two cohorts (297 and 3630 subjects in the T2DM+HBV and HBV cohort, respectively). The HBV cohort included on average younger patients (mean age 39.2 years) than the T2DM+HBV (54.9 years) and T2DM (63.3 years) cohorts. Patient characteristics for each cohort are presented in Table 2. The mean follow-up time of the study population in CPRD was 8.7 years for the T2DM+HBV cohort, 11.5 for the T2DM cohort and 6.2 years for the HBV cohort.

Cirrhosis

Cirrhosis cases were observed in less than five subjects in the T2DM+HBV cohort, while 379 cases (0.53%) and 31 cases (0.85%) were observed in cohorts T2DM and HBV, respectively. The calculated incidence rates for cirrhosis were 29.06 per 10 000 person-years (95% CI: 5.99–84.91) among subjects in the T2DM+HBV cohort, 2.68 (95% CI: 2.41–2.96) in the T2DM cohort, and 22.35 (95% CI: 15.19–31.72) in the HBV cohort (Table 3).

In each of the three cohorts, incidence rates were higher for males than females, for non-white compared with white ethnicity groups (except in the T2DM cohort), and for age groups at least 50 years compared with younger subjects (Table 4). Yearly incidence rates were relatively stable throughout the study (data not shown).

HBV infection was associated with a 14-fold increased risk for cirrhosis in T2DM patients [adjusted IRR = 14.06 (95% CI: 4.47–44.19)]. No increased risk of cirrhosis was identified in the T2DM+HBV cohort compared with the HBV cohort [adjusted IRR = 0.68 (95% CI: 0.21–2.27)] (Table 3).

Adjusting for calendar year and patient characteristics resulted in an increased IRR compared with the unadjusted estimate for the comparison of the T2DM+HBV and T2DM cohorts, and a slight reduction of the IRR for the comparison of the T2DM+HBV and HBV cohorts.

Based on estimated TTEs, the risk of progression to cirrhosis was higher in the T2DM+HBV cohort than in the T2DM cohort, with an estimated adjusted hazard ratio of 14.29 (95% CI: 4.55–44.92), and similar between the T2DM+HBV and HBV cohorts [adjusted hazard ratio = 0.69 (95% CI: 0.21–2.29)] (Supplementary Table

