Associations of severe liver diseases with cataract using data from UK Biobank: a prospective cohort study

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Summary

Background Liver disease is linked to series of extrahepatic multisystem manifestations. However, little is known about the associations between liver and eye diseases, especially cataract, the global leading cause of blindness. We aimed to investigate whether severe liver diseases, including non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), viral hepatitis, and liver fibrosis and cirrhosis, were associated with an increased risk of the cataract.

Methods A total of 326,558 participants without cataract at baseline enrolled in the UK Biobank between 2006 and 2010 were included in this prospective study. The exposures of interest were severe liver diseases (defined as hospital admission), including NAFLD, ALD, viral hepatitis and liver fibrosis and cirrhosis. The outcome was incident cataract. Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). Each liver disease was first treated as a binary time-varying variable to investigate its association with cataract, and then was treated as a ternary time-varying variable to examine the recent (liver disease within 0–5 years) *vs.* long-term (liver disease > 5 years) state associations with the risk of cataract.

Findings After a median follow-up of 13.3 years (interquartile range, 12.5–14.0 years), 37,064 individuals were documented as developing cataract. Higher risk of cataract was found in those with severe NAFLD (HR, 1.47; 95% CI, 1.33–1.61), ALD (HR, 1.57; 95% CI, 1.28–1.94) and liver fibrosis and cirrhosis (HR, 1.58; 95% CI, 1.35–1.85), but not in individuals with viral hepatitis when exposure was treated as a binary time-varying variable (P = 0.13). When treating exposure as a ternary time-varying variable, an association between recently diagnosed viral hepatitis and cataract was also observed (HR, 1.55; 95% CI, 1.07–2.23). Results from the combined model suggested they were independent risk factors for incident cataract. No substantial changes were found in further sensitivity analyses.

Interpretation Severe liver diseases, including NAFLD, ALD, liver fibrosis and cirrhosis and recently diagnosed viral hepatitis, were associated with cataract. The revelation of liver-eye connection suggests the importance of ophthalmic care in the management of liver disease, and the intervention precedence of patients with liver disease in the early screening and diagnosis of cataract.

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Research in context

Evidence before this study

We searched the PubMed database using the search terms [(non-alcoholic fatty liver disease OR NAFLD OR alcoholic liver disease OR ALD OR viral hepatitis OR liver fibrosis OR cirrhosis) AND cataract] on 19 September, 2023. The studies mainly focused on the association between viral hepatitis and cataract, and were limited by cross-sectional design or insufficient variable adjustment. Evidence on risk of cataract among patients with non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD) or liver fibrosis and cirrhosis was scarce.

Added value of this study

To our knowledge, this is the first large-scale prospective cohort study systematically investigating the associations between liver diseases and cataract. We found that those with severe liver diseases (defined as hospital admission), including NAFLD, ALD, liver fibrosis and cirrhosis and recently diagnosed viral hepatitis, had a higher risk of cataract. These liver diseases were furthered showed to be independent risk factors for incident cataract.

Implications of all the available evidence

Liver diseases were associated with risk of incident cataract. Ophthalmic care may need to be emphasized in the management of liver disease, and those with liver diseases may serve as potential target populations in the early screening and diagnosis of cataract. Additionally, further studies are required to elaborate the underlying mechanisms of liver-eye connection.

Introduction

Liver disease poses a serious burden on global public health with significant morbidity and mortality.[1] It generates 565 disability-adjusted life years (DALYs) per 100,000 population worldwide with respect to chronic liver disease, and accounts for approximately 2 million deaths per year at the global level, of which 1.16 million deaths are caused by cirrhosis.[1] Non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD) and viral hepatitis are the most common causes of cirrhosis.[2]

The liver undergoes series of metabolic and immune alternations in pathological conditions.[3,4] The diseased liver leads to abnormalities in numerous critical metabolic pathways,[5,6] and the activation of immune responses fuels hepatic and systemic inflammation.[7] On one hand, these pathophysiological alternations are implicated in the pathogenesis of various liver diseases and determine their outcomes, namely resolution or progression to fibrosis and cirrhosis.[3,8] On the other hand, metabolic changes and immune-mediated inflammation in liver disease play a pivotal role in the interplay between the liver and other organs, which can finally result in series of extrahepatic complications.[9] For example, those with NAFLD have a higher risk of developing cardiovascular disease such as cardiac arrhythmias.[10,11] The involved mechanisms might include altered metabolism in lipid,[12] methionine,[13] etc., as well as higher circulating pro-inflammatory cytokines resulting from immune responses.[14] Similar phenomena were also observed not only in ALD and viral hepatitis,[9,15–18] but also in liver fibrosis and cirrhosis,[5,19,20] the potential consequence of these liver diseases, owing to some resembled metabolic and immune patterns.

Cataract is the leading cause of global blindness characterized by opacification of the lens.[21,22] It has long been recognized that the metabolic derangement, such as diabetes and dyslipidemia, can accelerate the development of cataract.[23–25] There is also some evidence suggesting the role of immune components in the cataractogenesis.[26–29] Therefore, it is reasonable to speculate that, liver disease may increase the risk of cataract development owing to the metabolic and immune alternations. However, to the best of our knowledge, the association between liver disease and cataract has merely been investigated in viral hepatitis limited by cross-sectional design or insufficient variable adjustment.[30,31] NAFLD, ALD and liver fibrosis and cirrhosis, as described above, are also characterized by metabolic alternations and inflammation. The relationship between these important liver diseases and subsequent cataract has not been examined.

In this study, we aimed to fill these knowledge gaps and enrich the extrahepatic disease spectrum of liver disease in the UK Biobank (UKB) study, by systematically investigating whether severe liver diseases, including NAFLD, ALD, viral hepatitis and liver fibrosis and cirrhosis, were associated with an increased risk of the cataract. Our work provided an insight into liver-eye connection from an epidemiological perspective.

