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ORIGINAL ARTICLE

Prospective Study

Prevalence of cardiometabolic co-morbidities in patients with *vs* persons without chronic hepatitis B: The FitLiver cohort study

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Abstract

BACKGROUND

Chronic hepatitis B (CHB) affects > 300 million people worldwide. The combination of CHB and cardiometabolic co-morbidities increases the risk of liver-related morbidity and mortality. However, international guidelines for CHB treatment do not provide recommendations for follow-up examinations or treatment of patients with CHB and cardiometabolic comorbidities. In studies investigating cardiometabolic co-morbidity in patients with CHB, inconsistent findings have been observed, and both lower and higher prevalence of cardiometabolic co-morbidities compared to the general population have been reported. It is unclear whether patients with CHB living in Denmark have an increased prevalence of cardiometabolic co-morbidities.

AIM

To investigate the prevalence of cardiometabolic comorbidities in patients with CHB and matched non-CHB comparison group.

METHODS

We examined patients with CHB and age-, sex-, body mass index (BMI)-, and country-of-birth matched comparison group. Defining cardiometabolic co-morbidity: Obesity (BMI > 25 kg/m^2/abnormal waist-to-hip ratio), metabolic dysfunction-associated steatotic liver disease (MASLD), hypercholesterolemia (total-cholesterol > 5 mmol/L/statin use), hypertension (systolic ≥ 135 mmHg/diastolic ≥ 85 mmHg/antihypertensive medication) and type 2 diabetes (T2D) (2-hour oral glucose tolerance test glucose > 11.1 mmol/L/HbA1c > 48 mmol/mol/

antidiabetic medication). Physical activity was evaluated using maximal oxygen consumption (VO_2max), activity monitors, and a questionnaire.

RESULTS

We included 98 patients with CHB and 49 persons in the comparison group. The two groups were well-matched, showing no significant differences in age, sex, BMI, country-of-birth, education, or employment. Among patients with CHB, the following prevalence of cardiometabolic co-morbidity was found: 77% were obese, 45% had MASLD, 38% had hypercholesterolemia, 26% had hypertension, and 7% had T2D, which did not differ significantly from the comparison group, apart from lower prevalence of hemoglobin A1c (HbA1c) ≥ 48 mmol/L or known T2D. Both groups had low VO_2max of 27 mL/kg/minute in the patients with CHB and 30 mL/kg/minute in the comparison group, and the patients with CHB had a shorter self-assessed sitting time.

CONCLUSION

The patients with CHB and the comparison group were well-matched and had a similar prevalence of cardiometabolic comorbidities. Furthermore, both groups had low levels of physical fitness.

Key Words: Viral hepatitis B; Diabetes; Metabolic dysfunction-associated steatotic liver disease; Hypertension; Hypercholesterolemia; Obesity; Physical activity

Core Tip: This study assessed the prevalence of cardiometabolic comorbidities in patients with chronic hepatitis B (CHB) compared with a matched non-CHB group in Denmark. Both groups demonstrated similar prevalence of obesity, metabolic dysfunction-associated steatotic liver disease, hypercholesterolemia, hypertension, and type 2 diabetes (T2D). Notably, patients with CHB had a lower prevalence of hemoglobin A1c ≥ 48 mmol/mol or known T2D. Additionally, both groups exhibited low levels of physical fitness. This highlights the need for tailored management strategies to address cardiometabolic health issues in patients with CHB despite the comparable prevalence of comorbidities in the general population.

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INTRODUCTION

Chronic hepatitis B (CHB) is caused by persistent infection of the liver > 6 months with hepatitis B virus (HBV). The global prevalence of CHB is estimated to be > 300 million individuals[1], and it is the most common type of hepatitis worldwide. Untreated CHB can cause liver cirrhosis and hepatocellular carcinoma (HCC)[2]. Currently, there is no curative therapy; however, medical treatment can reduce the amount of virus in the blood, reducing CHB-induced morbidity and mortality by decreasing liver inflammation and fibrosis[3,4].

In Asian populations, it has been shown that patients with CHB have higher body mass index (BMI), consume more alcohol, and have poorer physical fitness compared to people without CHB[5]. In addition, approximately 33% are overweight and 50% physically inactive[6]. In general, obesity is associated with metabolic syndrome (*i.e.*, abdominal obesity, dyslipidaemia, hypertension, and glucose abnormality) and metabolic diseases such as type 2 diabetes (T2D), hypertension, hyperlipidaemia[7] and metabolic dysfunction-associated steatotic liver disease (MASLD)[8]. In studies investigating cardiometabolic co-morbidity in patients with CHB, inconsistent findings have been observed, and both lower and higher prevalence of cardiometabolic co-morbidities have been reported compared to the general population[9,10]. T2D and obesity are risk factors for HCC in patients with CHB[11,12]. However, none of the acknowledged HCC risk scoring systems incorporate cardiometabolic comorbidities as risk factors[3], and there is a lack of specific clinical guidance for managing patients with CHB with cardiometabolic comorbidities. The Danish and European guidelines for CHB management recommend screening patients for metabolic liver disease, with no recommendations for follow-up examinations or treatment of patients with CHB and cardiometabolic comorbidities, apart from those with impaired renal function[13]. A study investigating mortality among patients with CHB in Denmark found a prevalence of 4% for T2D compared to 2% in sex- and age-matched persons from the general population[14]. However, little information is available on patients with CHB living in Denmark regarding cardiometabolic co-morbidities.

