Original Research

Burden of liver disease progression in hospitalized patients with type-2 diabetes mellitus: a retrospective, longitudinal, cohort study

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Data sharing: subject to agreement

Abstract

Background and aims: There are uncertainties on the burden of liver disease in patients with type-2 diabetes (T2D).

Methods: We measured adjusted hazard ratios of liver disease progression to hepatocellular cancer and/or decompensated cirrhosis in a 2010-2020 retrospective, bicentric, longitudinal, cohort of 52,066 hospitalized patients with T2D.

Results: Mean age was 64±14 years and 58% were men. Alcohol use disorders accounted for 57% of liver-related complications and were associated with all liver-related risk factors. Non-metabolic liver-related risk factors accounted for 37% of the liver burden. T2D control was not associated with liver disease progression. The incidence (95% confidence interval) of liver-related complications and of competing mortality were 3.9 (3.5-4.3) and 27.8 (26.7-28.9) per 1000 person-years at risk, respectively. The cumulative incidence of liver disease progression exceeded the cumulative incidence of competing mortality only in the presence of a well-identified risk factors of liver disease progression, including alcohol use. The incidence of hepatocellular cancer was 0.3 (95% CI, 0.1-0.5) per 1000 person-year in patients with obesity and it increased with age. The adjusted hazard ratios of liver disease progression were 55.7 (40.5-76.6), 3.5 (2.3-5.2), 8.9 (6.9-11.5), and 1.5 (1.1-2.1), for alcoholic liver disease, alcohol use disorders without alcoholic liver disease, non-metabolic liver-related risk factors, and obesity, respectively. The attributable fractions of alcohol use disorders, non-metabolic liver risk-related risk factors, and obesity to the liver burden were 55%, 14%, and 7%, respectively.

Conclusions: In this analysis of data from two hospital-based cohorts of patients with T2D, alcohol use disorders, rather than obesity, contributed to most of the liver burden.

These results suggest that patients with T2D should be advised to drink minimal amounts of alcohol.

273/275 words

Lay summary

• There is uncertainty on the burden of liver-related complications in patients with type-2 diabetes

• We studied the risks of liver cancer and complications of liver disease in over 50,000 patients with type-2 diabetes

• We found that alcohol was the main factor associated with complications of liver disease

• This finding has major implications on the alcohol advice given to patients with type-2 diabetes

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease worldwide, affecting, on average, 25% of the adult population (1). NAFLD encompasses a wide range of diagnoses, from fatty liver to non-alcoholic steatohepatitis (NASH), that can progress to fibrosis, cirrhosis, and hepatocellular cancer (HCC). It is estimated that 5-10% of patients with NAFLD progress to NASH and fibrosis.(2) Increasing age and the parameters of the metabolic syndrome are all associated with the progression of fibrosis in NAFLD. Type-2 diabetes mellitus (T2D) is an important risk factor for the development and progression of NAFLD: about half of patients with T2D have NAFLD and one-third of patients with T2D may develop progressive liver disease.(3) The association of T2D with NAFLD increases the risk of advanced liver fibrosis, and of both liver-related and all-cause mortality.(4, 5) The prevalence of T2D is increasing worldwide,(6) and the economic burden of NAFLD is expected to grow exponentially.(7, 8) The EASL guidelines on NAFLD recommend that patients with T2D should be tested for the presence of NAFLD and fibrosis.(9) Yet, the risks of liver-related outcomes in patients with T2D are inconsistently reported in the literature. We therefore conducted a retrospective, longitudinal study in a large, multicentre cohort of patients with T2D to quantify the burden of liver disease, identify risk factors, and estimate attributable risks.

Methods

Data source

The data sources were the discharge databases, the medical records, and the biological databases of two teaching hospitals of the Assistance Publique-Hôpitaux de Paris (Cochin and Pitié Salpêtrière). Clinical data was extracted (AR, SB, PR) from the standardized discharge summaries that include: demographics; primary and associated discharge diagnosis codes according to the World Health Organisation International Classification of Diseases, tenth revision (ICD-10); medical procedures received during hospital stay; length of stay; entry and discharge modes (including in-hospital death). *The French Programme de Médicalisation des Systèmes d'Information* (PMSI) coding system was shown to be 100% specific for hard, including liver, outcomes.(10, 11)

All glycated hemoglobin measurements were extracted (JFM, MS, DR) and merged with the clinical dataset. Patient-level data check was performed for all patients who reached the primary outcome by three students (AM, JPB, CN) under the supervision of a senior investigator (LP). The Institutional Review Board of Assistance Publique-Hôpitaux de Paris approved the study and waived the need for informed consent from individual patients.

Study population

We selected, among all 2010-2020 patients with a discharge code for diabetes mellitus (ICD-10: E1; N=80,436), all adult patients with a type-2 diabetes mellitus (T2D) discharge code; without any other diabetes mellitus discharge code, including type-1 diabetes mellitus and other specified or non-specified diabetes mellitus.

Outcome measure

The main outcome was liver disease progression to a liver-related complication, including primary liver cancer and decompensated cirrhosis. Decompensated cirrhosis was defined as any of ascites, portal hypertension bleeding, hepatic encephalopathy, or non-obstructive jaundice. Competing events were death without a liver-related complication.

Exposures

The exposures were alcohol use disorders; non-metabolic liver-related risk factors; markers of the metabolic syndrome, including obesity, hypertension, and dyslipidemia; and non-liver related risk factors, including smoking. Alcohol use disorders were identified by three categories of discharge diagnosis codes: “alcoholic” liver disease (ICD-10: K70); another disease that was due to alcohol use disorders (for example ICD-10: K86.0 for “alcohol-induced” chronic pancreatitis); or mental and behavioral disorders due to former or current harmful use of alcohol (ICD-10: F10·1-F10·9, Z50·2).(11-13) Non-metabolic liver risk factors were all, well-identified, causes of chronic liver disease, including chronic hepatitis B with or without hepatitis delta coinfection; chronic hepatitis C (with or without an virological response to antivirals); and other primary causes of cirrhosis, including congenital malformations, inherited metabolic liver diseases, the Budd-Chiari syndrome, and autoimmune liver diseases. Metabolic syndrome was defined as the presence of two ot the following: obesity (ICD-10: E66), dyslipidemia (ICD-10: E78·0, E78·1, E78·2, E78·4, E78·5) or hypertension (ICD-10: I10, I11, I12, I13, R03·0). (14, 15) Poorly controlled T2D was defined as a persistent haemoglobin A1c level ≥7% for more than a year or the presence of complications of diabetes mellitus. Non-liver related risk factors were extrahepatic cancer; acquired immunodeficiency syndrome (AIDS); extra-hepatic diseases

requiring immunosuppression, such as connective tissue disorders; ischemic heart disease; and stage 3-5 chronic kidney disease.(11) The diagnostic code dictionary is provided in the supplementary material.

