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Mortality and cause of death in persons with chronic hepatitis B virus infection versus healthy persons from the general population in Denmark

Running title: *Chronic hepatitis B and mortality in Denmark*

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Abstract

The study aimed to determine adjusted all-cause mortality and cause of death in persons with chronic hepatitis B virus (HBV) infection compared with age – and sex-matched persons from the general population. We used nationwide registers to identify persons aged ≥ 18 years with chronic HBV infection in 2002-2017 in Denmark and included 10 age- and sex matched controls for each. Follow up was from 6 months after diagnosis until death, emigration, or December 31, 2017. Mortality rate ratios (MRRs) adjusted for age, sex, employment, origin, and comorbidity were calculated using Poisson regression. Unadjusted cause specific mortality rate ratios with 95% confidence intervals were calculated assuming a Poisson distribution. A total of 6,988 persons with chronic HBV infection and 69,847 controls were included. During a median follow up of 7.7 years (range 0.0-15.5), 315 (5%) persons with - and 1,525 (2%) without – chronic HBV infection died. The adjusted all-cause MRR was 1.5 (95% CI 1.2-2.0). Persons with chronic HBV infection had increased mortality due to liver disease including hepatocellular carcinoma (MRR 12.3 [8.6-17.7]), external causes (MRR 3.3 [2.5-4.7]), endocrine disease (MRR 3.2 [1.8-5.4]), genitourinary disease (MRR 3.2 [1.2-7.6]) and neoplasms (except hepatocellular carcinoma; MRR 1.6 [1.2-2.0]). In conclusion, this study showed an increased all-cause mortality in persons with chronic HBV infection in comparison with age- and sex-matched persons without chronic HBV infection which remained after adjustment for several confounding factors. Excess mortality was mainly associated with liver disease, but also external factors, endocrine disease, genitourinary disease, and neoplasms (excluding hepatocellular carcinoma).

Keywords: Hepatitis B, general population, DANHEP, nationwide, Scandinavia.

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Chronic hepatitis B virus (HBV) infection, defined as infection with hepatitis B virus (HBV) > 6 months, caused 900,000 deaths globally in 2015 and mortality is expected to increase [1,2]. In Denmark it has previously been estimated that approximately 11,000 persons live with chronic HBV infection[3]. It is recommended that all persons with chronic HBV infection are monitored by specialists in gastroenterology or infectious disease and treated if indicated. Treatment with nucleo(t)side analogues is free of charge for the individual person. Most with chronic HBV infection in Denmark have immigrated from Asia or the Middle East. Chronic HBV infectionrelated mortality in populations resembling the Danish, with low prevalence, mixed ethnicity, and access to management by specialists including antivirals, is not well documented.

Of the studies on mortality in persons with chronic HBV infection[4–20], some were conducted in Asia in patients with mainly genotype B or C, who were most likely infected at birth, comparable with around a third of the chronic HBV infection population in Denmark. Lifestyle and exposures may differ between participants in these studies and most people living in western Europe [4,13,20]. Other studies had small or selected study populations [5,9–12,14]. None of the population-based studies in populations resembling the Danish [7,17,19,21] included healthy controls. Therefore, it was not possible to determine if excess mortality in persons with chronic HBV infection remained after adjusting for important confounding factors including other risk factors for liver disease.

The objective of this study was to determine mortality rates (MRs) and compare all-cause mortality in persons with chronic HBV infection and the general population in Denmark after adjusting for possible confounders. Moreover, we aimed to describe the causes of death in persons with chronic HBV infection compared with the general population.

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Materials and Methods

We performed a register-based cohort study. All residents in Denmark are provided a unique ten-digit personal identification number (PIN) which is used in all public administrative registers. We used this PIN to link individual level information from several nationwide registers.

Materials

Persons with chronic HBV infection were identified in The Danish Database for Hepatitis B and C (DANHEP), the laboratory database DANVIR and the National Patient Registry (NPR). DANHEP has since 2002 enrolled all adult patients with chronic hepatitis B or C who attended care in a hospital department specialized in gastroenterology or infectious diseases [22]. DANHEP was also used to identify those treated with antivirals as only specialized hospital departments are authorized to dispense HBV therapy in Denmark. DANVIR has collected hepatitis virology and serology from laboratories in Denmark since 2000 [23]. The NPR was established in 1977, and contains date and diagnoses relevant for all in-and out-patient hospital contacts in Danish hospitals [24].

Date of death was retrieved from the Danish Civil Registration System (CRS) where all persons alive and living in Denmark are registered for administrative use [24,25]. Cause of death was retrieved from the Danish register of causes of death (DRCD) [26].