This study aimed to assess the prevalence of cardiometabolic co-morbidities (obesity, MASLD, hypercholesterolemia, hypertension, and T2D) among patients with CHB compared with a comparison group without CHB. Furthermore, we investigated whether there were any differences in physical fitness or activity.

MATERIALS AND METHODS

To investigate the effects of lifestyle-related behaviours and cardiometabolic co-morbidities in a population of patients with CHB living in the capital area of Copenhagen, Denmark, we initiated a prospective observational cohort study that included patients with CHB and an age-, sex-, BMI-, and country-of-birth matched comparison group without CHB. The cohort, called the "FitLiver Cohort", will include future follow-up visits planned two, five and ten years after inclusion.

This study assessed the baseline prevalence of cardiometabolic co-morbidities in a cohort of patients with CHB and a comparison group of persons without CHB. Furthermore, we compared baseline physical fitness and physical activity between the groups.

Study participants, eligibility, and recruitment

The inclusion criteria of the patients with CHB were CHB, defined as hepatitis B surface antigen (HBsAg) positivity > 6 months and age > 18 years. The exclusion criteria were hepatitis C virus (HCV) or human immunodeficiency virus (HIV) co-infection. The inclusion criteria for the matched comparison group was age > 18 years. Exclusion criteria were positive HBsAg, HCV, or HIV infection and uneven matching regarding age, sex, BMI, and country-of-birth to the patients with CHB. For both groups, pregnancy and the inability to understand and read Danish or English information to provide written informed consent were exclusion criteria.

Patients with CHB were recruited during regular outpatient visits to the Department of Infectious Diseases at the Copenhagen University Hospital, Hvidovre, Denmark. Eighteen patients with CHB were also included in a randomised clinical trial[15], and their results will be published elsewhere (paper submitted).

The participants in the comparison group were recruited through social media advertisements, posters in the hospital departments, and a medical trial recruitment company: "forskning.nu." We primarily included and examined patients with CHB and following sought participants for the comparison group. The matching criteria included age, sex, BMI, and country-of-birth.

The examinations were performed during two different visits to the Centre for Physical Activity Research, Copenhagen University Hospital, Rigshospitalet, Denmark, and the Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre, Denmark.

Outcomes

General examination: All participants were examined by a medical doctor who collected information about their medical history (including the level of education, relationship status, and moderate alcohol use), current medical treatment and diagnoses, electrocardiogram, and physical examination. Moderate alcohol use was defined as less than 10 units/week as defined by the Danish health authorities.

Body anthropometrics: The body composition, weight, height, waist circumference, and hip circumference were measured. Dual-energy X-ray absorptiometry was performed (Lunar Prodigy GE Healthcare, Madison, Wisconsin, encore software version 14, 10, 022) to determine total body fat mass and lean body mass. The participants were instructed to urinate immediately before the scans were performed.

Liver parameters: The general liver health was assessed through blood sampling of alanine aminotransferase (ALT), HBsAg status, hepatitis B viral load (HBV DNA), hepatitis D (HDV) status, hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs), hepatitis B e antigen (HBeAg), and Fibrosis Index-4 (FIB-4) through routine blood samples analysed by the Department of Biochemistry and the Department of Clinical Microbiology at Copenhagen University Hospital, Rigshospitalet, Denmark. We used anti-HBs levels ≥ 10 IU/L to indicate vaccine protection or immunity of HBV infection[15]. Transient elastography (TE) was performed using vibration-controlled TE (Fibroscan 502 Touch, DELRUS, Europe) to assess the fibrosis (TE-score) and controlled attenuation parameter (CAP) to assess hepatic steatosis. CAP cut-off values for hepatic steatosis were set at ≥ 248[16]. Participants were instructed to fast for three hours prior to the scan.

Cardiovascular parameters: Blood pressure measurements (Microlife BP B2 basic, Switzerland) were obtained after at least 15 minutes of rest. Fasting blood lipid profiles (total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides) were analysed using standard procedures at the Department of Clinical Biochemistry, Copenhagen University Hospital, Rigshospitalet, Denmark.

Glucose metabolism: The oral glucose tolerance test (OGTT) was performed to assess glucose metabolism. Participants arrived after an overnight fast. An intravenous catheter was placed in the anterior cubital region, and baseline blood samples, including hemoglobin A1c (HbA1c), were obtained. The participants then drank a glucose solution consisting of 75 g of glucose (water-free) dissolved in 300 mL of water in less than 2 minutes and rested for two hours in a semi-supine position. Following the intake of glucose solution, blood samples were drawn after 15, 30, 60, 90, and 120 minutes. Blood samples were analysed for glucose and insulin levels using standard procedures at the Department of Clinical Biochemistry, Copenhagen University Hospital, Rigshospitalet. Denmark. The area under the curve (AUC) for the glucose and insulin levels was calculated by computing a trapezoidal approximation of the integral under the curve. The Matsuda index, an index of whole-body insulin sensitivity, was calculated as 10000/square root of (fasting glucose × fasting insulin) × (mean glucose × mean insulin during OGTT). The conversion factor of insulin from pmol/L to μIU/L was set to 6.0[17]. The homeostasis model assessment for insulin resistance (HOMA-IR), was calculated from fasting plasma insulin and fasting plasma glucose levels using the HOMA2 calculator[18], which primarily is an index of hepatic insulin resistance.