Statistical Analysis

Using unique identifiers, we traced patients' trajectories in all units of the two hospitals. We did not trace patients' trajectories in other structures. Because primary liver cancer is often associated with long diagnosis delays, approximately 3 years for tumors with median growth rate,(16) we studied liver disease progression to a liver-related complication only among patients admitted to hospital from 2010 to 2020 who had no record of liver disease progression from 2010 to 2012. Because liver disease progression rate is non-linear after cirrhosis,(2) we restricted our incidence calculations to patients without cirrhosis diagnosed at study entry. Incidences were computed with the epiR package.(17) The effect of well-identified liver risk factors (alcohol use disorders, including alcoholic liver disease, and non-metabolic liver-related risk factors), and of the metabolic syndrome on liver disease progression were estimated with univariate and multivariate Cox proportional hazards models. Because of the differences in life-expectancies and alcohol consumption between males and women, we stratified all models on sex. To isolate the effect of non-metabolic liver-related risk factors, and of the components of the metabolic syndrome from alcohol use disorders (see table 1), the definitions of these variables were restricted to patients without alcohol use disorders. Because of the increased risk of liver disease progression with age and the open cohort study design, age was used as the timescale, with follow-up starting from Jan 1, 2010 until liver disease progression, in-hospital competing death, or right-censoring at last hospital discharge from 2010 to December 31, 2020.(18) All liver disease progression models fulfilled proportional hazards assumptions.

Attributable fractions combine information about incidence and adjusted hazard ratios estimates and denote the excess incidence of liver-related complications that would have been prevented in the 2010-2020 cohort if a risk factor (here alcohol use disorders, non-metabolic liver-related risk factors, and the metabolic syndrome) was absent.(19) All statistical tests were based on two-tailed P values, with $P<0.05$ considered to indicate statistical significance. All analyses were performed using RStudio statistical software (Version 1.2.5033 © 2009-2019 RStudio, Inc).

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Results

Characteristics of patients and interactions with alcohol use disorders

Of the 64,283 adult patients diagnosed with T2D, we excluded 12,217 (19.0%) patients with an ICD-10 code for another type of diabetes mellitus in their discharge summaries (see supplementary figure 1). The characteristics of the 52,066 patients are detailed in table 1. The mean ± standard deviation age at entry was 64 ± 14 years, the majority (72%) of patients were between 50 and 80 years old, and more than half (58%) were males. A well-identified cause of liver disease progression to a liver-related complication, including alcoholic liver disease and non-metabolic liver-related risk factors, was diagnosed in ~5% (4.7%) patients. Chronic viral hepatitis was present in ~2% of patients (1.3% with chronic hepatitis C and 0.8% with chronic hepatitis B). Cirrhosis was recorded in ~2% of patients. More than 2/3 (69.1%) of patients had at least one feature of the metabolic syndrome (obesity, dyslipidemia or hypertension) and a little more than 1/5 (22%) patients had a complete metabolic syndrome phenotype. Poorly controlled T2D was diagnosed in half (53.4%) of patients, including ~1/3 (36%) with one or more complications of T2D and ~2/3 with a serum HbA1c level (available for ~2/3 patients) ≥ 7% for a year or more. Smoking was recorded in 1/6 (16%) patients. At least one extrahepatic chronic condition was recorded in ~30% of patients. The majority (87%) of included patients had at least two hospital visits before liver disease progression [1,071 (2.1%) patients], non-liver related death [2,530 (4.9%) patients] or end of follow-up [48,465 (93%) patients] occurred. A total of 816 (76.2%) patients had liver disease progression as the primary diagnosis at discharge, including 264 (32.4%) with liver disease progression at study entry. Mean follow up was 21 months (median [range] 2 [0-148] months), which corresponded to a 90,469.75 person-

year observation period. A little more that 1/4 (28%) patients had one or more hospital stays for with T2D as the primary diagnosis at discharge.

The prevalence of alcohol use disorders was 7.5%. The interaction between patient characteristics and alcohol use disorders are detailed in table 1. Patients with alcohol use disorders were younger at inception (P<0.001), were censored younger (P<0.001), especially between [50-70) years, and were predominantly (P<0.001) males. Alcoholic liver disease was diagnosed in ~1/4 (24%) patients with alcohol use disorder. Patients with alcohol use disorders had more frequently non-metabolic liver-related risk factors [+7% (95%CI: 6%-8%], P<0.001); compensated cirrhosis [+13% (95% CI 12%-14%), P<0.001); features of the metabolic syndrome, including obesity [+13%, (95% CI 11%-14%), P<0.001], hypertension [+13%, (95% CI 11%-14%), P<0.001], and dyslipidemia [+11%, (95% CI 9%-13%), P<0.001]; complications of diabetes mellitus [+2%, (95% CI 0.0%-3%), P=0.031]; and non-liver-related risk factors [+8%, (95% CI 6%-9%), P<0.001], including smoking [+41%, (95% CI 40%-43%), P<0.001]. Ischemic heart disease (P = 0.6); outcome to chronic hepatitis C treatment (P = 0.3); and serum HbA1c levels were not associated with alcohol use disorders, although patients with alcohol use disorders had longer periods (P<0.001) with a serum HbA1c level ≥ 7%.

Outcome measure

The incidences of liver disease progression to a liver-related complication and of competing death were 3.9 (95% CI, 3.5-4.3) and 27.8 (95% CI, 26.7-28.9) per 1000 person-years at risk, respectively. The incidence of hepatocellular cancer was 0.8 (95% CI, 0.6-1.0) in patients without a well-identified risk factor of liver disease progression, including alcohol use disorders. The incidence of hepatocellular cancer was low in patients with obesity but increased after 70 years (table 2). Cumulative incidences of liver-related complications and of competing mortality by alcohol use

disorders, non-metabolic liver-related risk factors, obesity, and non-liver-related risk factors are presented in figure 2. The incidence of liver-related complications exceeded the incidence of competing death only in the presence of alcohol use disorders (before 65 years, panel A) or liver-related risk factors (Panel B). Otherwise, competing death exceeded the liver burden, including in the presence of obesity, and especially in the presence of non-liver-related risk factors (Panel C). Supplementary figure 2 presents the incidences of liver disease progression and of competing death during the observational period. The incidences of liver-related complications (P<0.001) and of competing death (P=0.006) decreased. The proportion of liver-related complications to competing death remained stable (P=0.08). Supplementary figure 3 presents the trends in alcohol use disorders, non-metabolic liver-related risk factors, and obesity in all patients and in patients with a liver-related complication. The proportion of patients with alcohol use disorders, non-metabolic liver-related risk factors, or obesity increased (P<0.001). The proportion of patients with a liver-related complications and with alcohol use disorders or obesity remained stable (P=0.485 and P=0.179, respectively). The proportion of patients with a liver-related complications and non-metabolic liver-related risk factors decreased (P<0.001).