Methods

Study population

The UKB is a large, prospective cohort study that enrolled over 500,000 participants across UK aged 37–73 years between 2006 and 2010 with a response

rate of 5.5%.[32] Extensive information was collected including data from touch-screen questionnaires, verbal interview, physical measures, biological samples and multimodal imaging. Further information about the study protocols is available online (https://www.ukbiobank.ac.uk/). This work was conducted under the application number 93118.

In this study, we excluded participants diagnosed with cataract at baseline (n = 14,238) and those who had records of cataract but the diagnosis or occurrence dates were lack of explicit clinical confirmation (n = 2721) (See "Incident cataract" section). We further excluded those who missed any data on covariates (n = 157,997). 856 participants lost to visit during a median follow-up of 13.3 years were also excluded. Eventually, a total of 326,558 participants were included for the final analysis. The flow chart was shown in Fig. 1.

Ethics

The UKB study was approved by the North West Multi-Center Research Ethics Committee. All participants provided informed consent through electronic signature upon recruitment.

Data on severe liver diseases

We defined severe liver diseases as hospitalization due to liver diseases as the previous study did.[33] Date and cause of hospital admission were obtained based on the hospital inpatient records through linkage to the Hospital Episode Statistics for England, Scottish Morbidity for Scotland, or Patient Episode Database for Wales. Patients with severe NAFLD, ALD, viral hepatitis or liver fibrosis and cirrhosis were ascertained based on the International Classification of Diseases (ICD)-9 and ICD-10 codes. Detailed information on ICD codes for each liver disease was described in Supplementary Table S1.

The UKB primary care data was another source of the health status of the participants and provided data recorded by health care professionals working at general practices. We used the Read v2 or CTV3 code mapping to the same ICD-10 codes described above to ascertained NAFLD, ALD, viral hepatitis and liver fibrosis and cirrhosis cases recorded at general practices (Supplementary Table S1). Given that less severe liver disease cases were thus included into exposure groups and only approximately 45% of the UKB cohort linked to primary care records, we did not include these patients into the main analyses under the definition of severe liver diseases. These patients recorded at primary level were combined with those hospitalized to form more complete liver disease sets, on which risk analyses would be conducted in sensitivity analyses to assess the robustness of our findings (see "Statistical analyses" section).

Incident cataract

Cataract diagnosis was ascertained by two steps. A complete cataract set was first determined using the "first occurrences" fields. The "first occurrences" fields provided by UKB defined each health outcome from different sources including self-report, primary care,

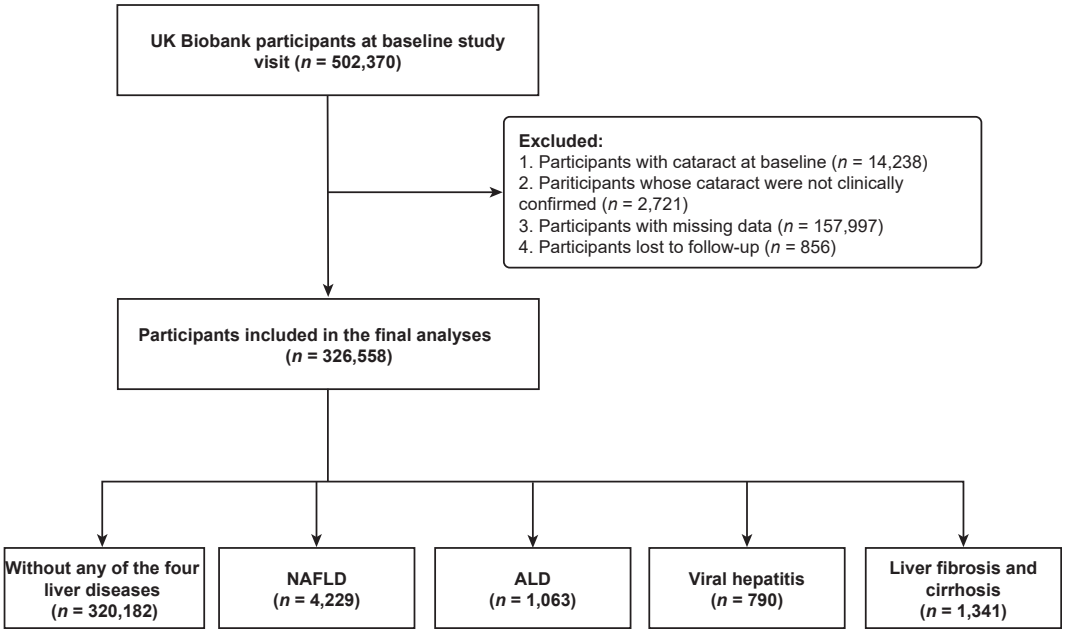

Fig. 1: **Flowchart showing the criterion of the study cohort from participants in the UK Biobank.** NAFLD, non-alcoholic fatty liver disease; ALD, alcoholic liver disease.

hospital inpatient data and death register records, which were mapped to unified ICD-10 codes with the earliest date of health outcome created. The data-field ID for cataract was described in Supplementary Table S2. No individual died of cataract. Those whose diagnosis or the incident dates of cataract without the support of primary care or hospital admissions data were considered as lack of explicit clinical confirmation, and were therefore excluded to ensure the accuracy of cataract ascertainment (n = 2,721, Fig. 1). The ICD-9 and ICD-10 codes for hospital inpatient data and Read codes for primary care data were also provided in Supplementary Table S2 based on clinical coding classification systems and maps in the UKB.

