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Diabetes and the risk of cirrhosis and HCC: An analysis of the UK Biobank

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Abstract

Background: Diabetes increases the risk of cirrhosis and HCC. We aimed to assess such associations given different diabetes statuses.

Methods: We included 449,497 participants in the UK Biobank cohort (mean age 56.7 ± 8.0 y; 45.5% male) and assessed the association between preclinical diabetes (prediabetes, having a high risk of diabetes), clinical diabetes (presence, duration, or glycemic control of type 2 diabetes), and incident liver cirrhosis and HCC by the Cox regression. Liver diseases were ascertained through inpatient records and national death registration. Gene-environment interaction was examined using the polygenic risk scores of cirrhosis and HCC.

Results: Compared with normoglycemia, having <5 years, ≥5 years of diabetes showed adjusted HRs (aHRs) of cirrhosis as 2.85 (2.45–3.32) and 3.43 (2.92–4.02), respectively, which was similarly observed in HCC. In diabetes, a level of hemoglobin A1c ≥ 7.5% showed aHRs of 1.37 (1.07–1.76) and 1.89 (1.10–3.25) for cirrhosis and HCC, respectively, compared with hemoglobin A1c < 6.5%. In non-diabetes, prediabetes presented aHRs of 1.41 (1.14–1.73) and 1.80 (1.06–3.04) of cirrhosis and HCC, respectively. Participants with a high risk of diabetes at baseline showed an aHR of 3.31 (2.65–4.13) for cirrhosis and 2.09 (1.15–3.80) for HCC. In those with a high genetic risk of HCC, having an increased risk of diabetes posed a significantly higher risk of HCC (aHR: 1.93, 1.45–2.58, $P_{interaction} = 0.005$), compared with those without a high genetic risk of HCC.

Conclusions: Not only diabetes but preclinical diabetes, longer diabetes duration, and higher baseline hemoglobin A1c were associated with an increased risk of incident cirrhosis and HCC in the general population.

Abbreviations: ALD, alcohol-related liver disease; FINDRISC, Finnish Diabetes Risk Score; GGT, gamma-glutamyl transferase; PRS, polygenic risk score; T2D, type 2 diabetes

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INTRODUCTION

Cirrhosis is the end stage of liver fibrosis, which substantially increases the risk of HCC. Despite its main causes, like alcohol abuse and HBV/HCV infection, the etiology of cirrhosis is shifting towards metabolic disorders across the world.[1] Diabetes, a well-recognized risk factor for cirrhosis, is characterized by hyperglycemia, insulin resistance, a life-long disease course, and systemic damage. Type 2 diabetes was identified as a strong risk factor for liver fibrosis and cirrhosis, but this association regarding different diabetes status, such as duration of diabetes and glycemic control, remained inconclusive, which may lead to varied clinical management strategies. Equating patients with newly diagnosed diabetes to those with longer periods could potentially incur bias in the estimation of the risk because uncontrolled glycemic level was disproportionately prevalent in those with earlier onset[2] and strongly correlated with increased liver stiffness.[3] Therefore, diabetes duration and glycemic control may confer a baseline risk of future liver diseases yet to be evaluated. Notably, before diabetes manifests itself, it is acknowledged that a long preclinical stage bridges its biological onset and clinical diagnosis.[4] The determination of whether individuals with prediabetes or those prone to diabetes are already at an increased risk of liver diseases poses great clinical and public health significance. On the other hand, the genetic factor has recently been profiled in developing cirrhosis and HCC in alcohol and dysmetabolism.[5,6] Whether an inherent predisposition to cirrhosis and HCC modified the relationship between the 2 diseases and diabetes status remained unclear.

Given the above knowledge gaps, the current study aimed to investigate associations between the presence of diabetes or prediabetes, duration of diabetes, glycemic control, and burden of diabetes with incident cirrhosis and HCC. We also examined whether genetic susceptibility to cirrhosis and HCC modified such associations.

METHODS

Study design and population

The study was based on the UK Biobank prospective cohort, initiated in 2006, including over 500,000 individuals aged between 40 and 69 years old. Participants were invited to 22 dedicated assessment centers across the UK. Eighty-nine percent of participants were recruited in England and the remaining in Scotland and Wales. Baseline assessment of questionnaires, physical examinations, and collection of blood samples was completed between 2006 and 2010. Individuals were linked to ongoing updated hospital records of disease diagnosis and cause of death coded by ICD-10 and ICD-9. Details of the cohort characteristics, procedures of data collection, and processing were available on the official website (https://www.ukbiobank.ac.uk). The UK Biobank study was approved by the North West—Haydock Research Ethics Committee (16/NW/0274), and written informed consent was obtained from all participants. We report our study according to the STROBE statement,[7] http://links.lww.com/HC9/A542. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

We focused on the associations of type 2 diabetes and its related characteristics with incident liver cirrhosis and HCC. Therefore, participants with type 1 diabetes and an age of diabetes diagnosis of less than 20 years old were excluded. Participants diagnosed with cirrhosis or HCC or having documented liver transplantation or liver surgery at baseline were excluded. Genetic predisposition was assessed by genetic risk scores derived from Caucasians, and therefore all non-Caucasians were excluded. We also ruled out participants with secondary causes of liver diseases that might lead to cirrhosis (Figure 1).

Exposure

We considered diabetes status as preclinical diabetes and clinical diabetes. We evaluated preclinical diabetes by the diagnosis of prediabetes and the Finnish Diabetes Risk Score (FINDRISC).[8] For clinical diabetes, we analyzed the presence of type 2 diabetes, duration of type 2 diabetes, and glycemic control.