Risk factors

Table 3 presents the characteristics of patients by outcome. Mean (standard deviation) age at liver disease progression to a liver-related complication was 65 (11) years, with an over-representation (63%) of the (60-70] age category. Patients with liver disease progression were predominantly (P<0.001) males. Alcohol use disorders, including alcoholic liver disease, and non-metabolic liver-related risk factors, accounted for more than 3/4 (76%) of the liver burden (P<0.001). An absence of sustained virological response to antivirals was associated (P<0.001) with liver disease progression in

chronic hepatitis C patients. Patients with compensated cirrhosis (P<0.001); obesity after 60 years old (P<0.001); hypertension (P<0.001); extra-hepatic cancer (P<0.001), moderate to severe chronic kidney disease (P<0.001); and smokers were at risk for liver disease progression.

Patients with competing mortality were almost eight years older [mean difference 7.9 (95% confidence interval, 7.1-8.7; P<0.001) years] than those with liver disease progression. Alcohol use disorders (P<0.001), non-metabolic liver-related risk factors (P<0.001); compensated cirrhosis (P=0.011); obesity after 60 years old (P<0.001); hypertension (P<0.001); extra-hepatic cancer (P<0.001); non-AIDS-related immunodeficiency disorder (P<0.019); ischemic heart disease (P<0.001); moderate to severe chronic kidney disease (P<0.001); and smoking (P<0.001) were risk factors for competing mortality.

Dyslipidemia, the metabolic syndrome, and poorly controlled T2D, including serum HbA1c levels were not associated with liver disease progression or competing mortality.

Multivariate associations

Table 4 presents the univariate and multivariate hazard ratios of liver disease progression and competing death in the cohort. The interaction of male sex, obesity, smoking, liver-related risk factors, and non-liver-related risk factors with alcohol use disorders is detailed in the univariate analyses. Male sex, obesity and smoking were associated with liver disease progression only in the presence of alcohol use disorders. Extrahepatic cancer remained associated with liver disease progression in the absence of alcohol use disorders. Figure 3 presents the adjusted hazard ratios for liver disease progression and for competing mortality, accounting for the interactions with aging and alcohol use disorders (see table 4 for the corresponding multivariate hazard

ratios). The risk for liver disease progression (in red) was higher than the risk for competing death (in black) for patients with alcoholic liver disease (P<0.001); non-metabolic liver-related risk factors (P<0.001); obesity without alcohol use disorders with adjusted hazard ratios of 1.54 (95% CI 1.11 – 2.13, P=0.01) and 1.26 (95% CI 1.13 – 1.40, P<0.001) for liver disease progression and competing mortality, respectively. Patients with non-liver related risk factors (including smoking) had a higher (P<0.001) risk for competing mortality than for liver disease progression. Patients with extra-hepatic cancer remained at risk for liver disease progression. Smoking was not an independent risk factor for liver disease progression.

Attributable fractions

After adjustment, alcohol use disorders, including alcoholic liver disease, contributed to more than half (55%) of the liver burden. The attributable fractions of non-metabolic liver-related risk factors and of non-liver-related risk factors were 14% and 3%, respectively. Obesity (without alcohol use disorders) accounted for 6% of the liver burden. Otherwise, undetermined risk factors contributed to liver disease progression in ~ 1/5 (21%) patients.

Discussion

In this 11-year cohort study of more than 50.000 adults with T2D, well-identified liver-related risk factors, including alcohol use disorders, contributed to ~70% of liver-related complications, while obesity and the metabolic syndrome to just ~7% of the burden. Alcohol use disorders contributed to more than half of the burden and were associated with all other risk factors of liver disease progression, including obesity. The incidence of liver-related complications exceeded the incidence of competing mortality only in the presence of well-identified liver-related risk factors, including alcohol use disorders. T2D patients with a metabolic syndrome phenotype had an incidence of hepatocellular cancer of 0.4 (95% CI, 0.2-0.7) per 1000 person-year at risk, and the incidence increased with age, especially after 70 years. The control of T2D including serum HbA1c levels, and smoking, were not risk factors of liver disease progression. This represents the largest study on the risks of liver-related complications of T2D patients.

In this cohort, the incidence of hepatocellular cancer was consistent with the estimates reported in other population-based studies on NAFLD, but lower than those reported in retrospective, histologically based, NAFLD/NASH studies. (20) In a meta-analysis of 86 studies that included 8,515,431 individuals from 22 countries, the annual incidences of hepatocellular cancer in NAFLD and NASH patients were 0.4 (95% CI, 0.3-0.7) and 5.3 (95% CI, 0.8-37.6) per 1,000 person-years at risk, respectively.(21). In a retrospective cohort study from the United States of America Veterans Health Administration, the incidence of hepatocellular carcinoma was 12.4 (10.7–14.2) per 1,000 person-years at risk in NAFLD patients with diabetes mellitus.(22) Based on our findings, these assumptions on the incidence of liver-related complications in NAFLD/NASH/T2D patients were over-estimations. Potential explanations include

selection bias, unmeasured confounding, including alcohol use disorders, and an absence of consideration of competing, non-liver related mortality, which is more prevalent than liver disease progression in patients with NAFLD, even in those with advanced fibrosis or cirrhosis.(22)

