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Hepatitis C and NAFLD as main causes of liver-related morbidity and mortality in the French general population: a Nationwide Study (NASH-CO study)

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Abbreviations

ALT: alanine aminotransferase

BMI: body mass index

CKD: chronic kidney disease

CVD: cardiovascular disease

DAA: direct-acting antiviral

EHC: extrahepatic cancer

FI: Forns index

FLI: fatty liver index

GGT: gamma glutamyl-transferase

HBP: high blood pressure

HBV: hepatitis B virus

HCC: cirrhosis and hepatocellular carcinoma

HCV: hepatitis C virus

IPTW: inverse-probability of treatment weighting

NAFLD: non-alcoholic fatty liver disease

NASH: non-alcoholic steatohepatitis

TG: triglyceride

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Oumarou Nabi, Nathanaël Lapidus, Karine Lacombe, and Lawrence Serfaty: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis.

Jerôme Boursier, Philippe Mathurin, Victor de Ledinghen: analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Jean-Michel Petit, Sofiane Kab, Adeline Renuy, Marie Zins: critical revision of the manuscript for important intellectual content.

Abstract

Background: The impact of NAFLD on health status and mortality has yet to be documented at the general population level. This study aimed to assess whether NAFLD was associated with hepatic and extrahepatic diseases and overall mortality, on the one hand, and to estimate its impact on health status and mortality compared to other liver-related diseases such as chronic hepatitis C or alcohol abuse, on the other hand.

Methods: The study population consisted of 154,900 participants from the nationwide Constances cohort. Non-invasive diagnosis of NAFLD and advanced fibrosis was performed using the fatty liver index and Forns index, respectively. Constances data were linked to hospitalization data to identify liver-related events, cardiovascular diseases (CVDs), extrahepatic cancers (EHCs), and chronic kidney disease (CKDs). Causal inference methods were used to estimate the impact of NAFLD on morbidity and mortality.

Results: The prevalence of NAFLD was 18.3% in subjects without other chronic liver diseases, among whom 2.7% had advanced fibrosis. A history of chronic hepatitis C (HCV) and B (HBV) was observed in 669 (0.4%) and 1311 (0.9%) subjects, respectively, whereas 15,714 (10.1%) individuals were recognized as heavy drinkers. The prevalence of advanced fibrosis was higher in HCV and NAFLD subjects (4.7% vs 2.7% vs 1.7% vs 1.6%, respectively, in HCV, NAFLD, heavy drinkers, and subjects with HBV). HCV remains the leading cause of hepatic-related complications (HR 9.75, 95% CI 6.63–14.33) before NAFLD (HR 2.63, 95% CI 1.96–2.87). NAFLD (HR 1.43, 95% CI 1.25–1.65) is the third leading cause of death behind HCV (HR 2.17, 95% CI 1.25–3.76) and binge drinking (HR 4.50, 95% CI 2.95–6.84). However, NAFLD remains the leading cause of CVD (HR 2.33, 95% CI 1.20–2.78) and CKD (HR 1.89, 95% CI 1.48–2.40).

Conclusion: This large general population-based cohort showed that NAFLD was associated with excess morbidity and mortality and demonstrated the fastest-growing trend. It challenges HCV infection in terms of hepatic morbidity and overall mortality.

Key words: NAFLD; advanced fibrosis; Fatty Liver Index; Forns Index; cardiovascular diseases; chronic kidney disease; extrahepatic malignancies, mortality

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Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease.¹ This syndrome ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) with varying amounts of fibrosis and cirrhosis.² Cohort studies have reported that the severity of liver fibrosis was the best predictor of liver-related mortality, but also of overall mortality in patients with biopsy-proven NAFLD.³ As a major risk factor for cirrhosis and hepatocellular carcinoma (HCC), NAFLD is possibly becoming the leading cause of liver transplantation and liver-related mortality.^{4,5} In addition to liver-related complications, NAFLD may promote cardiovascular disease (CVD), extrahepatic malignancy, or chronic kidney disease (CKD).⁶⁻⁸ However, few studies have investigated the burden of NAFLD at a general population level. Furthermore, few studies have directly compared NAFLD and the other chronic liver diseases (HCV, HBV, and heavy alcohol consumption) regarding their impact on morbidity and mortality.

