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Lean individuals with NAFLD have more Severe Liver Disease and Poorer Clinical Outcomes (NASH-CO Study)

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Abbreviations

ALT: Alanine Aminotransferases

ATC: Anatomical Therapeutic Chemical

AUDIT: Alcohol Use Disorders Identification Test

BMI: Body Mass Index

BPH: High Blood Pressure

CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration

CKD : Chronic Kidney Disease

CNIL : Commission Nationale Informatique et Libertés

CRN: Clinical Research Network

CVD: Cardiovascular disease

DM: Diabetes Mellitus

EHC: Extrahepatic cancer

FI: Forn's Index

FLI: Fatty Liver Index

GGT: Gamma Glutamyl Transferase

HCC: Hepatocellular carcinoma

HSC: Health Screening Center

ICD: International Classification of Diseases

INSERM: Institutional Review Board of the French National Institute of Health

NAFLD: Nonalcoholic fatty liver disease

NASH: Nonalcoholic Steatohepatitis

PY: Package per year

PNPLA3: patatin-like phospholipase domain-containing protein 3

SD: Standard Deviation

SNDS : Système National des données de Santé

TGs: triglycerides

TM6SF2: Transmembrane 6 Superfamily 2

WHO: World Health Organization

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Abstract

Background: The severity of liver injury and clinical outcomes in lean NAFLD subjects is a subject of debate and very few studies have been performed in the general population. The aim of this study was to compare subject characteristics and mortality between lean and non-lean NAFLD in a community setting.

Method: The study population included 169,303 participants from the nationwide Constances cohort. Subjects with excessive alcohol consumption, viral hepatitis or other liver diseases were excluded and 137,206 subjects were analyzed. The diagnosis of NAFLD and fibrosis

was performed using the Fatty Liver Index and the Forns Index. The median follow-up was 3.58 years.

Results: The prevalence of NAFLD was 5.3% (95%CI 5.2-5.4) in lean subjects, while 16.3% (95%CI 15.7-16.8) of NAFLD subjects were lean. Despite their better metabolic profile, the prevalence of advanced fibrosis was significantly higher in lean than in non-lean NAFLD (3.7% vs 1.7%, respectively $P < 0.01$). Among NAFLD subjects and after adjustment for demographics, metabolic risk factors and lifestyle, lean status was associated with advanced fibrosis (OR=1.26, 95%CI 1.20-1.65, $P=0.005$), an increased risk of liver-related events (aHR=5.84, 95%CI 4.03-8.46), chronic kidney disease (aHR=2.49, 95%CI 1.49-4.16), and overall mortality (aHR=3.01, 95%CI 2.21-4.11). Liver-related events and overall mortality were related to the severity of fibrosis, both in lean and non-lean NAFLD subjects, whatever the usual risk factors.

Conclusion: This study in a large community-based cohort confirms that NAFLD in lean subjects is more severe for fibrosis, the progression of liver disease, chronic kidney disease and overall mortality.

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

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease with an estimated worldwide prevalence ranging from 25% to 45%(1,2). Around 20% of patients with NAFLD have non-alcoholic steatohepatitis (NASH), the active form of NAFLD which may progress to cirrhosis, end-stage liver disease and hepatocellular carcinoma(3). Besides liver-related complications, it has been suggested that NAFLD could promote cardiovascular diseases (CVD), extrahepatic cancer (EHC) and chronic kidney disease (CKD) and may increase overall mortality(4).

Although obesity is a major risk factor, NAFLD can occur in individuals who are not obese and have a normal body mass index (BMI)(5,6). This is called lean NAFLD and was initially reported in Asian populations but has since been described in European and US populations(7). The prevalence and characteristics of lean NAFLD subjects have been recently evaluated in two meta-analyses(6,8). The estimated global prevalence of lean NAFLD ranged from 5.1% to 11.2% in the general population, with the highest prevalence in Asia, while the global prevalence of lean individuals in NAFLD patients ranged from 19.2% to 25.3%(6,8). Compared to healthy individuals, those with lean NAFLD more frequently had metabolic risk factors, a genetic predisposition such as patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) and transmembrane 6 superfamily 2 (*TM6SF2*) polymorphisms and higher liver or cardiovascular-related mortality(6,8). Compared to obese NAFLD, lean NAFLD individuals had fewer metabolic disorders and a similar prevalence of genetic polymorphisms for *PNPLA3* and *TM6SF2*(6). Two meta-analyses in biopsy-proven NAFLD patients have suggested that lean individuals had less severe histological findings including steatohepatitis and fibrosis(8,9). This was recently confirmed in the TARGET study showing lower rates of cirrhosis and comorbidities in lean Americans with biopsy-proven NAFLD(10). However, in a population study, non-invasive biomarkers have suggested a higher rate of advanced fibrosis in lean NAFLD subjects from the NAHNES cohort(11).

Despite a more favorable profile, it has been suggested that lean subjects with NAFLD may have a worse prognosis than obese subjects in the same condition. Although long-term follow-up studies in selected biopsy-proven NAFLD patients have provided contradictory results, three out of five studies have shown significantly higher rates of liver-related events and/or mortality in lean subjects(12–16). In two recent population-based studies, poorer outcomes have been suggested in lean or non-obese individuals with NAFLD(11,17). In a retrospective analysis of the UNOS data base, long-term graft and patient survival was worse in lean individuals transplanted for NASH while it was better in those transplanted for other indications(18).

To our knowledge, the impact of NAFLD on clinical outcomes and mortality in lean individuals has not been fully investigated in the general population in a European study. The aim of the present study was to assess in lean and non-lean NAFLD subjects from the Constances cohort: 1) the prevalence and risk factors associated with NAFLD, including lifestyle, 2) how NAFLD status and BMI affect the risk of clinical outcomes such as liver-related events, CVD, extrahepatic malignancies or CKD, and overall mortality.

Materials and Methods

Study Population

[AQ: Please cite Supplementary Figure 1 in the main text <http://links.lww.com/HEP/D714>.]

This longitudinal study was performed with data collected from participants included in the Constances cohort between 2012 and 2019. This "general purpose" has been previously described(19–21). Subjects recruited for Constances were included in the present analysis if they were at least 18 years old, with no history of excess alcohol consumption defined by a daily consumption >30 g/day in men and >20 g/day in women, no history of chronic HBV or HCV infection, or history of other liver diseases except NAFLD. The study was approved by the “Commission Nationale Informatique et Libertés” (CNIL), and ethical approval was

obtained from the Institutional Review Board of the French National Institute of Health (INSERM). All participants provided written informed consent for the use of their personal data for research.

