Development and validation of a model to predict incident chronic liver disease in the general population : The CLivD score

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Graphical abstract
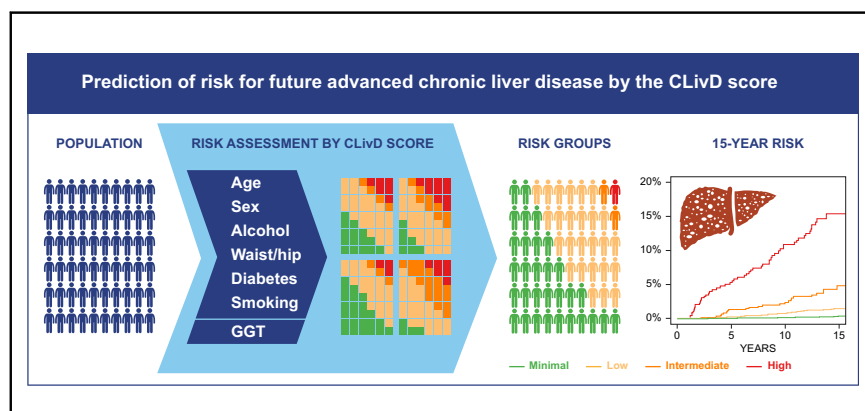
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Lay summary

Liver disease often progresses silently without symptoms and thus the diagnosis is often delayed until severe complications occur and prognosis becomes poor. In order to identify individuals in the general population who have a high risk of developing severe liver disease in the future, we developed and validated a **C**hronic **Liv**er **D**isease (CLivD) risk prediction score, based on age, sex, alcohol use, waist-hip ratio, diabetes, and smoking, with or without measurement of the liver enzyme gamma-glutamyltransferase. The CLivD score can be used as part of health counseling, and for planning further liver investigations and follow-up.

Highlights

- Liver disease tends to develop silently without symptoms and thus the diagnosis is often delayed.

- To improve early risk prediction, we developed and validated the CLivD score for use in the general population.

- The CLivD score is based on age, sex, alcohol use, waist-hip ratio, diabetes, smoking, with or without GGT values.

- The CLivD score provides accurate predictions of 15-year risk for future severe liver disease.

- The CLivD score could be used as part of health counseling, and for planning further liver investigations and follow-up.

Development and validation of a model to predict incident chronic liver disease in the general population: The CLivD score

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Background & Aims: Current screening strategies for chronic liver disease focus on detection of subclinical advanced liver fibrosis but cannot identify those at high future risk of severe liver disease. Our aim was to develop and validate a risk prediction model for incident chronic liver disease in the general population based on widely available factors.
Methods: Multivariable Cox regression analyses were used to develop prediction models for liver-related outcomes with and without laboratory measures (Model$_{lab}$ and Model$_{non-lab}$) in 25,760 individuals aged 40–70 years. Their data were sourced from the Finnish population-based health examination surveys FINRISK 1992-2012 and Health 2000 (derivation cohort). The models were externally validated in the Whitehall II (n = 5,058) and Copenhagen City Heart Study (CCHS) (n = 3,049) cohorts.
Results: The absolute rate of incident liver outcomes per 100,000 person-years ranged from 53 to 144. The final prediction model included age, sex, alcohol use (drinks/week), waist–hip ratio, diabetes, and smoking, and Model$_{lab}$ also included gamma-glutamyltransferase values. Internally validated Wolbers' C-statistics were 0.77 for Model$_{lab}$ and 0.75 for Model$_{non-lab}$, while apparent 15-year AUCs were 0.84 (95% CI 0.75-0.93) and 0.82 (95% CI 0.74-0.91). The models identified a small proportion (<2%) of the population with >10% absolute 15-year risk for liver events. Of all liver events, only 10% occurred in participants in the lowest risk category. In the validation cohorts, 15-year AUCs were 0.78 (Model$_{lab}$) and 0.65 (Model$_{non-lab}$) in the CCHS cohort, and 0.78 (Model$_{non-lab}$) in the Whitehall II cohort.
Conclusions: Based on widely available risk factors, the **C**hronic **Liv**er **D**isease (CLivD) score can be used to predict risk of future advanced liver disease in the general population.

Lay summary: Liver disease often progresses silently without symptoms and thus the diagnosis is often delayed until severe complications occur and prognosis becomes poor. In order to identify individuals in the general population who have a high risk of developing severe liver disease in the future, we developed and validated a **C**hronic **Liv**er **D**isease (CLivD) risk prediction score, based on age, sex, alcohol use, waist-hip ratio, diabetes, and smoking, with or without measurement of the liver enzyme gamma-glutamyltransferase. The CLivD score can be used as part of health counseling, and for planning further liver investigations and follow-up.

Introduction

Liver disease is increasingly contributing to the global healthcare burden,[1] and cirrhosis is the eleventh most common cause of death. Liver disease tends to develop without signs or symptoms and thus is often detected in the late stages based on complications such as ascites, jaundice, and variceal bleeding, with markedly poor prognosis.[2] In the UK, for instance, 50% of patients receive their diagnosis of cirrhosis following an emergency admission to the hospital because of complications of end-stage disease,[3] even though most of these patients have had prior contacts with primary healthcare.[4]

Identifying at-risk individuals before progression to advanced liver disease is an imperative. Early diagnosis could allow for risk communication with the affected patient, implementation of targeted lifestyle interventions, and consistent liver evaluation and follow-up. Existing screening strategies are based on currently acknowledged population-level risk factors, such as diabetes, obesity, and alcohol use. However, relying on these factors makes the number needed to screen unrealistically high,[5] along with carrying significant uncertainty regarding the risk of liver disease progression.