Covariates

Age at enrollment, year of birth, sex, ethnicity, alcohol intake frequency and smoking status were self-reported through a touchscreen questionnaire. The Townsend deprivation index was obtained based on participant's postcode. Alcohol intake frequency was categorized as daily or almost daily, 3 or 4 times a week, once or twice a week, 1–3 times a month, special occasions only and never. Smoking status was categorized as never, former and current. Physical activity was assessed based on International Physical Activity Questionnaire (IPAQ) guidelines and whether physical activity at or above moderate/vigorous/walking recommendation (150 min of walking or moderate activity per week or 75 min of vigorous activity according to 2017 UK Physical activity guidelines) was acquired.[34] Standing height and waist circumference were measured manually by trained nurses. Body mass index (BMI) was then calculated according to weight and standing height. Concentration of high-density lipoprotein cholesterol (HDL-C), triglycerides, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured in the blood sample collected at basement, while platelet (PLT) count was a result of hematological assays using whole blood before further processing. Fibrosis-4 index (FIB-4) was then calculated according to age, AST, ALT and PLT. History of hypertension, diabetes, chronic kidney disease and retinal diseases were obtained through a verbal interview by a trained nurse and the detailed definitions were provided in Supplementary Table S3.

Statistical analyses

The primary analysis was based on the complete dataset with no missing data. Baseline demographics and characteristics according to liver disease were described with quantitative variables presented as means and standard deviations (SDs) while categorical variables presented as frequencies and percentages.

Cox proportional hazards models with age as the time-axis were used to estimate the risk of cataract associated with NAFLD, ALD, viral hepatitis and liver fibrosis and cirrhosis represented as hazard ratios (HRs) and 95% confidence intervals (CIs). At the time of our analyses, the censoring date of hospital inpatient data was October 31, 2022 for England, July 31, 2021 for Scotland and February 28, 2018 for Wales. Censoring therefore occurred at this date, death or cataract onset, whichever occurred first. Model assumptions were checked using Schoenfeld residuals. To address potential immortal time bias,[35] each liver disease was treated as a binary time-varying variable as previous studies did,[36–39] that is, before/without the diagnosis of liver disease individuals were assigned to the unexposed group, and were assigned to the exposed group when liver disease was diagnosed until the end of follow-up. We further investigated the recent (liver disease within 0–5 years) *vs.* long-term (liver disease > 5 years) liver disease state associations with the risk of cataract, using a ternary time-varying variable which adopted the similar principle as the binary time-varying variable when taking values. To measure the single effect of each liver disease on cataract, risk association analysis was conducted firstly in separate model, without adjustment of other liver diseases. Given that four liver diseases in our study were not independent entities, as liver fibrosis and cirrhosis was associated with NAFLD, ALD and viral hepatitis,[20] certain liver disease may depend on other liver diseases to influence the cataract development. Therefore, to estimate the independence of effect exerted by each liver disease on incident cataract, four liver diseases were modeled together (combined model) as a previous study did,[36] that is, a total of 16 variables comprising 4 time-varying variables of liver diseases and 12 covariates in model 3 (see below) were included in the Cox proportional hazards models. Regardless of whether it was a separate model or a combined model, or whether a participant was diagnosed with a single or multiple liver diseases, the principle of taking values for each time-varying variable of liver disease remained consistent with the above descriptions. More details and illustrative examples were provided in Supplementary Methods.

A directed acyclic graph explaining the relationships between exposures, outcome and covariates was provided in Supplementary Fig. S1 to state the principle of confounders selecting. In addition to age as the time-axis, model was firstly adjusted for basic demographics including sex, year of birth, ethnicity and Townsend deprivation index (model 1). Model 2 was adjusted terms in model 1 and lifestyle factors including alcohol intake, smoking status and physical activities. Model 3 was further adjusted BMI, HDL-C, triglycerides, history of hypertension and history of diabetes, which served as not only the potential risk factors for cataract but also the components of metabolic syndrome.[40] Model 3 was considered as the best-fit model for the lowest score of Akaike information criterion (AIC) and Bayesian information criterion (BIC) among three models (Supplementary Table S4)

and was thus chosen as the primary model for subsequent analyses.

We further performed several subgroup analyses stratified by sex (male or female), ethnicity (British or others), Townsend deprivation index (high, medium or low), smoking status (never, former, or current), physical activity (above or below recommendation), BMI (high, medium or low), HDL-C (high, medium or low), triglycerides (high, medium or low), history of hypertension (yes or no), and history of diabetes (yes or no). Likelihood ratio tests were used to test interaction effects by comparing Cox models with or without an interaction term of strata factor and exposure.

To assess the robustness of our findings, we conducted several sensitivity analyses: (1) adjusting for more potential cataract risk factors and liver function biomarkers into Cox model, including waist circumference (another component of metabolic syndrome),[40] history of chronic kidney disease and history of retinal diseases as cataract risk factors,[22] as well as AST, ALT and FIB-4 index as liver function biomarkers; (2) excluding the liver diseases at baseline and only considering the liver diseases diagnosed during the follow-up as a previous study did[39]; (3) treating the first 2 years after liver diseases diagnosis as unexposed person-time to strengthen the causal inference; (4) adding individuals with liver diseases derived from primary care data into exposed groups; varying the definitions of recent and long-term liver disease states to a (5) 2-year time window and a (6) 8-year time window; (7) performing the same analysis in the original dataset with missing data as in the final dataset of 326,558 participants with complete data on all covariates. The percentages of participants with missing covariate data in physical activity, HDL-C, triglycerides, BMI, ethnicity, alcohol intake, smoking status and Townsend deprivation index were 19.8%, 14.4%, 6.6%, 2.0%, 0.2%, 0.2%, 0.2% and 0.1%, respectively. Multiple imputation was performed to impute these missing data and further details were described in Supplementary Methods. Frequencies and percentages of missing data according to liver disease were shown in Supplementary Table S5, and the pattern of data missingness presented by correlation matrix was shown in Supplementary Fig. S2; (8) varying the outcome of interest from incident cataract to incident cataract surgery. Codes used to define cataract surgery and participants included in this sensitivity analysis were described in Supplementary Methods; and (9) using the E-value methodology to assess the potential effect of unmeasured confounding.[41] This methodology estimated what the minimum risk ratio an unmeasured confounder would need to have between both liver disease and cataract to negate the observed associations in our study (see Supplementary Methods for details).[42]

All statistical analyses were performed by R version 4.3.0 (R Foundation for Statistical computing). A 2-sided P-value < 0.05 was considered statistically significant.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication.