The French Constances population-based cohort was designed as a large sample, representative for age, gender, and socioeconomic status of the French adult population aged 18–69 years, composed of more than 220,000 subjects included between 2012 and 2021.⁹ Using this cohort, the present study aimed to assess the burden of NAFLD and other chronic liver diseases on liver-related morbidity (hepatic events, CVD, extrahepatic malignancy, and CKD) and overall mortality in the general population.

Materials and Methods

Study sample

We conducted a longitudinal study with data collected at baseline and follow-up from participants included in the Constances cohort between 2012 and 2019. This cohort has been previously described.^{9,10} Subjects recruited in the Constances cohort were included in the present analysis if they were at least 18 years old and had no history or ongoing chronic hepatic disease such as autoimmune hepatitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin

deficiency, or known hepatotoxic drug intake (systemic corticosteroid therapy, methotrexate, tamoxifen, amiodarone). Next, the overall sample was split into five groups: (i) non-NAFLD subjects, corresponding to those with no history of excessive alcohol consumption defined by daily consumption above 30 grams per day in men and 20 grams per day in women, no history of chronic hepatitis B or C virus infection, and no history of other liver diseases including NAFLD; (ii) NAFLD subjects, corresponding to those with no history of excessive alcohol consumption, no history of chronic hepatitis B or C virus infection, and no history of other liver diseases except NAFLD; (iii) subjects with history of chronic hepatitis virus C; (iv) those with a history of chronic hepatitis B virus; and (v) those with excessive alcohol consumption (Supplementary Methods). Constances data were combined with the National Healthcare Database (Système National des Données de Santé, SNDS), which provided data on hospitalization and occurrence of death. The study was approved by the Commission Nationale Informatique et Libertés (CNIL), and ethics clearance was obtained from the Institutional Review Board of the French National Institute of Health (Authorization number: 910486). All participants provided written informed consent for the use of personal data for research.

Data collection at inclusion

Socio-demographic, comorbidity, and lifestyle data were obtained through standardized self-administered questionnaires. Socio-demographic data included age, gender, occupation and employment status, education level, and geographic origin. Alcohol consumption was assessed using the AUDIT questionnaire. The number of glasses per day was converted into grams per day of alcohol (1 glass=10 g of alcohol).

The health and morbidity data included history of cancer (colon, breast, prostate, lung, thyroid, ovary, uterus), cardiovascular events (arteritis of lower limbs, myocardial infarction, stroke, angina pectoris), blood hypertension, and diabetes. Body mass index (BMI) was calculated as the ratio of weight to height squared. Blood samples were made on a venous blood sample after

a 12-hour fasting period, and analyses were performed in the Health Screening Center (HSC) laboratories according to standards common to all. Available biological data of interest were blood glucose, serum creatinine, gamma glutamyl transferase (GGT), alanine aminotransferases (ALT), total cholesterol, high-density lipoprotein cholesterol, triglycerides (TGs), and platelets. Diabetes was defined by a blood glucose greater than 6.9 mmol/L after 12 hours of fasting according to the World Health Organization definition and/or antidiabetic therapy. The metabolic syndrome was defined according to the international diabetes federation. Chronic kidney disease (CKD) was defined as a glomerular filtration rate <60 mL/min/1.73m² calculated according to the CKD-EPI equation (Chronic Kidney Disease-Epidemiology Collaboration) (Supplementary Methods).