Collectively assessed cardiometabolic co-morbidities: To classify the cardiometabolic co-morbidities, we used pooled definitions based on examinations, medical treatment, and known diagnoses to define collectively assessed cardiometabolic co-morbidities. Obesity was defined as BMI > 25 kg/m^2 and/or abnormal waist-to-hip ratio (WHR) (> 0.90 for men and > 0.85 for women)[19]; MASLD as CAP > 248 dB/m and at least one of the following: BMI > 25 kg/m^2 or increased waist circumference (> 94 cm for men *vs* > 80 cm for women) or fasting glucose ≥ 5.6 mmol/L or HbA1c ≥ 39 mmol/L or known T2D diagnosis or medical treatment for T2D or blood pressure ≥ 130/85 mmHg or treatment with antihypertensive drugs or plasma HDL cholesterol ≤ 1.0 mmol/L for men and ≤ 1.3 for woman or plasma triglycerides ≥ 1.7 mmol/L or lipid-lowering treatment)[20]; Hypercholesterolemia (total cholesterol > 5 mmol/L)[21] and/or use of statins; Hypertension as systolic blood pressure of ≥ 135 mmHg and/or a diastolic blood pressure ≥ 85 mmHg[22] and/or use of antihypertensive medication[23]; T2D was defined as blood glucose > 11.1 mmol/L after a 2-hour OGTT, and/ or HbA1c > 48[24] and/or use of antidiabetic medicine intended to treat T2D.

Physical activity and fitness: We used graded cardiopulmonary exercise testing as described elsewhere[15,25] to determine the level of fitness indicated by maximal oxygen consumption (VO_2max), using a prediction model for choosing the watts and watt increase for each individual[26]. A Borg Rating of perceived exertion scale of 6–20 was used to obtain the self-assessed level of exhaustion[27]. Physical activity was measured for seven consecutive days at baseline and after the intervention using an axial accelerometer-based activity monitor (AX3; Axivity, Newcastle upon Tyne, United Kingdom). Moderate-to-vigorous physical activity (MVPA) was defined after the Freedson cut point, ≥ 1952 counts per minute[28], by use of the vertical axis of the accelerometer placed on the back, and days were removed if non-wear time was > 2700 minutes. The R packages devtools, and jbrond/physaccel were used to determine the intensity and physical activity types[29]. We had to remove day one because of the late start of activity registration (after 5:00 am), resulting in a mean of 5.6 days of AX3 wear for all participants, ranging from 1 to 7 days. We used the International Physical Activity Questionnaire-Short Form to assess self-assessed physical activity in Danish or English (Supplementary material).

Ethics

This study was approved by the Regional Committee of the Danish National Committee on Health Research Ethics (J.no. H-22055480), is regulated by the Danish Data Protection Agency (registration P-2023-24), and was carried out in accordance with the Helsinki Declaration for Ethics Standards in Human Trials.

Statistical analysis

Baseline characteristics were described using either the mean ± SD or medians [interquartile range (IQR)], depending on whether the data were symmetrically distributed.

Quantitative outcome variables were compared using the independent *t*-test or Wilcoxon rank-sum test according to the normality distribution. Fisher's exact test was used to analyse categorical data. R version 4.3.0 was used for the statistical analysis. For baseline characteristics, a P value of < 0.05 was considered significant. For the outcomes, the initial significance level for the study was $P < 0.05$ (reported as a tendency and $P < 0.05$; Table 1 and Table 2). However, we used Bonferroni corrections due to multiple outcomes, resulting in a significance level of $P < 0.002$ (reported as significant and $P < 0.05$; Table 1 and Table 2).

RESULTS

Study population

The participants were recruited between March 2022 and December 2023. We included 100 patients with CHB and 50 matched individuals from the comparison group but had to exclude three patients with CHB due to loss of HBsAg; one individual from the comparison group, who was diagnosed with CHB due to positive HBsAg > 6 months, was switched to the CHB group, resulting in 98 patients with CHB and 49 persons in the comparison group (Figure 1). Planned matching of the comparison group for age, sex, BMI, and country-of-birth was successful (Table 1). The level of education did not differ significantly between the groups. More patients with CHB were married or had partners. No participants reported excessive alcohol consumption. Fewer patients with CHB reported current alcohol consumption. There were no differences in smoking or drug use between the groups (Table 1).

Body anthropometrics

The groups were similar in body weight, WHR, total body fat content, total lean body mass, and abdominal obesity (Table 2).

Liver parameters

We found a tendency towards increased ALT and TE-score in patients with CHB (Table 2). Eight persons from the comparison group showed previous infection with HBV by positive anti-HBc, and 27 (55%) in the comparison group had protective anti-HBs, indicating a sufficient vaccination response or prior infection. Five (5%) patients with CHB were HBeAg positive, and one (1%) had positive anti-HDV. We found no differences in FIB-4 scores or CAP (Table 2). One participant from the comparison group did not have a FibroScan; therefore, one CAP and one TE score were missing.