The Danish Cancer Registry (DCR), supplied information on diagnosed malignancies [27]. Finally, the National Prescription Registry, which holds data on prescriptions filled after 1994, was used to identify Diabetes Mellitus diagnoses [28].

Study population

We enrolled all patients 18 years of age or older diagnosed with chronic HBV infection between January 1, 2002 and December 31, 2016. chronic HBV infection was defined as 1) inclusion in DANHEP and at least one

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positive HBsAg measurement, 2) a chronic HBV infection diagnosis in NPR, 3) two positive HBsAg measurements in DANVIR at least 6 months apart or one HBsAg with negative HBcIgM at the same time or positive HBsAg with no HBcIgM measured and a HBV endemic country of origin [3]. The reasoning for different definitions in the different registers is that diagnoses of chronic HBV infection in NPR and DANHEP were evaluated by the treating physician, while DANVIR simply supplies laboratory results. Finally, we included 10 age and sex matched controls without chronic HBV infection, per person with chronic HBV infection. Controls were not necessarily tested for HBV.

Definitions of exposures, confounding factors and outcomes

The specific ICD and ATC codes used to define outcomes and covariates are given in the supplemental material. Hepatocellular Carcinoma (HCC) was considered a liver related disease. Comorbidities were retrieved from the NPR, except for Diabetes Mellitus which was defined as a diagnosis in NPR or a filled prescription for an antidiabetic drug. As chronic hepatitis C (CHC) in the NPR seemed to be misclassified in some cases, when comparing with DANHEP registrations, we only accepted CHC diagnoses that were recorded at least twice in the NPR. Alcohol overuse was defined as any alcohol related diagnosis in the NPR except acute intoxication. To adjust for comorbidity, we calculated Charlson Comorbidity Index (CCI) score, based on diagnoses registered in the NPR and DCR. We used the version from 2011 by Quan et al. [29]. Chronic liver disease and HCC were excluded from the score as they are likely part of the causal pathway from chronic HBV infection to death. As some studies have found a link between Non-Hodgkin's Lymphoma (NHL) and chronic HBV infection, NHL was also excluded from the CCI score [30]. HIV and Diabetes Mellitus were included in the model independent of CCI. If a member of the study population did not have a certain diagnosis in the NPR or the DCR, it was assumed that they did not have the disease in question. We used employment status from CRS as a surrogate for socioeconomic status. Region of origin was determined by the birth country of the mother. Where data was missing, it was included in analyses as "unknown".

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Statistical analysis

The index date was set to 6 months after either the 18th birthday or the first date of inclusion in NPR, DANVIR or DANHEP, whichever came last. Controls were included at the same time as their case. Persons that died within 6 months of their first registration were excluded from analysis. Time at risk was from the index date until death, emigration/unknown status in CRS or December 31, 2017, whichever came first. We calculated crude and adjusted mortality rate ratios (MRRs) as well as liver related MRRs with 95% confidence intervals (95% CI). Moreover, we calculated unadjusted MRRs for chronic HBV infection patients versus controls for individual causes of death and 95% CIs assuming a Poisson distribution. Persons with HIV or CHC coinfection were excluded from the cause specific analysis. Overall survival probability was calculated using Kaplan Meier estimation. For cause specific deaths we calculated cumulative incidence functions and produced p-values using Gray's test.

Adjusted MRRs were calculated using Poisson regression and Quasi-Poisson regression in case of overdispersion. Employment, CCI, sex, region of origin, HIV, Diabetes Mellitus, and alcohol overuse and CHC were introduced into the model as baseline categorical covariates, while age was time dependent. As age and CCI did not show log linearity they were categorized. Age into 10-year groups and CCI into 4 groups, as there was no significant difference between models with 4 and 7 levels of CCI according to a log likelihood ratio test. Possible interactions between chronic HBV infection and CHC as well as chronic HBV infection and region of origin were tested using log likelihood ratio test. To assess if misclassification of chronic HBV infection in NPR had significantly influenced our results [31], we conducted a sensitivity analysis in which we excluded all with chronic HBV infection who were recorded in the NPR but not in DANHEP or DANVIR. To investigate if there was a survival difference in persons diagnosed with chronic HBV infection before development of cirrhosis and the general population, we conducted an adjusted analysis excluding persons with cirrhosis at baseline. All statistical tests for significance were two-sided with alpha=0.05. Statistical

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analysis was performed using STATA 16[32] and R 3.6.3 [33]. Reporting followed the STROBE cohort reporting guidelines [34].

The study was approved by the Danish Data Protection Agency (P-2019-829).