Type 2 diabetes cases were identified through hospital records by ICD-10 code E11-E14, ICD-9 code 250, the primary or secondary cause of death being diabetes, self-reported diabetes, insulin or hypoglycemic medication, random blood glucose $\geq$ 11.1 mmol/L, or HbA_{1c} $\geq$6.5%. We defined diabetes duration as the time from diagnosis to the baseline assessment. Glycemic control was evaluated by the baseline serum HbA_{1c} level. Normoglycemia was defined as the absence of diabetes and prediabetes.

For those without diabetes, prediabetes was defined as HbA_{1c} 6.0% to 6.4%.[9] The absolute risk of developing drug-treated type 2 diabetes in 10 years was assessed by the FINDRISC. The score was validated in large-scale cohorts of different races and widely used in clinical trials to select populations at risk for developing type 2 diabetes.[10,11] The risk is quantified as 0 to 25 points by evaluating baseline age, body mass index, waist circumference, history of antihypertensive medication, history of hyperglycemia, physical activity, diet (consumption of vegetables, fruits, or berries), and family history of diabetes. A higher score indicates a higher risk.

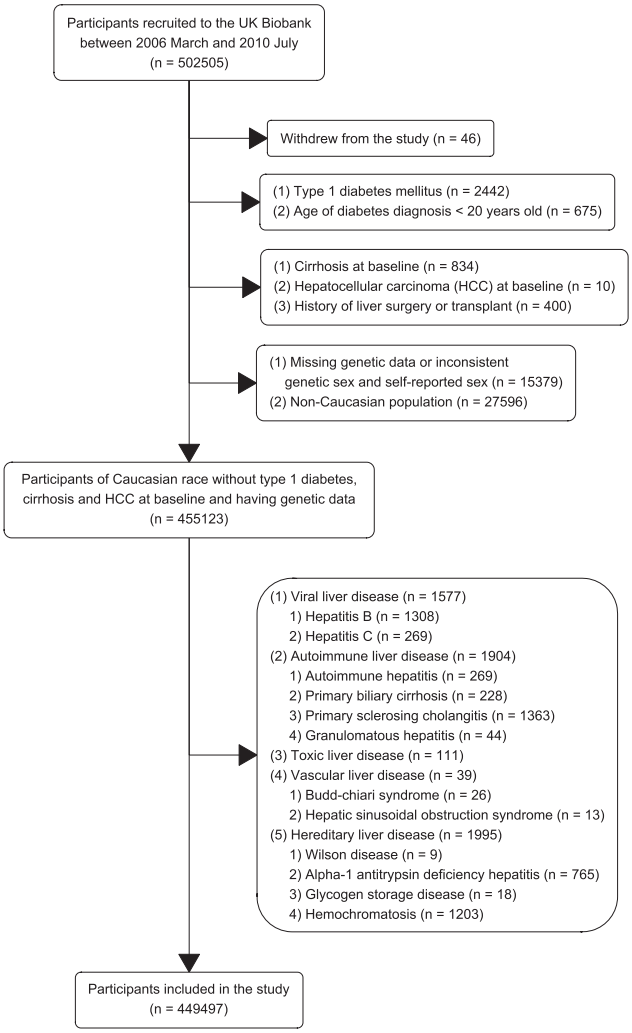


FIGURE 1 Flowchart of study population selection.

Outcomes

The primary outcome of interest was all-cause incident cirrhosis. Given the risk of HCC increases after the cirrhosis develops, we assessed the associations in participants without cirrhosis and HCC at baseline with incident HCC as a secondary outcome. We used electronic health records to identify the incident cases during the follow-up. The diagnosis of incident cirrhosis and HCC conformed to a previously examined panel of criteria.[12] Definitions of cirrhosis and HCC were detailed in Supplemental Methods, http://links.lww.com/HC9/A543 and Supplemental Table S1, http://links.lww.com/HC9/A543.

Covariates

Sociodemographic variables included age, sex, education, and socioeconomic status measured by the Townsend Deprivation Index in quintiles, assessment center, and annual household income. For lifestyles and health-related variables, smoking status was recorded as never, former, or current smoker. Alcohol consumption (grams per day) was calculated based on the total amount of drinking related to questionnaires (see Supplemental Methods, http://links.lww.com/HC9/A543). Physical activity was assessed by the International Physical Activity Questionnaire. Dyslipidemia was determined by serum cholesterol level or the presence of hypolipidemic treatment (Supplemental Table S1, http://links.lww.com/HC9/A543). Hypertension was defined by hospital diagnosis, self-reported hypertension, antihypertensive medication, or systolic/diastolic blood pressure $\geq$ 140/90 mm Hg (Supplemental Table S1, http://links.lww.com/HC9/A543). Body mass index was calculated as body weight (kg) divided by height squared (m^2). Genetic predisposition was quantified by a polygenic risk score and detailed in Supplemental Methods, http://links.lww.com/HC9/A543 and Supplemental Figure S1, http://links.lww.com/HC9/A543. NAFLD was defined by ICD-10 code (K760, K758), or a liver fat content > 5% measured by proton density fat fraction using liver MRI without significant alcohol intake (male < 30 g/d, female < 20 g/d).[13,14] The fibrosis-4 score was calculated as (age [year] $\times$ aspartate aminotransferase [U/L])/((Platelet count [10^9/L]) $\times$ (square root of alanine aminotransferase [U/L])).[15]

Statistical analysis

We estimated the association between diabetes status and the risk of incident cirrhosis and HCC by multivariable Cox proportional hazard models. The follow-up time of participants was censored at the date of diagnosis, date of death, or March 31, 2021. Nonlinear relationships were examined by restricted cubic spline with 4 knots specified. Variables with missing values (see Supplemental Table S2, http://links.lww.com/HC9/A543) were treated as dummy variables if they were included in regression models.