It is intriguing that liver-related events were diagnosed before competing deaths only in the presence of a well-identified risk factor of liver disease progression, including alcohol use, in our cohort. This finding was consistent with the reported interaction between alcohol use and the progression of other chronic liver diseases such as chronic hepatitis C, chronic hepatitis B, and hemochromatosis. When alcohol use disorders were present, liver disease progression occurred at a younger age than competing deaths from non-liver causes (11, 27, 28), as reported for NAFLD.(21, 29) Therefore, studies reporting high incidence rates of liver disease progression in NAFLD/NASH had probably unmeasured confounding liver-related risk factors, including alcohol use. (23-27) For example, alcohol use disorders interacted with all components of the metabolic syndrome in this cohort, including obesity; therefore unreported alcohol use may have contributed to liver disease progression in patients without any risk factor diagnosed. Smoking was a good example of unmeasured confounding. Smoking has been associated with NASH progression.(28) In our cohort, more than half of smokers had alcohol use disorders. Smoking was not an independent risk factor of liver disease progression in multivariate analysis and was most likely a proxy for unmeasured alcohol use disorders. Other interesting findings included an absence of relationship between T2D control and liver disease progression, as previously reported;(29) and a clear benefit of antiviral treatment of chronic hepatitis C patients with a sustained virological response to antiviral treatment. These findings

suggest that liver-related factors and alcohol use disorders drive preferentially liver disease progression of T2D patients, and that these factors should be diagnosed and treated.

Obesity has been inconsistently reported as a risk factor for liver disease progression.(30) In our cohort, obesity and the metabolic syndrome were independent risk factors of liver disease progression only if age and the interaction between obesity and alcohol use disorders were considered. The adjusted risk of obesity of 1.54 (95% CI 1.11 – 2.13, P=0.010) was consistent with previous estimates. (31) This rather low risk, compared with alcohol use disorders and other risk factors of chronic liver disease, probably explains, why the prevalence of obesity-associated hepatocellular carcinoma did not increase during the period while the prevalence of obesity increased. The decrease with time of the liver burden of T2D patients was also inconsistent with the increase in the prevalence of obesity and of the metabolic syndrome and was most likely due to competing deaths. Extra-hepatic cancer was a risk factor of liver disease progression, and we hypothesize that this was because of cancer treatment toxicity on a background of NAFLD/NASH.

Our study has clear strengths, as it is the first, large, multicenter cohort study designed to disentangle the burden of liver diseases of patients with T2D. Its longitudinal nature reduced the risks of reverse associations: all exposures were present before liver disease progression. The stringent selection of patients, the patient-level check of all liver-related events, the implementation of biology, including HbA1c levels, and the perimeter of the study limited the risks of selection, information and confounding bias. The attributable risks, which reflect the proportion of disease cases (here

hepatocellular carcinoma and decompensated cirrhosis) that can be attributed to an exposure (for example alcohol use disorders or non-metabolic liver risk factors) in the population (here, patients with T2D), were computed with multilevel Cox models with age as the time scale(32) to reduce statistical bias. Weaknesses include the fact that the study was hospital-based, and not designed to capture all competing deaths. Some patients could have been lost to follow-up in other hospitals, with a risk of underestimating the number of outcomes. The study is also limited by the presence of unmeasured exposures, including alcohol use. Therefore, our attributable risk measures for alcohol use disorders are most likely lower estimates. We also did not capture the effect of alcohol abstinence, which is well known to have a major impact on the risk of liver disease progression.(11)

In conclusion, we have shown that alcohol use disorders accounts for more than half of the liver burden of T2D patients and correlates with all other risk factors of liver disease progression. The contribution of the metabolic syndrome and of obesity, was lower (less than 10%) than previous estimations. Based on the finding of this study, T2D patients with alcohol use are those who should be prioritized for case-finding of advanced fibrosis. Alcohol use is a modifiable risk factor, and our data suggest that patients with T2D should be counseled to drastically minimize alcohol use. Overall, our results call for a more vigorous assessment of alcohol use in patients labeled as having NAFLD/NASH. (33, 34) Furthermore, models on the burden of NAFLD, including cost-effectiveness models for new treatments, should be adjusted for alcohol use.

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Author names in bold designate shared authorship

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Legends to figures

Figure 1: Competing risk analyses for alcohol use disorders, liver-related risk factors, metabolic syndrome, and non-liver-related risk factors

Cohort inception was 2010. Liver-related events were recorded after a 2010-2012 (3-year) washout period to reduce the risk of non-incident cases. Patients with cirrhosis at study entry were not included in the analysis. Liver disease progression to a liver-related complication was a composite outcome of primary liver cancer and of decompensated cirrhosis. Decompensated cirrhosis was defined as any of ascites, portal hypertension bleeding, hepatic encephalopathy, or non-obstructive jaundice.

Figure 2: Multivariate hazard ratios for liver disease progression to a liver-related complications and for competing mortality (death without liver disease progression) in patients with T2D

Hazard ratios were computed with multivariate Cox models stratified on sex, with age at last follow-up as the time scale. Alcohol use disorder was defined without alcoholic liver disease. Obesity, smoking, liver-related risk factors, ischemic heart disease, stage 3-5 (moderate to severe) chronic kidney disease, immundepression, and extra-hepatic cancer were defined without alcohol use disorders. Patients with cirrhosis at cohort inception were excluded from the analysis. Liver-related events were recorded after a 2010-2012 (3-year) washout period to reduce the risk of non-incident cases.

Figure 3: Adjusted attributable fractions for liver disease progression to a liver-related complications in patients with T2D

The attributable fraction reflects the number of liver events that would have been prevented in the absence of a risk factor. Attributable fractions were computed with cox models stratified on sex with age as the time scale, and adjusted for alcoholic liver

disease; alcohol use disorders without alcoholic liver disease; non-metabolic liver risk factors, obesity, and non-liver-related risk factors, without alcohol use disorders.

Tables

Table 1: Characteristics of T2D patients, stratified by alcohol use disorders

Characteristic	Overall N = 52,066[1]	Alcohol use disorders		p-value[2]
		No N = 48,158 (92%)[1]	Yes N = 3,908 (7.5%)[1]	
Age at inception	64 (14)	64 (14)	63 (12)	<0.001
Age categories at inception				<0.001
≤ 50	8,341 (16%)	7,818 (16%)	523 (13%)	
(50,60]	10,848 (21%)	9,838 (20%)	1,010 (26%)	
(60,70]	15,275 (29%)	13,932 (29%)	1,343 (34%)	
(70,80]	11,457 (22%)	10,670 (22%)	787 (20%)	
> 80	6,145 (12%)	5,900 (12%)	245 (6.3%)	
Age at last follow-up	65 (14)	65 (14)	65 (12)	<0.001
Sex				<0.001
Male	30,219 (58%)	27,029 (56%)	3,190 (82%)	
Female	21,847 (42%)	21,129 (44%)	718 (18%)	
Alcoholic liver disease	923 (1.8%)	0 (0%)	923 (24%)	<0.001