Definition of NAFLD and liver fibrosis

The fatty liver index (FLI) was chosen as a surrogate marker of NAFLD.¹¹ It has been successfully cross-validated in external populations.¹² Subjects with $FLI \geq 60$ were considered to have NAFLD based on the literature. The Forns index (FI) was chosen as a surrogate marker of liver fibrosis. It was calculated according to the published formula¹³ and has been previously validated as a marker of liver fibrosis in NAFLD¹⁰. The previously published thresholds were used to rule in or rule out advanced fibrosis (F3/F4), <4.2 and >6.9 , respectively. Subjects were classified as follows: non-NAFLD ($FLI < 60$), NAFLD ($FLI \geq 60$), NAFLD with mild fibrosis ($FLI \geq 60$ and Forns index < 4.2), NAFLD with intermediate fibrosis ($FLI \geq 60$ and Forns index $4.2-6.9$), and NAFLD with advanced fibrosis ($FLI \geq 60$ and Forns index > 6.9).

Follow-up study

Constances data were combined with the SNDS to collect data on hospitalization and death from January 1, 2012, to December 31, 2019.¹⁴ SNDS data were available during this period for 169,303 Constances participants. The follow-up period for each study participant was the time elapsed between the Constances baseline inclusion and December 31, 2019, the date of

death, or the last date of follow-up, whichever occurred first. The International Classification of Diseases (ICD-10) code was used to define liver-related events according to the recent expert panel consensus statement (compensated cirrhosis, hepatocellular carcinoma, decompensated cirrhosis),¹⁵ CVDs (arteritis of lower limbs, myocardial infarction, stroke, angina pectoris), EHCs (colon, breast, prostate, lung, thyroid, ovary, uterus), CKDs (chronic kidney disease, diabetic nephropathy, hypertensive nephropathy, kidney failure) (Supplementary Table 1), and overall mortality. Subjects with histories of cirrhosis-related complications or hepatocellular carcinoma, CVD, or EHC, or subjects with glomerular filtration rate (GFR) <60 mL/min/1.73 m² at baseline were excluded in the calculation of each category of incident events.

Statistical analysis

Continuous and categorical variables were expressed as means \pm standard deviation (SD) and percentages and compared using Student's t test and the χ^2 test, respectively (Supplementary Methods). We performed a longitudinal analysis to estimate the association of NAFLD and other chronic liver diseases with morbidities and overall mortality in the general population. In an initial set of analyses aimed at studying the prognosis associated with NAFLD and with fibrosis in NAFLD subjects, we excluded subjects with chronic hepatitis B and C, chronic liver diseases other than NAFLD, and those with excessive alcohol consumption. This sample was split (i) into two groups: participants without NAFLD (FLI <60) and those with NAFLD (FLI \geq 60); then (ii) into four groups: participants without NAFLD (FLI <60), those with NAFLD and mild (FLI \geq 60 and FI <4.2), intermediate (FLI \geq 60 and FI 4.2–6.9), and advanced fibrosis (FLI \geq 60 and FI >6.9).

In a second set of analyses, NAFLD subjects were compared to those with other chronic liver conditions. The overall study sample was split into five groups: non-NAFLD (FLI <60) and no other chronic liver condition, NAFLD (FLI \geq 60), HCV infection, HBV infection, and heavy alcohol consumption.

Mortality was studied with the standard Cox proportional hazard models and other clinical outcomes with the Fine-Gray model, including all-cause mortality as a competing event. The cumulative incidence function was estimated for each clinical outcome, and Gray's test was used to estimate the differences in the cumulative incidence functions between the groups. Standard Kaplan-Meier estimators were calculated for the all-cause mortality rate.

Propensity-score-based stabilized inverse-probability of treatment weighting (IPTW) was applied to handle confounding. Logistic and multinomial propensity scores for belonging to either one of the compared groups were derived from potential confounding factors such as socio-demographic characteristics (age, sex, geographic origin, education level), clinical and anthropometric variables (high blood pressure, diabetes, metabolic syndrome and BMI, waist circumference), lifestyle (smoking, soft drink, coffee intake, and regular exercise), and biological data (TGs, cholesterol, and ALT). The positivity assumption was graphically checked. We used the standardized mean difference to assess the balance of covariates before and after weighting. An absolute standardized mean difference less than 0.10 was deemed satisfactory. Fine and Gray models weighted by IPTW were used to estimate hazard ratios of liver-related events, CVD, EHC, and CKD with regards to the competing risk of death; and Cox proportional hazard models weighted by IPTW were used to estimate hazard ratios for overall mortality. Subjects presenting the studied clinical event in the 6 months following inclusion were excluded, so that they could not be attributed to a too recent change in the status of chronic liver conditions. Finally, in order to assess the trend of clinical outcomes and overall mortality in the risk groups over time, we tested the interaction between the study period and the risk groups in the previous models. A p value <0.05 was considered to be statistically significant. Analyses were performed using R Statistical Software version 4.1.0.