Table 1 Baseline demographic characteristics of patients with chronic hepatitis B and a comparison group without chronic hepatitis B, matched on age, sex, body mass index, and country-of-birth, *n* (%)

	All participants	Chronic hepatitis B	Comparison group	*P* value
Participants, *n*	147	98	49	
Age, years (range)	45 (19-78)	44 (25-74)	46 (19-78)	0.15
Sex, female	74 (50)	50 (51)	24 (49)	0.86
Country of birth				0.30
Denmark	20 (14)	12 (12)	8 (16)	
Eastern Europe	9 (6)	5 (5)	4 (8)	
Turkey	28 (19)	21 (21)	7 (14)	
MENA region	19 (13)	9 (9)	10 (20)	
Sub-Saharan Africa	11 (7)	7 (7)	4 (8)	
Asia	58 (39)	43 (44)	15 (31)	
South America	2 (1)	1 (1)	1 (2)	
Highest level of education				0.50
Primary school	17 (12)	14 (14)	3 (6)	
High school	10 (7)	6 (6)	4 (8)	
Vocational education	31 (21)	20 (20)	11 (22)	
Academic higher education	85 (58)	54 (55)	31 (63)	
Employment				0.29
Student	11 (7)	7 (7)	4 (8)	
Employed/self-employed	109 (74)	68 (69)	41 (84)	
Unemployed	10 (7)	8 (8)	2 (4)	
Retired	14 (10)	12 (12)	2 (4)	
Relationship status				
Married or with a partner	111 (76)	79 (80)	32 (65)	< 0.05
Substance intake				
Alcohol use currently	76 (52)	42 (43)	34 (69)	< 0.05
Smoking ever	61 (41)	41 (42)	20 (41)	1.00
Drug-use ever	12 (8)	7 (7)	5 (10)	0.53

The groups were compared using Fisher's exact test. A *P* value of < 0.05 is considered statistically significant. MENA: Middle East and Northern Africa.

Cardiovascular parameters

We found no statistically significant differences between the groups' measured lipid profiles or blood pressure (Table 2).

Glucose metabolism

None of the patients with CHB had elevated HbA1c levels (> 48 mmol/L) compared to six participants in the comparison group. We found tendencies of lower fasting glucose, lower measured HbA1c and number of individuals having 2-hour post-OGTT glucose values > 11.1 mmol/L in the CHB patients. However, a tendency towards a higher insulin AUC was observed in patients with CHB. We found no difference in the Matsuda index or HOMA-IR (Table 2). Three (0.4%) of plasma glucose samples, 21 (2.8%) of the plasma insulin samples, and two (1.4%) of the HbA1c samples were hemolyzed or lost during transfer between the departments.

Known cardiometabolic co-morbidity and current medication

We found no significant differences in the known diagnoses of hypercholesterolemia or hypertension. However, no patients with CHB were diagnosed with T2D compared to six (12%) in the comparison group. Patients with CHB used less anti-diabetic medication and more antiviral medication. We also found no significant differences in the use of lipid-lowering (statins) or antihypertensive medications (Table 2).

Table 2 Baseline clinical characteristics of patients with chronic hepatitis B and a comparison group without chronic hepatitis B matched on age, sex, body mass index, and country-of-birth, *n* (%)

	All participants	Chronic hepatitis B	Comparison group	*P* value
Participants, *n*	147	98	49	
Body anthropometrics				
Body weight, mean (± SD), kg	74.6 (± 17.4)	74.5 (± 17.7)	74.8 (± 16.8)	0.94
BMI, mean (± SD), kg/m^2	26.2 (± 4.9)	26.3 (± 5.16)	26.1 (± 4.43)	0.83
Waist-to-hip ratio (WHR), mean (± SD)	0.88 (± 0.09)	0.88 (± 0.09)	0.88 (± 0.08)	1.00
Total body fat, mean (± SD), %	32.6 (± 9.5)	32.9 (± 9.7)	32.0 (± 9.3)	0.59
Total lean body mass, median (IQR), kg	45.6 (17.5)	46.5 (18.3)	45.1 (13.3)	0.48
Abdominal obesity by WHR	85 (58)	56 (57)	29 (59)	0.86
Liver parameters				
ALT, median (IQR), U/L	27 (17)	28 (18)	24 (13)	< 0.05
Viral load, median (IQR), IU/mL	-	310 (2020)	-	
Anti-HDV positive	-	1 (1)	-	
HBeAg positive	-	5 (5)	-	
Anti-HBc positive	106 (72)	98 (100)	8 (16)	< 0.05[a]
Anti-HBs positive, level ≥ 10 IU/L	28 (19)	1 (1)	27 (55)	< 0.05[a]
Fib-4 score, median (IQR),	0.89 (0.53)	0.89 (0.52)	0.87 (0.58)	0.84
TE-score, median (IQR), kPa	4.5 (1.6)	4.7 (1.5)	4.4 (1.3)	< 0.05
CAP, mean (± SD), dB/m	250 (± 66)	248 (± 64)	255 (± 69)	0.52
Hepatic steatosis, CAP ≥ 248	73 (50)	47 (48)	26 (53)	0.60
Cardiovascular parameters				
Cholesterol, mmol/L	4.8 (1.1)	4.7 (1.1)	4.9 (1.1)	0.29
Hypercholesterolemia by cholesterol > 5 mmol/L	52 (35)	30 (31)	22 (45)	0.10
Triglycerides, median (IQR), mmol/L	1.0 (0.7)	1.0 (0.6)	1.1 (0.8)	0.43
LDL-cholesterol, median (IQR), mmol/L	3.0 (1.0)	2.8 (0.9)	3.2 (1.3)	0.13
HDL-cholesterol, median (IQR), median (IQR), mmol/L	1.3 (0.6)	1.3 (0.5)	1.4 (0.5)	0.12
Systolic blood pressure, mean (± SD), mmHg	119 (± 15)	118 (± 15)	122 (± 15)	0.13
Diastolic blood pressure, mean (± SD), mmHg	75 (± 10)	75 (± 11)	75 (± 9)	0.95
Glucose metabolism				
HbA1c, median (IQR), mmol/L	36 (6)	36 (6)	38 (5)	< 0.05
HbA1c ≥ 48 mmol/L	6 (4)	0	6 (12)	< 0.05[a]
Fasting glucose, median (IQR), mmol/L	4.9 (0.8)	4.9 (0.6)	5.1 (0.8)	< 0.05
Fasting insulin pmol/L	65 (58)	66 (53)	61 (79)	0.73
2-hour glucose, median (IQR), mmol/L	6.8 (2.2)	6.8 (1.8)	7.1 (3.8)	0.63
OGTT 2h glucose ≥ 11.1	17 (12)	8 (8)	9 (18)	0.10
OGTT glucose AUC, median (IQR), mmol/L/minute	899 (242)	879 (233)	905 (365)	0.53

