

Higher mortality among lean patients with nonalcoholic fatty liver disease despite fewer metabolic comorbidities

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Short Title: Extrahepatic manifestations and mortality in lean NAFLD

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Funding: Karn Wijarnpreecha was a recipient of the American Association for the Study of Liver Diseases (AASLD) Advanced/Transplant Hepatology Fellowship Award. Vincent L Chen was

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/apt.17424](https://doi.org/10.1111/apt.17424)

supported in part by an AASLD Clinical, Translational and Outcomes Research Award and an NIDDK K08 DK132312.

Conflict of interest statement for all authors: We do not have any financial or non-financial conflicts of interest.

Data Transparency Statement: Data available on request due to privacy/ethical restrictions

Authorship statement

Guarantor of article: Karn Wijarnpreecha and Vincent L Chen

Authors' contributions: Dr. Karn Wijarnpreecha was involved in study concept and design, acquisition, analysis, and interpretation of the data, drafting of the manuscript, and critical revision of the manuscript. Dr. Fang Li was involved in analysis and interpretation of the data, drafting and critical revision of the manuscript. Sori K Lundin was involved in analysis and interpretation of the data. Dr. Cui Tao was involved in interpretation of the data and critical revision of the manuscript. Dr. Deepika Suresh and Dr. Michael W Song were involved in data acquisition and validation. Dr. Vincent Chen was involved in study concept and design, analysis and interpretation of the data, critical revision of the manuscript, and study supervision. Dr. Anna SF Lok was involved in study concept and design, interpretation of data, critical revision of the manuscript, and study supervision.

ALL authors approved the final version of the article, including the authorship list.

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Key Words: hepatic steatosis; diabetes mellitus; NAFLD, cardiovascular diseases

Word Count: 5,562

4 Tables and 2 Figures

Abstract Word Count: 248 (≤ 250 words)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; ICD, International Classification of Diseases; IQR, interquartile range; LREs, liver-related events; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; PAD, peripheral arterial disease; PPV, positive predictive value; VCTE, vibration controlled transient elastography.

Abstract

Background & Aims: Nonalcoholic fatty liver disease (NAFLD) can develop in individuals who are not overweight. Whether lean persons with NAFLD have lower mortality and lower incidence of cirrhosis, cardiovascular diseases (CVD), diabetes mellitus (DM), and cancer than overweight/obese persons with NAFLD remains inconclusive. We compared mortality and incidence of cirrhosis, CVD, DM, and cancer between lean versus non-lean persons with NAFLD.

Methods: This is a retrospective study of adults with NAFLD in a single center from 2012 to 2021. Primary outcomes were mortality and new diagnosis of cirrhosis, CVD, DM, and cancer. Outcomes were modeled using competing risk analysis and Cox proportional hazards regression analysis.

Results: A total of 18,594 and 13,420 patients were identified for cross-sectional and longitudinal analysis, respectively: approximately 11% lean, 25% overweight, 28% class 1 obesity, and 35% class 2-3 obesity. Median age was 51.0 years, 54.6% were women. Median follow-up was 49.3 months. Lean patients had lower prevalence of metabolic diseases at baseline and lower incidence of cirrhosis and DM than non-lean patients and no difference in CVD, any cancer or obesity-related cancer during follow-up. However, lean patients had significantly higher mortality with incidence per 1,000 person-years of 16.67, 10.11, 7.37, and 8.99, respectively in lean, overweight, obesity class 1 and obesity class 2-3 groups, respectively.

Conclusions: Lean patients with NAFLD had higher mortality despite lower incidence of cirrhosis and DM, and similar incidence of CVD and cancer and merit similar if not more attention as non-lean patients with NAFLD.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease, affecting 25% of the population worldwide, and its clinical burden is expected to rise.¹ NAFLD is strongly associated with obesity and its comorbidities but can also develop in individuals who are not overweight (“lean NAFLD”).² The prevalence of lean NAFLD among the general population is 10–20% with most studies reported from Asian countries, and the highest prevalence reported in Mexico (37%).^{3–6}