Liver investigations triggered by abnormal aminotransferases alone or the detection of steatosis on imaging will miss a significant number of patients with liver disease.[6] Thanks to low positive-predictive values, reliance on these findings can lead to resource-consuming specialized investigations and over-diagnosis in many individuals who will never develop clinical liver disease.[7,8] Current risk stratification focuses on assessing the amount of liver fibrosis, but simple non-invasive liver fibrosis tests, such as non-alcoholic fatty liver disease (NAFLD) fibrosis score, fibrosis-4 (FIB-4), or aspartate aminotransferase to platelet ratio index (APRI), are of limited value in individuals in the general population compared to in highly selected NAFLD cohorts from specialist centers.[9,10] Significant alcohol use also impairs the performance of these tests,[11] and they were not originally designed to predict clinical liver outcomes.[12–14] Direct fibrosis biomarkers and special imaging methods, such as elastography, are additionally limited by cost, accessibility, and suboptimal performance in identifying early fibrosis stages and in the presence of alcoholic steatohepatitis.[15,16] All fibrosis tests reflect only the current state of the liver and not the factors driving disease progression.

Given that metabolic factors are also important in alcoholic-related liver disease and that alcohol use seems to affect metabolic liver disease,[17] population risk assessment should consider the combined contribution of alcohol and metabolic factors.[17–19] Risk prediction models that account for the combined contribution of several risk factors, analogous to the Framingham risk score or the European SCORE used in cardiovascular medicine,[20] would offer the opportunity to risk-stratify individuals before advanced liver disease arises.

Our aim was to develop and validate a simple prediction model – the **C**hronic **Liv**er **D**isease (CLivD) score – to quantify the risk of incident clinical liver disease in individuals in the general population, based on widely available and easily reproducible risk factors.

Material and methods
This study was conducted and reported in accordance with the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prediction or Diagnosis) guidelines.[21] Written informed consent from participants and research ethical approvals were obtained in all study cohorts.

Derivation cohort (Finland)
The population-based sample used for development of the risk model was extracted from the national FINRISK Studies from 1992, 1997, 2002, 2007, and 2012, and the Health 2000 survey from 2000-2001.[22,23] FINRISK studies are cross-sectional health-examination surveys that have been conducted in a systematic and standardized fashion by the Finnish Institute for Health and Welfare (previously National Public Health Institute) in Finland every 5 years since 1972. The surveys provide data on adults (25–74 years) from 4–6 regions in Finland. The sample were randomly drawn from the Finnish National Population Register and were stratified by region, sex, and 10-year age groups. The number of invitees has varied during 1992–2012 from 7,927 to 13,500, and participation rates have ranged from 65% to 76%.[23]

The Health 2000 Survey was also coordinated by the Finnish Institute for Health and Welfare (previously National Public

Health Institute), and originally comprised 8,028 adults aged ≥30 years, with a participation rate in the full examinations of 80%.[22] The cohort is considered representative of the entire Finnish population through a regional 2-stage stratified cluster sampling procedure. The methods, measurements, and protocols used in the FINRISK and Health 2000 studies are described in the supplementary information (p. 2–3).

The present study included individuals who were aged 40-70 years at baseline. We excluded those with a baseline diagnosis of liver disease in any registry (ICD-10: K70-K77, C22.0; ICD8/9: 570-573, 155.0); with a diagnosis of chronic viral hepatitis (ICD-10: B18); and current alcohol abstainers (*i.e.* they had used alcohol earlier and then stopped) (Table S1).

Follow-up data were obtained from several nationwide electronic health registers through linkage using the unique personal identity code assigned to all Finnish residents, as explained in detail in the supplementary information (p. 2–3). Follow-up ended in December 2016.

Validation cohort (Whitehall II)
The Whitehall II study is an ongoing cohort study of UK civil servants. A total of 10,308 adults (6,895 men and 3,413 women, aged 35–55) were originally recruited during 1985–1988 from London-based offices. Follow-up clinical examinations have taken place every 4-5 years since that time, with each wave taking 2 years to complete. Participants were linked electronically to national hospitalization, cancer, and mortality registers up to December 2019.[24] In studies of chronic diseases, the sensitivity and specificity of the Hospital Episode Statistics (HES) database are high.[24,25] Because the hospitalization register achieved a high level of national coverage from January 1997 onward, we set the start of follow-up time at the Whitehall II study's fifth follow-up examination (phase 5), which was undertaken in 1997–1999 and included 7,870 participants. We then applied the same exclusion criteria as in the derivation cohort (Table S1), except that we were could not fully exclude known baseline liver disease before 1997 based on registry coding.

Validation cohort (Copenhagen City Heart Study, CCHS)
The CCHS originally comprised a random sample of 19,698 individuals drawn from the Copenhagen Population Register in January 1976, from an urban population of ~90,000 inhabitants aged ≥20 years, as previously described.[26] Although additional samples have been included in follow-up examinations (1981–1983, 1991–1994, and 2001–2003), a total of 3,092 individuals have been examined in all 4 examinations. Because of the availability of necessary variables, we set the start of follow-up time at the fourth examination conducted in 2001–2003, comprising 6,238 individuals (49.5% of those invited). Participants were linked to well-validated Danish nationwide hospitalization, cancer, and mortality registers, which have previously been used successfully for liver outcomes.[27] We applied the same exclusion criteria as above (Table S1).

Definition of liver outcomes
Study endpoints were fatal and non-fatal advanced liver disease (requiring hospital admission or causing liver cancer or liver-related death). The ICD codes used for defining the outcomes are listed in Table S2.

Candidate predictors and missing data

The primary candidate variables of interest were objective, readily available, and reproducible factors identified *a priori* based on previously published data, clinical rationale, and their ease of use in primary care settings (Tables S3 and S4). Alcohol use and smoking data were based on questionnaires (supplementary information, p. 3–4). Waist and hip circumferences were measured using standard techniques.[22,23] Diabetes was defined as a fasting serum glucose ≥7.0 mmol/L (126 mg/dl), taking diabetic medication, or having a prior known diabetes diagnosis.

Baseline data with ≤5% missingness were imputed by multiple imputation using the predictive mean matching method (supplementary information, p. 6). In the derivation cohort, data on exercise, binge drinking, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and homeostasis model assessment of insulin resistance (HOMA-IR) were missing in ≥15% because these variables had not been assessed in all subcohorts. Missingness rates for all other variables were 0%–5% (Table S3).