The association of type 2 diabetes with incident cirrhosis and HCC was examined according to the presence of diabetes or prediabetes compared with non-diabetes or normoglycemia. In diabetes, we subdivided participants by a 5-year cutoff of diabetes and repeated the analysis. Regarding glycemic control, we categorized subjects by HbA_{1c} as <6.5% (reference group), 6.5%–7%, 7.0%–7.5%, and $\geq$7.5% for diabetes.[16] Finally, we linked the FINDRISC to the future risk of cirrhosis and HCC in non-diabetes; we divided participants by quintile of FINDRISC and used the lowest quintile as the reference group.

We performed several additional analyses to support our results. In sensitivity analyses, we used alternate definitions of cirrhosis and HCC, further excluded participants with alcohol-associated liver disease and

alcohol use disorder, or adjusted for the presence of NAFLD. When the outcome was HCC, we additionally adjusted for the presence of incident cirrhosis. We used the Fine-Gray subdistribution hazard models to consider competing risks. We examined whether genetic background modified the association of diabetes status with incident cirrhosis and HCC, each using the tertile of cirrhosis polygenic risk score and HCC polygenic risk score for stratification. Exploratory subgroup analyses were performed by stratifying participants according to age, sex, liver chemistry, and fibrosis-4 score.

A 2-sided p-value < 0.05 was considered statistically significant. All analyses were performed in R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute, USA). R packages used in the analyses were detailed in Supplemental Methods, http://links.lww.com/HC9/A543.

RESULTS

Characteristics of participants included in the study

In the present study, we included 449,497 participants (mean age 56.7 ± 8.0 y, 45.5% male). At baseline, 22,934 participants had type 2 diabetes (Table 1). Over a median of 12.0 (interquartile range: 11.3–12.7) years of follow-up, 1824 cases of incident cirrhosis and 272 HCC were recorded. About half (149/272, 54.8%) of HCC developed in participants without cirrhosis. Compared with subjects without diabetes and prediabetes, participants with diabetes tended to be male, had lower household income, less physical activity, more alcohol consumption, and a higher prevalence of NAFLD (Table 1).

Risk of hepatic outcomes posed by prediabetes, diabetes, and duration of diabetes

We observed that diabetes and prediabetes were significant predictors of incident cirrhosis and HCC (Table 2). Compared with normoglycemia, prediabetes was associated with a 41% higher risk for incident cirrhosis [adjusted HR (aHR) 1.41, 95% CI: 1.14–1.73] and an 80% higher risk for HCC (aHR: 1.80, 95% CI: 1.06–3.04). The presence of diabetes showed an overall 3-fold higher risk for cirrhosis (aHR: 3.12, 95% CI: 2.77–3.53, Table 2) and a 5-fold higher risk for HCC (aHR: 5.68, 95% CI: 4.25–7.59, Model 3). No significant interaction between diabetes and genetic risk of cirrhosis or HCC was observed ($P_{interaction} = 0.095$ for cirrhosis; 0.081 for HCC, Figure 2). Considering the duration of diabetes, participants with ≥ 5 years of diabetes showed a higher incidence and risk of outcomes than those with < 5 years of diabetes (Table 2, Supplemental Figure S2, http://links.lww.com/HC9/A543). Compared with normoglycemia, the aHRs of cirrhosis for having < 5 years and ≥ 5 years of diabetes were 2.85 (95% CI: 2.45–3.32) and 3.43 (95% CI: 2.92–4.02), respectively, and the incidence rates per 100,000 person-years were 145.65 and 188.73, respectively. For HCC, this risk was markedly higher, showing aHRs of 4.40 (95% CI: 3.03–6.38) and 7.25 (95% CI: 5.16–10.19) for having < 5 years and ≥ 5 years of diabetes, respectively. These associations were not modified by the genetic risk of cirrhosis or HCC ($P_{interaction} = 0.940$ for cirrhosis; 0.308 for HCC, Supplemental Figure S3, http://links.lww.com/HC9/A543).

Association between glycemic control and risk of hepatic outcomes in subjects with diabetes

We further assessed the association between glycemic control and incident cirrhosis and HCC in patients with diabetes. A lower HbA_{1c} level predicted a lower risk of both diseases. Given that HbA_{1c} is lower than 7.5%, we observed a decreasing trend in risk for cirrhosis and HCC (Supplemental Figure S4, http://links.lww.com/HC9/A543). Conversely, using HbA_{1c} <6.5% as reference, those with higher HbA_{1c} showed greater risk of incident cirrhosis (aHR: 0.97, 95% CI: 0.74–1.28 for HbA_{1c} between 6.5% and 7%; aHR: 1.14, 95% CI: 0.84–1.55 for HbA_{1c} between 7% and 7.5%; aHR: 1.37, 95% CI: 1.07–1.76 for HbA_{1c} ≥ 7.5%, Table 3). A similar trend was observed regarding HCC (aHR: 1.42, 95% CI: 0.82–2.48 for HbA_{1c} between 6.5% and 7%; aHR: 1.94, 95% CI: 1.06–3.53 for HbA_{1c} between 7% and 7.5%; aHR: 1.89, 95% CI: 1.10–3.25 for HbA_{1c} ≥ 7.5%, Table 3). Meanwhile, the association did not vary by the duration of diabetes ($P_{interaction} = 0.536$ for cirrhosis; 0.909 for HCC, Supplemental Figure S5, http://links.lww.com/HC9/A543).