Data collection at baseline

Selected subjects were invited to complete questionnaires and to attend a Health Screening Center (HSC) for a comprehensive health examination(21). Socio-demographic and lifestyle data were obtained by a standardized self-administered questionnaire at home. Socio-demographic data included age, gender, occupation and employment status, education and geographic origin. Alcohol consumption was assessed using the AUDIT questionnaire(22). The history of alcohol consumption was assessed at baseline and each year across study period based on an AUDIT questionnaire regarding the alcohol consumption in the last 12 months. The number of glasses per day was converted into the amount of grams per day of alcohol. On this basis, the level of alcohol consumption was classified into 3 groups: no consumption, moderate consumption (≤ 30 g/day in men and ≤ 20 g/day in women), and excessive consumption otherwise. Tobacco use was assessed using similar procedure by a standardized self-administered. The number of cigarettes per day was converted into the number of packs per year (P/Y), and split in to 3 groups (No use,]0-10] P/Y and >10 P/Y). Changes of alcohol consumption and tobacco use during follow-up are shown on supplementary Table 1 <http://links.lww.com/HEP/D713>. Health and morbidity data were recorded by a physician in the HSC(21). This included histories of chronic HBV or HCV infection, other liver diseases, high blood pressure, diabetes, CVD, extrahepatic cancer (or malignancy) and CKD examination (Supplementary methods <http://links.lww.com/HEP/D713>). Diabetes was defined either on the basis of self-reporting and/or blood glucose >6.9 mmol/L and/or antidiabetic therapy at baseline. The Body Mass Index (BMI) was calculated at baseline as the ratio of weight to height squared. Subjects were

considered to be lean with a BMI $<25\text{kg/m}^2$, or $<23\text{ kg/m}^2$ if they were of Asian ethnicity and as overweight with a BMI 25-29.9 or 23-27.4 if they were of Asian ethnicity and obese with a BMI $\geq 30\text{ kg/m}^2$, or $\geq 27.5\text{ kg/m}^2$ if Asian ethnicity. Weight loss ($>5\text{kg}$) was recorded each year and based on declarative data, across the follow-up period. Blood samples were taken from a venous blood sample after a 12-hour fast and analyses were performed in the HSC laboratories according to general standards. Biological data included blood glucose, serum creatinine, gamma glutamyl transferase (GGT), alanine aminotransferases (ALT), total cholesterol, high-density lipoprotein cholesterol, triglyceride (TGs) and platelets (Supplementary methods <http://links.lww.com/HEP/D713>). The metabolic syndrome was defined according to the international diabetes federation(23). Chronic kidney disease was defined according to a glomerular filtration rate $<60\text{ ml/min/1.73m}^2$ calculated according to the CKD-EPI equation (Chronic Kidney Disease-Epidemiology Collaboration).

Definition of NAFLD and liver fibrosis

Liver biopsy, ultrasound or imaging examinations were not performed within the framework of the Constances cohort. The fatty liver index (FLI) was then chosen as a surrogate marker of NAFLD(24). It has been successfully cross-validated in external populations(25,26) and in lean subjects(27). Subjects with $\text{FLI} \geq 60$ were considered to have NAFLD according to the literature. As the measurement of AST was not available in Constances for the calculation of the FIB-4 as well as the other scores, the Forns Index (FI)(28) was then chosen as a surrogate marker of liver fibrosis. It has been previously validated as a marker of liver fibrosis in a large cohort of biopsy-proven NAFLD(19). Moreover, FI has been shown as accurate predictor of morbi mortality in NAFLD patients(29). Subjects were classified as follows: non-NAFLD ($\text{FLI} < 60$), NAFLD ($\text{FLI} \geq 60$), NAFLD with mild fibrosis ($\text{FLI} \geq 60$ and $\text{FI} < 4.2$), NAFLD with intermediate fibrosis ($\text{FLI} \geq 60$ and FI between 4.2-6.9) and NAFLD with advanced fibrosis ($\text{FLI} \geq 60$ and $\text{FI} > 6.9$).

Follow-up study

Constances data were linked to hospitalization data and deaths which were recorded in the Systeme National des données de Santé (SNDS) from 2012 to December 31, 2019(30). International Classification of Diseases (ICD-10) codes were used to define liver-related events according to the recent expert panel consensus statement (compensated cirrhosis, hepatocellular carcinoma, decompensated cirrhosis)(31), CVD (arteritis of lower limbs, myocardial infarction, stroke, angina pectoris), EHC (colon, breast, prostate, lung, thyroid, ovary, uterus), CKD (Supplementary Table 2 <http://links.lww.com/HEP/D713>), and overall mortality (Supplementary methods <http://links.lww.com/HEP/D713>). Subjects with history of cirrhosis-related complications or hepatocellular carcinoma, were excluded from the analysis. Those with history of CVD, EHC or subjects with GFR <60 mL/min/1.73m² at baseline were excluded in the calculation of each category of incident events.

Statistical analysis

Baseline distributions were expressed as means for continuous variables and percentages for categorical variables with their 95% confidence intervals (95%CI). Multinomial univariate and multivariate regression models including the usual clinically relevant risk factors and based on our previous works(19,32,33), such as socio-demographic characteristics, clinical and anthropometric variables, lifestyle and biological data were built to identify risk factors associated with NAFLD at baseline in relation to BMI (Supplementary methods <http://links.lww.com/HEP/D713>).

In a second set of analyses, we performed a longitudinal analysis to assess the impact of NAFLD on clinical outcomes and overall mortality. The overall sample was split into 3 groups: lean participants with NAFLD, non-lean (overweight and obese) with NAFLD, and non-NAFLD. Mortality was studied with the standard Cox proportional hazards 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 the Gray's test was used to estimate the differences in the cumulative incidence functions between the groups. A standard Kaplan-Meier curve was estimated for all-cause mortality. Propensity-score-based stabilized inverse-probability weighting (IPTW) was applied to handle confounding. A multinomial propensity score for belonging to the three compared groups was derived by boosted logistic regression or multinomial regression models, from potential usual clinically relevant confounding factors (Supplementary methods <http://links.lww.com/HEP/D713>).