Statistical analyses

We developed two types of risk prediction models: one based on non-laboratory measures only (Model$_{non-lab}$) and one including laboratory measures (Model$_{lab}$). Candidate variables were tested for association with liver outcomes by univariable and multivariable Cox regression analyses with incident liver disease within 15 years as the outcome. Predictors with univariate p <0.2 were considered in multivariable analysis. Of correlated variables (Spearman correlation coefficient >0.6), we chose the variable judged to be clinically more important. The final model was selected by a combination of backward and forward stepwise elimination techniques (supplementary information, pp. 6–14); however, age was retained in the model as a measure of exposure time regardless of statistical significance. Non-linear associations were investigated using restricted cubic splines. Two-way interactions among the variables in the final model and with sex were investigated and included in the final model if they improved model performance based on the Akaike information criterion, C-statistic and likelihood ratio test. Variables with >5% missingness rates were subsequently tested in the complete-case dataset for whether they improved model performance (supplementary information, p. 11–12).

From the final models (Model$_{non-lab}$ and Model$_{lab}$), we calculated prognostic risk scores for each person as a linear predictor, *i.e.* a weighted sum of the variables in the model, where the weights were the Cox regression coefficients. A high-risk score indicates higher risk of liver events. Based on this risk score, participants were classified into 4 risk groups defined by the predicted 15-year absolute cumulative probability of liver events using the cut-offs 0.5%, 5%, and 10%. We considered 15-year risk because of the time it usually takes for clinical liver endpoints to develop from early-stage liver disease,[28] and risk stratification on a shorter timescale would have risked suboptimal discrimination. The cumulative probability calculation was based on cause-specific Cox regression considering death without liver disease as a competing-risk event.[29] We assessed cause-specific Cox regression model performance in terms of discrimination (Wolbers' C-statistic and time-dependent AUC) and calibration. Internal validation was based on bootstrap resampling. The Aalen-Johansen competing-risk method was used to estimate the cumulative incidence of liver outcomes within risk groups. Using the prognostic scores, we assessed the model's C-statistic in subgroups of the derivation cohort by sex, alcohol risk use (average alcohol intake >30 g/day for men and >20 g/day for women), and baseline NAFLD (fatty liver index ≥30[30] and non-risk drinking). To address the impact of possible pre-existing undiagnosed liver disease, we also performed landmark analysis set at 1 or 3 years after baseline. We also performed analyses by all liver events (including milder forms of liver disease; ICD-10: K70-K77, C22.0; ICD8/9: 570-573, 155.0), liver death, all-cause death, and incident cardiovascular disease (defined as previously described).[31]

External validation of Model$_{non-lab}$ was performed in the Whitehall II and CCHS cohorts, but we externally validated Model$_{lab}$ only in the CCHS cohort because gamma-glutamyltransferase (GGT) was unavailable in Whitehall II. Data were analyzed with R software version 3.6.1.

Results

The Finnish derivation cohort comprised 25,760 individuals, the Whitehall II cohort had 5,058 individuals, and the CCHS cohort had 3,049 individuals (Table 1). Compared with the Finnish cohort, the Whitehall II cohort had a higher proportion of men (70% *vs.* 48%), fewer lifetime alcohol abstainers (3% *vs.* 9%), fewer smokers (12% *vs.* 23%), and less diabetes (4% *vs.* 8%). The CCHS cohort had a slightly higher mean age (56.8 *vs.* 54.0 years), more alcohol use (13 *vs.* 8 drinks/week), more smokers (36% *vs.* 23%), and less diabetes (4% *vs.* 8%) than the Finnish cohort (Table 1).

Median follow-up time was 12.9 years (IQR 7.8–17.8; range 0.0–23.0; 318,616.0 person-years) in the derivation cohort, 21.6 years (IQR 21.2–21.8; range 0.1–22.4; 102,710.3 person-years) in the Whitehall II cohort, and 16.0 years (IQR 15.5–16.6, range 0.3–17.2, 45,027.4 person-years) in the CCHS cohort. The number of incident liver events (hospitalization, cancer, or death) was 273 in the derivation cohort, 54 in Whitehall II, and 64 in CCHS, and the absolute rates of incident liver outcomes per 100,000 person-years were 85.7, 52.6, and 144.4, respectively. All-cause mortality rates per 100,000 person-years were 937.4 in the derivation cohort, 810.0 in Whitehall II, and 1,494.6 in CCHS. Median years from baseline to first liver event were 9.3 (IQR 4.5–12.8) in the derivation cohort, 14.4 (IQR 9.4–17.5) in Whitehall II, and 15.5 (IQR 9.1–16.4) in CCHS.

Model development, performance measure, and internal validation

The phases of the model-building procedures are detailed in the supplementary information (pp. 8–14). The final multivariable model based on non-laboratory values only (Model$_{non-lab}$) included age, sex, waist-hip ratio, average alcohol consumption, diabetes, and smoking status. The model with laboratory values (Model$_{lab}$) included all of these variables and GGT (Fig. 1). There was a significant interaction between sex and smoking (effect of smoking stronger for men) and between sex and GGT (effect of GGT stronger for women) (Fig. S4).

Table 2 shows apparent and internal validation performance statistics of both models. Model$_{lab}$ had an optimism-corrected Wolbers' C-statistic of 0.77 for discrimination of incident liver disease and an apparent 15-year AUC of 0.84 (Table 2). Calibration plots are shown in Fig. S13). For Model$_{non-lab}$, the optimism-corrected C-statistic was 0.75, and apparent 15-year AUC, 0.82.

Table 1. Baseline demographics in the Finnish derivation cohort and the UK validation cohort.