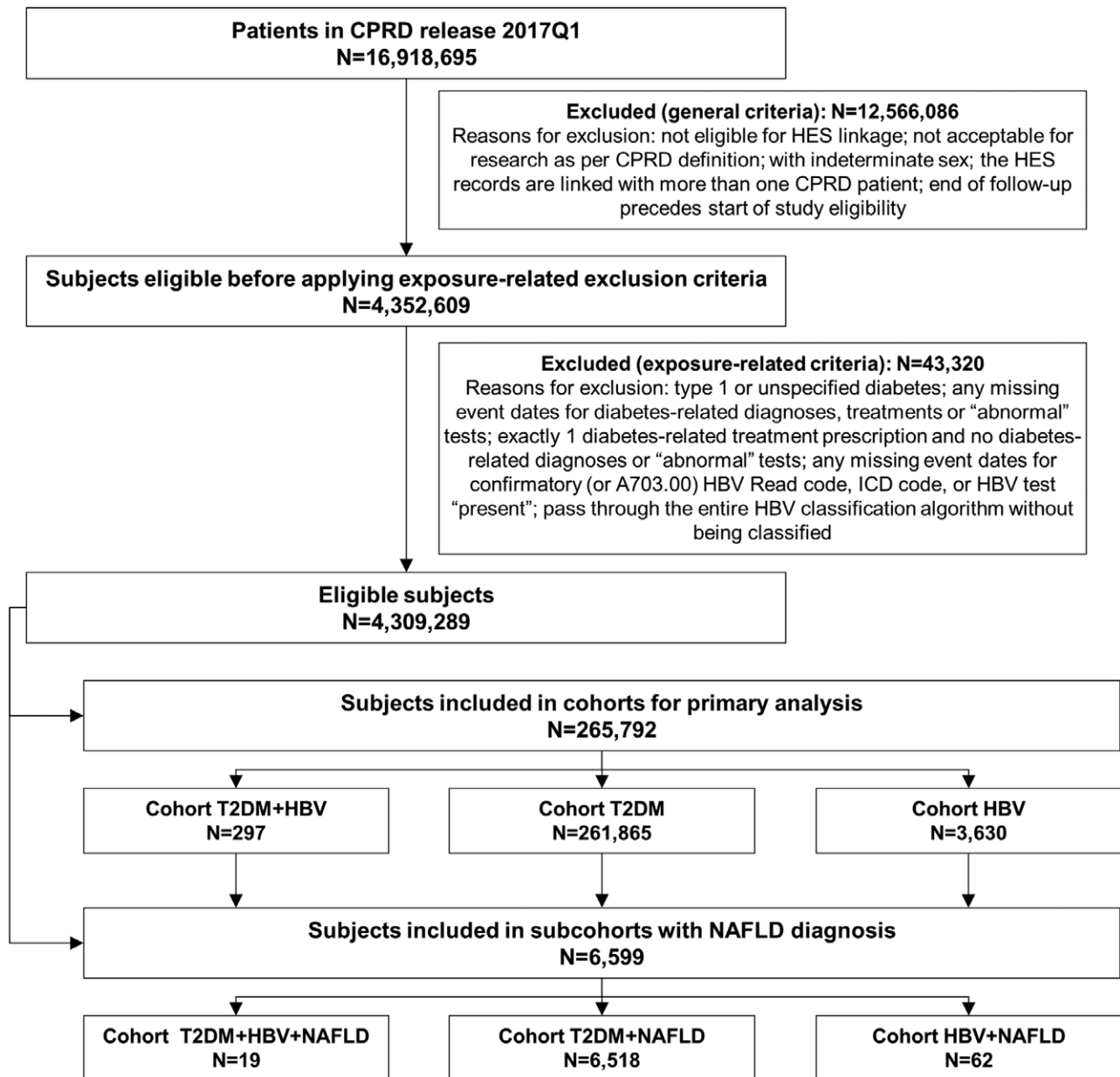


Fig. 1. Patient flow. CPRD, Clinical Practice Research Database; HBV, hepatitis B virus; HES, hospital episode statistics; ICD, International Classification of Disease; N, number of subjects; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

S4_1, Supplemental digital content 4, <http://links.lww.com/EJGH/A456>).

In secondary analyses in subpopulations with NAFLD diagnosis, the size of the cohorts was reduced significantly, with only 19 subjects in the T2DM+NAFLD+HBV cohort, 6518 subjects in the T2DM+NAFLD cohort and 62 in the NAFLD+HBV cohort. No cirrhosis cases were identified in the T2DM+NAFLD+HBV cohort. The unadjusted incidence rates for cirrhosis were 16.92/10 000 person-years (95% CI: 12.97–21.69) and 85.24 (95% CI: 10.32–307.91) in the T2DM+NAFLD and NAFLD+HBV cohorts, respectively.

During the clinical profile review, the positive predictive value of the cirrhosis classification algorithm was 94% against the double independent review of the case profiles (inter-reviewer agreement 99%).

Hepatocellular carcinoma

HCC was observed in less than five patients in the T2DM+HBV cohort, 3159 patients in the T2DM cohort and 15 patients in the HBV cohort. The adjusted IRRs, when comparing the T2DM+HBV cohort to the two other cohorts were 2.83 (95% CI: 1.06–7.55) for the T2DM cohort and 1.39 (95% CI: 0.46–4.20) for the HBV cohort (Table 3).