Results

At the time of analysis, baseline data were available for 199,341 participants. After excluding subjects who withdrew their consent, had other causes of liver diseases, or missing data for NAFLD assessment, and participants whose data were not available in the SNDS, 154,900 were included in the final analysis and defined the overall sample (Figure 1). Their baseline characteristics were not different from those of the excluded participants (data not shown, available on request). A total of 25,753 had NAFLD, which corresponded to 18.3% (95% CI 18.2–18.4) of the general population without HCV, HBV, excessive alcohol consumption, and other chronic liver diseases, and 16.7% of the entire population including those with HCV, HBV, and excessive alcohol consumption. Overall, 669 (0.4%, 95% CI 0.3–0.5) subjects had a history of HCV, 1311 (0.9%, 95% CI 0.8–1.0) had a history of HBV, and 15,714 (10.1%, 95% CI 10.0–10.2) had excessive alcohol consumption. The baseline characteristics of the study sample are reported in Table 1.

Clinical outcomes and overall mortality according to the presence of NAFLD in subjects without HCV, HBV, and excessive alcohol consumption

Data for the analysis of clinical outcomes and overall mortality were available in 137,206 participants. Among them, 25,753 (18.3%, 95% CI 18.2–18.4) had NAFLD (Figure 1). After a median follow-up of 3.62 years (range 0.07–7.95), 682 subjects developed a hepatic event (including 122 with HCC), 2050 had an incident cardiovascular event, 471 evolved towards CKD, 1954 were diagnosed with an extrahepatic malignancy, and 1166 died. The cumulative incidence of liver-related events, CVDs, CKD, and overall mortality were significantly associated with the presence of NAFLD compared to those without NAFLD (Figure 2 and Supplementary Figures 1 and 2). Raw and IPTW-weighted analyses for the risk of clinical outcomes and overall mortality according to the presence of NAFLD are shown in Table 2 (and Supplementary Table 2). The presence of NAFLD compared to subjects without NAFLD after

IPTW remained associated with an increased risk of liver-related events (HR 2.63, 95% CI 1.96–2.87), CVD (HR 2.33, 95% CI 1.20–2.78), CKD (HR 1.89, 95% CI 1.48–2.40), and overall mortality (HR 1.43, 95% CI 1.25–1.65). The risk of extrahepatic malignancies was not associated with the NAFLD status. Liver-related and extrahepatic clinical outcomes as well as overall mortality in NAFLD subjects according to the fibrosis degree are shown in Figure 2 (and Supplementary Figure 3). The grade of fibrosis was associated with risks of hepatic events, CVD, extrahepatic malignancy, CKD, and overall mortality (Table 3).

Clinical outcomes and overall mortality according to the presence of chronic liver diseases

To estimate and compare the impact of various chronic liver diseases on the incidence of morbidities and mortality, we split the entire study sample (previous sample plus those with excessive alcohol consumption or HCV and HBV disease) into five groups: 111,453 subjects without NAFLD (FLI <60), 25,753 subjects with NAFLD, 669 with HCV, 1311 with HBV, and 15,714 with excessive alcohol consumption (Figure 1). Baseline characteristics of subjects according to chronic liver conditions are shown in Table 1.