	Derivation cohort	Validation cohort	
Country	Finland	UK	Denmark
N	25,760	5,058	3,049
Age	54.1 (8.5)	55.6 (6.0)	56.8 (8.6)
Sex			
Men	12,354 (48.0)	3,520 (69.6)	1,447 (47.5)
Women	13,406 (52.0)	1,538 (30.4)	1,602 (52.5)
Alcohol use (drinks per week)*	8.1 (14.6)	11.3 (11.7)	13.3 (12.2)
Lifetime alcohol abstainer	2,299 (8.9)	160 (3.2)	
Current smoker	5,833 (22.8)	592 (11.7)	1,110 (36.4)
Waist–hip ratio	0.91 (0.09)	0.89 (0.09)	0.87 (0.09)
Diabetes	2,151 (8.4)	224 (4.4)	111 (3.6)
Gamma-glutamyltransferase (U/L)	37.1 (57.1)		41.5 (36.9)
Additional variables tested in the derivation cohort only			
Binge drinking**			
Less often	8,717 (73.2)		
Monthly	1,670 (14.0)		
Weekly or more often	1,516 (12.7)		
Smoking			
Never	13,509 (53.4)		
Previous smoker	6,194 (24.4)		
<10 cigarettes/day	1,276 (5.0)		
10–19 cigarettes/day	2,086 (8.2)		
20+ cigarettes/day	2,291 (9.0)		
Exercise (>20 minutes)			
At least 2 times a week	13,509 (57.9)		
2–4 times a month	5,660 (26.0)		
Less often	3,499 (16.1)		
Waist circumference (cm)	92.2 (13.5)		
Body mass index (kg/m^2)	27.4 (4.6)		
Alanine aminotransferase (U/L)	27.60 (18.11)		
Aspartate aminotransferase (U/L)	28.85 (14.09)		
Low-density lipoprotein cholesterol (mmol/L)	3.54 (0.96)		
High-density lipoprotein cholesterol (mmol/L)	1.43 (0.39)		
Non–high-density lipoprotein cholesterol (mmol/L)	4.28 (1.09)		
Triglycerides (mmol/L)	1.54 (1.00)		

Results are given as n (%) or mean (± SD).
*1 drink = 10 g ethanol.
**Defined as 5 or more alcoholic drinks per occasion.

Over the 15-year follow-up, the apparent C-statistic was ∼0.8 in Model$_{lab}$, and Model$_{non-lab}$ (Fig. S6). In all sensitivity analyses, the apparent C-statistic remained >0.75 for Model$_{lab}$ and >0.71 for Model$_{non-lab}$ (Table 3). Model discrimination improved with restriction of outcomes to liver-related deaths only (Table 3).

In a subpopulation of 1,253 individuals from the FINRISK cohorts with available platelet data, apparent Wolbers' C were 0.72 for FIB-4 and 0.70 for APRI, compared to 0.88 for Model$_{lab}$ and 0.86 for Model$_{non-lab}$.

Risk stratification

Fig. 2 shows the cumulative incidences of liver events by risk group, considering death without liver disease as a competing-risk event. The models could identify a small proportion (<2%) of the population with >10% absolute risk of developing liver events within 15 years. In the minimal-risk groups, 15-year risks were <0.4%, and only 10% of all liver events in the population occurred in the minimal-risk group.

Nomogram

Fig. 3 and 4 show the nomograms for estimation of an individual's 15-year (Model$_{lab}$ and Model$_{non-lab}$) absolute risks of advanced clinical liver disease based on cause-specific Cox regression.

External validation

Applying a cause-specific Cox model with the risk score based on Model$_{lab}$ as a single covariate to the CCHS cohort gave a Wolbers' C-statistic of 0.78 and a 15-year AUC of 0.78 (95% CI 0.68-0.87) (Table 2). For Model$_{non-lab}$, the corresponding C-statistics and 15-year AUCs were 0.65 and 0.65 (95% CI 0.55–0.76) in the CCHS cohort, and 0.74 and 0.79 (95% CI 0.70–0.88) in the Whitehall II cohort (Table 2). Comparisons of hazard ratios and absolute incidence estimates between risk groups in the various cohorts are shown in Fig. S11 and S12 and in Table S9. Assessment of relatedness between the derivation and Whitehall II samples are shown in the supplementary information, p. 17–18 and Fig. S14.

In the Whitehall II cohort, the Model$_{non-lab}$ score increased during follow-up among both those who developed liver events and those who did not, but the score was consistently higher in the liver-event group (Fig. S15).