Based on the estimated TTE, the risk of progression to HCC was significantly higher in the T2DM+HBV cohort than in the T2DM cohort, with an estimated adjusted hazard ratio of 2.85 (95% CI: 1.07–7.61) and similar between the T2DM+HBV and HBV cohorts [adjusted hazard ratio=1.40 (95%CI: 0.46–4.24)] (Supplementary File S4, Table S4_1, Supplemental digital content 4, <http://links.lww.com/EJGH/A456>).

Table 2. Patient characteristics

	T2DM + HBV cohort (N = 297)	T2DM cohort (N = 261 865)	HBV cohort (N = 3630)
Mean age ($\pm$ SD), years	54.9 ($\pm$ 13.9)	63.3 ($\pm$ 14.7)	39.2 ($\pm$ 12.5)
Age group, n (%)			
18–29 years	8 (2.7)	3771 (1.4)	791 (21.8)
30–39 years	35 (11.8)	13 577 (5.2)	1310 (36.1)
40–49 years	70 (23.6)	30 332 (11.6)	835 (23.0)
50–59 years	78 (26.3)	52 082 (19.9)	440 (12.1)
60–69 years	63 (21.2)	66 841 (25.5)	162 (4.5)
70–79 years	25 (8.4)	58 874 (22.5)	65 (1.8)
$\geq$ 80 years	18 (6.0)	36 388 (13.9)	27 (0.7)
Sex, n (%)			
Female	113 (38.0)	123 416 (47.1)	1857 (51.1)
Male	184 (62.0)	138 449 (52.9)	1773 (48.9)
Ethnicity, n (%)			
White	128 (43.1)	208 988 (79.8)	1398 (38.5)
Mixed	<5 (1.3)	1295 (0.5)	93 (2.6)
Asian or Asian British	41 (13.8)	14 064 (5.4)	335 (9.2)
Black	63 (21.2)	6290 (2.4)	742 (20.4)
Other ethnic groups	40 (13.5)	4392 (1.7)	606 (16.7)
Not stated	21 (7.1)	26 836 (10.2)	456 (12.6)
BMI, n (%)			
Underweight	7 (2.3)	3275 (1.3)	193 (5.3)
Normal	40 (13.5)	22 800 (8.7)	667 (18.4)
Overweight	65 (21.9)	51 104 (19.5)	572 (15.8)
Obese	93 (31.3)	74 584 (28.5)	313 (8.6)
Unknown	92 (31.0)	110 102 (42.0)	1885 (51.9)
Alcohol consumption, n (%)			
Drinker	67 (22.6)	66 462 (25.4)	765 (21.1)
Nondrinker	61 (20.5)	25 336 (9.7)	781 (21.5)
Exdrinker	8 (2.7)	4211 (1.6)	59 (1.6)
Unknown	161 (54.2)	16 5856 (63.3)	2025 (55.8)
Tobacco smoking, n (%)			
Smoker	36 (12.1)	32 535 (12.4)	563 (15.5)
Nonsmoker	105 (35.4)	63 226 (24.2)	1 283 (35.4)
Exsmoker	54 (18.2)	47 196 (18.0)	270 (7.4)
Unknown	102 (34.3)	118 908 (45.4)	1 514 (41.7)
Dyslipidaemia, n (%)			
Present	56 (18.9)	45 557 (17.4)	124 (3.4)
Absent	241 (81.1)	216 308 (82.6)	3 506 (96.6)
HBV-vaccination, n (%)			
Vaccinated	29 (9.8)	10 215 (3.9)	355 (9.8)
Unvaccinated	268 (90.2)	251 650 (96.1)	3 275 (90.2)

Due to a confidentiality agreement with the Clinical Practice Research Database, cells with counts <5 are not reported.

HBV, hepatitis B virus; n (%), number (percentage) of subjects in a certain category; N, number of subjects in each group; T2DM, type 2 diabetes mellitus.