Non-metabolic liver-related risk factors	1,761 (3.4%)	1,366 (2.8%)	395 (10%)	<0.001
Chronic hepatitis C	683 (1.3%)	500 (1.0%)	183 (4.7%)	<0.001
Chronic hepatitis C with an SVR	535 (79%)	396 (80%)	139 (77%)	0.3
Chronic hepatitis B	427 (0.8%)	362 (0.8%)	65 (1.7%)	<0.001
Other chronic liver diseases	765 (1.5%)	566 (1.2%)	199 (5.1%)	<0.001
Compensated cirrhosis	1,074 (2.1%)	515 (1.1%)	559 (14%)	<0.001
Metabolic syndrome	11,570 (22%)	10,199 (21%)	1,371 (35%)	<0.001
Obesity	15,109 (29%)	13,520 (28%)	1,589 (41%)	<0.001
Dyslipidemia	16,859 (32%)	15,197 (32%)	1,662 (43%)	<0.001
Hypertension	28,369 (54%)	25,782 (54%)	2,587 (66%)	<0.001
Diabetes mellitus with complications	18,962 (36%)	17,476 (36%)	1,486 (38%)	0.030
Current or past smoker	8,207 (16%)	6,102 (13%)	2,105 (54%)	<0.001
Non-liver-related risk factors	14,984 (29%)	13,575 (28%)	1,409 (36%)	<0.001
Cancer	6,478 (12%)	5,745 (12%)	733 (19%)	<0.001
AIDS	557 (1.1%)	488 (1.0%)	69 (1.8%)	<0.001

Immunodeficiency disorder	1,025 (2.0%)	917 (1.9%)	108 (2.8%)	<0.001
Ischemic heart disease	4,521 (8.7%)	4,191 (8.7%)	330 (8.4%)	0.6
Moderate to severe chronic kidney disease	4,286 (8.2%)	3,822 (7.9%)	464 (12%)	<0.001
Serum HbA1c ≥ 7%	18,062 (64%)	16,419 (64%)	1,643 (63%)	0.8
Mean serum HbA1c level	7.61 (4.57)	7.62 (4.71)	7.47 (2.75)	<0.001
Max serum HbA1c level	8.19 (14.68)	8.14 (12.71)	8.68 (27.42)	0.3
Number of HbA1c measurements ≥ 7%	2.46 (2.25)	2.41 (2.17)	2.88 (2.88)	<0.001
Number of HbA1c measurements	3 (3)	3 (3)	4 (4)	<0.001
Follow-up, months	21 (32)	20 (31)	26 (35)	<0.001
Outcome				<0.001
Death without a liver-related complication	2,530 (4.9%)	2,265 (4.7%)	265 (6.8%)	
Progression to a liver-related complication	1,071 (2.1%)	463 (1.0%)	608 (16%)	
Alive without a liver-related complication	48,465 (93%)	45,430 (94%)	3,035 (78%)	

Metabolic syndrome was defined as the presence of obesity with either hypertension or dyslipidemia. Compensated cirrhosis was defined as the record of cirrhosis before a liver-related complication. Liver-related complication were defined as a composite outcome of hepatocellular carcinoma and of decompensated cirrhosis (any of ascitis, portal

hypertension bleeding, non-obstructive jaundice, encephalopathy). Competing death was defined as death or palliative care without a liver-related complication. Abbreviations: AIDS: Acquired immunodeficiency syndrome; HbA1c: glycated hemoglobin; SVR: sustained virological response; T2D: type-2 diabetes mellitus

1 Mean (SD); n (%)

2 Wilcoxon rank sum test; Pearson's Chi-squared test

Table 2: Incidences of liver-related complications and of competing death in T2D patients, per 1000 person-years at risk

Indicator	Estimate (95% CI)
Incidence of liver-related complications	3.90 (3.50-4.33)
Incidence of hepatocellular carcinoma	1.57 (1.32-1.85)
Incidence of decompensated cirrhosis	2.24 (1.94-2.57)
Incidence of competing death	27.8 (26.72-28.91)
Incidence of hepatocellular carcinoma without a well-identified risk factor of liver disease progression	0.79 (0.61-1.02)
Incidence of hepatocellular carcinoma with metabolic syndrome	0.41 (0.21-0.74)
Incidence of hepatocellular carcinoma with obesity age < 70	0.25 (0.10-0.52)
Incidence of hepatocellular carcinoma with obesity age ≥ 70	1.58 (0.64-3.26)

Table 3: Characteristics of T2D patients, stratified by outcome

Characteristic		Outcome			
	Overall, N = 52,066[1]	**Death without a liver-related complication,** N = 2530 (4.9%)[1]	**Progression to a liver-related complication,** N = 1071 (2.1%)[1]	**Alive without a liver-related complication,** N = 48,465 (93%)[1]	**p-value**[2]
Age at inception	64 (14)	71 (12)	65 (11)	63 (14)	<0.001
Age categories at inception					<0.001
≤ 50	8,341 (16%)	113 (4.5%)	107 (10.0%)	8,121 (17%)	
(50,60]	10,848 (21%)	321 (13%)	213 (20%)	10,314 (21%)	
(60,70]	15,275 (29%)	693 (27%)	383 (36%)	14,199 (29%)	
(70,80]	11,457 (22%)	764 (30%)	286 (27%)	10,407 (21%)	
> 80	6,145 (12%)	639 (25%)	82 (7.7%)	5,424 (11%)	
Age at last follow-up	65 (14)	73 (12)	65 (11)	65 (14)	<0.001
Sex					<0.001
Male	30,219 (58%)	1,677 (66%)	835 (78%)	27,707 (57%)	

Female	21,847 (42%)	853 (34%)	236 (22%)	20,758 (43%)	
Alcohol use disorders	3,908 (7.5%)	265 (10%)	608 (57%)	3,035 (6.3%)	<0.001
Alcoholic liver disease	923 (1.8%)	22 (0.9%)	531 (50%)	370 (0.8%)	<0.001
Non-metabolic liver-related risk factors	1,761 (3.4%)	117 (4.6%)	394 (37%)	1,250 (2.6%)	<0.001
Chronic hepatitis C	683 (1.3%)	31 (1.2%)	171 (16%)	481 (1.0%)	<0.001
Chronic hepatitis C with an SVR	535 (79%)	28 (90%)	102 (61%)	405 (85%)	<0.001
Chronic hepatitis B	427 (0.8%)	22 (0.9%)	77 (7.2%)	328 (0.7%)	<0.001
Other chronic liver diseases	765 (1.5%)	69 (2.7%)	204 (19%)	492 (1.0%)	<0.001
Compensated cirrhosis	1,074 (2.1%)	48 (1.9%)	403 (38%)	623 (1.3%)	<0.001
Metabolic syndrome	11,570 (22%)	406 (16%)	249 (23%)	10,915 (23%)	<0.001
Obesity by age category					<0.001
< 60 years	7,512 (50%)	124 (25%)	110 (35%)	7,278 (51%)	