Results

We identified 7,040 persons with chronic HBV infection who met the inclusion criteria. Of these, 52 died within six months of diagnosis and were excluded from analysis; 33% died from HBV, HCC or NHL. Overall, 6,988 with chronic HBV infection and 69,847 controls were included in the study. In the chronic HBV infection group 3,414 (49%) were registered in DANHEP implying link to specialized care. Of these, 555 (16%) initiated treatment at some point during follow-up. Baseline characteristics are listed in table 1. The study population was relatively young (median age at baseline 36 years, range (18-92)). There were more with a region of origin other than Denmark, unemployment, and comorbidities in the chronic HBV infection group. The prevalence of Diabetes Mellitus was 4% in the chronic HBV infection group and 2% in controls. This may in part reflect the composition of the groups with respect to region of origin. Among persons without chronic HBV infection, the Diabetes Mellitus prevalence in those from Denmark and Central/South East Asia was 2% while it was 3% among persons from North Africa/West Asia, 1% in persons from Europe and 4% among persons from Sub-Saharan Africa. In persons with chronic HBV infection the baseline prevalence of Diabetes Mellitus was 5% in persons from Denmark, 3% in persons from Central/South East Asia, 5% in those from North Africa/West Asia, 3% in persons from Europe and 4% in persons from Sub-Saharan Africa. Hepatitis B e antigen (HBeAg) status was registered for 3,187 with chronic HBV infection in DANHEP of whom 80% were HBeAg negative at first measurement. We did not have consistent information on hepatis D virus (HDV) co-infection in persons with chronic HBV infection. Among those registered in DANHEP, 1,102 had an HDV RNA test registered and 42 (4%) of them were positive for HDV RNA. Likewise, we did not have information on disease phase for all with chronic HBV infection. Among 2,194 registered in DANHEP with available HBV DNA concentration, HBeAg status and Alanine Aminotransferase (ALT) level at

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baseline, 810 (37%) had HBV DNA < 2,000 International Units (IU)/ml, ALT within normal range and negative HBeAg (HBeAg negative chronic HBV infection). At baseline 315 (5%) and 156 (0.2%) with and without chronic HBV infection had liver cirrhosis according to the NPR or the pathology registry. Median follow-up time was 7.3 (0.0-15.5) and 7.8 (0.0-15.5) years for persons with chronic HBV infection and controls respectively. Total risk time was 52,548 years for persons with chronic HBV infection and 549,430 for controls. During the study period 315 (5%) with chronic HBV infection and 1,525 (2%) controls died.

Figure 1 shows a Kaplan Meier plot of the survival probability for persons with chronic HBV infection and the general population (P<0.001 log-rank test). Survival probability after 10 years of follow-up was 94.3% (93.6-95.0) and 97.4% (97.2-97.5) in persons with and without chronic HBV infection respectively.

The crude all-cause MR was 6.0/1,000 person years for persons with chronic HBV infection and 2.8/1,000 person years in controls (crude MRR 2.2 (95%CI; 1.9-2.6)). Table 2 shows mutually adjusted MRRs. After adjustment the chronic HBV infection group had a 50% (MRR 1.5 (95%CI; 1.2-2.0)) increased MR. There was no statistically significant effect of CHC, HIV or region of origin. However, higher age, male sex, higher CCI, Diabetes Mellitus, and alcohol overuse all increased the MR. Similar results were found in a sensitivity analysis excluding 1,637 persons with a chronic HBV infection diagnosis in NPR and no chronic HBV infection registration in either DANHEP or DANVIR. In this analysis the adjusted MRR for persons with chronic HBV infection compared with the general population was 1.9 (95% CI 1.5-2.5). Likewise, our analysis excluding individuals with cirrhosis at baseline similar results for all-cause mortality (MRR 1.4 (95% CI; 1.1-1.7)). Finally, we performed the same analysis separately for persons with and without Danish origin. In the group without Danish origin we compared 4,597 with chronic HBV infection with 8,768 controls. In this analysis we found an adjusted MRR of 2.3 (95% CI 1.4-3.7) between persons with chronic HBV infection and controls. In the analysis of persons with Danish origin, we excluded all with alcohol related diagnoses, persons only registered in the NPR and persons with HIV or CHC coinfection. The analysis included 1,237 with chronic HBV infection and 10,721 controls and produced an adjusted MRR of 1.7 (1.2-2.5).