Table 3. Unadjusted and adjusted incidence rate ratio of cirrhosis and hepatocellular carcinoma comparing type 2 diabetes mellitus+hepatitis B virus cohort with type 2 diabetes mellitus and hepatitis B virus cohorts

Number of cases/incidence rate (95% CI ^a)			Incidence rate ratio (95% CI)		
T2DM+HBV cohort	T2DM cohort	HBV cohort	Compared cohorts	Unadjusted ^b	Adjusted ^c
Cirrhosis					
<5/ 29.06 (5.99–84.91)	379/ 2.68 (2.41–2.96)	31/ 22.35 (15.19–31.72)	T2DM+HBV vs T2DM	10.86 (2.23–31.98)	14.06 (4.47–44.19)
			T2DM+HBV vs HBV	1.30 (0.25–4.17)	0.68 (0.21–2.27)
Hepatocellular carcinoma					
<5/ 38.31 (10.44–98.09)	3 159/ 22.30 (21.53–23.09)	15/ 10.72 (6.00–17.69)	T2DM+HBV vs T2DM	1.72 (0.47–4.40)	2.83 (1.06–7.55)
			T2DM+HBV vs HBV	3.57 (0.86–11.21)	1.39 (0.46–4.20)

Incidence rates are expressed in cases per 10000 person-years. Due to a confidentiality agreement with the Clinical Practice Research Database, cells with counts less than 5 are not reported.

CI, confidence interval; HBV, hepatitis B virus; T2DM, type 2 diabetes mellitus.

^a95% CIs based on the exact Poisson confidence interval.

^b95% CIs based on the exact binomial Clopper–Pearson CI.

^c95% CIs based on multiple Poisson regression model, adjusted for calendar year, age group, sex, ethnicity, BMI, tobacco smoking status, dyslipidemia and HBV vaccination.

Results of sensitivity analyses (Supplementary File S4, Supplemental digital content 4, <http://links.lww.com/EJGH/A456>)

Relaxing the exclusion criteria related to history of other liver disease resulted in an expected increase in the size of the T2DM+HBV, T2DM and HBV cohorts, as well as in the number of cirrhosis cases captured in the follow up. Compared with the initial number of cases in cohort

T2DM+HBV, sensitivity analyses identified 24 and six cases, when not applying or modifying the medical history of liver disease exclusion criteria, respectively. Not applying the exclusion criteria resulted in a statistically significant adjusted IRR comparing the incidence rate in T2DM+HBV and HBV subcohorts, in contrast with the results of the primary analyses comparison of cohort T2DM+HBV vs cohort HBV. When modifying exclusion criteria, the resulting adjusted IRR remained at similar estimates and

Table 4. Incidence rates for cirrhosis, by patient characteristics, per 10 000 person-years