Association between the risk of hepatic outcomes and FINDRISC in subjects without diabetes

In subjects without diabetes, the risk of developing diabetes, using FINDRISC as a proxy, was nonlinearly associated with the risk of incident cirrhosis and HCC ($P_{nonlinearity} < 0.001$ for cirrhosis; $= 0.001$ for HCC, Figure 3, A and B). We subsequently divided the participants by quintiles of FINDRISC as 0–4 points, 5–7 points, 8–10 points, 11–12 points, and greater than or equal to 13 points (Figure 3, C). Compared with the lowest quintile (0–4 points), the risk of cirrhosis rose significantly from the second (aHR: 1.62, 95% CI: 1.28–2.04) to the highest (aHR: 3.31, 95% CI: 2.65–4.13) quintile of FINDRISC. The

TABLE 1 Characteristics of participants stratified by prediabetes or diabetes

	Overall (n = 449497)	Normoglycemia (n = 413268)	Prediabetes (n = 13295)	Diabetes (n = 22934)
Demographic				
Age, y	56.73 (8.03)	56.42 (8.06)	60.71 (6.43)	59.97 (6.97)
Sex, male, n (%)	204556 (45.51)	184198 (44.57)	6310 (47.46)	14048 (61.25)
BMI, kg/m^2	27.37 (4.75)	27.04 (4.50)	30.33 (5.56)	31.75 (5.89)
Follow-up, year	12.03 [11.31, 12.73]	12.04 [11.32, 12.74]	11.93 [11.12, 12.71]	11.87 [11.00, 12.64]
Alcohol intake, g/day	16.60 (17.58)	16.70 (17.49)	15.09 (18.38)	15.58 (18.73)
FINDRISC, point	8.70 (4.58)	8.12 (4.04)	11.37 (3.87)	17.91 (3.91)
Education, n (%)				
Vocational	52442 (11.67%)	47304 (11.45%)	1819 (13.68)	3319 (14.47)
Lower Secondary	120838 (26.88)	111760 (27.04)	3428 (25.78)	5650 (24.64)
Upper Secondary	50778 (11.30)	47371 (11.46)	1237 (9.30)	2170 (9.46)
College or University	144131 (32.06)	136142 (32.94)	2838 (21.35)	5151 (22.46)
Others	76910 (17.11)	66777 (16.16)	3810 (28.66)	6323 (27.57)
Unknown	4398 (0.98)	3914 (0.95)	163 (1.23)	321 (1.40)
Household income, pound, n (%)				
< 18,000	85227 (18.96)	74612 (18.05)	3762 (28.30)	6853 (29.88)
18,000–30,999	98407 (21.89)	89718 (21.71)	3230 (24.29)	5459 (23.80)
31,000–51,999	101941 (22.68)	95495 (23.11)	2421 (18.21)	4025 (17.55)
52,000–100,000	80157 (17.83)	76438 (18.50)	1255 (9.44)	2464 (10.74)
> 100,000	21238 (4.72)	20459 (4.95)	280 (2.11)	499 (2.18)
Unknown	62527 (13.91)	56546 (13.68)	2347 (17.65)	3634 (15.85)
Townsend deprivation index, n (%)				
Quintile 1 (least deprived)	93892 (20.89)	87776 (21.24)	2395 (18.01)	3721 (16.22)
Quintile 2	93558 (20.81)	86909 (21.03)	2554 (19.21)	4095 (17.86)
Quintile 3	92034 (20.47)	85026 (20.57)	2617 (19.68)	4391 (19.15)
Quintile 4	88619 (19.72)	81180 (19.64)	2705 (20.35)	4734 (20.64)
Quintile 5 (most deprived)	80862 (17.99)	71896 (17.40)	3007 (22.62)	5959 (25.98)
Unknown	532 (0.12)	481 (0.12)	17 (0.13)	34 (0.15)
Physical activity, n (%)				
Low	67623 (15.04)	60330 (14.60)	2378 (17.89)	4915 (21.43)
Medium	148947 (33.14)	137601 (33.30)	4150 (31.21)	7196 (31.38)
High	148043 (32.94)	138512 (33.52)	3677 (27.66)	5854 (25.53)
Unknown	84884 (18.88)	76825 (18.59)	3090 (23.24)	4969 (21.67)
Smoking behavior, n (%)				
Current	46465 (10.34)	41554 (10.05)	2279 (17.14)	2632 (11.48)
Former	158933 (35.36)	143232 (34.66)	5165 (38.85)	10536 (45.94)
Never	242498 (53.95)	227094 (54.95)	5787 (43.53)	9617 (41.93)
Unknown	1601 (0.36)	1388 (0.34)	64 (0.48)	149 (0.65)
Laboratory tests				
ALT, U/L	23.42 (13.83)	22.89 (13.35)	28.03 (16.07)	30.31 (17.94)
AST, U/L	26.10 (10.23)	25.89 (9.86)	28.22 (12.46)	28.56 (14.10)
GGT, U/L	36.77 (40.00)	35.48 (37.88)	47.81 (50.26)	53.58 (60.46)
Albumin, g/L	45.25 (2.60)	45.27 (2.59)	44.73 (2.65)	45.06 (2.82)
Total bilirubin, μmol/L	9.12 (4.37)	9.16 (4.40)	8.07 (3.65)	8.92 (4.24)
HbA_{1c}, %	5.43 (0.56)	5.32 (0.31)	6.15 (0.14)	6.89 (1.32)
Diabetes history				
Age of diabetes onset, y	—	—	—	54.76 (8.56)
Diabetes duration, y	—	—	—	5.21 (6.10)

TABLE 1. (*continued*)