[60-70)	4,632 (31%)	160 (33%)	119 (38%)	4,353 (30%)	
≥ 70 years	2,965 (20%)	207 (42%)	82 (26%)	2,676 (19%)	
Dyslipidemia	16,859 (32%)	652 (26%)	239 (22%)	15,968 (33%)	<0.001
Hypertension	28,369 (54%)	1,662 (66%)	693 (65%)	26,014 (54%)	<0.001
Diabetes mellitus with complications	18,962 (36%)	812 (32%)	321 (30%)	17,829 (37%)	<0.001
Serum HbA1c ≥ 7%	18,062 (64%)	610 (55%)	272 (46%)	17,180 (64%)	<0.001
Mean serum HbA1c level	7.61 (4.57)	7.14 (1.45)	6.71 (1.57)	7.64 (4.69)	<0.001
Max serum HbA1c level	8.19 (14.68)	7.60 (3.26)	7.31 (2.14)	8.23 (15.13)	<0.001
Number of HbA1c measurements ≥ 7%	2.46 (2.25)	2.11 (1.79)	2.18 (2.33)	2.48 (2.26)	<0.001
Number of HbA1c measurements	3 (3)	3 (3)	3 (4)	3 (3)	0.002
Non-liver-related risk factors	14,984 (29%)	1,734 (69%)	455 (42%)	12,795 (26%)	<0.001
Cancer	6,478 (12%)	1,138 (45%)	281 (26%)	5,059 (10%)	<0.001

AIDS	557 (1.1%)	22 (0.9%)	18 (1.7%)	517 (1.1%)	0.094
Immunodeficiency disorder	1,025 (2.0%)	67 (2.6%)	15 (1.4%)	943 (1.9%)	0.019
Ischemic heart disease	4,521 (8.7%)	447 (18%)	76 (7.1%)	3,998 (8.2%)	<0.001
Moderate to severe chronic kidney disease	4,286 (8.2%)	466 (18%)	140 (13%)	3,680 (7.6%)	<0.001
Current or past smoker	8,207 (16%)	589 (23%)	234 (22%)	7,384 (15%)	<0.001
Follow-up, months	21 (32)	21 (29)	1 (7)	21 (32)	<0.001

Metabolic syndrome was defined as the presence of obesity with either hypertension or dyslipidemia. Compensated cirrhosis was defined as the record of cirrhosis before a liver-related complication. Liver-related complications were defined as a composite outcome of hepatocellular carcinoma and of decompensated cirrhosis (any of ascitis, portal hypertension bleeding, non-obstructive jaundice, encephalopathy, with a previous record of compensated cirrhosis). Competing death was defined as death or palliative care without a liver-related complication. Abbreviations: AIDS: Acquired immunodeficiency syndrome; HbA1c: glycated hemoglobin; SVR: sustained virological response; T2D: type-2 diabetes mellitus

1 Mean (SD); n (%)

2 Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 4: Univariate and multivariate hazard ratios for liver-related complications and competing mortality for in-hospital T2D patients

	Competing mortality without liver disease progression		Progression to a liver-related complication	
	HR (95% CI)	**aHR (95% CI)**	**HR (95% CI)**	**aHR (95% CI)**
Male sex	**1.56 (1.43-1.69)*** **		**2.04 (1.6-2.59)*** **	
Male sex w/o AUD	**1.47 (1.35-1.6)*** **		1.28 (0.986-1.67)	
Alcoholic liver disease	0.895 (0.48-1.67)	1.61 (0.86–3.00)	**79.6 (63.2-100)*** **	**55.7 (40.50–76.61)*** **
AUD w/o alcoholic liver disease	**2.28 (2-2.6)*** **	**4.13 (3.58–4.78)*** **	**1.89 (1.32-2.72)*** **	**3.45 (2.29–5.19)*** **
Obesity	**1.23 (1.11-1.36)*** **		**1.37 (1.07-1.75)***	
Obesity w/o AUD	**1.14 (1.02-1.27)***	**1.26 (1.13–1.40)*** **	**0.71 (0.52-0.96)***	**1.54 (1.11–2.13)***
Smoking	**1.94 (1.77-2.13)*** **		**1.57 (1.21-2.03)*** **	
Smoking w/o AUD	**1.65 (1.48-1.83)*** **	**1.28 (1.15–1.44)*** **	**0.593 (0.40-0.89)***	0.72 (0.47–1.10)
Liver risk factors	**2.02 (1.66-2.46)*** **		**22.1 (17.7-27.6)*** **	
Liver risk factors w/o AUD	**1.93 (1.57-2.39)*** **	**1.75 (1.44–2.14)*** **	**13.4 (10.4-17.3)*** **	**8.9 (6.90–11.48)*** **

Ischemic heart disease	**1.62 (1.46-1.79)*** **		**0.613 (0.41-0.92)***	
Ischemic heart disease w/o AUD	**1.54 (1.39-1.71)*** **	**1.76 (1.58–1.96)*** **	**0.431 (0.27-0.70)*** **	0.79 (0.48–1.31)
Stage 3-5 CKD	**1.54 (1.39-1.7)*** **		1.01 (0.728-1.4)	
Stage 3-5 CKD w/o AUD	**1.39 (1.25-1.55)*** **	**1.38 (1.24–1.54)*** **	**0.426 (0.26-0.69)*** **	**0.6 (0.36–0.99)***
Immunodepression	**1.29 (1.04-1.6)***		1.33 (0.76-2.32)	
Immunodepression w/o AUD	**1.33 (1.07-1.66)*** **	**1.44 (1.16–1.80)****	1.11 (0.59-2.08)	1.29 (0.68–2.42)
Extrahepatic cancer	**5.06 (4.68-5.48)*** **		**3.42 (2.75-4.24)*** **	
Extrahepatic cancer w/o AUD	**4.33 (3.99-4.69)*** **	**4.86 (4.47–5.29)*** **	**2.24 (1.76-2.84)*** **	**4.05 (3.07–5.34)*** **