	T2DM+HBV cohort (N=297)		T2DM cohort (N=261 865)		HBV cohort (N=3630)	
	Cases (n)	Incidence rate (95% CI)	Cases (n)	Incidence rate (95% CI)	Cases (n)	Incidence rate (95% CI)
Age group						
18–29 years	0	0.00 (0.00–1218.48)	<5	1.18 (0.14–4.27)	<5	7.75 (0.94–28.01)
30–39 years	0	0.00 (0.00–273.48)	7	1.01 (0.41–2.09)	<5	6.21 (1.28–18.16)
40–49 years	0	0.00 (0.00–116.81)	21	1.25 (0.77–1.91)	11	30.80 (15.37–55.10)
50–59 years	<5	33.82 (0.86–188.44)	74	2.38 (1.87–2.98)	8	43.67 (18.85–86.04)
60–69 years	<5	89.73 (10.87–324.15)	130	3.23 (2.70–3.83)	5	70.18 (22.79–163.77)
70–79 years	0	0.00 (0.00–375.65)	105	3.25 (2.66–3.94)	<5	72.28 (8.75–261.11)
≥80 years	0	0.00 (0.00–687.35)	40	3.19 (2.28–4.34)	0	0.00 (0.00–429.33)
Sex						
Female	<5	26.21 (0.66–146.03)	171	2.59 (2.22–3.01)	11	15.10 (7.54–27.02)
Male	<5	30.73 (3.72–110.99)	208	2.75 (2.39–3.15)	20	30.38 (18.55–46.91)
Ethnicity						
White	0	0.00 (0.00–60.33)	343	2.92 (2.61–3.24)	14	23.50 (12.85–39.43)
Mixed	0	0.00 (0.00–6274.03)	0	0.00 (0.00–5.04)	0	0.00 (0.00–103.98)
Asian or Asian British	<5	69.59 (1.76–387.75)	17	2.41 (1.40–3.85)	<5	35.12 (9.57–89.92)
Black	<5	69.00 (1.747–384.45)	<5	0.35 (0.01–1.95)	8	34.26 (14.79–67.50)
Other ethnic groups	<5	65.55 (1.66–365.24)	<5	1.97 (0.54–5.05)	<5	17.23 (4.70–44.13)
Not stated	0	0.00 (0.00–332.97)	14	1.22 (0.67–2.05)	<5	5.47 (0.14–30.47)
BMI						
Underweight	0	0.00 (0.00–1087.23)	<5	3.29 (0.90–8.42)	<5	15.63 (0.40–87.06)
Normal	0	0.00 (0.00–285.03)	21	1.81 (1.12–2.77)	6	25.41 (9.32–55.30)
Overweight	<5	45.84 (1.16–255.39)	58	2.03 (1.54–2.63)	<5	9.10 (1.21–36.11)
Obese	0	0.00 (0.00–97.84)	126	3.13 (2.60–3.72)	6	59.58 (21.86–129.68)
Unknown	<5	53.27 (6.45–192.42)	170	2.83 (2.42–3.30)	16	20.36 (11.63–33.06)
Alcohol consumption						
Drinker	0	0.00 (0.00–117.65)	77	2.29 (1.81–2.86)	<5	18.58 (6.03–43.37)
Nondrinker	<5	61.01 (1.54–339.91)	34	3.16 (2.19–4.42)	<5	20.03 (6.50–46.75)
Exdrinker	0	0.00 (0.00–1999.98)	<5	1.20 (0.15–4.33)	<5	125.92 (15.25–454.87)
Unknown	<5	33.39 (4.04–120.62)	266	2.78 (2.46–3.14)	19	22.29 (13.42–34.81)
Tobacco smoking						
Smoker	0	0.00 (0.00–238.05)	51	3.25 (2.42–4.27)	<5	15.95 (3.29–46.60)
Nonsmoker	0	0.0 (0.00–87.08)	61	2.10 (1.60–2.69)	11	26.83 (13.39–48.01)
Exsmoker	0	0.00 (0.00–171.10)	58	2.74 (2.08–3.54)	<5	11.18 (0.28–62.29)
Unknown	<5	77.41 (15.96–226.22)	209	2.76 (2.40–3.16)	16	22.88 (13.08–37.15)
Dyslipidaemia						
Present	0	0.00 (0.00–154.34)	51	2.16 (1.61–2.84)	<5	25.70 (0.65–143.17)
Absent	<5	35.78 (7.38–104.57)	328	2.78 (2.49–3.10)	30	22.26 (15.01–31.77)
HBV vaccination						
Vaccinated	0	0.00 (0.00–256.36)	7	1.44 (0.58–2.96)	<5	5.84 (0.15–32.55)
Unvaccinated	<5	32.76 (6.76–95.75)	372	2.72 (2.45–3.01)	30	24.68 (16.65–35.23)

Due to a confidentiality agreement with the Clinical Practice Research Database, cells with counts less than 5 are not reported. CI, confidence interval; HBV, hepatitis B virus; n, number of cases; N, number of subjects in each group.

statistical significance as the IRRs in the primary analyses (Supplementary File S4, Table S4_3, Supplemental digital content 4, <http://links.lww.com/EJGH/A456>).

