ORIGINAL ARTICLE

OPEN

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

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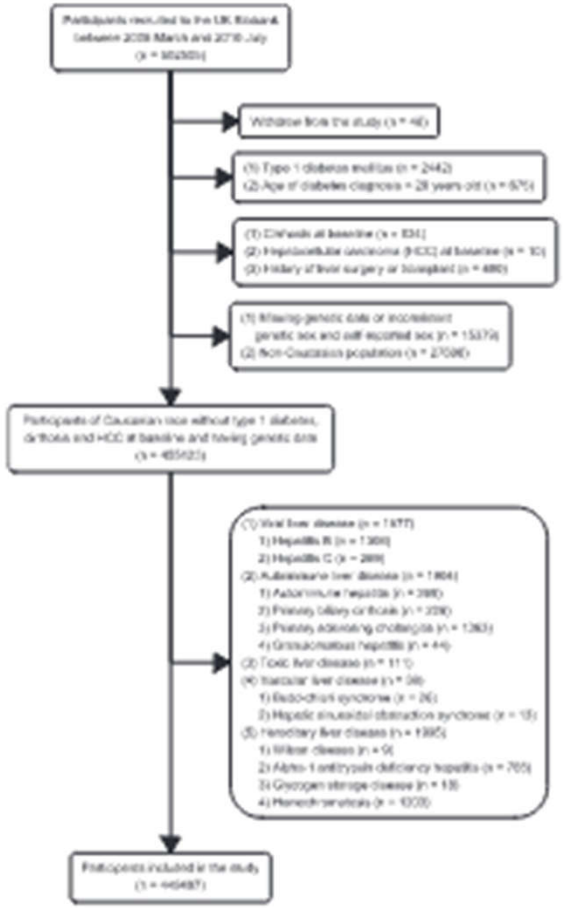
Background: Diabetes increases the risk of cirrhosis and HCC. We aimed to assess such associations given different diabetes statuses.

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 pre-clinical 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.


Participants recruited to the UK Biobank between 2006 March and 2010 July (n = 502505)
Withdrew from the study (n = 46)
(1) Type 1 diabetes mellitus (n = 2442)
(2) Age of diabetes diagnosis < 28 years old (n = 675)
(1) CirrhosIs at baseline (n = 834)
(2) Hepatocellular carcinoma (HCC) at baseline (n = 10)
(3) History of liver surgery or transplant (n = 480)
(1) Missing genetic data or inconsistent genetic sex and self-reported sex (n = 15379)
(2) Non-Caucasian population (n = 27088)
Participants of Caucasian race without type 1 diabetes, cirrhosis and HCC at baseline and having genetic data (n = 455123)
(1) Viral liver disease (n = 1477)
1) Hepatitis B (n = 1308)
2) Hepatitis C (n = 269)
(2) Autoimmune liver disease (n = 1804)
1) Autoimmune hepatitis (n = 998)
2) Primary biliary cirrhosis (n = 339)
3) Primary sclerosing cholangitis (n = 1383)
4) Granulomatous hepatitis (n = 44)
(3) Toxic liver disease (n = 511)
(4) Vascular liver disease (n = 38)
1) Budd-chiari syndrome (n = 26)
2) Hepatic sinusoidal obstruction syndrome (n = 13)
(5) Hereditary liver disease (n = 1995)
1) Wilson disease (n = 9)
2) Alpha-1 antitrypsin deficiency hepatitis (n = 705)
3) Glycogen storage disease (n = 18)
4) Hemochromatosis (n = 1030)
Participants included in the study (n = 449487)

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.

FUNDING INFORMATION

ORIGINAL CONTRIBUTION | ARTICLES IN PRESS

Combination of Breast Ultrasound With Magnetic Resonance Imaging in the Diagnosis of Non-mass-like Breast Lesions Detected on Ultrasound: A New Integrated Strategy to Improve Diagnostic Performance

Rui-Lan Niu • Jun-Kang Li • Bo Wang • ... Nai-Qin Fu • Gang Liu • Zhi-Li Wang • Show all authors

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characteristic curve (AUC), sensitivity and specificity of US, MRI and the integrated diagnostic strategy using US combined with MRI for NMLs were 0.730, 93.7% and 52.3%; 0.849, 94.7% and 75.0%; and 0.901, 92.6% and 87.5%, respectively. Compared with US or MRI alone, the integrated diagnostic strategy significantly increased the AUC ($p < 0.001$, $p = 0.007$) and specificity ($p < 0.001$, $p = 0.034$) while maintaining high sensitivity ($p = 0.774$, $p = 0.551$). In the validation set, the integrated strategy of US combined with MRI (AUC = 0.899) also had good performance compared with US (AUC = 0.728) or MRI (AUC = 0.838).