The NAFLD subjects had significantly more metabolic disorders and a higher prevalence of ALT above the normal threshold compared to the other groups (Table 1). The prevalence of advanced fibrosis among subjects with NAFLD was 2.7% (95% CI 2.5–2.9). The chronic liver condition with the highest prevalence of fibrosis was HCV (4.9%, 95% CI 4.6–5.2) (Table 1). After a median follow-up of 3.60 years (range 0.06–7.86), 885 subjects developed a hepatic event (including 135 with HCC). The other observed events were 2560 CVDs, 560 CKDs, 2273 extrahepatic malignancies, 21 liver transplantations, and 1382 deaths. The risk of clinical outcomes and overall mortality were significantly associated with chronic liver diseases compared to those without NAFLD and other chronic liver diseases (Figure 3 and Supplementary Figure 4).

Raw and IPTW-weighted analyses of the risk of clinical outcomes and overall mortality according to the presence of chronic liver disease are shown in Table 4 (and Supplementary Table 3). Compared to subjects without NAFLD, HCV chronic hepatitis remained the leading cause of liver-related events (HR 9.75, 95% CI 6.63–14.33), followed, respectively, by NAFLD (HR 2.63, 95% CI 1.96–2.87), excessive alcohol consumption (HR 1.57, 95% CI 1.23–2.32), and HBV chronic hepatitis (HR 1.47, 95% CI 1.21–3.54). When each chronic liver disease is compared in NAFLD subjects (Supplementary Tables 4 and 5 and Supplementary Figures 5 and 5 bis), HCV chronic hepatitis remained the leading cause of liver-related events followed by NAFLD. However, in the trend analysis over the study period of inclusion, NAFLD was the fastest-growing cause of hepatic events (interaction HR 1.40, 95% CI 1.05–1.85 per year) (Supplementary Table 6). NAFLD was also the only condition with an increasing association over the study period regarding CVD (HR 1.06, 95% CI 1.02–1.10), CKD (HR 1.15, 95% CI 1.05–1.27), and death (HR 1.41, 95% CI 1.33–1.49) (Supplementary Table 6).

Discussion

To our knowledge, this study is the first European survey to prospectively evaluate the burden of NAFLD and to compare NAFLD to other chronic liver diseases (HCV, HVB) and heavy alcohol consumption in terms of clinical outcomes and mortality in a community setting. Compared to non-NAFLD subjects and those with other chronic liver diseases, those with NAFLD were older, mostly males, and had more metabolic disorders and liver injuries, such as ALT above the normal threshold and liver fibrosis. Our study showed that: 1) NAFLD, regardless of the severity of histological features, was associated with liver-related events, extrahepatic clinical outcomes, and overall mortality; 2) there was a dose-dependent relationship between the severity of liver fibrosis and the occurrence of clinical outcomes and overall mortality; 3) compared to excessive alcohol consumption and hepatitis virus infections, NAFLD was the fastest-growing cause of liver-related morbidity, although HCV currently

remains the leading cause of death; and, lastly, 4) compared to hepatitis virus infections and excessive alcohol consumption, NAFLD was the leading and the most common cause of extrahepatic morbidities, such as CVD and CKD, and overall mortality.

Findings from community-based studies are conflicting and continue to fuel controversy. Several prospective Asian community-based studies have shown conflicting results. Indeed, contrary to Lee et al. who demonstrated from a Korean population-based cohort that NAFLD was associated with a higher risk of digestive and esophageal malignancies,¹⁶ Zhou et al. reported from a Chinese cohort that patients with NAFLD had a benign prognosis.¹⁷ Lazo et al. found no association between non-alcoholic fatty liver disease or non-alcoholic steatohepatitis and all-cause mortality, CVD, cancer, or liver disease in the US general population.¹⁸ Our results showed a strong association of clinical outcomes such as liver-related complications or extrahepatic clinical outcomes (CVD, CKD) and all-cause mortality. As in previous studies in biopsy-proven NAFLD patients,^{3,16,19,20} we found a dose-response relationship between the grade of fibrosis and the incidence of clinical outcomes or all-cause mortality. Our results support that NAFLD is associated with an increased risk of hepatic and extrahepatic clinical outcomes and worse long-term prognosis.