	Overall (n = 449497)	Normoglycemia (n = 413268)	Prediabetes (n = 13295)	Diabetes (n = 22934)
Diabetes treatment, n (%)				
None	—	—	—	9935 (43.32)
Only insulin	—	—	—	1066 (4.65)
Only oral medication	—	—	—	10320 (45.00)
Insulin and oral medication	—	—	—	1613 (7.03)
Comorbidities, n (%)				
Incident cirrhosis	1824 (0.41)	1303 (0.32)	97 (0.73)	424 (1.85)
Incident HCC	272 (0.06)	157 (0.04)	16 (0.12)	99 (0.43)
Baseline hypertension	250477 (55.72)	221354 (53.56)	10001 (75.22)	19122 (83.38)
Baseline dyslipidemia	248765 (55.34)	217196 (52.56)	10575 (79.54)	20994 (91.54)
Baseline ALD	27500 (6.12)	24436 (5.91)	1069 (8.04)	1995 (8.70)
Baseline alcohol use disorder	21313 (4.74)	18919 (4.58)	799 (6.01)	1595 (6.95)
Baseline NAFLD	10555 (2.3)	8790 (2.1)	444 (3.3)	1321 (5.8)

Note: Continues variables were mean (SD) or median [interquartile range], and categorical variables were numbers (%).
Abbreviations: ALD, alcohol-related liver disease; FINDRISC, Finnish Diabetes Risk Score; GGT, gamma-glutamyl transferase.

incidence rate for cirrhosis was 19.53, 24.93, 36.73, and 46.36 per 100,000 person-years in the second, third, fourth, and highest quintile of FINDRISC, respectively. The trend remained similar regarding HCC, albeit with an attenuated association. Interaction analysis indicated that in participants with a high genetic risk of HCC, every 5-point increment of FINDRISC was associated with a significantly greater risk of HCC (aHR: 1.93, 1.45–2.58, $P_{interaction} = 0.005$, Figure 4).

Additional analyses

By sensitivity analyses, we found the associations between diabetes status and risk of cirrhosis and HCC was robust when using alternate definition of liver outcomes, excluding participants with alcohol-associated liver disease and alcohol use disorder, or adjusting for the presence of NAFLD (Supplemental Table S3, http://links.lww.com/HC9/A543). An array of post hoc subgroup analyses regarding prediabetes (Supplemental Figure

TABLE 2 Effects of prediabetes, diabetes, and diabetes duration on risk of incident cirrhosis and hepatocellular carcinoma

			Diabetes		
	Normoglycemia	Prediabetes	< 5 y	≥ 5 y	Overall
Incident cirrhosis					
Cirrhosis cases/total cases, No.	1303/413268	97/13295	220/13248	204/9686	424/22934
Rate/100,000 person, y	26.69	63.72	145.65	188.73	163.62
Model, HR (95% CI)					
1	1 [Reference]	1.85 (1.50–2.28)	3.88 (3.36–4.49)	4.54 (3.90–5.28)	4.21 (3.76–4.72)
2	1 [Reference]	1.45 (1.18–1.79)	2.99 (2.57–3.48)	3.59 (3.06–4.20)	3.28 (2.91–3.70)
3	1 [Reference]	1.41 (1.14–1.73)	2.85 (2.45–3.32)	3.43 (2.92–4.02)	3.12 (2.77–3.53)
Incident HCC					
HCC cases/total cases, No.	157/413268	16/13295	41/13248	58/9686	99/22934
Rate/100,000 person, y	3.21	10.49	27.04	53.38	38.04
Model, HR (95% CI)					
1	1 [Reference]	2.25 (1.34–3.77)	5.79 (4.08- 8.20)	9.34 (6.84–12.73)	7.38 (5.70–9.57)
2	1 [Reference]	1.81 (1.07–3.05)	4.39 (3.05–6.32)	7.20 (5.19–10.00)	5.63 (4.26–7.43)
3	1 [Reference]	1.80 (1.06–3.04)	4.40 (3.03–6.38)	7.25 (5.16–10.19)	5.68 (4.25–7.59)

Notes: Model 1 indicates that analysis was adjusted for age (years), sex (male/female), education (6 categories), Townsend deprivation index (6 categories), and income (6 categories). Model 2 indicates adjustment for Model 1 and alcohol consumption (g/day), smoking behavior (current/former/never), physical activity (low/medium/high/unknown), and body mass index (kg/m^2). Model 3 indicates adjustment for Model 2 and baseline presence of hypertension (yes/no), dyslipidemia (yes/no), assessment center (22 categories), and polygenic risk score (scaled continuous variable) for cirrhosis or HCC, respectively.