Conclusion

The integrated diagnostic strategy of US combined with MRI exhibited good performance for breast NMLs compared with either modality used alone, which can improve the diagnostic specificity while maintaining high sensitivity.

Original Investigation

October 23, 2023

Endogenous and Exogenous Thyrotoxicosis and Risk of Incident Cognitive Disorders in Older Adults

Roy Adams, PhD[1]; Esther S. Oh, MD, PhD[1,2]; Sevil Yasar, MD, PhD[2]; et al

Results A total of 65 931 patients were included in the analysis (median [IQR] age at first visit, 68.0 [65.0-74.0] years; 37 208 [56%] were female; 46 106 [69.9%] were White). Patients exposed to thyrotoxicosis had cognitive disorder incidence of 11.0% (95% CI, 8.4%-14.2%) by age 75 years vs 6.4% (95% CI, 6.0%-6.8%) for those not exposed. After adjustment, all-cause thyrotoxicosis was significantly associated with risk of cognitive disorder diagnosis (adjusted hazard ratio, 1.39; 95% CI, 1.18-1.64; $P < .001$) across age groups. When stratified by cause and severity, exogenous thyrotoxicosis remained a significant risk factor (adjusted hazard ratio, 1.34; 95% CI, 1.10-1.63; $P = .003$) with point estimates suggestive of a dose response.

Conclusions and Relevance In this cohort study among patients 65 years and older, a low TSH level from either endogenous or exogenous thyrotoxicosis was associated with higher risk of incident cognitive disorder. Iatrogenic thyrotoxicosis is a common result of thyroid hormone therapy. With thyroid hormone among the most common prescriptions in the US, understanding the negative effects of overtreatment is critical to help guide prescribing practice.

Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection

Published , 5/25/2023

The Infectious Diseases Society of America and the American Association for the Study of Liver Diseases have collaboratively developed evidence-based guidance regarding the diagnosis, management, and treatment of hepatitis C virus (HCV) infection since 2013. A panel of clinicians and investigators with extensive infectious diseases or hepatology expertise specific to HCV infection periodically reviews evidence from the field and update existing recommendations or introduce new recommendations as evidence warrants.

This update focuses on changes to the guidance since the previous 2020 published update, including ongoing emphasis on recommended universal screening; management recommendations for incomplete treatment adherence; expanded eligibility for simplified chronic HCV infection treatment in adults with minimal monitoring; updated treatment and retreatment recommendations for children as young as 3 years; management and treatment recommendations in the transplantation setting; and screening, treatment, and management recommendations for unique and key populations.

Review | March 9, 2023 |

Hepatitis B core-related antigen: A novel and promising surrogate biomarker to guide anti-hepatitis B virus therapy

Takako Inoue, Takehisa Watanabe, Yasuhito Tanaka

Clin Mol Hepatol. 2023;29(4):851-868.

The current requirement for biomarkers to detect hepatitis B virus (HBV) infection is polarized. One is a fully-automated and highly sensitive measurement system; the other is a simple system for point-of-care testing (POCT) in resource-limited areas. Hepatitis B core-related antigen (HBcrAg) reflects intrahepatic covalently closed circular DNA and serum HBV DNA. Even in patients with undetectable serum HBV DNA or HBsAg loss, HBcrAg may remain detectable. Decreased HBcrAg levels are associated with reduction of the occurrence of hepatocellular carcinoma (HCC) in chronic hepatitis B. Recently, a fully-automated, novel high-sensitivity HBcrAg assay (iTACT-HBcrAg, cut-off value: 2.1 logIU/mL) has been developed. This attractive assay has been released in Japan very recently. iTACT-HBcrAg can be useful for monitoring HBV reactivation and prediction of HCC occurrence, as an alternative to HBV DNA. Moreover, monitoring HBcrAg may be suitable for determining the therapeutic effectiveness of approved drugs and novel drugs under development. Presently, international guidelines recommend anti-HBV prophylaxis for pregnant women with high viral loads to prevent mother-to-child transmission of HBV. However, >95% of HBV-infected individuals live in countries where HBV DNA quantification is not available. Worldwide elimination of HBV needs the scaling-up of examination and medication services in resource-limited areas. Based on this situation, a rapid and easy HBcrAg assay as a POCT is valuable. This review provides the latest information regarding the clinical use of a new surrogate marker, HBcrAg, in HBV management, based on iTACT-HBcrAg or POCT, and introduces novel agents targeting HBV RNA/protein. **(Clin Mol Hepatol 2023;29:851-868)**