OGTT Insulin AUC, median (IQR), pmol/L/minute	56295 (49073)	66311 (54818)	45952 (33450)	< 0.05
Matsuda Index, median (IQR)	3.7 (3.5)	3.6 (2.8)	3.8 (4.5)	0.57
HOMA-IR, median (IQR)	1.2 (1.1)	1.3 (1.0)	1.2 (1.5)	0.81
Known cardiometabolic co-morbidity				
Hypercholesterolemia	18 (12)	9 (9)	7 (15)	0.40
Hypertension	16 (11)	11 (11)	7 (15)	0.60
Type 2 diabetes	6 (4)	0 (0)	6 (12)	< 0.05[a]
Current medication				
Lipid-lowering medicine	14 (10)	8 (8)	6 (12)	0.55
Antihypertensive medication	19 (13)	12 (12)	7 (14)	0.79
Anti-diabetic medicine	6 (4)	1 (1)	5 (10)	< 0.05
Antiviral medicine	23 (16)	22 (22)	1 (2)	< 0.05[a]
Collectively assessed cardiometabolic co-morbidity				
Obesity	112 (76)	75 (77)	37 (76)	1.00
MASLD	69 (47)	44 (45)	25 (51)	0.48
Hypercholesterolemia	65 (44)	37 (38)	28 (57)	< 0.05
Hypertension	42 (29)	25 (26)	17 (35)	0.25
Type 2 diabetes	17 (12)	8 (8)	9 (18)	0.10

[a]*P* < 0.05 indicates statistical significance after Bonferroni correction. A *P* value of < 0.05 is considered to show a trend.

According to normality distribution, continuous data is presented in mean (± SD) or median (interquartile range). Quantitative outcome variables were compared using the independent *t*-test and Mann-Whitney *U* test according to normality distribution. Fisher's exact test was used to analyze categorical data. Definitions of collectively assessed cardiometabolic co-morbidity: Obesity is defined as body mass index > 25 or abnormal waist-to-hip ratio; metabolic dysfunction-associated steatotic liver disease; hypercholesterolemia as total cholesterol > 5 mmol/L or use of statins; hypertension is defined as measured systolic blood pressure of ≥ 135 mmHg and or a diastolic blood pressure ≥ 85 mmHg and or use of antihypertensive medication; type 2 diabetes (T2D) is defined as blood glucose > 11 mmol/L after a 2-hour oral glucose tolerance test, or hemoglobin A1c > 48 or use of antidiabetic medicine intended to treat T2D. ALT: Alanine aminotransferase; AUC: Area under the curve; BMI: Body mass index; CAP: Controlled attenuation parameter; FIB-4: Fibrosis index 4 factors; HbA1c: Hemoglobin A1c; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; HDL: High-density lipoprotein; Anti-HBc: Hepatitis B core antibodies; Anti-HBs: Hepatitis B surface antibodies; Anti-HDV: Hepatitis D virus antibodies; IQR: Interquartile range; LDL: Low-density lipoprotein; MASLD: Metabolic dysfunction-associated steatotic liver disease; TE: Transient elastography; WHR: Waist-to-hip ratio.

Collectively assessed cardiometabolic co-morbidity

In the patients with CHB, we found a collectively assessed prevalence of 77% being obese, 45% having MASLD, 38% having hypercholesterolemia, 26% having hypertension, and 8% having T2D. There were no significant differences between the groups; however, there was a tendency towards lower hypercholesterolemia in patients with CHB (Table 2).

Physical activity and fitness

Patients with CHB had lower self-assessed sitting time than those in the comparison group, a tendency toward lower VO_2 max, and a tendency toward lower self-assessed MVPA. There was no difference in the self-assessed walking activity. The activity monitors showed no differences between the groups in MVPA or sedentary time (Table 3). Nine activity monitor measurements were lost or fell off the participants: Six in the CHB group and three in the comparison group.