IPTW-weighted Fine-Gray model was applied to estimate the competing risk hazard ratios of liver-related events, CVD, extrahepatic malignancies, CKD and cause-specific hazard ratios for overall mortality. We performed subgroup analyses in NAFLD subjects according to BMI (lean with NAFLD versus non-lean with NAFLD), and in lean NAFLD subjects according to the presence of fibrosis. Thus, the lean NAFLD participant sample was split into two groups: lean NAFLD with advanced fibrosis, and lean NAFLD without advanced fibrosis. These analyses were performed according to the same approach described above. A 6-month latency period since inclusion was imposed so that the incidence of a clinical event could be attributed to the presence of diabetes and/or NAFLD. Thus, to avoid an immortal time bias, the follow-up of subjects began 6 months after the collection of baseline NAFLD status. Because participants may lose weight or change lifestyle over time, we finally performed sensitivity analyses accounting for these potential variations. 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, SNDS data were available in 169,303 participants. After excluding subjects who withdrew their consent, had a history of excessive alcohol consumption, chronic viral hepatitis, other causes of liver disease, or missing data for calculation of FLI, 137,206

subjects were included in the final analysis and defined as the overall population (Figure 1). Their baseline characteristics are shown in Table 1. Distribution of BMI was as follows: 79,789 (58.2%) lean, 39,992 (29.1%) overweight and 17,425 (12.7%) subjects with obesity. According to $FLI \geq 60$, a total of 25,753 subjects were considered to have NAFLD (weighted prevalence 18.3%, 95%CI 18.2-18.4), including 3664 with lean NAFLD (Figure 1).

Prevalence of lean NAFLD

The weighted prevalence of lean NAFLD in the overall population was 2.9% (95%CI 2.8-3.0), which was similar between men and women (2.9%, 95%CI 2.8-3.1 vs 3.0%, 95%CI 2.8-3.1) (Supplementary Table 3 <http://links.lww.com/HEP/D713>). The highest prevalence was found in 29-38 year old subjects (5.6%, 95%CI 5.3-6.0) while the lowest prevalence in >69 year old subjects (0.9%, 95%CI 0.6-1.2) (Supplementary Table 3 <http://links.lww.com/HEP/D713>). The highest prevalence of lean NAFLD was found in Asian individuals (14.4%, 95%CI 13.0-15.7) which reached 30.1% (95%CI 27.2-33.0) in those who were 29-38 years old (Supplementary Table 3 <http://links.lww.com/HEP/D713>). The prevalence of NAFLD in lean, overweight and obese subjects was 5.3% (95%CI 5.2-5.4), 28.5 % (95%CI 28-29) and 79.2% (95%CI 79.1-79.3), respectively. The prevalence of NAFLD in lean subjects increased to 25.1% (95%CI 22.7-27.5) in those with type 2 diabetes, to 7.8% (95%CI 6.8-7.8) with HBP, 16.4% (95%CI 15.4-17.4) with hypercholesterolemia, 18.1% (95%CI 17.0-19.2) with hypertriglyceridemia and to 18.8% (95%CI 17.7-19.8) with elevated ALT. In lean subjects with a combination of diabetes, HBP, hypercholesterolemia, hypertriglyceridemia, the prevalence of NAFLD ranged from 3.3% in those with no risk factors to 86.1% in those with all risk factors (Supplementary Figure 2 <http://links.lww.com/HEP/D715>). The distribution of BMI in NAFLD subjects was as follows: lean 16.3% (95%CI 15.7-16.8), overweight 41% (95%CI 40.3-41.8) and obesity

42.7% (95%CI 42.0-43.4). [AQ: Please cite Supplementary Figure 3 in the text <http://links.lww.com/HEP/D716>].

Baseline characteristics according to BMI in NAFLD patients

Table 1 shows the baseline characteristics of subjects according to BMI and NAFLD. Lean NAFLD subjects were significantly younger than non-lean NAFLD and were more often women, with fewer metabolic abnormalities (51.9% had no evident metabolic risk factors), significantly higher rates of moderate alcohol consumption and tobacco use, and were more frequently of Asian origin with a lower level of education. The independent risk factors of NAFLD were quite similar between lean and non-lean subjects on multivariate analysis except for younger age and Asian ethnicity in lean subjects (Table 2). The prevalence of comorbidities including CVD, EHC and CKD were similar between lean and non-lean NAFLD subjects (Table 1).

Liver injury at baseline is more severe in lean individuals with NAFLD

Patients with lean NAFLD had elevated ALT (34.3%, 95%CI 34.1-34.5 vs 21.0%, 95%CI 20.7-21.3) and advanced fibrosis according to FI >6.9 (3.6%, 95%CI 3.4-3.8 vs 1.7%, 95%CI 1.5-1.9, P<0.01) significantly more frequently than those with non-lean NAFLD (Table 1). The independent parameters associated with advanced fibrosis (FI >6.9) in NAFLD subjects were lean status (OR=1.26, 95%CI 1.20-1.65, P=0.005), male gender (OR=2.67, 95%CI 1.90-3.83, P<0.001), diabetes (OR=2.47, 95%CI 1.85-3.30, P<0.001), hypertriglyceridemia (OR=2.72, 95%CI 2.01-2.36, P<0.001), elevated ALT (OR=5.18, 95%CI 3.89-6.90, P<0.001), soda intake (OR=1.58, 95%CI 1.14-2.15, P=0.004), coffee intake (OR=0.76, 95%CI 0.57-0.98, P=0.006) and Asian origin (OR=5.45, 95%CI 1.98-12.64, P=0.002). (Supplementary Table 4 <http://links.lww.com/HEP/D713>).