NAFLD is associated with a wide spectrum of extrahepatic diseases, such as cardiovascular diseases (CVD), metabolic diseases (diabetes mellitus [DM], hypertension, dyslipidemia), chronic kidney diseases (CKD), or cancers.^{7,8} Several cross-sectional studies have evaluated prevalence of hepatic and extra-hepatic diseases among lean versus obese individuals with NAFLD. A cross-sectional analysis of the TARGET-NASH study cohort with 3,386 NAFLD patients in the US found a lower prevalence of cirrhosis, DM, and CVD in lean individuals compared to overweight/obese individuals.² Another study from Austria with 4,091 NAFLD participants had similar findings with lower prevalence of metabolic diseases (DM, metabolic syndrome, hypertension, dyslipidemia) and lower Framingham risk score for CVD but no significant difference in prevalence of coronary artery disease in lean patients compared with overweight/obese patients.⁹ By contrast, a recent Korean study with 4,786 NAFLD patients found higher atherosclerotic CVD scores among lean persons.¹⁰ However, cross-sectional studies can only show an association but not a cause-effect relationship.

Data on the impact of baseline body mass index (BMI) on the incidence of outcomes such as cirrhosis, CVD, cancers, and mortality among patients with NAFLD are limited. One longitudinal

study on the natural history of NAFLD in lean subjects included 1,090 US participants with biopsy-proven NAFLD followed for a mean of 133 ± 81.3 months demonstrated increased overall-mortality in lean patients compared to non-lean patients despite lower prevalence of metabolic diseases and advanced fibrosis.¹¹ A retrospective cohort study from the Olmsted county database with 4,834 NAFLD patients with median follow-up of 6.4 years showed similar findings with higher overall mortality in the lean persons and no significant differences in risk of cirrhosis, hepatic decompensation, CVD events, or malignancy between lean and obese persons.¹² Finally, a recent multi-center study from Western countries with 1,339 participants with biopsy-proven NAFLD with median follow-up of 94 months, demonstrated lower prevalence of non-alcoholic steatohepatitis (NASH), advanced fibrosis, and DM among lean versus obese individuals but no significant differences in overall-mortality or incidence of liver-related events between lean versus non-lean participants.⁵ Notably, the criteria for inclusion and the definition of outcomes in these published studies were not uniform. Given these inconsistencies, we conducted a comprehensive evaluation of multiple outcomes in a large cohort of patients with NAFLD with the aim to compare the mortality and incidence of cirrhosis, CVD, DM, and cancers between lean versus overweight and obese individuals with NAFLD.

Methods

Study population

This is a retrospective cohort study of adult patients diagnosed with NAFLD at the University of Michigan Health System between January 1, 2012 and December 1, 2021. The study was approved by the institutional review board of the University of Michigan.

Inclusion criteria were the presence of NAFLD defined as hepatic steatosis without an alternative etiology (**Supplementary Table 1**). We identified patients with hepatic steatosis on imaging or biopsy based on a validated natural language processing algorithm previously described¹³, or vibration controlled transient elastography (VCTE) showing controlled attenuation parameter (CAP) >250 db/m.¹⁴ In brief, the algorithm screened imaging or biopsy reports for the terms “fatty” or “steato” appearing in the same sentence as “liver” or “hepat”, then excluded reports with terms of negation (“no hepatic steatosis”) or evaluation (“rule out hepatic steatosis”). This algorithm had been previously shown to have a positive predictive value (PPV) >95%.¹³ Over 95% of our cohort had an initial diagnosis of NAFLD at our center based on imaging, 3.4% based on transient elastography and 1.6% on liver biopsy.

The study has two components: a cross-sectional analysis to compare prevalent/baseline clinical characteristics and comorbidities of lean versus non-lean patients with NAFLD, and a longitudinal analysis to determine mortality and incidence of clinical outcomes of lean versus non-lean patients. The index date was defined as the date when a patient was first diagnosed with NAFLD at our center. Follow-up time was defined as the interval from the index date to the date of the last clinical encounter, death, or study end date (December 1, 2021), whichever was earlier. For both cross-sectional and longitudinal analyses, we excluded participants with (i) age <18 or >80 years (n = 1,627); (ii) other causes of liver disease (n = 4,577); (iii) significant alcohol