Note: Hazard ratios were computed with univariate and mulitivariate Cox models with age as the time-scale. Boldness indicates statistical significance: *P<0.05; **P<0.01; ***P<0.0001. Patients with cirrhosis at cohort inception and patients with a liver-related event between 2010-2012 were excluded from the analysis. Liver-related events were recorded after a 2010-2012 (3-year) washout period to reduce the risk of non-incident cases. w/o: without; AUD: alcohol use disorders, CKD: chronic kidney disease; HR: hazard ratio; aHR: adjusted hazard ratio

Figure 1

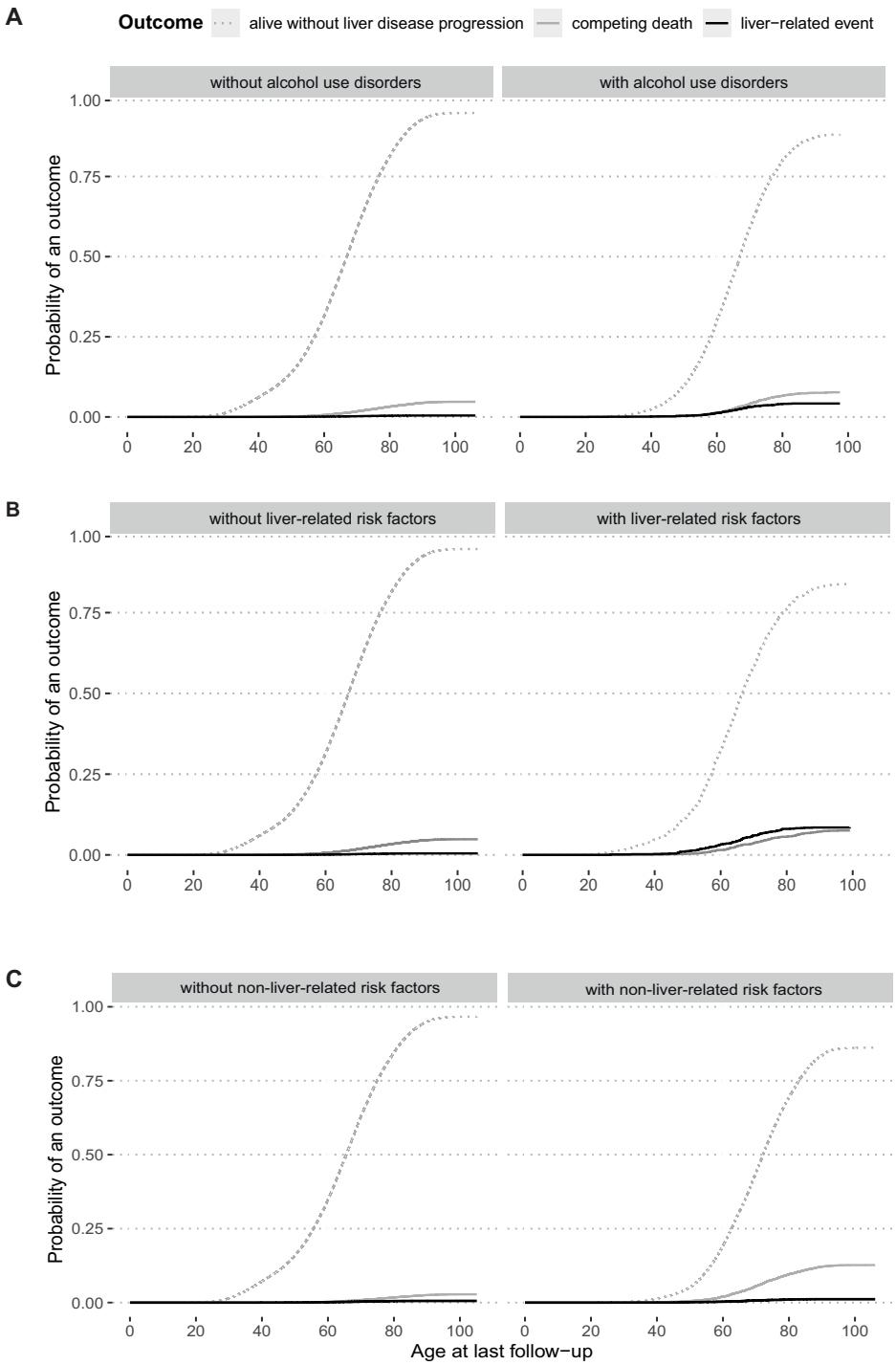
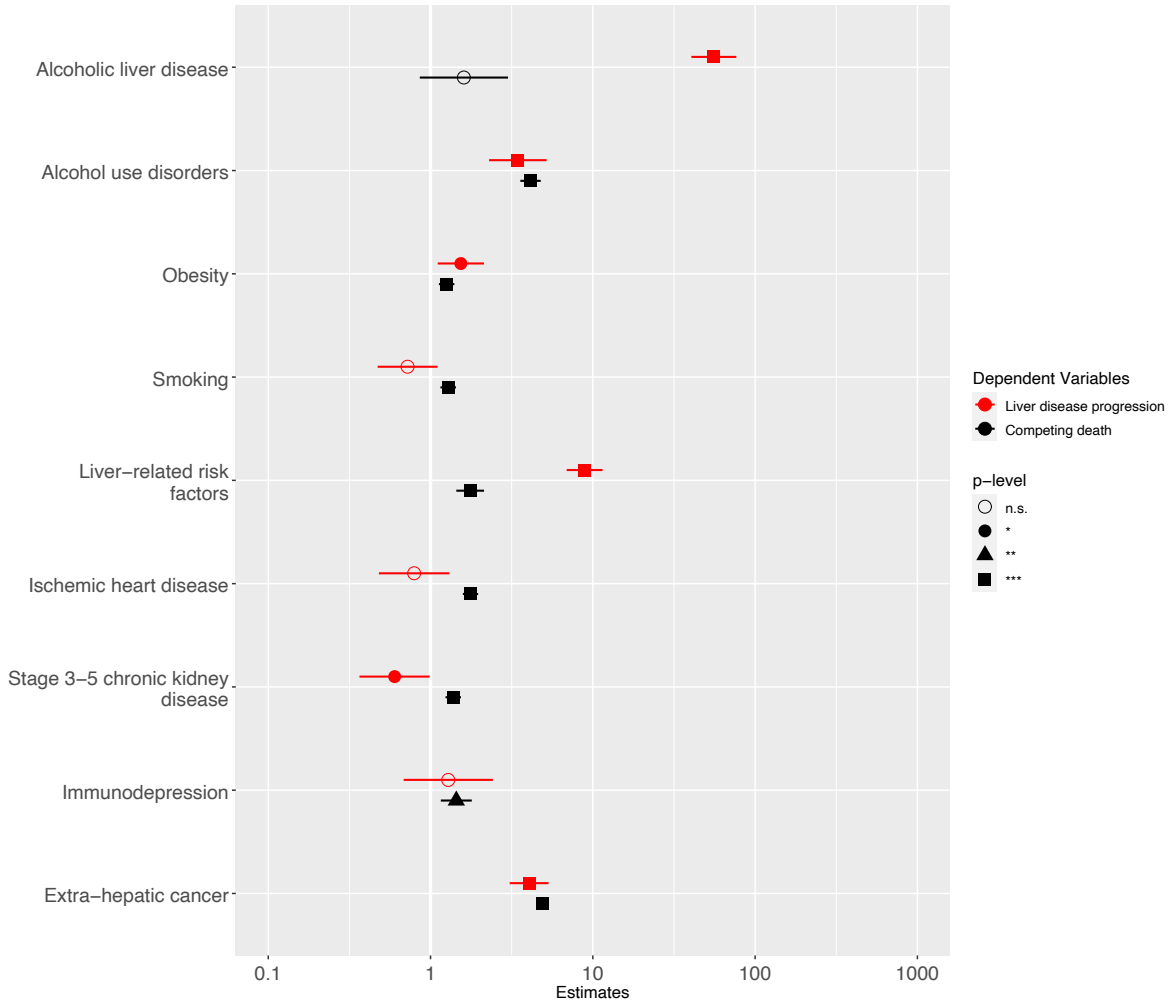