Discussion

We have developed and validated a chronic liver disease risk prediction model – the CLivD score – based on affordable and widely available variables to quantify an individual's absolute risk of developing advanced chronic liver disease. Use of this novel model enables the identification of high-risk individuals
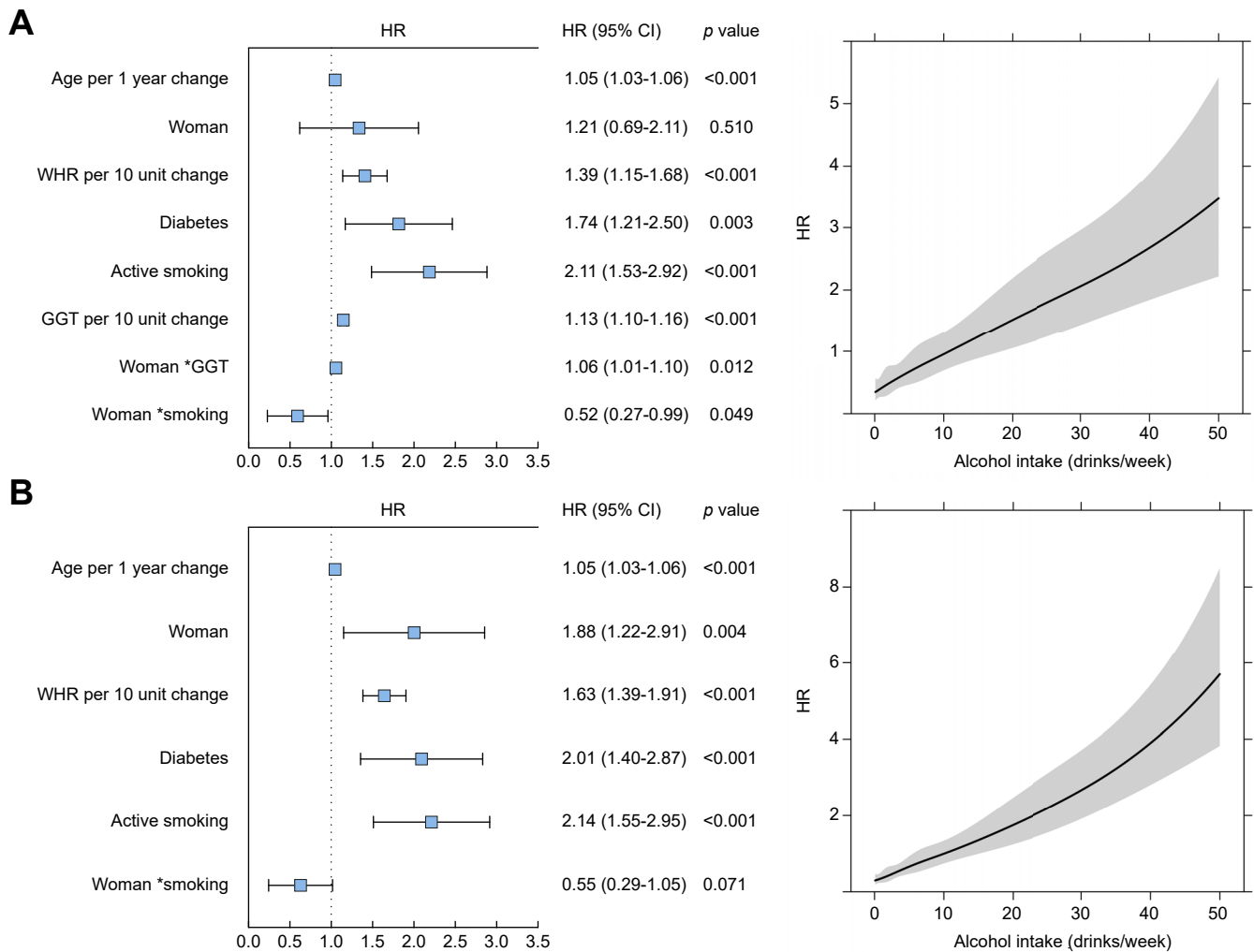
Fig. 1. HRs of model variables for liver-related outcomes and relationship between alcohol use and liver-related outcomes. Forest plot showing the HRs and 95% CIs for liver-related outcomes and the variables in (A) Model$_{lab}$ and (B) Model$_{non-lab}$, and plots showing the non-linear relationship between alcohol use and liver-related outcomes. GGT, gamma-glutamyltransferase; HRs, hazard ratios; WHR, waist-hip ratio.

in the general population before development of advanced liver fibrosis, considering the combined contribution of several risk factors and avoiding dichotomization between alcohol risk drinkers or non-risk drinkers.[17,32,33] Risk estimation with the non-laboratory version of the model can be completed by anyone online or using color-coded scoring sheets (Fig. 3 and 4; example shown in Fig. S16) without the need for a single blood test, for example, as part of liver-oriented public health campaigns. This accessibility could increase the applicability and dissemination of risk estimations in the general population.

Table 2. Model diagnostics.

	Model$_{lab}$	Model$_{non-lab}$
Derivation cohort		
Wolbers' C-statistic, apparent	0.816	0.790
Wolbers' C-statistic, optimism corrected*	0.771	0.747
Time-dependent AUC at 15 years, apparent	0.841 (0.753-0.929)	0.823 (0.736-0.909)
Whitehall II (validation cohort)		
Wolbers' C-statistic		0.739
Time-dependent AUC at 15 years		0.789 (0.695-0.882)
Copenhagen City Heart Study (validation cohort)		
Wolbers' C-statistic	0.777	0.652
Time-dependent AUC at 15 years	0.777 (0.683-0.871)	0.653 (0.549-0.756)

95% CIs given in parentheses.
*Determined by bootstrapping 200 samples of the derivation data.

Table 3. Sensitivity analyses in the derivation cohort showing apparent Wolbers' C-statistic as a measure of model performance.

Subgroups	N	Liver events	Model$_{lab}$ C-statistic	Model$_{non-lab}$ C-statistic
Landmark at 1 year of follow-up	25,650	256	0.819	0.792
Landmark at 3 years of follow-up	21,827	224	0.812	0.782
Men	12,354	194	0.811	0.797
Women	13,406	79	0.781	0.712
Complete-case analysis	24,229	262	0.815	0.789
Alcohol risk drinkers*	1,704	86	0.767	0.711
Non-risk drinkers	22,783	149	0.759	0.719
Non-alcoholic fatty liver disease**	13,153	118	0.762	0.714

Alternative outcomes	N	Events	Model$_{lab}$ C-statistic	Model$_{non-lab}$ C-statistic
All liver events***	24,229	407	0.718	0.686
Liver death	24,229	153	0.836	0.812
All-cause death	24,229	2,993	0.695	0.682
Cardiovascular events	24,229	2,753	0.639	0.629

*Average alcohol intake >30 g/day for men and >20 g/day for women.
**Fatty liver index >30 and a non-risk drinker.
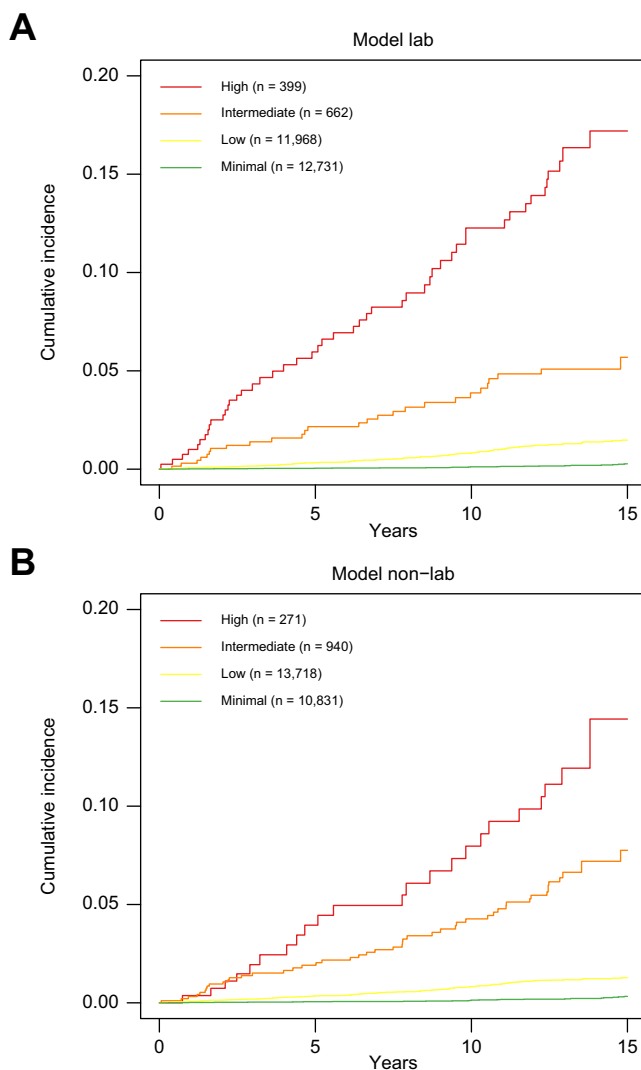***ICD-10 codes K70-77 and C22.0, and ICD-8/9 codes 570-573, 155.0.