Cardiometabolic co-morbidity in treated and untreated patients with CHB

In a sub-analysis of the patients with CHB treated with antiviral medicine compared with untreated, we found that patients with CHB on antiviral treatment had a tendency of higher WHR mean 0.91 (± 0.06) *vs* 0.86 (± 0.09) in the untreated group, a tendency of lower levels of cholesterol of median 4.3 mmol/L (IQR: 0.8) *vs* 4.9 mmol/L (IQR: 1.1) in the untreated group, a tendency of lower levels of HDL cholesterol of median 1.2 mmol/L (IQR: 0.4) *vs* 1.3 mmol/L (IQR: 0.6), and significantly lower HBV DNA of median 0 IU/mL (IQR: 7.8) compared to 852 IU/mL (IQR: 3747), respectively. We found no differences in BMI, indices of glucose metabolism, triglycerides, LDL cholesterol, ALT, HBeAg, Fib-4 score, TE score, CAP, or VO_2max (Supplementary Table 1).

Table 3 Physical activity of patients with chronic hepatitis B and a comparison group from the general population matched on age, sex, body mass index, and country-of-birth

	All participants	Chronic hepatitis B	Comparison group	*P* value
Participants, *n*	147	98	49	
VO_2max, mean (± SD), mL/kg/minute	28.0 (± 7.7)	26.9 (± 7.5)	30.2 (± 7.6)	< 0.05
Self-assessed physical activity				
MVPA, median (IQR), minute/week	120 (353)	68 (262)	188 (406)	< 0.05
Walking activity, mean (± SD), minute/week	243 (± 548)	290 (± 538)	180 (± 364)	0.10
Sitting time, mean (± SD), minute/week	2100 (± 2047)	1680 (± 1470)	2625 (± 1680)	< 0.05[a]
Measured physical activity				
MVPA, median (IQR), minute/week	388 (230)	357 (257)	424 (204)	0.23
Walking activity, mean (± SD), minute/week	624 (± 232)	628 (± 248)	615 (± 201)	0.76
Sitting time, mean (± SD), minute/week	3471 (± 981)	3536 (± 992)	3345 (± 957)	0.27
Sedentary time, median (IQR), minute/week	8399 (656)	8449 (735)	8393 (567)	0.65

[a]*P* < 0.05 indicates statistical significance after Bonferroni correction. A *P* value of < 0.05 is considered to show a trend.
According to normality distribution, data is given in mean (± SD) or median (interquartile range). Quantitative outcome variables were compared using the independent *t*-test and Mann-Whitney *U* test according to normality distribution. Fisher's exact test was used to analyze categorical data. IQR: Interquartile range; MVPA: Moderate-to-vigorous physical activity; VO_2max: Maximal oxygen consumption.

DISCUSSION

In this baseline assessment of the prospective FitLiver Cohort Study, which included patients with CHB and a matched comparison group, we found that matching the two groups according to sex, age, BMI, and country-of-birth reflected a similar prevalence of cardiometabolic co-morbidities. However, we found that known diagnosis of T2D, and the number of persons with increased HbA1c levels was higher in the comparison group. We found tendencies toward a lower prevalence of collectively assessed hypercholesterolemia in patients with CHB compared to the comparison group. Furthermore, we found no differences in the collectively assessed obesity, MASLD, or hypertension. Individuals from the comparison group had a higher self-assessed sitting time, a tendency toward higher MVPA, and a tendency toward higher VO_2max compared to patients with CHB.

Owing to the matching of BMI in this study, it is not surprising that body anthropometrics were similar between the groups. Both groups were, on average, overweight with a BMI > 25, which is similar to the general Danish population, in which approximately 50% were assessed to have a BMI > 25[30]. The collective assessment of obesity, including increased WHR and BMI, further increased the percentage to 76% in both groups, indicating a risk of future cardiometabolic co-morbidities[31].

By investigating liver parameters, we found a tendency of increased ALT and TE-scores in patients with CHB, assessed to indicate inflammation and fibrosis in the liver, which is less surprising both due to chronic inflammation in the liver caused by HBV and due to the combination of CHB, obesity, hyperglycaemia, and dyslipidemia, which have been shown to increase ALT levels in patients with CHB[32]. Relatively few of the patients with CHB were HBeAg positive. Only 1% were anti-HDV positive (no measured HDV-RNA), indicating a generally less active viral infection, also shown by the modest median of 310 IU/mL in HBV DNA, which is probably also associated with the 22% of patients with CHB who received antiviral treatment suppressing viral load. The suggestion of less active viral replication was further confirmed by the median ALT, FIB-4, and TE scores being within normal ranges. The finding of previous HBV infection among individuals in the comparison group of 16% shows that this group of people has a higher exposure to HBV compared to the general Danish population (estimated prevalence of 3%)[33]. However, only 55% had protective antibodies indicating positive vaccination status or cleared previous infection protecting against future HBV infection among the comparison group. Since vaccination against HBV is not part of the general Danish vaccination program, this might indicate a need to improve the vaccination status among populations at a higher risk of HBV exposure. Hepatic steatosis, indicated by CAP > 248, showed a prevalence of 50% in all participants, with a tendency of less (48%) in the patients with CHB compared to the comparison group (53%), and a MASLD prevalence of 47% in all participants which is higher than in a recent American assessment of MASLD prevalence of 32.45%[34]. Furthermore, the previous term, non-alcoholic fatty liver disease, was assessed to have a global prevalence of 29.8%, whereas European countries had an estimated prevalence of