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Figure 2 shows crude cause specific MRRs comparing 6,410 persons with chronic HBV infection with the age and sex matched control population (n=69,740) after excluding persons from either population with CHC or HIV co-infection. During 52,548 and 549,430 person-years in persons with chronic HBV infection and controls, 15 (0.2%) with chronic HBV infection and 6 (0.009%) controls died from HCC, whereas 72 (1.1%) with chronic HBV infection and 516 (0.7%) of the controls died from other neoplasms (MRR 1.6 (95%CI; 1.2-2.0). After removing pancreatic cancer and NHL the MRR was 1.4 (95%CI;1.1-1.9). In the chronic HBV infection group, 39 (0.6%) died from external causes such as accidents, poisonings, and intentional self-harm. Amongst controls 135 (0.2%) persons died from external causes corresponding to an MRR of 3.3 (95% CI; 2.5-4.7). Moreover, 18 (0.3%) with chronic HBV infection and 65 (0.01%) controls died from endocrine disease mainly Diabetes Mellitus (94%). This corresponded to a three times higher MR from endocrine disease in persons with chronic HBV infection (MRR 3.2 (95% CI; 1.8-5.4)). Death from genitourinary disease, mainly chronic renal insufficiency (69%), was also more common in persons with chronic HBV infection (MRR 3.2 (95% CI; 1.2-7.6)). In contrast we found no differences in MRs from psychiatric, circulatory, or respiratory causes. Mortality from diseases of the digestive system was also comparable in the two groups once liver disease was excluded. Finally, chronic HBV infection patients had a higher rate of death due to liver-related causes such as cirrhosis, HCC, acute exacerbation of liver disease with a crude MRR of 12.3 (95%CI; 8.6-17.7). In the total study population, the liver related MRR was 6.9 (95%CI; 4.1-11.7) after adjustment for age, sex, employment status, area of origin, CCI, Diabetes Mellitus, alcohol overuse, and co-infection with CHC and HIV. The liver related MRR was 1.5 (1.3 -1.7) when persons with cirrhosis at baseline were removed from analysis. Cumulative incidence functions showed increased risk of death from liver-, genitourinary- and endocrine disease as well as external causes and neoplasms in persons with chronic HBV infection.

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Discussion

In this nationwide register-based cohort study of mortality and cause of death in people with chronic HBV infection compared with the general population we found a 50% increased all-cause MR in those with chronic HBV infection after adjustment. Excess death was mainly related to liver disease, (21% of observed death in chronic HBV infection patients versus 4% in the control group). However, rates of death from external factors, endocrine disease, genitourinary disease, and neoplasms (excluding HCC) were also increased in persons with chronic HBV infection.

The association between chronic HBV infection and increased all-cause mortality was in line with previous studies conducted in low - [5,7,16,17,19,21] and high endemic areas [13,14,20,35] finding MRRs or age and sex standardized mortality ratios (SMRs) of 1.2-2.3 in persons with chronic HBV infection compared with the general population or a control group.

Previous studies also found increased liver-related mortality in persons with chronic HBV infection with SMRs ranging from 10-22, [5,7,13,16,17,19–21,35]. We were able to control for several confounding factors in our study, which might explain why we found a lower liver related MRR compared with studies that did not adjust for comorbidity. After adjustment we still found that the rate of liver related death in persons with chronic HBV infection was almost 7 times higher than the rate in the general population, suggesting that chronic HBV infection is an independent driver of liver related death in Denmark. Both all-cause mortality and liver-related mortality was increased in persons with chronic HBV infection an no cirrhosis at time of their chronic HBV infection diagnosis. This may reflect that just over half (51%) were not registered in one of the departments responsible for chronic HBV infection care in Denmark. Consequently, they were likely not monitored regularly and did not have access to antiviral treatment, which is exclusively dispensed by hospitals. Moreover, cirrhosis may have been underdiagnosed in the subset of the population that was not assessed by a specialist. The suboptimal link to care is likely also the reason for the low treatment uptake

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seen in the chronic HBV infection population. Globally, it is estimated that 19% with chronic HBV infection require treatment, however only 8% received antiviral treatment during follow up [36].

As expected, higher age, male sex, alcohol overuse, and comorbidity were associated with increased rate of all-cause mortality. It would also have been interesting to see the effect of antiviral treatment, however, we feared that the indication for such treatment might skew the result as it is mainly recommended for persons with signs of liver disease progression. Likewise, we would have liked to stratify by disease phase and HDV coinfection. However, we did not have this information for most individuals with chronic HBV infection. We controlled for alcohol overuse based on NPR diagnoses. As many with harmful alcohol use are not admitted to hospital, alcohol overuse was most likely underestimated which could lead to bias in either direction. We would expect HIV, CHC, and chronic HBV infection/CHC coinfection to be associated with increased mortality, however we did not find any association. For CHC and CHC/chronic HBV infection a possible explanation for this is that the only source of information on CHC was the NPR, where this diagnosis has previously been underreported [31]. According to a recent estimate the prevalence of CHC is 0.2% in Denmark [37]. Consequently, we would expect to find 140 persons with CHC in the control group, however we only found 48. This could lead to an underestimation of the effect of CHC. In contrast, HIV is well documented in the NPR. However, the number of people with HIV included in this study (2.7% of cases and 0.08% of controls), may have been too low to see any effect. Moreover, frequent contact with the healthcare system, and the fact that tenofovir disoproxil is often included in the HIV treatment regime may have lowered mortality in persons co-infected with HIV.