A

B

Fig. 2. Cumulative incidence of liver-related outcomes by risk group. Cumulative incidence of liver-related outcomes by risk group estimated by (A) Model$_{lab}$ and (B) Model$_{non-lab}$ in the derivation cohort using the Aalen-Johansen cumulative incidence function. Risk groups were defined by the predicted 15-year probability of liver outcomes as <0.05% (minimal), 0.05%–4.9% (low), 5%–9.9% (intermediate), and ≥10% (high).

In the derivation cohort, optimism-corrected Wolbers' C-statistics as a measure of model discrimination in the competing-risk setting were 0.77 for the model with laboratory data and 0.75 for the model without laboratory data. In the validation cohort, the C-statistic for the model with GGT was 0.78. These estimates are reasonable considering that the models were developed to predict rare outcomes in unselected populations. For comparison, for the largest multinational risk charts with laboratory data to predict 10-year cardiovascular disease risk, the C-statistic varies in a range of 0.69–0.83 by country.[34]

The non-laboratory factors included in the CLivD score (age, sex, alcohol use, abdominal obesity, diabetes, and smoking) are acknowledged population risk factors for cirrhosis and have an established or suspected causal relationship with liver fibrosis and/or liver cancer.[9,32,35–41] In this context, age is a measure of exposure time and not a risk factor *per se*. Flexible non-linear analyses revealed that even light alcohol use was associated with liver outcomes, which is in agreement with previous longitudinal studies.[37]

GGT is a readily available biomarker and more sensitive and accurate than ALT or AST for predicting future liver disease.[13,42] However, the correlation between serum GGT and severity of liver disease in cross-sectional studies is only modest.[13,43,44] By reflecting whole-body oxidative stress, serum GGT may instead mirror mechanisms that lead to disease and thus serve as a marker of disease risk rather than of existing liver disease.[45,46] Oxidative stress mainly related to mitochondrial dysfunction is indeed considered pivotal in the pathophysiology of chronic liver disease and cirrhosis.[47,48] Although GGT has traditionally been used as a marker of alcohol intake, the correlation between GGT and amount of alcohol intake is poor (r <0.3).[49]

The prediction models are based on hazard rates derived from several combined, large, and well-characterized Finnish population cohorts with longitudinal follow-up for clinically relevant liver outcomes (hospital admission, cancer, death) ascertained from reliable national registries. We were able to assess multiple acknowledged risk factors identified *a priori* and account for their complex non-linear relationships and joint contribution. Because they are built on reproducible and widely available risk factors, the models likely can be applied with relative ease in clinical practice by nurses or general practitioners and are amenable to further external validation.

WOMEN

Age

0	12	24	36	Points

50   60   70   Years

Waist-hip ratio

9	13	18	22	26	31	35	40	44	49	53	57	63	Points

0.75 0.80 0.85 0.90 0.95 1.00 1.05 1.10 1.15 1.20 1.25 1.30   Ratio

Alcohol intake

0	13	23	28	34	41	47	52	57	62	Points

3   7   10   14   21   28   35   42   49   Drinks/week

Diabetes

0	15	Points

No   Yes

GGT (Non-smokers)

5	10	14	19	23	28	33	37	42	47	51	56	60	65	70	74	79	84	88	93	97	Points

10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200

GGT (Smokers)