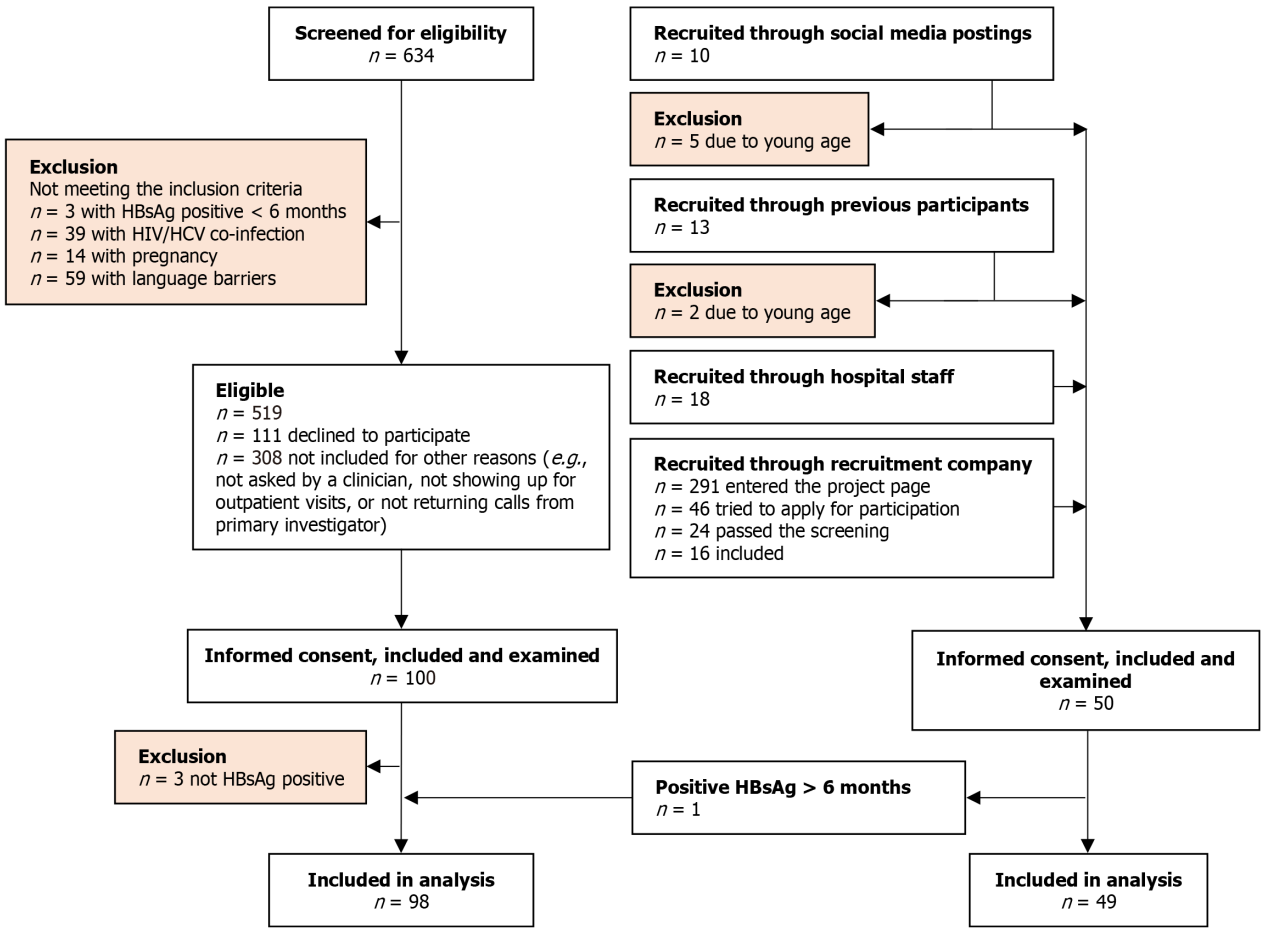

Figure 1 Flowchart of screening and inclusion of patients with chronic hepatitis B and a comparison group without chronic hepatitis B matched on age, sex, body mass index, and country-of-birth in the FitLiver cohort. HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.

31%[35]. This indicates that both of our study participant groups had an increased prevalence of MASLD compared to the general population.

Hypercholesterolemia can be defined in several ways. In a study from United States, the prevalence of hypercholesterolemia in the general population was 47%, defined by LDL-cholesterol level of ≥ 130 mg/dL (3.25 mmol/L)[36]. In contrast, a French study found a prevalence of hypercholesterolemia in the general population of 27% with LDL-cholesterol greater than 160 mg/dL (4.0 mmol/L) or reimbursement for lipid-lowering drugs[37]. In our study, we found a median LDL cholesterol of 3.0 mmol/L, while the comparison group had a non-significantly higher median of 3.2 (IQR: 1.3) compared to 2.8 (IQR: 0.9) in the patients with CHB. We based our collective assessment of hypercholesterolemia on total cholesterol, current use of statins, or known diagnoses and found a prevalence of 38% in the patients with CHB, which makes it challenging to compare with the above-mentioned studies.

The prevalence of collectively assessed hypertension in the patients with CHB was 26% and 35% in the comparison group. A Danish assessment of hypertension by essential screening showed a prevalence of 26%[38] which is similar to our findings.