Results

Cohort description

The study included a total of 326,558 participants with no missing data. Among these, 157,180 were males and 169,378 were females, with a mean age at enrollment of 56.1 years. 6376 participants were diagnosed with at least one liver disease at baseline or during the follow-up. Among these with liver diseases, most participants were diagnosed with NAFLD (327 cases at baseline; 3902 cases during the follow-up), followed by liver fibrosis and cirrhosis (198 cases at baseline; 1143 cases during the follow-up) and ALD (282 cases at baseline; 781 cases during the follow-up), and the least number of participants diagnosed with viral hepatitis (334 cases at baseline; 456 cases during the follow-up).

Baseline demographics and characteristics by liver disease are presented in Table 1. Compared with individuals not diagnosed with any of the four liver diseases, those in either liver disease group were more likely to be male, more deprived, current smoker, have lower physical activity and have a history of hypertension and diabetes. Additionally, individuals diagnosed with NAFLD, ALD or liver fibrosis and cirrhosis tend to have higher BMI and triglycerides levels, whereas those with viral hepatitis showed no significant differences on these measures compared with individuals without any of the four liver diseases.

Severe liver diseases and risk of incident cataract

The incidence pattern of cataract for each liver disease was described in Table 2. During a median follow-up of 13.3 years (interquartile range, 12.5 to 14.0 years), 37,064 participants were documented as developing cataract. Incident cases under the exposure of NAFLD, ALD, viral hepatitis and liver fibrosis and cirrhosis were 420, 89, 67 and 153, respectively, and the corresponding incident cases per 100,000 person-years were 2210.05, 1655.12, 1040.85 and 2424.16, respectively. The associations between severe liver diseases and cataract were shown in Table 3 based on Cox proportional hazards models. Individuals with NAFLD had a 47% increased risk of cataract (HR, 1.47; 95% CI, 1.33–1.61; P < 0.0001) in model 3. This increased risk was even higher 5 years after the NAFLD diagnosis (HR, 1.52; 95% CI, 1.31–1.78; P < 0.0001) compared with the first 5 years (HR, 1.43; 95% CI, 1.26–1.62; P < 0.0001). Similar higher adjusted hazard ratios for cataract were also found in those with ALD (HR, 1.57; 95% CI, 1.28–1.94; P < 0.0001) or liver fibrosis and cirrhosis (HR, 1.58; 95%

	Overall	No diagnosis of any of the four liver diseases	NAFLD	ALD	Viral hepatitis	Liver fibrosis and cirrhosis
No. of participants	326,558	320,182	4229	1063	790	1341
Age at enrollment, mean (SD), yrs	56.1 (8.1)	56.1 (8.1)	56.0 (7.8)	55.7 (7.6)	54.8 (7.7)	58.1 (7.4)
Year of birth, *n* (%)						
1931–1940	20,098 (6.2)	19,733 (6.2)	238 (5.6)	48 (4.5)	34 (4.3)	107 (8.0)
1941–1950	138,556 (42.4)	135,878 (42.4)	1728 (40.9)	428 (40.3)	283 (35.8)	688 (51.3)
1951–1960	104,763 (32.1)	102,523 (32.0)	1530 (36.2)	391 (36.8)	305 (38.6)	395 (29.5)
1961–1970	63,141 (19.3)	62,048 (19.4)	733 (17.3)	196 (18.4)	168 (21.3)	151 (11.3)
Sex, *n* (%)						
Male	157,180 (48.1)	153,603 (48.0)	2183 (51.6)	831 (78.2)	493 (62.4)	794 (59.2)
Female	169,378 (51.9)	166,579 (52.0)	2046 (48.4)	232 (21.8)	297 (37.6)	547 (40.8)
Ethnicity, *n* (%)						
British	290,613 (89.0)	285,095 (89.0)	3712 (87.8)	938 (88.2)	577 (73.0)	1187 (88.5)
Others	35,945 (11.0)	35,087 (11.0)	517 (12.2)	125 (11.8)	213 (27.0)	154 (11.5)
Townsend deprivation index, mean (SD)	−1.4 (3.0)	−1.4 (3.0)	−0.5 (3.3)	0.5 (3.7)	0.5 (3.8)	−0.3 (3.5)
Alcohol intake, *n* (%)						
Daily or almost daily	69,523 (21.3)	68,083 (21.3)	789 (18.7)	527 (49.6)	147 (18.6)	316 (23.6)
3 or 4 times a week	78,523 (24.0)	77,446 (24.2)	734 (17.4)	159 (15.0)	139 (17.6)	199 (14.8)
Once or twice a week	84,485 (25.9)	83,137 (26.0)	976 (23.1)	100 (9.4)	174 (22.0)	263 (19.6)
1–3 times a month	35,713 (10.9)	35,002 (10.9)	533 (12.6)	36 (3.4)	83 (10.5)	132 (9.8)
Special occasions only	34,506 (10.6)	33,584 (10.5)	696 (16.5)	49 (4.6)	104 (13.2)	190 (14.2)
Never	23,808 (7.3)	22,930 (7.2)	501 (11.8)	192 (18.1)	143 (18.1)	241 (18.0)
Smoking status, *n* (%)						
Never	179,028 (54.8)	176,318 (55.1)	1926 (45.5)	307 (28.9)	295 (37.3)	558 (41.6)
Former	113,904 (34.9)	111,428 (34.8)	1676 (39.6)	373 (35.1)	296 (37.5)	537 (40.0)
Current	33,626 (10.3)	32,436 (10.1)	627 (14.8)	383 (36.0)	199 (25.2)	246 (18.3)
Physical activity, *n* (%)[b]						
Above recommendation	266,638 (81.7)	261,767 (81.8)	3194 (75.5)	836 (78.6)	613 (77.6)	1006 (75.0)
Not meeting recommendation	59,920 (18.3)	58,415 (18.2)	1035 (24.5)	227 (21.4)	177 (22.4)	335 (25.0)
BMI, mean (SD), kg/m^2	27.3 (4.7)	27.2 (4.6)	31.2 (5.5)	28.6 (5.1)	27.0 (4.7)	30.2 (5.8)
HDL-C, mean (SD), mmol/L	1.4 (0.4)	1.5 (0.4)	1.3 (0.4)	1.5 (0.5)	1.4 (0.4)	1.3 (0.4)
Triglycerides, mean (SD), mmol/L	1.7 (1.0)	1.7 (1.0)	2.3 (1.3)	2.0 (1.3)	1.7 (1.0)	1.9 (1.1)
History of hypertension, *n* (%)						
Yes	82,846 (25.4)	80,172 (25.0)	1850 (43.7)	503 (47.3)	238 (30.1)	597 (44.5)
No	243,712 (74.6)	240,010 (75.0)	2379 (56.3)	560 (52.7)	552 (69.9)	744 (55.5)
History of diabetes, *n* (%)						
Yes	14,847 (4.5)	13,926 (4.3)	705 (16.7)	140 (13.2)	57 (7.2)	268 (20.0)
No	311,711 (95.5)	306,256 (95.7)	3524 (83.3)	923 (86.8)	733 (92.8)	1073 (80.0)