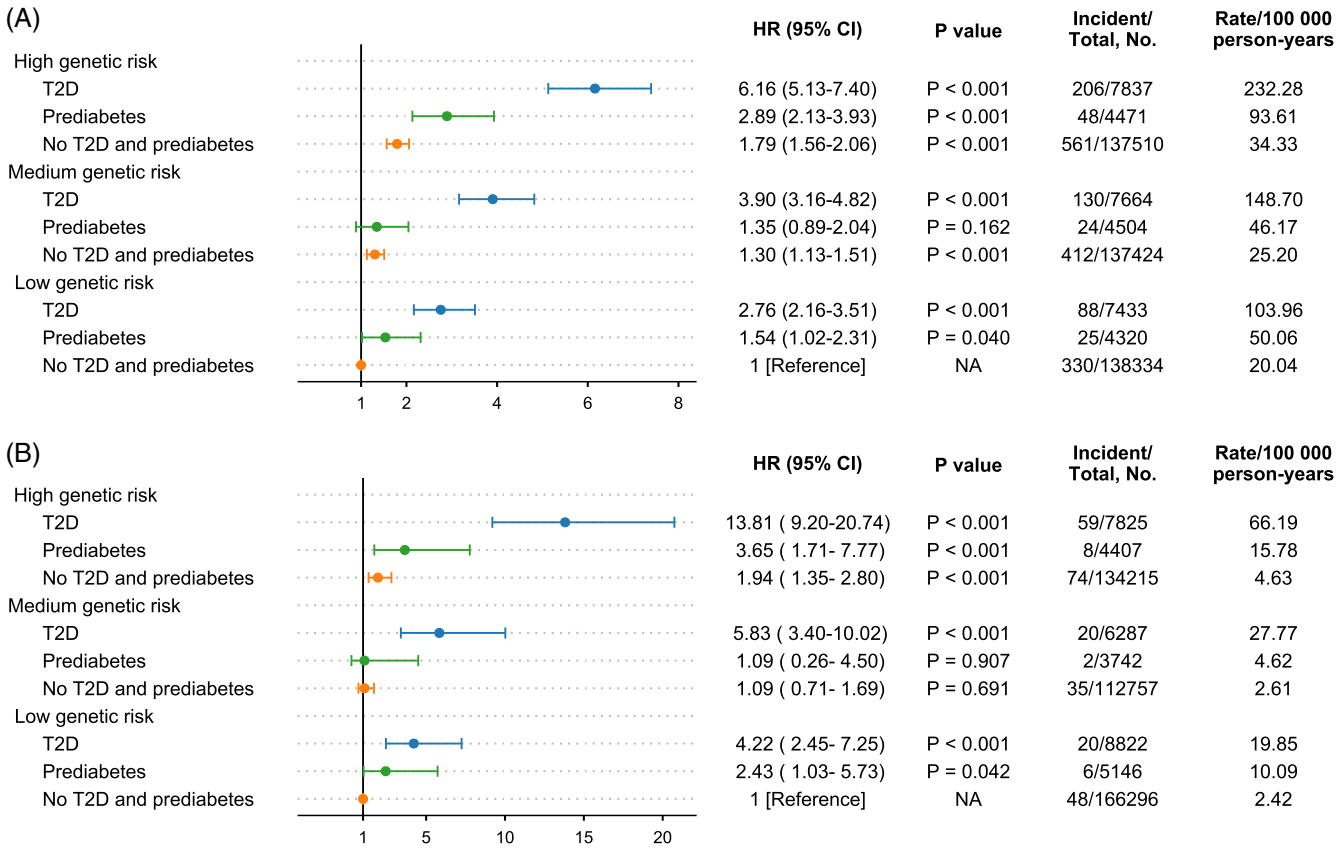
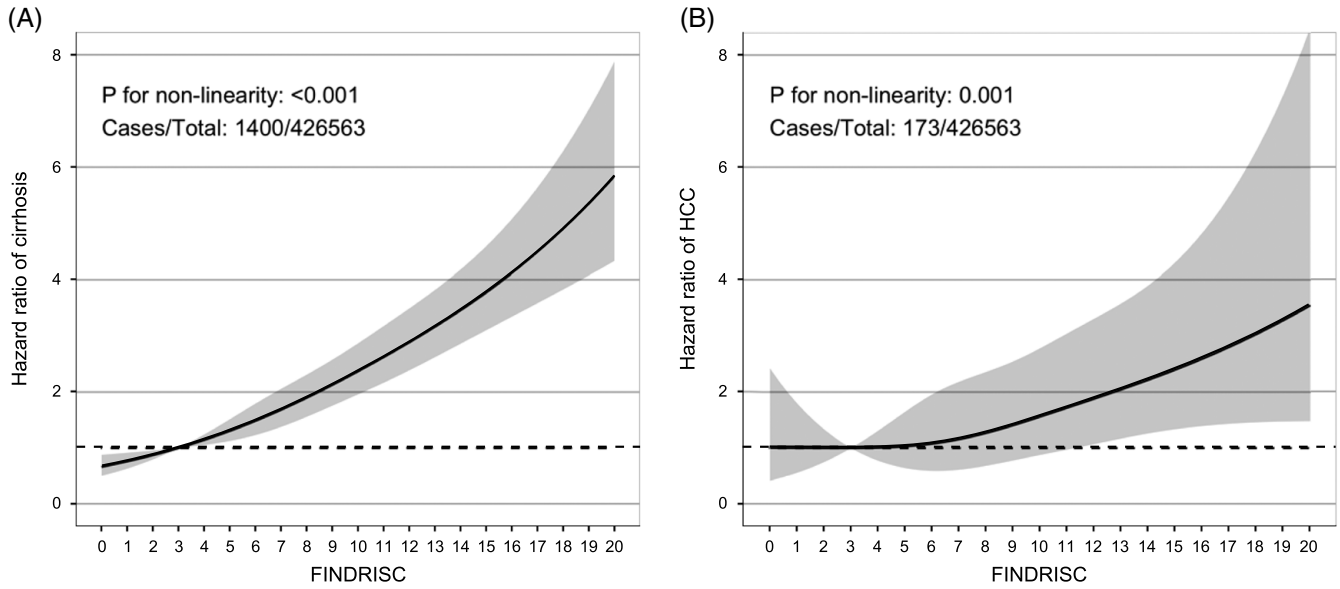


FIGURE 2 Risk of incident cirrhosis and HCC according to genetic risk and presence of diabetes or prediabetes. (A) Risk of incident cirrhosis; (B) Risk of incident HCC. Tertile of genetic risk for cirrhosis or HCC (low, medium, and high) was evaluated by polygenic risk scores, respectively. The P for interaction was 0.095 for cirrhosis and 0.081 for HCC, calculated by including a product term of diabetes status and the polygenic risk score of cirrhosis or HCC, respectively, adjusting for Model 3. Abbreviation: T2D, type 2 diabetes.