The finding of no diagnosed T2D in the patients with CHB was surprising, since a previous nationwide Danish registry study found a T2D prevalence of 4% among patients with CHB, with a median age of 36 years[14]. Our study collectively assessed T2D by including elevated HbA1c, increased 2-hour glucose levels after an OGTT, or documented diagnosis and treatment with antidiabetic medication. In Denmark, HbA1c is commonly used to diagnose T2D; surprisingly, we found that all patients with CHB had levels below 48 mmol/L. However, HbA1c levels may not be as reliable in certain populations, such as those with hemoglobinopathies, iron deficiency due to anemia, and specific ethnic backgrounds[39]. A higher insulin AUC in patients with CHB suggests an increased insulin requirement to maintain normal blood glucose levels, possibly indicating increased insulin resistance in patients with CHB. However, we found no difference in HOMA-IR. The collectively assessed T2D in both the patients with CHB, and the comparison group was higher than the estimated prevalence of T2D in Denmark at 5.5%[40].

Our study found low VO_2max values in both groups (27 mL/kg/minute in patients with CHB and 30 mL/kg/minute in the comparison group) when compared with a cross-sectional German study investigating normal VO_2max values at a similar age. They found a mean VO_2max of 35 mL/kg/minute in men and 29 mL/kg/minute in women[41]. The World Health Organization recommends 150-300 minutes of moderate-intensity, 75-150 minutes of vigorous-intensity physical activity, or some equivalent combination of moderate-intensity and vigorous-intensity aerobic physical activity per week

[42]. In a Korean cohort following 9727 patients with CHB starting antiviral treatment, they found that patients who were physically active for more than 150 minutes of moderate-intensity aerobic exercise each week (assessed by self-assessed physical activity questionnaires) had a lower risk of HCC[43]. Our study found that self-assessed MVPA in both groups was lower than recommended. However, interestingly, the measured MVPA seemed to comply with the recommendations and showed no difference between the groups, although tendencies of lower MVPA and higher sitting and sedentary times were observed in patients with CHB, suggesting an explanation for the lower physical fitness state found by the tendency of decreased VO_2max.

The comparison of treated and untreated patients with CHB showed significant differences only in viral load, which was expected. However, there were tendencies of lower total cholesterol and HDL cholesterol, which have been found previously[44] in patients with CHB treated with antiviral medicine.

Strengths and limitations

A strength of this study is the combination of clinical history and clinical and biochemical findings, including OGTT, to better describe the prevalence of cardiometabolic comorbidities among patients with CHB. Matching with the comparison group enabled the elimination of known confounding factors when comparing the groups prospectively. However, the study was limited by selection or volunteer bias, as participants who willingly agreed to participate may have different characteristics from those of the target population. The suggestion that the included patients with CHB were healthier than the general CHB population in Denmark can be supported by the fact that none of the CHB patients had been diagnosed with T2D and had low alcohol use, which probably also reflects the recommendation of low alcohol use when having CHB[13]. Selection- or volunteer bias can result in the inclusion of a healthier population in research studies, as the examinations require time, ability, and willingness to undergo extensive health examinations[45].

CONCLUSION

In this baseline assessment of the FitLiver Cohort Study, we found that the patients with CHB and the comparison group were well-matched and had a similar prevalence of cardiometabolic comorbidities. Furthermore, both groups had a low mean VO_2max, indicating lower physical fitness, and the patients with CHB had a shorter sitting time than those in the comparison group.

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FOOTNOTES

Author contributions: Jespersen S, Weis N, Pedersen BK, and Krogh-Madsen R conceived the study; Jespersen S, Krogh-Madsen R, Weis N, Pedersen BK, and Madsbad S contributed to protocol development and study design; Jespersen S and Weis N screened for eligible patients and included them; Jespersen S and Fritt-Rasmussen A integrated and quality-checked the data; Jespersen S and Fritt-Rasmussen A performed the experiments and collected the data; Jespersen S performed the statistical analyses; Jespersen S wrote the first article draft; All authors read the manuscript, critically revised it for important intellectual content, and approved the final version.

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Institutional review board statement: This study was approved by the Regional Committee under the Danish National Committee on Health Research Ethics (J.no. H-22055480), is regulated by the Danish Data Protection Agency (registration P-2023-24) and was carried out in accordance with the Helsinki Declaration for ethics standards in human trials.

Clinical trial registration statement: This study was not registered in a clinical trials registry. As an observational, prospective cohort study, it does not meet the typical criteria for clinical trial registration, which generally applies to interventional studies such as randomized controlled trials. However, we have adhered to relevant ethical guidelines and reporting standards, such as the STROBE guidelines, to ensure the rigorous conduct and transparent reporting of our research.

Informed consent statement: All participants signed an informed consent form prior to their inclusion in the study. The consent process included a thorough explanation of the study's purpose, procedures, potential risks, and benefits. Participants were informed of their right to withdraw from the study at any time without any negative consequences. Additionally, the confidentiality of their data was assured, and all data were anonymized to protect participant privacy.

Conflict-of-interest statement: Weis N has been a clinical investigator for Merck, Sharp and Dohme. The authors declare no conflicts of interest.

Data sharing statement: The public release of raw data is restricted by Denmark's national legislation, specifically the Data Protection Act § 10 and the Data Disclosure Proclamation Act. According to these laws, we are only permitted to provide pseudonymized data to the Journal after obtaining approval from the Data Protection Authorities (Data Protection Act § 10, section 3, nr. 3). Interested parties, including reviewers, can request access to the data; however, such access is contingent upon approval from the Danish Data Protection Agency for the transfer of data from the Capital Region to the Journal. Suppose a journal intends to share pseudonymized data with others. In that case, it must establish a suitable legal basis for doing so and ensure that the data are used exclusively for scientific research purposes.

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