NAFLD, non-alcoholic fatty liver disease; ALD, alcoholic liver disease; SD, standard deviation; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol. [a]Descriptive characteristics by liver disease were presented as means with standard deviations for quantitative variables and as frequencies and percentages for categorical variables. Participants could develop more than one liver disease so the column 4–7 were not mutually exclusive groups. [b]Physical activity that met the 2017 UK Physical activity guidelines (150 min of walking or moderate activity per week or 75 min of vigorous activity) was defined as above recommendation.

Table 1: **Baseline characteristics of the included participants by liver disease.**[a]

CI, 1.35–1.85; P < 0.0001). Additionally, the risk of cataract was higher during the first 5 years (ALD: HR, 1.66; 95% CI, 1.22–2.27; P = 0.0013. Liver fibrosis and cirrhosis: HR, 1.67; 95% CI, 1.35–2.06; P < 0.0001) rather than 5 years after ALD (HR, 1.51; 95% CI, 1.14–2.00; P = 0.0042) or liver fibrosis and cirrhosis (HR, 1.48; 95% CI, 1.17–1.88; P = 0.0013) diagnosis. Viral hepatitis was not associated with cataract when treated as a binary time-varying exposure (HR, 1.20; 95% CI, 0.95–1.53; P = 0.13). Nonetheless, an increased risk of cataract was observed in the first 5 years since viral hepatitis was diagnosed (HR, 1.55; 95% CI, 1.07–2.23; P = 0.019), and this association cannot be observed in later years (HR, 1.03; 95% CI, 0.75–1.41; P = 0.86). These results did not change when four liver diseases were included in a combined model, though the associations between liver diseases and cataract were partly attenuated (Fig. 2). Results from this combined model also suggested that NAFLD, ALD and liver fibrosis and cirrhosis, as well as viral hepatitis in the first five years were independent risk factors for incident cataract (Fig. 2).

	Not exposed to liver disease	Expose to liver disease
Non-alcoholic fatty liver disease		
Person-years at risk	4,078,033	19,004
Incident cases	36,644	420
Incident cases per 100,000 person-years	898.57	2210.05
Alcoholic liver disease		
Person-years at risk	4,091,660	5377
Incident cases	36,975	89
Incident cases per 100,000 person-years	903.67	1655.12
Viral hepatitis		
Person-years at risk	4,090,600	6437
Incident cases	36,997	67
Incident cases per 100,000 person-years	904.44	1040.85
Liver fibrosis and cirrhosis		
Person-years at risk	4,090,726	6311
Incident cases	36,911	153
Incident cases per 100,000 person-years	902.31	2424.16

[a]For those diagnosed with liver disease during the follow-up, their person-years at risk from the baseline to the diagnosis of liver disease were assigned to the "not exposed to liver disease" group, while their person-years at risk since the diagnosis of liver disease were assigned to the "expose to liver disease" group.

Table 2: **Cataract incidence by each liver disease.[a]**

Subgroup analyses

As shown in Fig. 3A, physical activity significantly decreased the effect of viral hepatitis on incident cataract (HR, 0.93; 95% CI, 0.69–1.26 *vs.* HR, 2.02; 95% CI, 1.34–3.05, P for interaction = 0.0020), but such a modification pattern was not observed in NAFLD, ALD or liver fibrosis and cirrhosis (P for interaction = 0.67, 0.39 and 0.79, respectively). As for illness history, the risk-increasing effect of viral hepatitis on cataract were significantly higher in those with history of hypertension (HR, 1.55; 95% CI, 1.12–2.16 *vs.* HR, 0.90; 95% CI, 0.64–1.28, P for interaction = 0.021) (Fig. 3B), while diabetes significantly lowered the effect of NAFLD (HR, 1.16; 95% CI, 0.95–1.43 *vs.* HR, 1.51; 95% CI, 1.35–1.69, P for interaction = 0.0043) on incident cataract (Fig. 3C). No significant interactions were found between liver diseases and sex, ethnicity, Townsend deprivation index, smoking status, HDL-C and triglycerides (Supplementary Table S6).