TABLE 3 Association between baseline hemoglobin A1c level and incident cirrhosis or hepatocellular carcinoma in diabetic subjects

	HbA_{1c} <6.5%	6.5% ≤ HbA_{1c} <7%	7% ≤ HbA_{1c} <7.5%	HbA_{1c} ≥7.5%
Incident cirrhosis				
Cirrhosis cases/total cases, No.	146/9030	84/5071	57/2951	115/4956
Rate/100,000 person, y	142.69	146.36	170.96	206.71
Model, HR (95% CI)				
1	1 [Reference]	1.02 (0.78–1.33)	1.17 (0.86–1.60)	1.43 (1.12–1.83)
2	1 [Reference]	0.98 (0.74–1.28)	1.14 (0.84–1.56)	1.40 (1.09–1.79)
3	1 [Reference]	0.97 (0.74–1.28)	1.14 (0.84–1.55)	1.37 (1.07–1.76)
Incident HCC				
HCC cases/total cases, No.	28/9030	23/5071	18/2951	27/4956
Rate/100,000 person, y	27.26	39.92	53.78	48.24
Model, HR (95% CI)				
1	1 [Reference]	1.44 (0.83–2.50)	1.90 (1.05–3.44)	1.91 (1.13–3.25)
2	1 [Reference]	1.41 (0.81–2.45)	1.94 (1.07–3.51)	1.95 (1.14–3.33)
3	1 [Reference]	1.42 (0.82–2.48)	1.94 (1.06–3.53)	1.89 (1.10–3.25)

Notes: Model 1 adjusted for age (y), sex (male/female), education (6 categories), Townsend deprivation index (6 categories), and income (6 categories). Model 2 adjusted for Model 1 and alcohol consumption (g/day), smoking behavior (current/former/never), physical activity (low/medium/high/unknown) and BMI (kg/m^2). Model 3 adjusted for Model 2 and baseline presence of hypertension (yes/no), dyslipidemia (yes/no), assessment center (22 categories), and polygenic risk score (scaled continues variable) for cirrhosis or HCC, respectively.



(C)

	HR (95% CI)	P value	Incident/ Total, No.	Rate/100 000 person-years
FINDRISC ≥13	2.09 (1.15-3.80)	P = 0.015	41/56249	6.22
	3.31 (2.65-4.13)	P < 0.001	305/56249	46.36
FINDRISC 11-12	1.36 (0.71-2.61)	P = 0.356	23/52812	3.70
	2.73 (2.17-3.44)	P < 0.001	228/52812	36.73
FINDRISC 8-10	1.25 (0.69-2.28)	P = 0.456	38/104229	3.08
	1.99 (1.60-2.48)	P < 0.001	307/104229	24.93
FINDRISC 5-7	0.96 (0.50-1.83)	P = 0.902	23/89972	2.16
	1.62 (1.28-2.04)	P < 0.001	208/89972	19.53
FINDRISC 0-4	1 [Reference]	NA	16/85126	1.58
	1 [Reference]	NA	118/85126	11.62

FIGURE 3 Association between FINDRISC and incident cirrhosis and HCC in subjects without diabetes. (A and B) Nonlinear association presented by restricted cubic spline with 4 knots specified, using FINDRISC = 3 as reference level. (C) HR, incident cases, and incident rate of cirrhosis and HCC across the FINDRISC quintile. The analyses were adjusted for age (y), sex (male/female), education (6 categories), Townsend deprivation index (6 categories) and income (6 categories). Abbreviation: FINDRISC, Finnish Diabetes Risk Score.

S6, http://links.lww.com/HC9/A543), diabetes (Supplemental Figure S7, http://links.lww.com/HC9/A543), and diabetes duration (Supplemental Figure S8, http://links.lww.com/HC9/A543) were conducted, which showed a consistent effect of these factors on liver outcomes. The risk of HCC was similar to cirrhosis when controlling the presence of incident cirrhosis. To account for competing risks, the Fine-Gray model was used, and a comparable risk was found for cirrhosis and HCC regarding prediabetes, diabetes, and its duration (Supplemental Table S4, http://links.lww.com/HC9/A543). The cutoff of diabetes duration used in the analyses was justified by comparing cumulative incidence curves (Supplemental Figure S9, http://links.lww.com/HC9/A543).

DISCUSSION

In this large prospective cohort study of middle and elderly adults, individuals with prediabetes, less than 5 years of diabetes, and greater than or equal to 5 years of diabetes showed an increasingly higher risk of incident cirrhosis and HCC. Regarding glycemic control, a lower baseline HbA_{1c} level was associated with a lower risk of future cirrhosis and HCC in subjects with type 2 diabetes. Subjects without type 2 diabetes but at high risk of developing it were also prone to cirrhosis and HCC, and this link between diabetes and HCC was likely exacerbated by HCC genetic risk. These lines of evidence may inform the