Risk of clinical outcomes and mortality in lean and non-lean NAFLD subjects with non NAFLD subjects as reference group

After a median follow-up of 3.75 years (range 0.08-7.91) in the overall population, 649 subjects developed liver-related events, including 119 HCC, 1901 developed CVD, 410 CKD, 1854 extra hepatic malignancies, 18 underwent liver transplantation (Supplementary Table 5 <http://links.lww.com/HEP/D713>) and 1148 died. The cumulative incidence of liver-related events, CVD, extrahepatic malignancies, CKD and deaths in lean NAFLD, non-lean NAFLD and non-NAFLD subjects are shown on Figure 2 (and Supplementary Figure 4 <http://links.lww.com/HEP/D717>). The 5-year incidence rate for liver-related events in these three groups was 7.89 vs 1.57 vs 0.99 per 1000 person-years ($P<0.0001$), CVD 2.03 vs 2.61 vs 2.16 per 1000 person-years ($P<0.0001$), extrahepatic malignancies 4.43 vs 3.59 vs 2.13 per 1000 person-years, CKD 5.58 vs 3.02 vs 1.09 per 1000 person-years ($P<0.0001$) and all cause death 5.01 vs 2.15 vs 1.38 per 1000 person years ($P<0.0001$), respectively. The analysis for the risk of clinical outcomes and death in lean and non-lean NAFLD subjects is shown in Table 3. After IPTW-weighting (models containing age, gender, geographic origin, educational level, diabetes, HBP, hypercholesterolemia, ALT, alcohol consumption, tobacco use, soda intake, coffee consumption and physical exercise), lean NAFLD subjects had a significantly increased risk of liver-related events (aHR=8.72, 95%CI 6.23-12.20), CKD (aHR=5.33, 95%CI 3.30-8.62) and all-cause death (aHR=3.74, 95%CI 2.97-4.72) compared to non-NAFLD subjects, while non-lean NAFLD subjects had a significantly increased risk of liver-related events (aHR=1.50, 95%CI 1.09-2.06) and CVD (aHR=1.71, 95%CI 1.44-2.04). The IPTW-weighted risk of EHC was not significantly increased in either lean or non-lean NAFLD subjects (Table 3). In sensitivity analysis, accounting weight loss or lifestyle changes (alcohol or tobacco use) during follow-up period did not affect significantly, the risk of

clinical outcomes and overall mortality in lean NAFLD compared to non-lean NAFLD subjects (Supplementary Table 6 <http://links.lww.com/HEP/D713>).

The impact of lean status on clinical outcomes in NAFLD subjects

After a median follow-up of 3.75 years (range 0.08-7.91), 261 of the 22,089 NAFLD subjects developed liver-related events, including 33 HCC, 719 developed CVD, 176 CKD, 458 extrahepatic malignancies, while 8 were transplanted (Supplementary Table 5 <http://links.lww.com/HEP/D713>) and 371 died. The cumulative incidence of liver-related events, extrahepatic malignancies, CKD and death, was significantly influenced by lean status, but not CVD (Supplementary Figure 5 <http://links.lww.com/HEP/D718>). Raw and IPTW-weighted analysis for the risk of clinical outcomes and death according to BMI in NAFLD subjects is shown in Table 4. Lean NAFLD subjects had a significantly increased risk of liver-related events (aHR=5.84, 95%CI 4.03-8.46), CKD (aHR=2.49, 95%CI 1.49-4.16), and overall mortality (aHR=3.01, 95%CI 2.21-4.11) than non-lean NAFLD subjects and after IPTW-weighting (models including age, gender, geographic origin, educational level, diabetes, HBP, hypercholesterolemia, ALT, alcohol consumption, tobacco use, soda intake, coffee consumption and physical exercise). The raw and IPTW-weighted risk of extrahepatic malignancies was not significantly influenced by the BMI in NAFLD subjects (Table 4).

Clinical outcomes in lean NAFLD subjects according to the severity of liver fibrosis

After a median follow-up of 4.51 years (range 0.08-7.83), 76 of the 3664 lean NAFLD subjects developed liver-related events, including 9 HCC, 49 developed CVD, 32 CKD, 54 extrahepatic malignancies while 1 was transplanted (Supplementary Table 5 <http://links.lww.com/HEP/D713>) and 100 died. The 5-year incidence rate (per 1000 person-years) of liver-related events, CKD, and death was significantly higher in lean NAFLD subjects with advanced fibrosis than in those without (37.40 vs 12.26, $P<0.001$, 14.30 vs 5.57,

P=0.009 and 34.15 vs 10.26, P=0.011, respectively). There was a significantly increased risk of all types of clinical events and death on univariate analysis in lean NAFLD with advanced fibrosis compared to those without (Supplementary Table 7 <http://links.lww.com/HEP/D713>). On multivariate analysis, after adjustment for age, gender, geographic origin, educational level, diabetes, HBP, hypercholesterolemia, ALT, alcohol consumption, tobacco use, soda intake, coffee consumption and physical exercise, lean NAFLD subjects with advanced fibrosis had a significantly increased risk of liver-related events (aHR=6.19, 95%CI 4.35-8.82) and overall mortality (aHR=3.40, 95%CI 2.53-4.59) (Supplementary Table 7 <http://links.lww.com/HEP/D713>). Results were similar in non-lean NAFLD with or without advanced fibrosis (data not shown). Compared to non-NAFLD, lean NAFLD without advanced fibrosis remained associated with a significantly increased risk of clinical outcomes and overall mortality (Supplementary Figure 4 <http://links.lww.com/HEP/D717> and Supplementary Table 7 <http://links.lww.com/HEP/D713>).

Discussion

To our knowledge, this is the largest population-based study to prospectively evaluate the burden of NAFLD on clinical outcomes and mortality in lean individuals. The estimated prevalence of NAFLD among lean subjects was 5.3%. In this unselected population, lean NAFLD was associated with a better metabolic profile, different lifestyle, and a higher rate of advanced fibrosis at baseline than non-lean NAFLD. After adjustment for the usual risk factors and lifestyle, lean status remained associated with a higher rate of advanced fibrosis and poorer clinical outcomes for liver-related events and chronic kidney disease, while the risk of death from all causes was more than 3 times higher than in non-lean NAFLD. Clinical outcomes were related to the severity of fibrosis, both in lean and non-lean NAFLD subjects. The Constances is a large population-based cohort representative of the French general population aged 18 and over(20). The scores for non-invasive markers such as the FLI and FI