Discussion

To our knowledge, this is the first study to assess the risk of developing cirrhosis or HCC associated with HBV infection in patients with NAFLD. When using T2DM as a proxy for NAFLD, we found that in patients with both T2DM and HBV, the risk of cirrhosis was 14-fold increased compared with patients with T2DM only. However, no increase in the risk of cirrhosis was observed for patients with both conditions when compared to those with HBV only, under strict exclusion criteria of medical history of liver disease.

Although a direct comparison to our results was hindered by the case definition used, a previous study assessing the incidence of cirrhosis between 1998 and 2009 in England found that, among 5119 incident cases of cirrhosis, most were due to alcohol consumption [18]. Estimated incidence rates for other etiologies were: 0.34/10 000 person-years for viral hepatitis, 0.30/10 000 person-years for autoimmune/metabolic diseases and

0.77/10 000 person-years for cryptogenic etiology [18]. Emphasis was put on the increasing number of cases of cryptogenic cirrhosis, which were likely attributable to end-stage NAFLD [18,19]. The study also evidenced an increase of around 50% in cirrhosis incidence rates over the considered period [18], while our analysis showed that the incidence of cirrhosis with nonalcoholic etiology was relatively stable from 2000 to 2015. However, both studies showed a higher cirrhosis incidence in males and adults at least 50 years of age. In our analysis, higher cirrhosis incidence ratios were also observed in non-white versus white ethnicity groups, in particular for the T2DM+HBV group, consistent with previous reports showing differences between ethnic groups [20,21]. The underlying cause is likely to be complex, encompassing both genetic and behavioral factors (e.g., nutrition) and requires further elucidation.

In our analysis, NAFLD diagnosis led to increased incidence rates of cirrhosis among T2DM and among HBV patients, although no cases were identified in the T2DM+NAFLD+HBV cohort and comparison with patients presenting all three conditions was not possible. The analysis was also limited by the relatively small sizes of the cohorts including patients with both HBV and

NAFLD. Of note, a recent cohort study including 83 339 Korean adults showed that HBV infection was significantly associated with a lower risk of developing NAFLD, suggesting a possibly protective effect of HBV on the development of NAFLD [11]. This has been previously hypothesized and can be explained by the impact of HBV infection on lipid metabolism; however, further elucidation of the involved mechanism is needed [22,23].

In our study, the incidence of HCC varied by cohort between 10.72/10 000 person-years in patients with HBV only and 38.31/10 000 person-years in those with both T2DM and HBV. In the UK, most liver cancer cases are liver cell carcinomas, of which a high proportion is represented by HCC [24,25]. A marked increase in liver cell cancer cases has been observed over the past decades, with age-standardized incidence rates increasing from 0.56/10 000 people in 2003 to 0.96/10 000 people in 2015 [25], making HCC an even more pressing health concern. HBV chronic infection is already established as a major risk factor for HCC worldwide, and several studies showed that Diabetes Mellitus is associated with elevated risk of HCC incidence and mortality [26,27]. Our analysis also estimated a slightly increased risk for HCC in patients with both T2DM and HBV compared to those with HBV only. With T2DM being used as a proxy for NAFLD, these data are consistent with previously reported associations between NAFLD and increased HCC incidence [28].

The main limitation of the study was the lack of clinical ascertainment, leading to potential misclassification of the cases. Another important limitation was the small case count, as HBV infection is a rare disease in the UK, with an incidence of 1.13/100 000 people reported for 2011 [29]. Moreover, given the potentially long progression time from NAFLD onset or HBV-infection to NAFLD- or HBV-related cirrhosis, the available follow-up period in CPRD might not be long enough to include the onset of the cirrhosis outcome. Furthermore, including both prevalent and new-onset cases in cohort definitions can hinder interpretation of some analysis, in particular those on TTE. Immortal time bias was inherent to the study design, as only HBV-infected individuals who survived to become type 2 diabetic were included in the T2DM+HBV cohort, and individuals dying before acquiring T2DM remained in the HBV cohort. A further limitation was the difficulty in identifying chronic HBV and its phases and NAFLD and its progression stages, as no detailed clinical reports were available in the data for the conditions. Moreover, differential misclassification of NAFLD and HBV between T2DM and nondiabetic subjects was a possibility, resulting from information bias due to closer clinical monitoring of liver function for T2DM subjects, and leading to a higher likelihood for NAFLD and HBV to be identified in T2DM subjects. The use of several healthcare databases might have allowed for the identification of a larger number of cases, both for HBV and NAFLD and the simultaneous use of data from two or more European databases was considered in the early development of the study design. However, a feasibility analysis showed this approach to be hindered by the differences in the definition of cases used from one database to another and limitations in terms of direct access to the data.