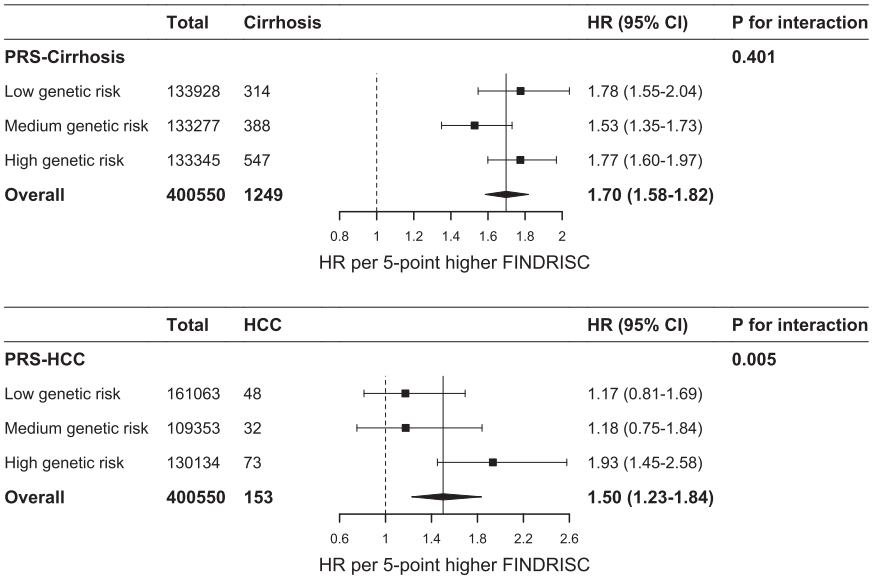


FIGURE 4 Risk of incident cirrhosis and HCC in nondiabetic subjects with different FINDRISC according to cirrhosis or HCC genetic risk. The upper and lower panel represent the risk of cirrhosis or HCC of participants grouped by PRS, respectively. HRs were calculated for every 5-point increment of FINDRISC, adjusting for age. The total number of subjects and incident cirrhosis and HCC were shown, respectively. P for interaction was calculated by including a product term of FINDRISC and PRS of cirrhosis or HCC in the Cox model, respectively, adjusting for age. Abbreviations: FINDRISC, Finnish Diabetes Risk Score; PRS, polygenic risk score.

refinement of diabetes management regarding liver diseases.

Comparing subjects with diabetes to those without diabetes and prediabetes, the relative risk of cirrhosis (aHR: 3.12) was largely consistent with a cohort study of 6251 adult patients with chronic hepatitis C,[17] which concluded that new-onset diabetes hastened the development of cirrhosis (aHR: 2.51) and decompensated cirrhosis (aHR: 3.56). In the current large cohort without viral hepatitis but which was substantially affected by dysmetabolism (50% of participants with hypertension or dyslipidemia), diabetes posed a similar additional risk. By contrast, in a prospective study of 0.5 million adults with lower body mass index and fewer metabolic risk factors, the risk of cirrhosis was lower (aHR: 1.81).[18] Therefore, metabolic disorders could contribute to the development of cirrhosis regardless of viral hepatitis and alcohol consumption, highlighting the urgent need for effective management for those harboring metabolic risk factors, especially diabetes, to prevent cirrhosis and HCC. In addition, we found that diabetes status is associated with incident cirrhosis independent of genetic predisposition. This implied that screening for diabetes is more suitable to be exercised in the at-risk population regardless of one's genetic propensity to liver fibrosis or cirrhosis.

The longer duration of diabetes appeared to be linked to liver-related outcomes, but the association was poorly profiled. Pang et al reported the highest risks of cirrhosis and liver cancer in individuals with 0–2 years of diabetes (HR: 2.62) but attenuated in those with a longer period of time.[18] On the contrary, by exploring nonlinear associations, we showed that having greater than or equal to 5 years of diabetes at baseline was associated with a higher risk of future cirrhosis and HCC compared to those with a shorter duration of diabetes. The attenuated associations in previous studies might be explained by unobserved changes in treatment exposure and health-related behaviors during follow-up. Our study found that the longer duration of diabetes heightened cirrhosis and HCC risk after accounting for the competing risk of death.

Long-term glycemic control contributed to advanced liver fibrosis as a 1% higher HbA_{1c} related to 15% (adjusted OR: 1.15) higher risk independent of type 2 diabetes.[3] Data from the UK Biobank cohort showed a relatively weaker association between HbA_{1c} and liver diseases in those with type 2 diabetes compared with the risk posed by diabetes per se. A possible reason for this modest association was that a lower baseline HbA_{1c} level was associated with a relatively healthier lifestyle and a type 2 diabetes of milder severity (55.7% of diabetic subjects with $HbA_{1c} < 6.5\%$ and without diabetes treatment) and shorter duration (median, 3.0 y), which resulted in less severe steatosis and subsequent liver fibrosis.[19]

Diabetes is preceded by a preclinical stage that is undetectable for several years.[4] Few studies have looked at the link between preclinical diabetes and liver fibrosis. In a cross-sectional study of 4207 adults in the United States, neither liver fibrosis nor cirrhosis was associated with prediabetes.[20] Herein, we demonstrated that in non-diabetes, prediabetes (HbA_{1c} 6.0–6.4%) and an elevated risk of future diabetes were associated with a significantly higher risk of future cirrhosis. However, the modest increase in the risk of HCC might be partly explained as a carryover effect

from cirrhosis. Given the large number of people without diabetes but are at significantly elevated risk of future diabetes and cirrhosis, subjects in the preclinical stage of diabetes may account for a considerable burden of incident cirrhosis and HCC, both of which are potentially preventable.

Our study has limitations. We could not assess NASH-related cirrhosis due to a lack of histological data in such a large cohort. Imaging-based assessment of NAFLD, when performing sensitivity analyses, demonstrated the robustness of the association between diabetes and cirrhosis. Identifying cirrhosis and HCC relied on inpatient records, which may be incapable of capturing all cases. To attenuate the bias, we employed an externally validated panel of ICD codes and carefully considered its feasibility in the current study. Regarding the generalizability of the results, we estimated associations exclusively from Caucasians of middle and old age, hence the caution for extrapolating the conclusion to the population of other races and age groups. As an epidemiologic study, our results could not establish a causal relationship between diabetes status and the development of liver cirrhosis. Also, we used FINDRISC to assess the risk of developing diabetes, which contained several factors that may be associated with cirrhosis or HCC independent of diabetes.

In conclusion, preclinical and clinical stages of diabetes were associated with the risk of incident cirrhosis and HCC. This could help with clinical surveillance of these advanced liver diseases, allowing for early diagnosis, more accurate risk stratification, and improved disease prognosis.

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

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