Sensitivity analyses

Several sensitivity analyses were conducted to assess the robustness of our findings (Supplementary Tables S7–S14). Compared with the results from the main analyses, the results from sensitivity analyses (1) to (8) showed no substantial changes of the effects of NAFLD, ALD and liver fibrosis and cirrhosis as well as their recent or long-term states on cataract (Supplementary Tables S7–S14). As for viral hepatitis, there was still no association between it and cataract when treated as a binary time-varying variable (Supplementary Tables S7–S10,S13–S14). Nevertheless, the finding that the viral hepatitis in the first five years increased the risk of cataract still held in

	Hazard ratio (95% CI)		
	Liver disease exposure (time varying)	Time since liver disease diagnosed	
		>0–5yrs	>5yrs
Non-alcoholic fatty liver disease			
Model 1[a]	1.73 (1.57–1.91)	1.66 (1.47–1.88)	1.85 (1.58–2.15)
Model 2[b]	1.67 (1.52–1.84)	1.61 (1.42–1.82)	1.78 (1.53–2.08)
Model 3[c]	1.47 (1.33–1.61)	1.43 (1.26–1.62)	1.52 (1.31–1.78)
Alcoholic liver disease			
Model 1[a]	1.82 (1.48–2.24)	1.88 (1.38–2.56)	1.77 (1.34–2.35)
Model 2[b]	1.72 (1.39–2.12)	1.83 (1.34–2.50)	1.64 (1.24–2.17)
Model 3[c]	1.57 (1.28–1.94)	1.66 (1.22–2.27)	1.51 (1.14–2.00)
Viral hepatitis			
Model 1[a]	1.23 (0.97–1.57)	1.59 (1.10–2.28)	1.06 (0.77–1.45)
Model 2[b]	1.20 (0.94–1.52)	1.55 (1.07–2.22)	1.02 (0.74–1.40)
Model 3[c]	1.20 (0.95–1.53)	1.55 (1.07–2.23)	1.03 (0.75–1.41)
Liver fibrosis and cirrhosis			
Model 1[a]	1.85 (1.57–2.16)	2.00 (1.62–2.47)	1.68 (1.32–2.14)
Model 2[b]	1.76 (1.50–2.07)	1.92 (1.55–2.37)	1.60 (1.26–2.03)
Model 3[c]	1.58 (1.35–1.85)	1.67 (1.35–2.06)	1.48 (1.17–1.88)

CI, confidence interval. [a]Model 1, adjusted for sex, year of birth, ethnicity, and Townsend deprivation index with age as the time-axis. [b]Model 2, included covariates from model 1 plus alcohol intake, smoking status, physical activity with age as the time-axis. [c]Model 3, included covariates from model 2 plus body mass index, concentration of HDL-C, concentration of triglycerides, history of hypertension and history of diabetes with age as the time-axis. HDL-C, high-density lipoprotein cholesterol.

Table 3: **Associations between severe liver diseases as time-varying exposures and subsequent cataract as the outcome.**

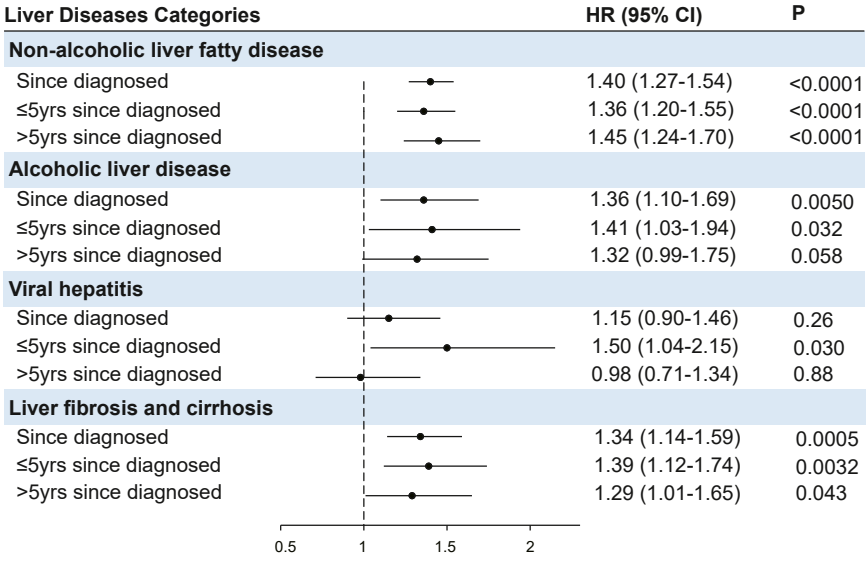

***Fig. 2:* Associations between severe liver diseases and cataract in the combined model.** The hazard ratios for developing cataract were estimated using Cox proportional hazards models adjusted for sex, year of birth, ethnicity, Townsend deprivation index, alcohol intake, smoking status, physical activity, body mass index, concentration of HDL-C, concentration of triglycerides, history of hypertension and history of diabetes with all four liver diseases modeled together. Each liver disease was treated as a binary or ternary time-varying variable and age was used as the time-axis. A P value below 0.05 was considered statistically significant. HR, hazard ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol.

sensitivity analyses from (1) to (8), although this association was slightly weakened in the model merging primary care data into the exposure group (Supplementary Table S10. HR 1.43; 95% CI, 0.99–2.07; P = 0.059). For the HRs in model 3 of NAFLD (HR, 1.47), ALD (HR, 1.57), liver fibrosis and cirrhosis (HR, 1.58) and recently diagnosed viral hepatitis (HR, 1.55) associated with incident cataract, the E-values were 2.30, 2.52, 2.53 and 2.47, respectively.

Discussion

In this large-scale prospective cohort study of 326,558 UK Biobank participants, we found severe NAFLD, ALD, liver fibrosis and cirrhosis and recently diagnosed viral hepatitis were associated with an increased risk of cataract. Previous relevant studies have only investigated the association between viral hepatitis and cataract,[30,31] and were limited by cross-sectional design or insufficient variable adjustment. Our work, to our knowledge, was the first large-scale prospective study systematically investigating associations between liver diseases and cataract.