8	12	17	21	26	31	35	40	45	49	54	58	63	68	72	77	82	86	91	95	100	Points

10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200   U/L

MEN

Age

0	12	24	36	Points

50   60   70   Years

Waist-hip ratio

9	13	18	22	26	31	35	40	44	49	53	57	63	Points

0.75 0.80 0.85 0.90 0.95 1.00 1.05 1.10 1.15 1.20 1.25 1.30   Ratio

Alcohol intake

0	13	23	28	34	41	47	52	57	62	Points

3   7   10   14   21   28   35   42   49   Drinks/week

Diabetes

0	15	Points

No   Yes

Non-smokers

GGT

0	3	6	9	13	16	19	22	25	28	32	35	38	41	44	47	51	54	57	60	63	Points

10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200   U/L

Smokers

GGT

20	23	26	29	33	36	39	42	45	48	52	55	58	61	64	67	71	74	77	80	83	Points

10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200   U/L

Score

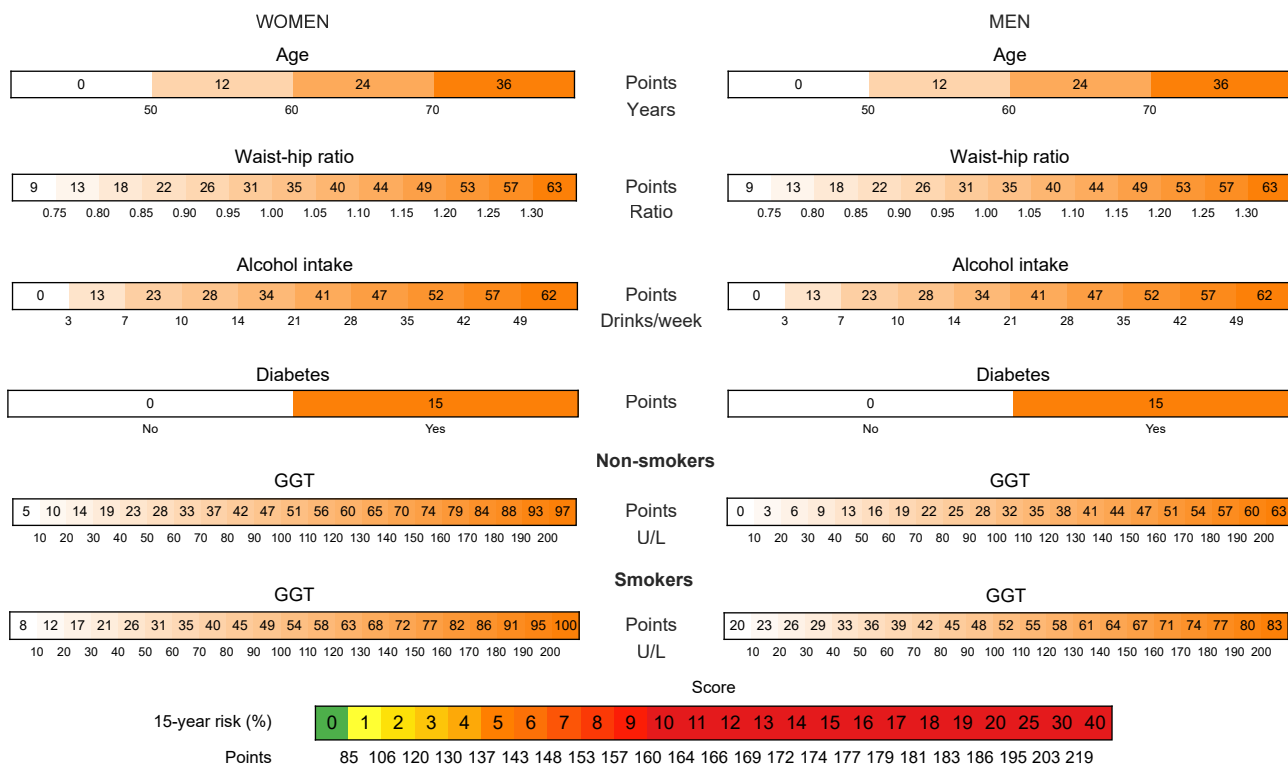| 15-year risk (%)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	25	30	40
Points	85	106	120	130	137	143	148	153	157	160	164	166	169	172	174	177	179	181	183	186	195	203	219	

Fig. 3. Nomogram to calculate an individual's 15-year absolute risks of developing clinical liver-related outcomes based on the risk prediction model with laboratory data (Model_{lab}). GGT, gamma-glutamyltransferase.

Although waist–hip ratio was measured in this study according to standardized protocols, accuracy of self-measurements of this ratio is good.[50,51]

Strengths of our study include external validation in UK and Danish populations with similar inclusion and exclusion criteria, and similar definitions of exposures and outcomes as in the derivation cohort. The ability to include liver-related hospitalizations is a major strength of our study, because this inclusion reduces the risk of omitting cases with clinically significant liver disease. Differences in incidence rates among cohorts are likely the result of a different case mix and different length of follow-up.

Study limitations include an uncertainty in risk estimates when dealing with relatively rare outcomes and long-term predictions, as is the case with clinical liver disease. The low number of outcomes in the validation cohorts limited our ability to obtain accurate incidence estimates by risk subgroup, and for this reason, we did not perform model re-calibration. We assessed risk factors only once, at baseline, but this is often also the reality in the clinic when making predictions of future risks. More validation studies are needed in larger samples and in ethnically diverse populations. More study is also needed before the models can be applied in those with chronic viral hepatitis or abstainers with a history of alcohol consumption, since both of these were exclusion criteria in this study. We acknowledge that reliance on registry linkage omits undiagnosed liver disease and less severe cases that may have been largely managed in primary care, but we specifically sought to examine complicated liver disease, not subclinical liver fibrosis. Future studies should analyze whether inclusion of additional variables could improve model performance.

Comparison to previous studies

Current population-based screening strategies focus on detecting prevalent subclinical advanced liver fibrosis using various non-invasive fibrosis tests, such as FIB-4 and APRI.[52] However, non-invasive fibrosis tests were not designed for screening the general population or predicting clinical liver-related outcomes.[9,53] In a smaller subpopulation analysis, C-statistics for FIB-4 and APRI were 0.72 and 0.70, respectively. These are comparable to those reported in a large Swedish population-based study (0.70 and 0.67), although it is unclear whether competing risks were adequately accounted for in that study.[13] Importantly, in that latter study, 65%–69% of liver outcomes within 10 years occurred in the low-risk categories, so that FIB-4 or APRI screening would have missed them.[13] In comparison, in our study, only 8%–10% of liver outcomes within 15 years occurred in the lowest laboratory-based CLivD-score category. Further comparison to non-invasive fibrosis tests is needed in larger cohorts.

A strong advantage of our risk factor-based model, compared to a specific diagnosis of advanced liver fibrosis, is the ability to identify high-risk persons before they progress to advanced fibrosis. The CLivD score could complement fibrosis tests by serving as the initial basis for further fibrosis testing and follow-up. Such targeted fibrosis screening could substantially reduce the numbers needed to screen and the false-positive rates among screened individuals, but this requires specific investigation.