We found either negative or no association between being from another region than Denmark and mortality. Persons with chronic HBV infection and Denmark as country of origin were older and more comorbid compared with persons with other regions of origin. This may in part be a result of routes of infection. In DANHEP, the most common route of infection in persons with chronic HBV infection from areas other than Denmark is vertical transmission (29%). In contrast it is intravenous drug use (25%) and

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sexual transmission (17%) in persons with chronic HBV infection originating from Denmark. Although we strived to control for comorbidities, it is likely that there is some residual confounding due to lifestyle and disease not treated in hospitals. We suspected that the higher rate of vertical transmission and thus longer disease duration among persons with other countries of origin might affect the impact of chronic HBV infection on death. When we restricted our study to persons with countries of origin other than Denmark the MRR for chronic HBV infection was 2.3. However, this trend was not confirmed by a significant interaction between chronic HBV infection related mortality and region of origin, in our main model.

When looking at cause specific mortality we found excess death from external factors in chronic HBV infection patients. This may reflect that a subset of this group has comorbidities such as large alcohol or drug consumption increasing mortality due to external factors. In the NPR 7% in the chronic HBV infection group had a disorder due to psychoactive drug use compared with only 0.6% in the general population.

We also found an increased rate of death from neoplasms in persons with chronic HBV infection. Much of this (17%) was due to HCC. However, persons with chronic HBV infection also had a higher rate of death from pancreatic cancer. Previous studies of cancer and pancreatic cancer in chronic HBV infection have produced mixed results [38–41]. Andersen et al. studied cancer incidence in Denmark in persons with and without chronic HBV infection, and found no increased incidence of all-type cancer or pancreatic cancer [39]. Contrary to Andersen et al., we did not account for ethnicity and alcohol use. Not all oncology units have guidelines in line with screening recommendations prior to immunosuppressive therapy [42]. However, it is possible that persons diagnosed with cancer are more likely to be screened for HBV as a precaution prior to chemotherapy. Consequently, it is possible that the some of the effect of chronic HBV infection on death from neoplasms can be explained by surveillance bias.

The rate of death from endocrine disease was three times higher in persons with chronic HBV infection. Although previous studies have found this association [21], it may in part be explained by confounding factors

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such as country of origin, however even after stratifying on region of origin, diabetes was more prevalent in persons with chronic HBV infection.

Likewise, increased death from genitourinary disease was reported by Duberg and Amin et al. [7,21]. However, we found that only 29% of those who died from kidney disease were diagnosed more than 6 months after their chronic HBV infection diagnosis, suggesting that surveillance bias may play a role for this finding. Moreover, chronic kidney disease could be related to the higher prevalence of Diabetes Mellitus seen in the chronic HBV infection group.

A strength of this study is that persons with chronic HBV infection were identified from two hospital-based nationwide registries, including outpatients and a laboratory-based registry [22,24,37], which helped minimize selection bias due to more severe disease in hospitalized patients. Contrary to previous studies in similar settings [7,21], we were able to compare with an age - and sex-matched control group randomly sampled from the general population which enabled us to control for some important confounding factors.

Our study also had several limitations. Although identifying chronic HBV infection cases through laboratory tests may have limited selection bias, we do not know to which extend the control population had contact with the primary health care system. This could cause us to overestimate to effect of chronic HBV infection on death. As mentioned, another limitation to our study was the discrepancy between countries of origin in the chronic HBV infection and control group. The validity of chronic HBV infection registrations in NPR is also a possible limitation, as they have previously been shown to have low positive predictive value (PPV) for chronic HBV infection (63.8, 49.5-76.0) [24]. However, in our sensitivity analysis excluding all only registered in the NPR yielded results similar to those of our main analysis.

Additionally, this study is limited by cause-specific mortality being derived from the DRCD. As autopsy rates have declined (10% in 2011) and as it was previously shown that 30% of causes of death on death certificates had to be altered post autopsy, there is risk of misclassification [43]. Persons with chronic HBV

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infectioncould be more likely to have a liver-related diagnosis as the primary cause of death, causing unbalanced misclassification and an up to 30% overestimation of liver-related mortality in persons with chronic HBV infection.