No study to date has examined the associations of NAFLD and ALD with cataract. In the present work, we demonstrated that both NAFLD and ALD increased the risk of cataract development. Though the exact biological mechanisms remain elusive, the altered microenvironment surrounding lens owing to the metabolic changes of NAFLD and ALD may serve as a possible pathway in caractogenesis. Both NAFLD and ALD are characterized by metabolic changes.[4,43] For instance, NAFLD and ALD can lead to an increase of circulating homocysteine (Hcy),[44,45] which is able to induce endoplasmic reticulum stress and promote the generation of reactive oxygen species (ROS) in human lens epithelial cells (LECs).[46] Its association with cataract risk has been observed in an epidemiological study.[47] Research has also found a reduction of glutathione (GSH) level in NAFLD and ALD,[44,48] which may engender crystallin degeneration and subsequently lead to the opacification of lens.[49] Additionally, Vitamin D deficiency associated with these two liver diseases may also play a possible role in the cataract formation.[26,50,51] In addition to metabolic aspect, the activated immune response in NAFLD and ALD can result in systemic inflammation that characterized by the upregulation of pro-inflammatory cytokines.[9,14,52,53] Recent animal experiments suggested the role of immune cells migrating from the surrounding vasculature to the lens in cataractogenesis.[28,29] Liver disease may indirectly assist immune cells in invading the lens to accelerate cataract formation, through the increased pro-inflammatory cytokines which have the effect of augmenting leukocyte-endothelial adhesion, increasing vascular permeability and promoting transendothelial migration.[54–56] Despite these speculations, laboratory studies on liver disease and cataract are still very

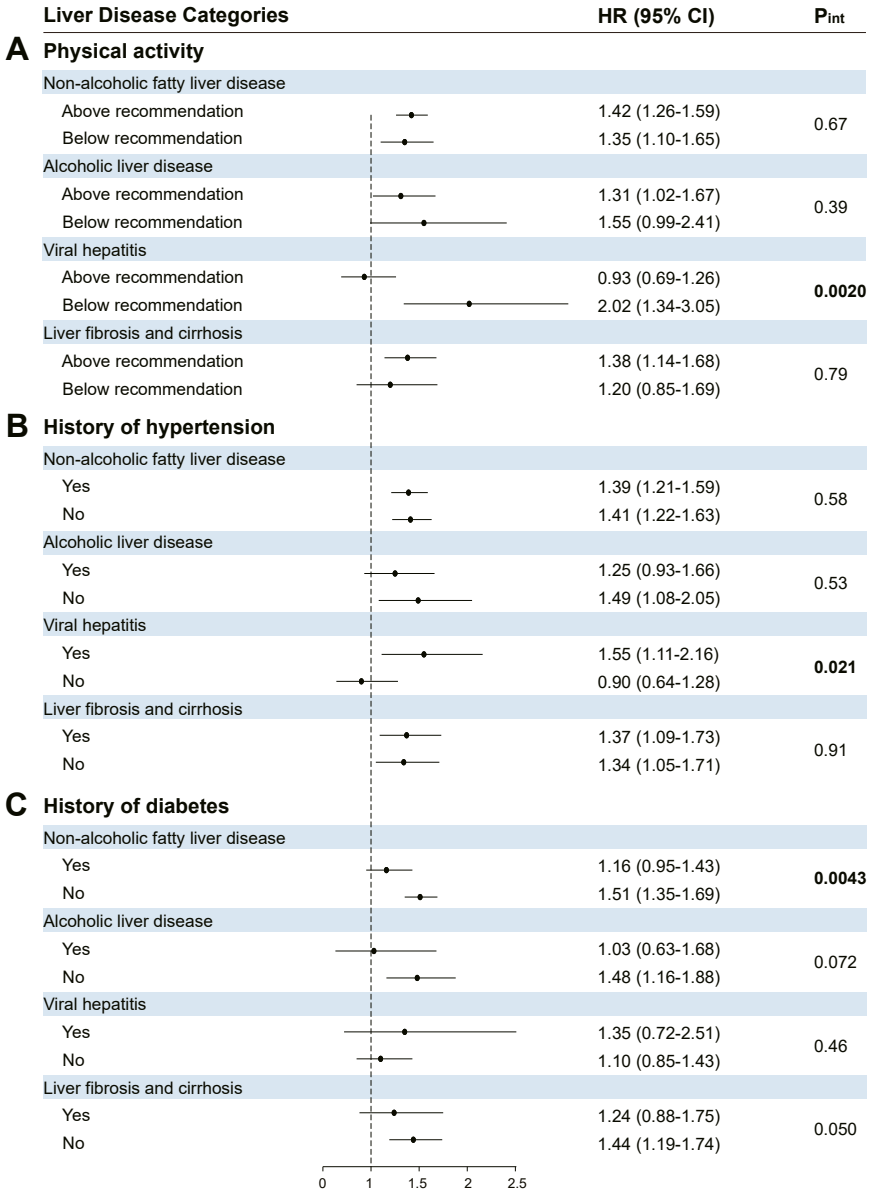

***Fig. 3:* Associations between severe liver diseases and cataract in the combined model according to potential risk factors.** The effects of each liver disease on incident cataract according to (A) physical activity, (B) history of hypertension, and (C) history of diabetes were estimated by combined Cox proportional hazards models adjusted for sex, year of birth, ethnicity, Townsend deprivation index, alcohol intake, smoking status, physical activity, body mass index, concentration of HDL-C, concentration of triglycerides, history of hypertension and history of diabetes except for the strata factor in each subgroup. Age was used as the time-axis. Physical activity that met the 2017 UK Physical activity guidelines (150 min of walking or moderate activity per week or 75 min of vigorous activity) was defined as above recommendation. A P value below 0.05 was considered statistically significant. HR, hazard ratio; CI, confidence interval; P_{int}, P value for interaction; HDL-C, high-density lipoprotein cholesterol.

limited, and more investigation is required to elucidate the mechanisms underlying the liver-eye connection.