Keywords: Hepatitis B core-related antigen (HBcrAg); Covalently closed circular DNA (cccDNA); HBV reactivation; Point-of-care testing; RNA destabilizer

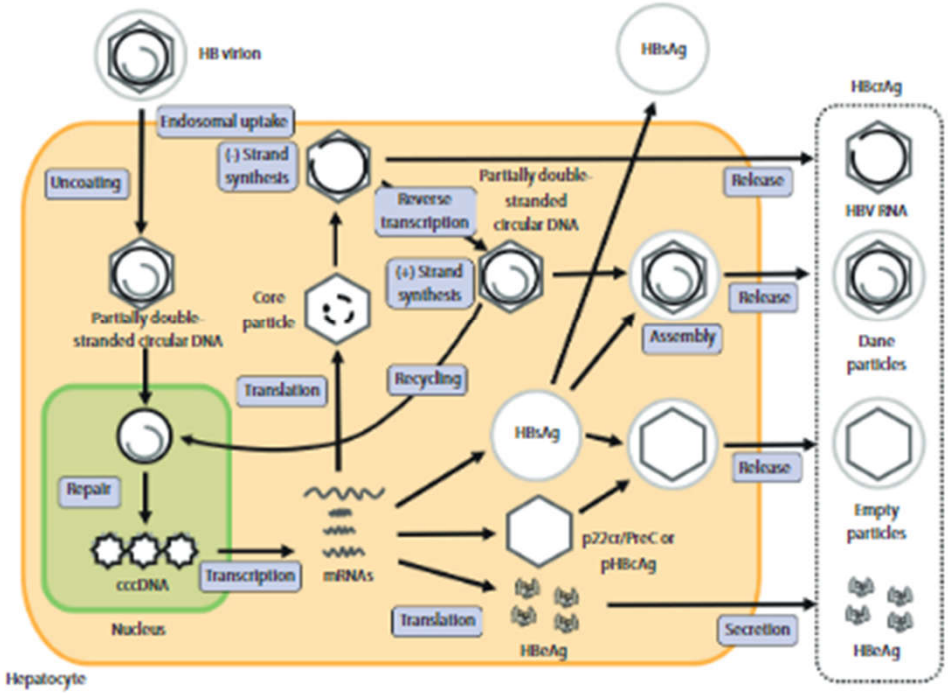
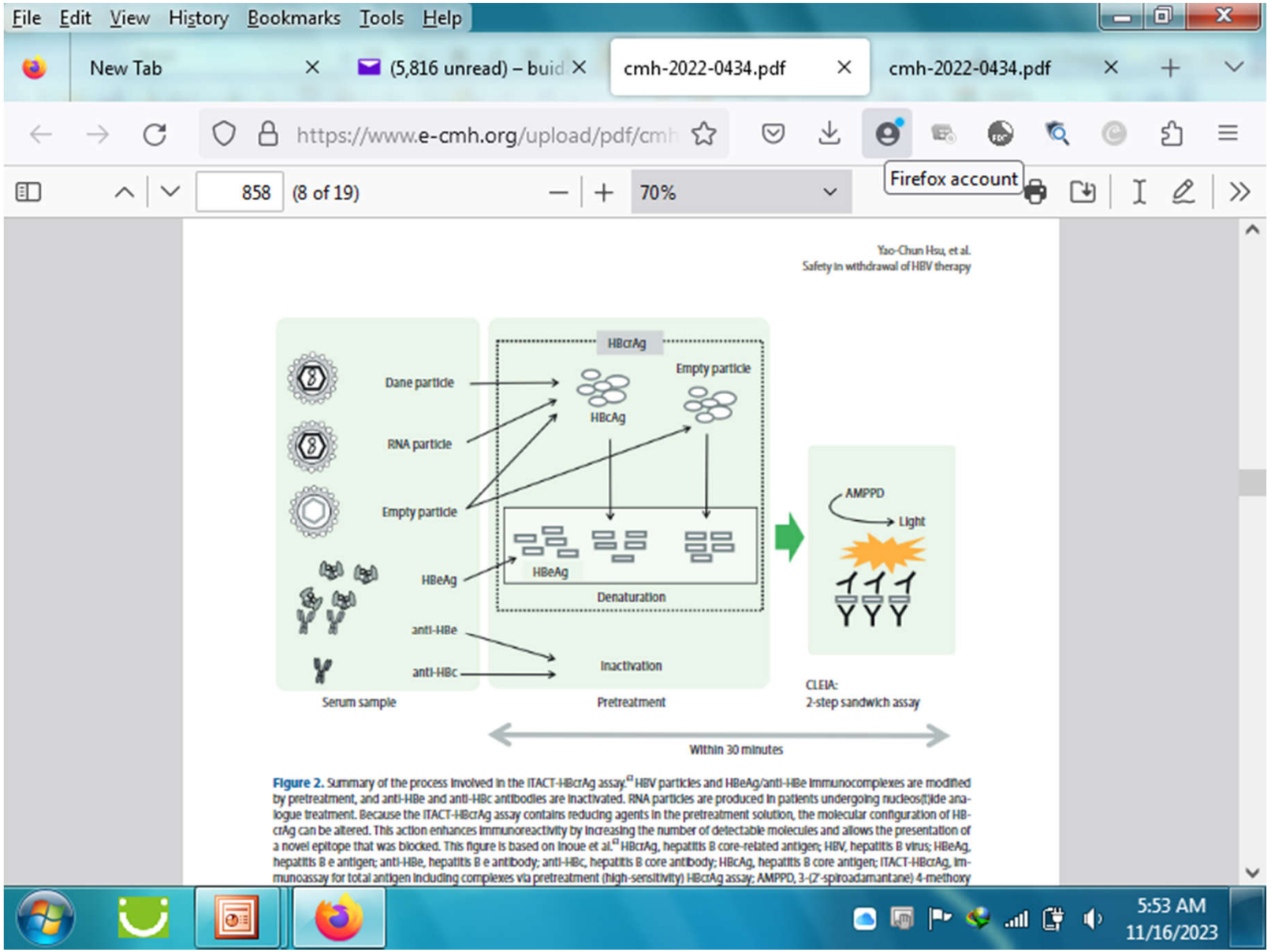