Finally, to consider the competing risk of dying from other causes we produced cumulative incidence curves of mortality related to liver-, endocrine- and genitourinary disease, neoplasms and external causes that confirmed increased risk of death due to these causes in persons with chronic HBV infection.

In conclusion, this nationwide register-based study provides evidence of excess liver related and overall mortality in chronic HBV infection patients compared with age – and sex-matched persons from the general population in an HBV low endemic country where all residents have access to management by specialists and treatment free of charge for the individual. After adjustment, a 50% increased all-cause mortality rate was maintained in persons with chronic HBV infection. Our findings highlight the importance of eliminating chronic HBV infection also in low endemic settings.

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Abbreviations

HBV:	Hepatitis B virus
WHO:	World Health Organization
MR:	Mortality Rate
PIN:	Personal Identification Number
DANHEP:	The Danish Database for Hepatitis B and C
NPR:	National Patient Registry
CRS:	Civil Registration System
DRCD:	Danish Registry of Causes of Death
DCR:	Danish Cancer Registry
HBeAg	Hepatitis B e Antigen
HCC:	Hepatocellular carcinoma
CHC:	Chronic Hepatitis C
CCI:	Charlson Comorbidity Index
NHL:	Non-Hodgkin's Lymphoma
CI:	Confidence interval
MRR:	Mortality Rate Ratio
HDV:	Hepatitis D Virus
ALT:	Alanine Aminotransferase
SMR:	Standardized Mortality Rate Ratio
PPV:	Positive Predictive Value

Data availability
Data from Danish public registers used for this study are not publicly available.

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Figures

Figure 1: Kaplan Meier plot of overall survival probability in persons with chronic hepatitis B and sex and age matched persons from the general population 2002-2017.

P-value <0.001 produced by log rank testing; significance level 0.05. HBV: Hepatitis B Virus

Figure 2: Unadjusted cause specific mortality rate ratios in people with chronic hepatitis B virus infection and age and sex matched persons from the general population in Denmark 2002-2017.

95% confidence intervals were calculated assuming a Poisson distribution. Persons with HIV or chronic hepatitis C coinfection were excluded from this analysis.

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Table 1: Baseline characteristics of the study population

	Chronic hepatitis B virus infection	Control
N	6,988	69,847
Age	35.6 (28-47)	35.6 (28-47)
Male sex	3,705 (53)	37,017 (53)
Region of origin:		
Denmark	2,391 (34)	61,079 (87)
Europe	823 (12)	3,892 (6)
Northern Africa and Western Asia	1,001 (14)	1,817 (3)
Sub-Saharan Africa	989 (14)	682 (1)
Central and south-east Asia	1,664 (24)	1,977 (3)
Other/unknown	120 (2)	400 (1)
Employment:		
Employed	2,546(36)	46,571 (67)
Unemployed	1,582 (23)	4,437 (6)
Disability	814 (12)	3148 (5)
Student/retired/unknown	2,046 (29)	15,691 (22)
Diabetes Mellitus	290 (4)	1,504 (2)
HIV	186 (3)	59 (0)
Chronic Hepatitis C	401 (6)	48 (0)
Alcohol	532 (8)	1,192 (2)
Psychoactive drug use	481 (7)	434 (0.6)

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Charlson Comorbidity Index score	0 (0-0)	0 (0-0)
Cirrhosis	315 (5)	156 (0)
Death from any cause	315 (5)	1,525 (2)
Death from liver cause	75 (1)	63 (0)
Risk time (years)	52,548	549,430

Continuous variables are presented with medians (interquartile range). Categorical variables are presented with frequency (%).