Our results are particularly relevant for patient management and the improvement of monitoring. Indeed, it is usually claimed that advanced fibrosis, but not simple steatosis is the best predictor of long-term prognosis. However, our results suggest that this dictum is not entirely true. We found that whatever the level of fibrosis, all NAFLD patients remain particularly at risk of dying or developing hepatic or extrahepatic complications. HCV and heavy alcohol consumption were once considered the first and second cause of chronic liver disease, respectively, ahead of HBV, which ranked third.²¹⁻²³ Our results suggest that NAFLD is now the leading cause of all-cause mortality and extrahepatic morbidities, such as CVD and CKD, and the fastest-growing cause for liver-related morbidity compared to chronic hepatitis

virus infections (HCV and HBV) and excessive alcohol consumption. Previous studies have demonstrated the increasing trend in NAFLD-related hepatic complications and liver transplants worldwide.^{4,5} In the US, although HCV remained the leading etiology of chronic liver disease among new liver transplant waitlist registrations, NASH demonstrated the greatest increase from 2004 to 2013 and had already become the second leading etiology of liver transplantation in 2013.⁴ This tendency had already been observed since 2011 from the US National Health and Nutrition Examination Surveys collected from 1988 to 2008. Those surveys showed that the main causes of chronic liver diseases remained stable during the study period, except NAFLD, which increased steadily.²¹ Since 2011, the landscape of HCV treatment has evolved rapidly, with the approval of direct-acting antiviral (DAA) agents. In 2017, Goldberg et al.²⁹ have theorized that the burden of active HCV infection on cirrhosis and HCC (compensated or decompensated) has decreased since the introduction of highly efficacious DAA therapy. The rising prevalence of NAFLD coupled with the stabilization and expected decline in HCV-related clinical outcomes due to DAA therapy will soon result in NAFLD overtaking HCV as the leading etiology of chronic liver disease. Another potential explanation for these observations might be etiology-specific differences in disease progression. In our study, the prevalence of metabolic disorders (such as diabetes or hyperlipidemia) was significantly higher in NAFLD subjects than in other chronic liver diseases. In our study population, as in several other studies,^{24,25} NAFLD subjects seem to have more metabolic disorders and a poorer lifestyle (high prevalence of smoking and alcohol consumption in the NAFLD subjects). Although these associations with the prevalence of NAFLD are not new, it has been demonstrated that metabolic disorders such as diabetes, high blood pressure, dyslipidemia, smoking, and lack of regular exercise contribute to disease progression and NAFLD-related mortality.²⁴⁻²⁷ On top of liver-related complications and mortality, several previous studies^{24,28} have demonstrated that extrahepatic clinical outcomes,

such as CVD, extrahepatic malignancies, and CKD, and their related mortality were strongly influenced by metabolic disorders and amplified in the presence of NAFLD. Thus, due to the rising prevalence of obesity, diabetes, and metabolic syndrome in the last two decades, we could observe a high incidence of NAFLD and resulting complications.^{29,30} These results underscore the need for a comprehensive approach to NAFLD patient management and suggest the need to reinforce and focus efforts on preventing and treating metabolic disorders, and to advise patients to reduce and maintain appropriate body weight and to optimize lifestyle regardless of the level of fibrosis.

Our study has several limitations. The non-invasive biomarkers we used to assess the prevalence of NAFLD or advanced fibrosis may lead to a (probably non-differential) misclassification bias and decrease the power of our analyses to identify associations with clinical outcomes or mortality. However, the performance of imaging methods such as ultrasound or elastometry, which have been used for the screening of NAFLD and fibrosis, also have such limitations. MRI or liver biopsy, which are the gold standards for NAFLD diagnosis and measuring liver injuries, cannot be used on a large scale, such as in the general population. In conclusion, this large general population-based cohort showed that NAFLD was associated with excess morbidity and mortality and demonstrated the fastest-growing trend. It challenges HCV infection in terms of hepatic morbidity and overall mortality. In addition, given the increasing rates of obesity and diabetes, NAFLD may soon become the first cause of the burden of hepatic and extrahepatic morbidities and mortality in western countries.