Identification of individuals in the general population who are at risk of future liver disease can support informing them about liver-related risks and how to reduce these risks. Knowledge
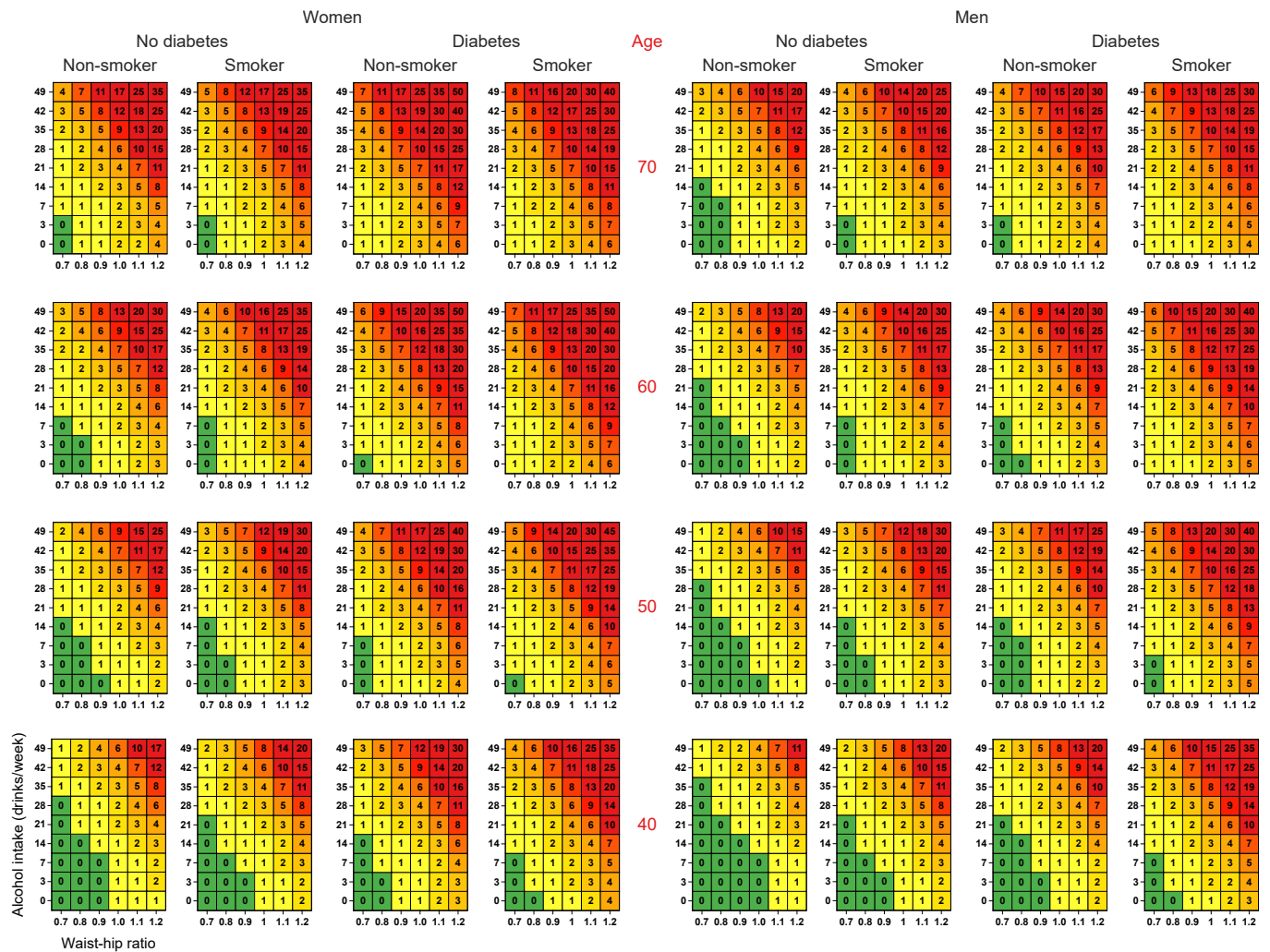
Fig. 4. Nomograms to calculate an individual's 15-year absolute risk of developing clinical liver-related outcomes based on the risk prediction model without laboratory data (Model$_{non-lab}$).

about being at high risk can support healthy lifestyle changes, such as a reduction of harmful drinking.[54] Furthermore, the prediction model could help target lifestyle intervention resources and therapeutic decisions based on risk, and possibly also help assess response to such interventions.

Alcohol use, smoking, abdominal obesity, and serum GGT are all modifiable.[55–61] The change in serum GGT level correlates with the improvement in hepatic steatosis following lifestyle interventions.[62] Interventions targeted at reducing an individual's CLivD score or components of the score would likely lead to reductions in the risk of clinical liver disease, but this possibility also needs further study. In addition, the CLivD score should not replace current diagnostic tests when there is suspicion of prevalent liver disease.

In conclusion, the CLivD score is a simple prediction model based on easily accessible risk factors for predicting future risk of advanced chronic liver disease. Using the CLivD score, risk estimation can be performed by anyone through the internet or by using the related scoring sheets. The model identifies individuals at high risk and provides data to support lifestyle changes. At the primary health-care level, the CLivD score can be used to identify individuals who should be referred for further liver assessment.

More validation studies and a health-economics evaluation of this approach are needed.

Abbreviations

ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; CLivD score, **C**hronic **Liv**er **D**isease score; FIB-4, fibrosis-4; GGT, gamma-glutamyltransferase; HES, Hospital Episode Statistics; HOMA-IR, homeostasis model assessment of insulin resistance; ICD, International Classification of Diseases; NAFLD, non-alcoholic fatty liver disease.

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Authors' contributions

Study concept: FÅ, PKL, MF, ABu, AJ. Study design and enrollment of participants and data collection: FÅ, PKL, ABu, ABr, SEB, BGN, PP, VS., SM, AL, MP, AJ, MF. Data analysis: FÅ, PKL, ABu, KMP, MB, SEB, PP. Data interpretation: FÅ, PKL, ABu, ABr, KMP, MB, SEB, BGN, PP, VS., SM, AL, MP, AJ, MF. First draft: FÅ. Critical revision for important intellectual content: FÅ, PKL, ABu, ABr, KMP, MB, SEB, BGN, PP, VS., SM, AL, MP, AJ, MF.

Data availability statement

FINRISK and Health 2000 data are available from the THL biobank based on a research application, as explained on the website of the THL biobank (https://thl.fi/en/web/thl-biobank/for-researchers). Whitehall II data are available to bona fide researchers for research purposes. Please refer to the Whitehall II data sharing policy at http://www.ucl.ac.uk/whitehallII/data-sharing. Copenhagen City Heart Study data are also available through research application.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.02.021.

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