have been validated in several studies as surrogate markers of NAFLD and fibrosis in the general population and have been shown to accurately detect fatty liver and advanced fibrosis(19,24–26,29). Based on these validated markers, we found a similar prevalence of NAFLD among lean subjects (5.3%) and a similar prevalence of lean individuals among NAFLD subjects (16.3%) to that reported in US and Korean community-based epidemiological studies(34,35). The prevalence of NAFLD reached 85% in lean subjects combining metabolic risk factors, corresponding to a high-risk subgroup that requires screening for NAFLD. Compared to non-lean NAFLD, lean NAFLD subjects were younger, mostly women, less likely to have components of the metabolic syndrome and more often Asian, which supports data from previous community-based studies(36,37). Consistent with prior studies, highest prevalence of lean NAFLD was found in Asian individuals(37). However, there may be important differences among individuals of Asian ethnicity between East/South/SE/Central Asians. Unfortunately, Constances do not provide this type of data. Despite a better metabolic profile, lean NAFLD was associated with a higher prevalence of elevated ALT and advanced fibrosis according to FI than non-lean NAFLD (3.7% vs 1.7%, respectively). On multivariate analysis, lean status remained associated with advanced fibrosis, independent from demographics, metabolic risk factors and lifestyle. These results are contradictory to those reported in biopsy-proven NAFLD patients. Indeed, two meta-analyses have suggested that lean individuals have a lower rate of extensive fibrosis and NASH, which was confirmed in the US TARGET cohort(6,9,10). A small prospective study in Hong Kong reported a similar prevalence of extensive fibrosis between obese and non-obese individuals with biopsy-proven NAFLD(13). It could be argued the heterogeneity of studies because all were hospital-based as shown in a meta-analysis(9). The reasons of indicating the liver biopsy could be abnormal liver test and/or additional risk factor for NASH, suggesting bias in the selection of patients. In a recently published population-based

study, extensive fibrosis assessed by FIB4 was more prevalent in lean than in non-lean NAFLD subjects from the US NHANES cohort(11).

Our large community-based cohort confirms that lean NAFLD is associated with adverse liver-related events, including the occurrence of HCC. We found an increased risk of liver-related events in lean NAFLD subjects compared to overweight/obese NAFLD subjects with a Hazard Ratio of 5.84 (95%CI 4.03-8.46) after adjustment (IPTW-weighted) for a large number of confounding factors. Liver-related events were assessed according to the recent expert report which provided a reference standard to code compensated cirrhosis, HCC and decompensated cirrhosis(31). The risk of incident chronic kidney disease was also found to be increased in lean NAFLD subjects with an IPTW-weighted HR of 2.49 (95%CI 1.49-4.16). The risk of incident CVD and extrahepatic malignancies were not significantly influenced by lean status after adjustment for confounding factors. Cardiovascular diseases risk was significantly increased in non-lean NAFLD individuals, suggesting that obesity itself is a major risk factor for CVD independent of NAFLD. Finally, overall mortality was significantly increased in lean NAFLD subjects when compared with non-lean NAFLD with an IPTW-weighted HR of 3.01 (95%CI 2.21-4.11), which is consistent with the largest US community-based study(11). A higher prevalence of advanced fibrosis in lean NAFLD subjects may partly explain these clinical findings. Fibrosis grade has been shown as an independent predictor of survival in NAFLD patients(38). Here, we found that grade of fibrosis was predictive of clinical outcomes in both lean and non-lean NAFLD subjects. Data on the course of fibrosis, especially in lean NAFLD subjects without advanced fibrosis, was not available in Constances.

At this time, there is no definitive explanation why, despite a more favorable metabolic profile, lean NAFLD subjects have an increased risk for elevated ALT, advanced fibrosis, liver-related events, and overall mortality when compared to non-lean NAFLD subjects.

Changes of BMI prior to baseline or during follow-up may influence our results. In this setting, we have checked history of obesity or overweight in lean subjects which was a very rare event. Poorer outcomes in lean NAFLD individuals may reflect weight loss related to advanced disease. However, we excluded participants with decompensated cirrhosis at baseline and we adjusted morbi-mortality analysis for weight loss during follow-up. We were not able to analyze weight gain in lean NAFLD during follow-up. However, a recent multicentric study in biopsy proven NAFLD patients showed no impact of weight change on long-term events(12).

Several pathogenic hypotheses may be addressed. Insulin resistance (IR) which is a driver of fibrogenesis in NAFLD patients, is present in lean NAFLD but to a lesser degree than in obese NAFLD patients as shown in a meta-analysis(9). Body composition in terms of fat mass, fat distribution and muscle mass, plays a major role in the development of NAFLD and its severity(39,40). In the Rotterdam cohort, assessment of body composition by DXA showed that sarcopenia was more prevalent in lean NAFLD subjects and associated with the severity of liver disease(41). Bile acids (BAs) and microbiota may play a role in the pathogenesis of NAFLD in lean individuals. While BAs may have protective effect through FXR activation, alterations in both total BAs levels and composition have been noted in both rodents and humans with NAFLD/NASH(42). In this setting, it was shown that increased levels of BAs are associated with NASH progression and fibrosis severity(43,44). In a Western multicentric study, the serum levels of BAs, especially secondary BAs, were significantly higher among lean NAFLD patients compared with their non lean counterparts(44). Moreover, patients with lean NAFLD had a distinct microbiota profile with an increased abundance of members belonging to the *Clostridium* genus as well as *Ruminococcaceae*, which are involved in the formation of BAs. In another study from Asia, fecal and blood microbiota profiles were different between lean and non lean NAFLD individuals(45). The lack of liver histology did

not allow to correlate with the severity of liver disease. Genetic predisposition may partly explain liver disease severity and poorer clinical outcomes in lean NAFLD subjects.

However, a recent meta-analysis did not find different prevalence of *PNPLA3* and *TM6SF2* polymorphisms between lean and obese NAFLD patients(6). It was confirmed in a recent large cohort of biopsy proven lean NAFLD patients(12). Other genetic polymorphisms, such as *HSD17B13* which is associated with the severity of NASH, should be tested in larger and longitudinal cohorts(46). In our study, Asian ethnicity was strongly associated with lean NAFLD and was an independent predictor of advanced fibrosis. A Japanese study showed that a genetic polymorphism (*PNPLA3 rs738409*) was more frequent in Asian subjects with NAFLD, especially since its prevalence was more prominent in lean NAFLD(36).

As previously suggested by Hagström et al, the differences in dietary patterns and other lifestyle parameters might affect disease progression in lean NAFLD subjects(14). In our study, we found higher rates of moderate alcohol consumption or tobacco use in lean compared with non-lean NAFLD subjects. During follow-up, significantly more lean NAFLD subjects had increased alcohol consumption or tobacco use. However, after adjustment for alcohol and tobacco, there was no significant impact on the severity of fibrosis nor clinical outcomes.