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Table 1: General characteristics of study sample and according to chronic liver diseases

	Overall sample N=154,900	Non-NAFLD (FLI <60) N=111,453	NAFLD (FLI ≥60) N= 25,753	Excessive alcohol consumption N=15,714	HCV N=669	HBV N=1311
Age (years), mean [SD]	47·0 [13·3]	45·6 [13·2]	52·4 [11·8]	48·0 [14·2]	55·8 [9·1]	54·5 [11·2]
Male sex, n (%)	71,510 (47·1)	46,895 (41·4)	15,328 (66·9)	9063 (60·0)	315 (54·4)	579 (50·7)
BMI (kg/m ²), n (%)	18,628 (12·3)	3341 (3·0)	13287 (58·0)	1796 (12·5)	97 (17·4)	166 (15·4)
HBP, n (%)	16,795 (11·3)	8370 (7·6)	6115 (27·3)	2138 (14·5)	116 (20·0)	213 (18·8)
Waist circumference (cm), mean [SD]	84·94 [12·9]	80·8 [9·5]	103·9 [9·5]	87·3 [13·3]	88·5 [13·3]	87·3 [13·1]
Diabetes, n (%)	7733 (5·2)	2473 (2·2)	3946 (15·6)	807 (5·5)	41 (7·1)	76 (6·7)
hypercholesterolemia, n (%)	11,801 (8·0)	5991 (5·4)	4103 (18·5)	1573 (10·7)	61 (10·6)	147 (13·0)
ALT>N, n (%)	17,907 (11·8)	7404 (6·5)	8006 (35·0)	2321 (16·1)	129 (23·3)	130 (11·9)
GGT>N, n (%)	16,839 (11·1)	6232 (5·5)	7558 (33·0)	2877 (19·9)	113 (20·5)	148 (13·5)
FI, n (%)	1115 (0·7)	305 (0·3)	517 (2·7)	249 (1·7)	27 (4·9)	17 (1·6)
Geographic origin, n (%)						
European	142,541 (93·9)	105,612 (94·2)	20,978 (92·7)	14,325 (95·3)	474 (84·2)	850 (76·4)
Overseas France	1326 (0·9)	978 (0·9)	228 (1·0)	99 (0·7)	7 (1·2)	16 (1·4)
Asian	1075 (0·7)	844 (0·8)	117 (0·5)	73 (0·5)	4 (0·7)	43 (3·9)
Sub-Saharan African	1595 (1·1)	1119 (1·0)	263 (1·2)	99 (0·7)	27 (4·8)	115 (10·3)
North African	3648 (2·4)	2490 (2·2)	828 (3·7)	244 (1·6)	44 (7·8)	60 (5·4)
Other	1508 (1·0)	1087 (1·0)	219 (1·0)	178 (1·2)	7 (1·2)	29 (2·6)
Education level (years), n (%)						
≤8	4657 (3·1)	2788 (2·5)	1354 (5·9)	459 (3·0)	40 (6·9)	56 (4·9)
9–15	97,896 (64·5)	70,863 (62·6)	17,098 (74·6)	9479 (62·8)	414 (71·5)	755 (66·2)
≥16	49,140 (32·4)	39,491 (34·9)	4458 (19·5)	5156 (34·2)	125 (21·6)	330 (28·9)
Tobacco >10 pack/year, n (%)	57,177 (37·7)	38,870 (34·4)	9519 (41·5)	8822 (57·8)	270 (46·6)	428 (37·5)
Soft drink ≥1/d, n (%)	31,265 (20·6)	23,801 (21·0)	4294 (18·7)	3091 (20·5)	101 (17·4)	192 (16·8)
Exercise ≥2h/w, n (%)	52,658 (34·7)	41,950 (37·5)	5632 (25·1)	4920 (32·9)	165 (29·4)	391 (35·0)
Coffee ≥1 cup/d, n (%)	12,799 (8·4)	9046 (8·2)	2350 (10·5)	1344 (9·0)	55 (9·9)	106 (9·6)

Table 2: Raw (unweighted) and IPTW-weighted associations between clinical outcomes and presence of NAFLD