Figure 1. Schema of the life cycle of HBV and HBcrAg. The cccDNA is present as minichromosomes. There are 5 to 50 per hepatocyte. The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Safety in withdrawal of HBV therapy
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Empty particle
HBeAg
anti-HBe
anti-HBc
HBcAg
Empty particle
HBeAg
Denaturation
Inactivation
AMPPD
Light
Serum sample
Pretreatment
CLEIA:
2-step sandwich assay
Within 30 minutes
Figure 2. Summary of the process involved in the ITACT-HBcrAg assay.[17] HBV particles and HBeAg/anti-HBe immunocomplexes are modified by pretreatment, and anti-HBe and anti-HBc antibodies are inactivated. RNA particles are produced in patients undergoing nucleos(t)ide analogue treatment. Because the ITACT-HBcrAg assay contains reducing agents in the pretreatment solution, the molecular configuration of HBcrAg can be altered. This action enhances immunoreactivity by increasing the number of detectable molecules and allows the presentation of a novel epitope that was blocked. This figure is based on Inoue et al.[17] HBcrAg, hepatitis B core-related antigen; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; anti-HBe, hepatitis B e antibody; anti-HBc, hepatitis B core antibody; HBcAg, hepatitis B core antigen; ITACT-HBcrAg, Immunoassay for total antigen including complexes via pretreatment (high-sensitivity) HBcrAg assay; AMPPD, 3-(2'-spiroadamantane) 4-methoxy
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