Our study has several limitations. The causality and temporality between metabolic risk factors or comorbidities and NAFLD could not be confirmed due to the cross-sectional design. For example, we cannot exclude that diabetes is a consequence rather than a cause of NAFLD. Another limitation is the use of non-invasive serum biomarkers to assess the presence of NAFLD and advanced fibrosis. Imaging methods, such as US or Fibroscan, which are more accurate than biomarkers for the detection of NAFLD and fibrosis, are difficult to apply on a large scale such as in the general population. Because AST measurements were not performed in the subjects Constances cohort, we could not compare our data to other fibrosis

biomarkers such as FIB4 or NAFLD fibrosis scores. Finally, we could not assess the impact of NASH in our study population, because liver biopsy is the gold standard for this diagnosis. Other weaknesses of the study are the small representation of African or Asian populations, short median follow-up of 3.58 years, limited information on insulin resistance, no morphometric data beyond BMI, no data addressing genetic polymorphisms, and reliance on ICD-10 codes for clinical outcomes without primary medical record data.

In conclusion, this large, prospective, community-based cohort provides real-world evidence that lean NAFLD subjects have more progressive liver disease and poorer clinical outcomes, independent from the usual risk factors and lifestyle. Because of the fairly low prevalence of NAFLD in lean subjects, NAFLD screening should target those patients with metabolic abnormalities and/or unexplained cytolysis. The poorer prognosis of NAFLD in lean individuals may encourage the inclusion of these patients in clinical trials.

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Figure 1: Flow chart

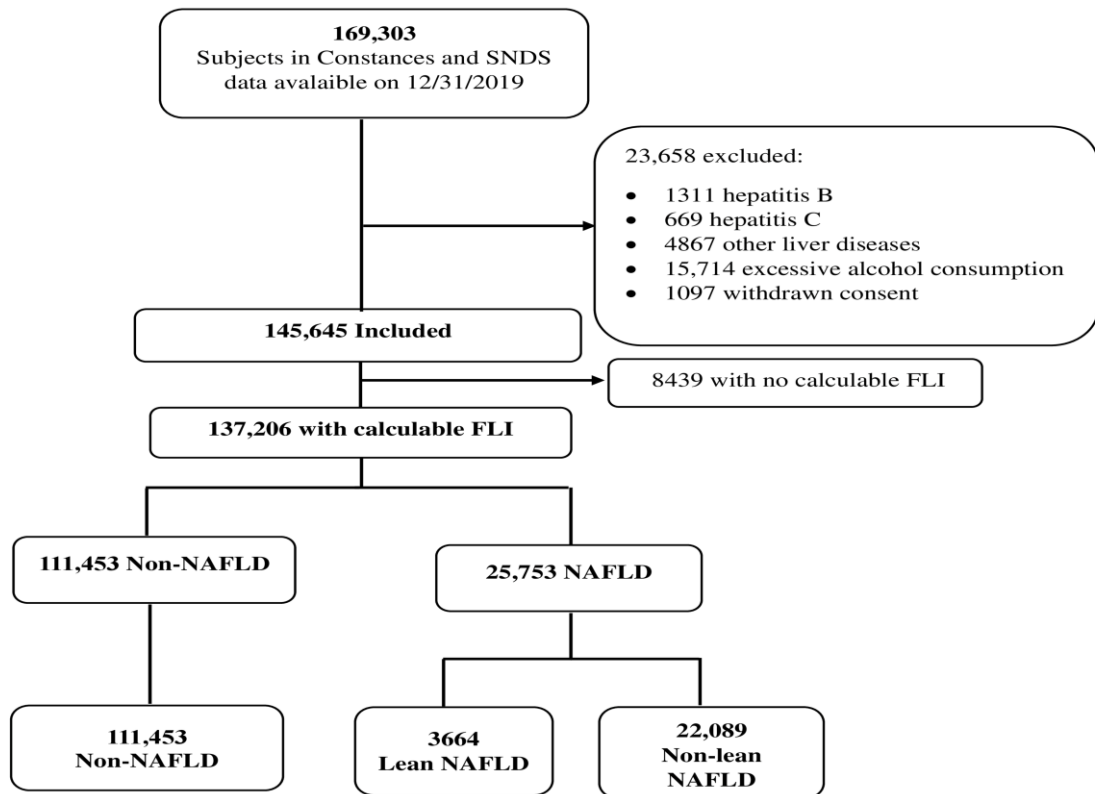


Figure 2: Cumulative incidence of (A) liver-related events, (B) cardiovascular disease, (C) chronic kidney disease and (D) all cause death in lean NAFLD, non-lean NAFLD and non-NAFLD subjects