	Unweighted		IPTW-weighted	
	NAFLD (FLI \geq 60) N=25,753		NAFLD (FLI \geq 60) N=25,753	
	HR (95% CI)	p	HR (95% CI)	p
Hepatic events	2.85 (2.43–3.34)	<0.001	2.63 (1.96–2.87)	<0.001
Cardiovascular diseases	2.73 (2.49–2.99)	<0.001	2.33 (1.20–2.78)	<0.001
Extrahepatic malignancies	1.42 (1.28–1.58)	<0.001	1.09 (0.90–1.23)	0.894
Chronic kidney disease	3.22 (2.65–3.91)	<0.001	1.89 (1.48–2.40)	<0.001
Death	1.93 (1.70–2.19)	<0.001	1.43 (1.25–1.65)	<0.001

Reference group: subjects without NAFLD (FLI <60)

Table 3: Raw (unweighted) and IPTW-weighted associations between grade of fibrosis and clinical events or overall mortality in NAFLD subjects

	Unweighted				IPTW-weighted			
	NAFLD and advanced fibrosis (FLI \geq 60 and FI >6.9)		NAFLD and intermediate fibrosis (FLI \geq 60 and FI 4.2–6.9)		NAFLD and advanced fibrosis (FLI \geq 60 and FI >6.9)		NAFLD and intermediate fibrosis (FLI \geq 60 and FI 4.2–6.9)	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Hepatic events	11.1 (7.84–15.7)	<0.001	1.19 (0.91–1.57)	0.212	8.61 (5.04–14.7)	<0.001	1.11 (0.77–1.61)	0.563
Cardiovascular diseases	5.02 (3.57–7.06)	<0.001	1.30 (0.97–2.69)	0.086	2.38 (1.92–3.08)	0.012	1.01 (0.83–1.24)	0.897
Extrahepatic malignancies	5.79 (3.92–8.56)	<0.001	2.56 (2.09–3.14)	<0.001	1.88 (1.16–3.06)	0.011	1.19 (0.92–1.55)	0.188
Chronic kidney disease	4.76 (2.63–8.62)	<0.001	1.63 (1.19–2.22)	0.002	2.80 (1.66–3.71)	<0.001	1.01 (0.73–1.33)	0.939
Death	5.39 (3.68–7.88)	<0.001	1.49 (1.19–1.87)	<0.001	2.97 (1.94–4.56)	<0.001	1.06 (0.82–1.38)	0.637

Reference group: NAFLD with mild fibrosis (FLI \geq 60 and FI <4.2)

Table 4: IPTW-weighted analysis of clinical outcomes risks according to the presence of chronic liver diseases and in heavy drinkers (reference group = non-NAFLD, FLI <60)

	NAFLD (FLI \geq 60)		Excessive alcohol consumption		HBV		HCV	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Hepatic events	2.63 (1.96–2.87)	<0.001	1.57 (1.23–2.32)	<0.001	1.47 (1.21–3.54)	<0.001	9.75 (6.63–14.33)	<0.001
Cardiovascular diseases	2.33 (1.20–2.78)	<0.001	1.21 (1.07–2.20)	<0.027	1.74 (1.25–2.43)	0.001	1.80 (1.13–2.88)	0.013
Extrahepatic malignancies	1.09 (0.90–1.23)	0.894	1.59 (0.88–2.89)	0.126	1.09 (0.74–1.63)	0.657	1.11 (0.63–1.96)	0.728
Chronic kidney disease	1.89 (1.48–2.40)	<0.001	1.69 (1.02–3.25)	0.015	0.76 (0.24–2.38)	0.633	0.50 (0.07–3.54)	0.484
Death	1.43 (1.25–1.65)	<0.001	4.50 (2.95–6.84)	<0.001	1.23 (0.74–2.05)	0.432	2.17 (1.25–3.76)	0.006

Figure titles

Figure 1: Flowchart

Figure 2: Cumulative incidence of hepatic events and overall mortality according to the presence of NAFLD and the grade of fibrosis in NAFLD subjects

Figure 3: Cumulative incidence of hepatic events and overall mortality according to the presence of chronic liver diseases and in heavy drinkers