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Table 2: Crude and mutually adjusted all-cause mortality rate ratios in patients with chronic hepatitis B virus infection and sex - and age-matched persons from the general population in Denmark 2002-2017.
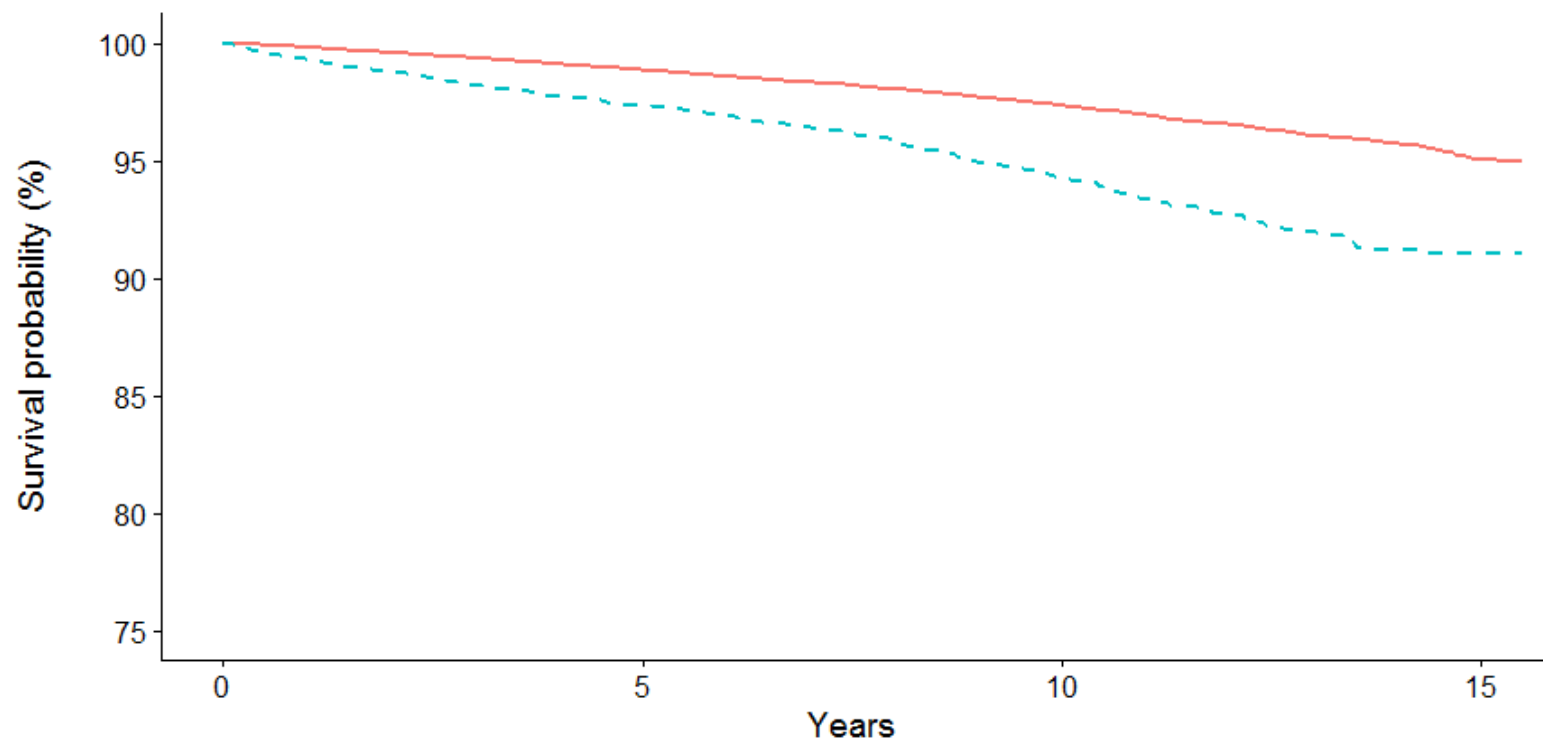
	Unadjusted mortality rate ratio (95% CI)	Mutually adjusted mortality rate ratio (95% CI)
Chronic hepatitis B	2.2 (1.9-2.6)	1.5 (1.2-2.0)
Chronic hepatitis C	3.0 (1.0-9.4)	1.3 (0.2-10.6)
Chronic hepatitis B and C	1.9 (1.2-3.2)	0.5 (0.2-1.3)
Age <40	Ref	Ref
Age 40-49	2.8 (2.3-3.4)	3.2(2.2-4.7)
Age 50-59	7.0 (5.8-8.4)	6.8 (4.7-9.7)
Age >=60	25.4 (21.5-30.1)	15.5 (11.2-21.4)
Male sex	2.0 (1.8-2.2)	1.7 (1.4-2.0)
Employed	Ref	Ref
Unemployed	2.9 (2.5-3.5)	3.6 (2.6-5.0)
Disability	10.0 (8.9-11.3)	3.9 (3.0-5.1)
Other	4.0 (3.6-4.5)	3.4 (2.7-4.2)
CCI 0	Ref	Ref
CCI 1-2	4.1 (3.7-4.6)	1.9 (1.5-2.4)
CCI 3-4	17.1 (13.7-21.4)	2.9 (1.9-4.4)
CCI >4	14.4 (11.1-18.7)	4.0 (2.5-6.5)
Region: Denmark	Ref	Ref
Region: Central/ South East Asia	0.5 (0.4-0.7)	0.5 (0.3-0.9)
Region: Europe	0.8 (0.7-1.0)	0.8 (0.5-1.2)