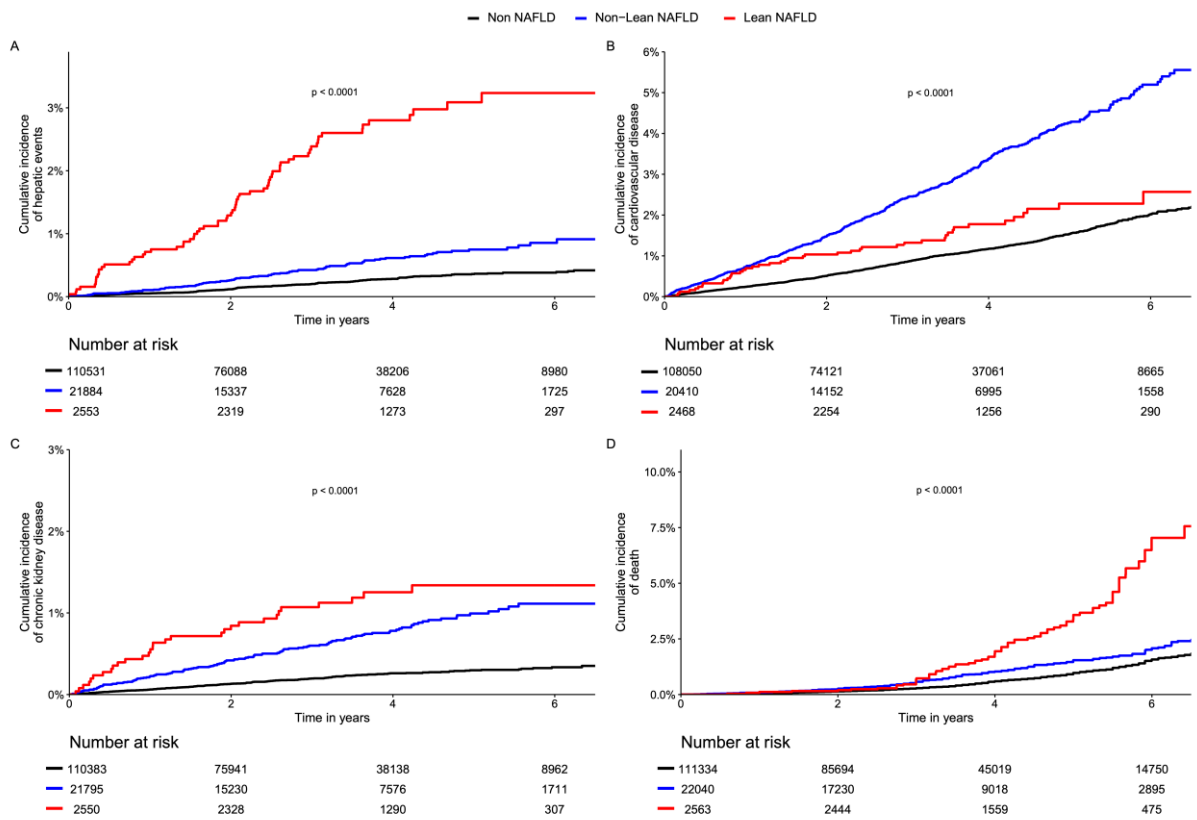


Table 1 : General characteristics at baseline of overall population and according to BMI and presence of NAFLD (FLI \geq 60)

	Overall population n = 137,206	Non-NAFLD n = 111,453	Non-lean NAFLD n = 22,089	Lean NAFLD n = 3664
Age(years), mean (95%CI)	46.8 (46.7-46.9)	48.6 (48.5-48.7)	54.9 (54.8-55.0)	45.1 (44.7-45.5)
Male sex, % (95%CI)	45.8 (45.7-45.9)	41.0 (40.9-40.1)	69.6 (69.5-69.7)	43.7 (43.5-43.9)
BMI (Kg/m²), mean (95%CI)	24.8 (24.7-24.9)	24.1 (24.0-24.2)	30.9 (30.8-31.0)	22.3 (22.2-22.4)
Waist circumference (cm), mean (95%CI)	84.7 (84.6-84.8)	82.1 (82.0-82.2)	103.2 (103.1-103.3)	78.6 (78.3-78.9)
Diabetes, % (95%CI)	5.3 (5.1-5.5)	2.4 (2.3-2.5)	17.9 (17.7-18.1)	10.5 (10.1-10.9)
Hypertriglyceridemia, % (95%CI)	12.2 (12-12.4)	7.3 (7.1-7.5)	36.1 (36.0-36.2)	27.0 (26.8-27.2)
Hypercholesterolemia, % (95%CI)	11.5 (11.3-11.7)	7.2 (7.0-7.4)	32.3 (32.0-32.6)	25.1 (24.8-25.4)
HBP, % (95%CI)	10.6 (10.5-10.7)	10.7 (10.4-11.1)	31.6 (31.5-31.7)	30.6 (30.2-31.0)
ALT >N, % (95%CI)	11.3 (11.2-11.4)	7.3 (7.2-7.5)	21.0 (20.7-21.3)	34.3 (34.1-34.5)
GGT>N, % (95%CI)	10.1 (10.0-10.2)	10.7 (10.5-10.9)	17.8 (17.4-18.2)	31.1(30.8-31.4)
Forns Index, mean (95%CI)	-	-	3.69 (1.55)	4.16 (1.49)
Advanced fibrosis (FI>6.9), % (95%CI)	-	-	1.7 (1.5-1.9)	3.6 (3.4-3.8)
Alcohol >10g/day, % (95%CI)	25.1 (25.0-25.2)	23.3 (23.0-23.6)	29.0 (28.7-29.3)	43.8 (43.6-44.0)
Tobacco >10 pack/year, % (95%CI)	21.1 (21.0-21.2)	20.2 (19.9-20.5)	23.9 (23.6-23.3)	28.4 (28.2-28.6)
Physical activity \geq2 h/week, % (95%CI)	25.9 (25.8-26.0)	24.7 (24.6-24.8)	27.2 (26.8-27.7)	28.3 (27.9-28.7)
Soda \geq1/d, % (95%CI)	4.0 (3.8-4.2)	3.6 (3.3-3.9)	5.3 (4.9-5.7)	4.9 (4.6-5.2)
Coffee \geq1 cup/day, % (95%CI)	28.9 (28.7-29.9)	28.5 (28.2-28.8)	30.1 (29.9-30.3)	31.8 (31.6-32.0)

Geographic origin, % (95%CI):				
Western countries	93.0 (92.9-93.1)	94.8 (94.7-94.9)	88.0 (87.9-88.1)	74.3 (74.2-74.4)
Overseas France	1.1 (1.0-1.1)	1.2 (1.1-1.3)	0.4 (0.3-0.6)	0.7 (0.3-1.0)
Asian	0.9 (0.8-1.0)	0.5 (0.4-0.6)	0.4 (0.3-0.5)	14.4 (13.0-15.7)
Sub-Saharan Africa	0.5 (0.4-0.6)	0.5 (0.4-0.5)	0.4 (0.3-0.5)	0.6 (0.3 -1.0)
North African	4.5 (4.4-4.6)	3.1 (3.0-3.2)	10.7 (10.3-11.2)	10.1 (9.0-11.3)
Schooling level, % (95%CI):				
≤8 years	4.5 (4.3-4.7)	2.5 (2.4-2.6)	15.1 (14.5-15.7)	9.5 (8.2-10.9)
9-11 years	25.2 (25.0-25.5)	24.0 (23.7-24.2)	31.1 (30.7-31.5)	31.6 (31.2-33.0)
12-15 years	37.9 (37.6-38.0)	38.6(38.5-38.7)	31.6 (31.5-31.7)	42.5 (42.4-42.6)
≥16 years	32.4 (32.3-32.5)	34.9 (34.8-35.0)	22.2 (22.1-22.3)	16.4 (16.2-16.6)
History of, % (95%CI):				
Cardiovascular diseases	10.1 (9.9-10.2)	3.9 (3.6-4.1)	13.7 (13.2-14.2)	14.1 (13.5-14.6)
Extrahepatic malignancies	5.5 (5.4-5.6)	5.7 (5.5-5.9)	5.2 (4.5-6.1)	5.6 (4.8-6.4)
Chronic kidney disease	3.2 (3.0-3.3)	3.1 (2.8-3.3)	3.0 (2.8-3.3)	3.3 (2.6-4.0)

Table 2: Univariate and multivariate analysis of risk factors for NAFLD according to the BMI (non-NAFLD subjects are the reference group).