We also observed an association of liver fibrosis and cirrhosis with cataract in our study. Similar to NAFLD and ALD, metabolic alternation is also a critical component of liver fibrosis and cirrhosis.[19,20] In animal models, liver fibrosis was associated with increased serum levels of ceramides,[57] which may result in ROS generation and apoptosis in human LECs.[58] Methionine metabolism and Hcy can also be altered,[5,59] potentially contributing to the occurrence of cataract.[47] As a possible outcome of several liver diseases, liver fibrosis

and cirrhosis presents a more severe inflammation landscape.[20] Increased circulating pro-inflammatory cytokines may also promote immune cell-mediated cataract development as described above. Of course, these speculations require further laboratory investigations.

The association between viral hepatitis and cataract has been investigated previously.[30,31] A cross-sectional study of 10,037 Koreans reported both hepatitis B virus (HBV) and hepatitis C virus (HCV) group had higher odds ratios (ORs) for cataract (HBV: OR, 1.07; 95% CI, 1.00–1.14; P = 0.048. HCV: OR, 1.40; 1.40; 95% CI, 1.12–1.76; P = 0.003).[30] Another retrospective study of 58,260 participants with an average follow-up of 5 years, showed participants with HCV had a higher HR for cataract development (HR, 1.23; 95% CI, 1.14–1.32; P < 0.001).[31] Though consistent with our results with respect to association of recently diagnosed viral hepatitis with cataract, this study did not adjust for important variables such as BMI, smoking status and alcohol intake into their model, and did not investigate the effect of long-term state of viral hepatitis. Our study addressed these deficiencies and provided robust evidence for the association between viral hepatitis and cataract. We found that only recent viral hepatitis diagnosed within 5 years was associated with an increased risk of cataract. The specific mechanisms remained largely unknown, as viral hepatitis showed complicated metabolic profiles.[60] It was shown that the infection of hepatotropic viruses like HCV was associated with metabolic derangements including insulin resistance and diabetes that may accelerate cataract formation,[60] while some evidence also showed that both acute and chronic viral hepatitis had a lower prevalence of hyperlipidemia,[61–63] which appeared to be a protective factor for cataract. The situation is further complicated by systemic inflammation brought about by the activated immune responses.[64,65] More investigation is therefore required to elucidate the exact relationship between viral hepatitis and cataract.

In subgroup analyses, we found physical activity and hypertension could respectively decrease and increase the risk-increasing effect of viral hepatitis on cataract. These phenomena may be explained by the fact that exercise can reduce the level of systemic inflammation brought about by the viral hepatitis,[66] while hypertension can exacerbate liver injury which may amplify the inflammation.[67] Intriguingly, though both NAFLD and diabetes are risk factors of cataract,[22] we found the effect of NAFLD on cataract was lower in those with diabetes. The existence of such an interaction pattern can be supported by other studies to some extent, which showed in patients with type 2 diabetes mellitus, those who developed NAFLD had a lower frequency of cataract.[68,69] Admittedly, the underlying mechanisms require to be further investigated.

Although our study has several strengths, the following limitations need to be declared. First, the low response rate and health volunteer bias of the UKB cohort suggest that it is not representative of general UK population,[70] though the risk factor associations in the UK Biobank seem to be generalizable.[71] Second, we excluded many participants owing to the substantial missing data on some covariates such as physical activity, which might potentially introduce selection bias, even though analysis based on imputed complete dataset reached similar conclusions to the main analysis. Third, there existed multiplicity issue in our study because in separate models and combined models, a total of 26 analyses were performed, resulting in increased type I error. At the Bonferroni significance level (P < 0.0019, 0.05/26), most of the results in separate models survive with the exception of the recently diagnosed ALD and viral hepatitis, while several results of the combined models fail to meet the significance threshold. Thus, these results, especially the effect independence of four liver diseases, should be interpreted cautiously. Fourth, the outcome of interest, cataract, is a slowly progressive process, and the time of its being documented might be influenced by factors such as different frequency of ophthalmic examinations among groups, the subjective tolerance of patients to the vision impairment and the location of lens opacity. These factors might introduce potential bias, though analysis using incident cataract surgery as the outcome showed the same association pattern. Fifth, the observational design of our study precluded the establishment of causal relationships, and the residual confounding might still exist. Nevertheless, the E-value methodology suggested for association of NAFLD, ALD, liver fibrosis and cirrhosis or recently diagnosed viral hepatitis with cataract, an unmeasured confounder would need to have a corresponding association of at least 2.30, 2.52, 2.53, or 2.47 on the risk ratio scale with both exposure and outcome to explain away our main results. Given that the well-established risk factor diabetes had the strongest association with cataract in model 3 while its hazard ratio was around 1.72, which was much lower than the above E-values, we did not think there existed such an unmeasured but strong confounder that could explain away the observed associations.

In conclusion, severe NAFLD, ALD, liver fibrosis and cirrhosis and recently diagnosed viral hepatitis were associated with a higher risk of incident cataract. Considering that liver disease is increasingly advocated as a multisystem disease, these results are of significance for the comprehensive management of liver disease. Our work also provided evidence for early intervention in those with liver disease for prevention of cataract in the context of global population aging.

Contributors

XZ designed the study. CC and LW analyzed and interpreted the data. CC drafted the manuscript. CC, LW, WH and YZ accessed and verified the underlying data. XZ, FW, JX and YL critically reviewed the

manuscript. All authors approved the final version of the draft. All authors had full access to all the data in the study and had final responsibility to submit for publication.

Data sharing statement

All data relevant to the study were acquired from the UK Biobank Resource under application number 93118. Data can be accessed through applications on UK Biobank website (https://www.ukbiobank.ac.uk/).

Declaration of interests

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102424.

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