One of the main strengths of this study was the large size of the population included in the analyses, which allowed the assessment of incidence ratios by patient

characteristics (like age group, ethnicity, underlying conditions and behavioral factors), bringing important information about differences between subpopulations. Another strength was the quality of the data which contributed to the robustness of the analysis. Moreover, the algorithms used to construct definitions and identify cases can be used in future studies measuring outcomes related to these conditions; the algorithm used for cirrhosis was validated. In addition, sensitivity analyses were performed and their results support the robustness of the main findings.

This retrospective study, using linked routinely collected primary care and hospitalization datasets and validated algorithms to identify cases, provides a blueprint for similar studies in other countries as well as periodic re-evaluations in the future.

Conclusion

HBV infection increased significantly (14-fold) the risk for cirrhosis and hazard of progression to cirrhosis among patients with T2DM, a condition that was used as proxy for NAFLD in our study. Although our data only confirms already-established conclusions on the risk associated with HBV infection, it did not provide evidence of an increased risk of cirrhosis in patients with T2DM and HBV infection compared with those HBV infection only. Our study provides a strong model for evaluation of the same outcomes in other countries, in order to provide a global perspective on the impact of HBV infection in patients with NAFLD. Finally, preventing both HBV and T2DM can help reduce the burden of cirrhosis and HCC.

Figure 2 represents a Focus on Patient Section, which elaborates on the research clinical relevance to be shared to patients by Health Care Professionals.

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Conflicts of interest

G.F. and T.C. were employees of P95 during the conduct of the study; A.S. and T.V. are employees of P95. P95

Focus on the Patient

What is the context?

- Non-alcoholic fatty liver disease (NAFLD) is a common causes of liver damage, with more than 30% of the population in the United States, Australia and parts of Europe being affected. In its most severe form, NAFLD can lead to fibrosis, cirrhosis and hepatocellular carcinoma (HCC). NAFLD is strongly associated with type 2 diabetes mellitus (T2DM), with up to 70% of T2DM patients also having NAFLD.
- Another important cause of liver damage is hepatitis B virus (HBV)-infection, which in its chronic form can lead to cirrhosis and/or HCC and ultimately to death. Currently, an estimated 3.5% of the world population is living with chronic HBV infection.

What is new?

- This study assessed if HBV infection increases the risk of progression of liver disease to cirrhosis HCC in people with fatty liver or T2DM.
- The data was collected retrospectively from a large database of anonymous patient medical records from general practitioners and hospitalization records in the United Kingdom.

What is the result?

- The study estimates a 14-fold increased risk of cirrhosis and 3-fold increased risk of HCC in patients with HBV and T2DM compared to patients with T2DM only. The risk associated with HBV infection is similar to the risk among non-diabetics.

Fig. 2. Focus on patient section.

received fees from GSK for performing this work and other work unrelated to this study. Y.H. participated in GSK advisory boards, consulted for P95 and was an investigator in clinical studies evaluating anti-HBV compounds, conducted by Janssen Pharmaceutica. T.V. received personal fees from GSK during the conduct of the study. Y.F. is an external consultant for GSK. D.R. and A.G. are employees of GSK and hold stock options/unrestricted shares from the sponsoring company.

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