	Univariable		Multivariable	
	Lean NAFLD	Non-lean NAFLD	Lean NAFLD	Non-lean NAFLD
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Age (per 1-year increase)	0.99 (0.99-1.00)	1.06 (1.05-1.06)*	0.98 (0.98-0.99)*	1.04 (1.03-1.04)*
Male sex	1.73 (1.62-1.86)*	5.17 (5.01-5.33)*	0.86 (0.77-1.06)	3.10 (2.95-3.26)*
Diabetes	6.38 (5.65-7.21)*	11.00 (10.38-11.65)*	3.07 (2.56-3.76)*	3.35 (3.11-3.65)*
HBP	1.06 (0.95-1.18)	1.95 (1.45-2.03)*	1.00 (0.86-1.17)	1.96 (1.89-2.05)*
ALT >N	9.02 (8.26-10.99)*	6.01 (5.81-6.23)*	10.81 (9.63-12.32)*	6.29 (5.99-6.66)*
Cholesterol >N	5.11 (4.73-6.29)*	6.67 (5.78-8.03)*	11.89 (9.83-13.22)*	5.01 (4.37-5.42)*

Tobacco >10 pack/year	2.04 (1.91-2.20)*	1.65 (1.62-1.69)*	1.78 (1.62-2.00)*	1.65 (1.60-1.71)*
Alcohol >10 g/day	1.82 (1.69-1.95)*	1.79 (1.25-2.19)*	1.76 (1.31-2.09)*	1.44 (1.22-1.57)*
Soda ≥1/day	1.99 (1.61-2.17)*	1.81 (1.29-2.24)*	1.71 (1.08-2.13)*	1.76 (1.58-2.18)*
Coffee ≥1 cup/day	0.56 (0.51-0.61)*	0.65 (0.63-0.67)*	1.00 (0.89-1.13)	1.32 (1.25-1.39)*
Physical activity ≥2h/week	0.82 (0.76-0.88)*	0.74 (0.63-0.81)*	0.72 (0.57-0.80)*	0.73 (0.59-0.85)*
Schooling >12 years	0.54 (0.49-0.60)*	0.52 (0.37-0.69)*	0.53 (0.44-0.62)*	0.55 (0.43-0.68)*
Geographic origin				
Western countries (reference)	1	1	1	1
Asian	2.33 (2.11-2.73)*	0.98 (0.79-1.19)	2.19 (1.86-2.99)*	1.10 (0.73-1.49)
Sub-Saharan Africa	1.07 (0.99-1.16)	1.18 (0.96-1.39)	0.84 (0.41-0.98)*	1.76 (0.99-2.59)
North Africa	3.28 (2.67-4.12)*	4.99 (3.79-5.23)*	3.12 (2.48-4.01)*	3.17 (2.55-3.96)*

*P<0.05

Table 3: Raw and IPTW-weighted hazard ratios of clinical outcomes and death in lean and non-lean NAFLD subjects (non NAFLD subjects as reference group)

	Raw (reference group = non-NAFLD)				IPTW-weighted* (reference group = non-NAFLD)			
	Lean NAFLD		Non-lean NAFLD		Lean NAFLD		Non-lean NAFLD	
	HR	p	HR	p	aHR	p	aHR	p
	(95%CI)		(95%CI)		(95%CI)		(95%CI)	
Hepatic events			2.13		8.72		1.50	
	9.42 (7.27-12.22)	<0.001	(1.69-2.68)	<0.001	(6.23-12.20)	<0.001	(1.09-2.06)	<0.001

Cardiovascular diseases			2.86		1.47		1.71	
	1.58 (1.20-	0.00	(2.58-	<0.	(0.64-	0.69	(1.44-	<0.
	2.09)	1	3.17)	001	2.07)	9	2.04)	001
Extrahepatic malignancies			1.41		1.22		1.14	
	1.47 (1.13-	0.00	(1.24-	<0.	(0.87-	0.25	(0.88-	0.32
	1.93)	5	1.60)	001	1.71)	4	1.48)	7
Chronic kidney disease			3.13		5.33		2.17	
	4.96 (3.41-	<0.	(2.50-	<0.	(3.30-	<0.	(1.53-	<0.
	7.21)	001	3.92)	001	8.62)	001	3.07)	001
Death			1.54		3.74		1.23	
	4.47 (3.70-	<0.	(1.33-	<0.	(2.97-	<0.	(1.08-	0.00
	5.40)	001	1.78)	001	4.72)	001	1.73)	6

* Adjusted for age, gender, geographic origin, educational level, diabetes, HBP, hypercholesterolemia, GGT, ALT, alcohol consumption, tobacco use, soda intake, coffee consumption and physical exercise

Table 4: Raw and IPTW-weighted hazard ratios of clinical outcomes and death in NAFLD subjects according to the BMI

	Raw (reference group= non-lean NAFLD)		IPTW-weighted* (reference group= non-lean NAFLD)	
	Lean with NAFLD		Lean with NAFLD	
	HR (95%CI)	P	aHR (95%CI)	P
Hepatic events	4.46 (3.31-6.02)	<0.001	5.84 (4.03-8.46)	<0.001
Cardiovascular diseases	0.56 (0.42-0.74)	<0.001	0.55 (0.38-0.81)	0.002
Extrahepatic malignancies	1.04 (0.78-1.38)	0.785	1.08 (0.72-1.62)	0.721
Chronic kidney disease	1.59 (1.08-2.35)	0.019	2.49 (1.49-4.16)	<0.001
Death	2.90 (2.34-3.61)	<0.001	3.01 (2.21-4.11)	<0.001

* Adjusted for age, gender, geographic origin, educational level, diabetes, HBP, hypercholesterolemia, GGT, ALT, alcohol consumption, tobacco use, soda intake, coffee consumption and physical exercise