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Region: North Africa/West Asia	0.7 (0.5-0.9)	0.5 (0.3-0.8)
Region: Sub-Saharan Africa	0.6 (0.4-1.0)	0.5 (0.2-1.1)
Region: Other	0.1 (0.8-0.8)	0.2 (0.01-2.0)
Diabetes Mellitus	6.2 (5.4-7.1)	1.6 (1.2-2.1)
HIV	2.8 (1.8-4.6)	0.9 (0.3-2.1)
Alcohol	6.8 (6.0-7.8)	1.9 (1.4-2.5)

CI: Confidence interval. Unadjusted 95% CI assuming Poisson distribution. Mutually adjusted mortality rate ratios from Quasi-Poisson regression model.
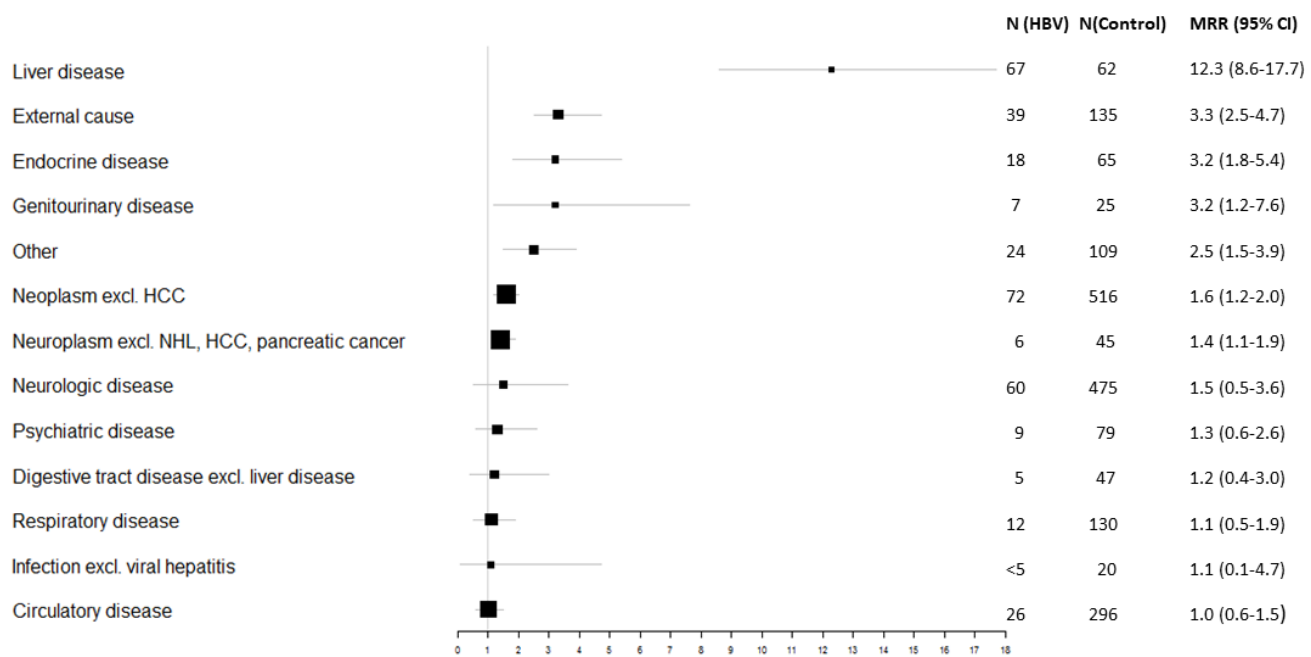
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		N (HBV)	N(Control)	MRR (95% CI)
Liver disease		67	62	12.3 (8.6-17.7)
External cause		39	135	3.3 (2.5-4.7)
Endocrine disease		18	65	3.2 (1.8-5.4)
Genitourinary disease		7	25	3.2 (1.2-7.6)
Other		24	109	2.5 (1.5-3.9)
Neoplasm excl. HCC		72	516	1.6 (1.2-2.0)
Neuroplasm excl. NHL, HCC, pancreatic cancer		6	45	1.4 (1.1-1.9)
Neurologic disease		60	475	1.5 (0.5-3.6)
Psychiatric disease		9	79	1.3 (0.6-2.6)
Digestive tract disease excl. liver disease		5	47	1.2 (0.4-3.0)
Respiratory disease		12	130	1.1 (0.5-1.9)
Infection excl. viral hepatitis		<5	20	1.1 (0.1-4.7)
Circulatory disease		26	296	1.0 (0.6-1.5)

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