A
Outcome
alive without liver disease progression
competing death
liver−related event
without alcohol use disorders
with alcohol use disorders
Probability of an outcome
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
B
without liver-related risk factors
with liver-related risk factors
C
without non-liver-related risk factors
with non-liver-related risk factors
Age at last follow−up

Figure 2


Alcoholic liver disease
Alcohol use disorders
Obesity
Smoking
Liver−related risk factors
Ischemic heart disease
Stage 3−5 chronic kidney disease
Immunodepression
Extra−hepatic cancer
0.1
1
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Estimates
Dependent Variables
Liver disease progression
Competing death
p−level
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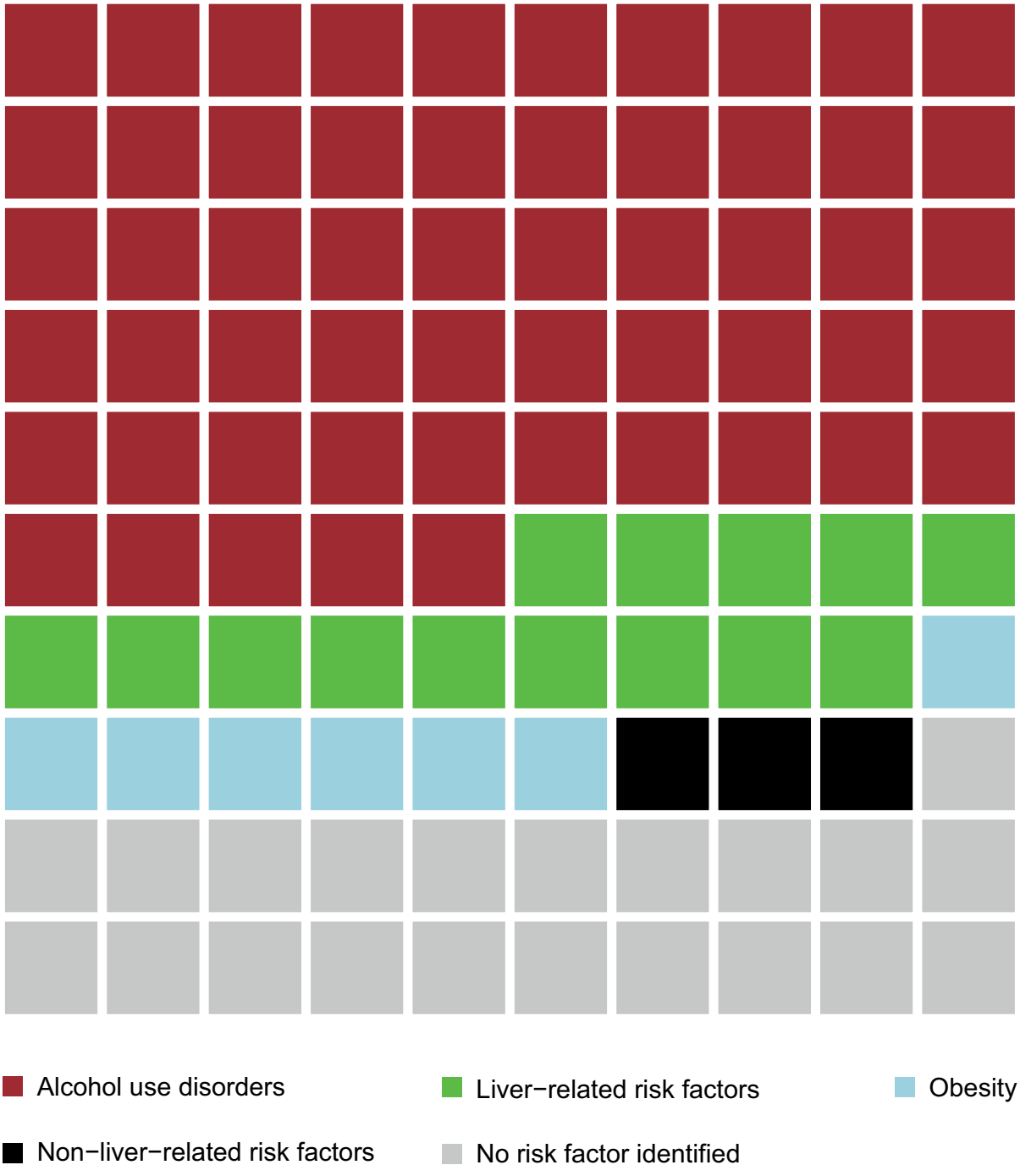
Figure 3


Alcohol use disorders
Liver−related risk factors
Obesity
Non−liver−related risk factors
No risk factor identified