consumption defined as >7 drinks/week in women and >14 drinks/week in men (n = 690)¹⁵; (iv) BMI <18.5 kg/m² (n = 199); (v) cancer diagnosis other than non-melanoma skin cancer up to 1 year after the index date (n = 8,535) since low BMI in these patients may be due to the cancer; (vi) previous history of bariatric surgery (n = 550); (vii) unknown race/ethnicity data, or missing important laboratory data such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or platelet (n = 17,087) within 12 months of the index date; or (viii) baseline cirrhosis with portal hypertension, ascites, esophageal varices, or hepatic encephalopathy since ascites may affect BMI (n = 1,247). For the longitudinal analysis, we further excluded those with a follow-up time of less than 365 days. (Figure 1)

Study Outcomes and Variable Definitions

For the cross-sectional analysis, the primary outcomes were the prevalence of cirrhosis, CVD, metabolic diseases, and chronic kidney disease (CKD) stage 3-5. Specifically, CVD comprised four types of diseases: coronary artery disease (CAD), cerebrovascular accident (CVA), peripheral arterial disease (PAD), and congestive heart failure (CHF). Metabolic diseases included DM, dyslipidemia, and hypertension. The prevalence of diseases of interest was defined as any diagnosis before or up to 90 days after the index date.

For the longitudinal analysis, the primary outcomes were overall mortality and incidence of CVD, cirrhosis, liver-related events (LREs) (ascites, variceal bleeding, hepatic encephalopathy, or HCC), DM, obesity-related cancer, and any cancer. We excluded patients with baseline cirrhosis from LREs incidence analysis because the interest of our study was identifying progression from non-cirrhotic NAFLD to LREs, rather than from compensated cirrhosis to

decompensation. Obesity-related cancer included malignant neoplasms of gastrointestinal tract and liver, breast, thyroid gland, uterus, ovary, kidney, as well as multiple myeloma.¹⁶ We evaluated the association between Fibrosis-4 (FIB-4) as non-invasive fibrosis score and the incidence of liver cirrhosis and LREs among NAFLD patients stratified by BMI category.¹⁷ Mortality was identified based on linkage to the Michigan Department of Vital and Health Records database; all deaths occurring in the state of Michigan are required to be reported to the Department. Cause of death was mainly based on International Classification of Diseases (ICD-10-CM) code provided. Causes of death were then grouped into organ/system-level cause. We manually reviewed the medical records of 20 patients who died at our hospital and found that the ICD-10 code assigned by the Michigan Death Index corresponded with the primary or a contributing cause of death in 19 (95%) of cases. Incident disease was defined as any new diagnosis after 365 days from the index date among patients with no prevalent disease.

The majority of outcomes and comorbidities were diagnosed based on ICD codes ¹⁶ **(Supplementary Table 1)**. For cirrhosis, we demonstrated that the ICD codes used had a positive predictive value (PPV) of 86%.¹⁸ We additionally assessed the sensitivity of ICD codes for cirrhosis and found that 46% of 582 NAFLD patients with evidence of cirrhosis on imaging had at least one ICD code for cirrhosis within 6 months of the imaging with no meaningful differences in sensitivity (41-51%) or specificity ($\geq 98\%$) across BMI categories. Previous studies have validated the accuracy of diagnosis of CVD based on ICD codes with PPV greater than 90% ^{19–21} and large epidemiologic studies found PPV of 80% for diagnosis of all malignant tumors by ICD coding.^{22–25} Chronic kidney disease (CKD) stage 3-5 was based on an estimated glomerular filtration rate of less than 60 ml/min/1.73m².²⁶

Body Mass Index

The NAFLD cohort was stratified into 4 subgroups based on average BMI values within a 6-month period around the index date. The World Health Organization recommendations for Asian and non-Asian BMI cutoffs^{27,28} were applied to categorize patients into lean, overweight, class 1 obesity, and class 2-3 obesity.

Given that weight and therefore BMI category may change during follow-up, we conducted a sensitivity analysis in which only patients whose weight category did not change during follow-up were included.

Genotyping and genetic analysis

A subset of our cohort was enrolled in Michigan Genomics Initiative, a prospective cohort of Michigan Medicine patients undergoing genotyping for research purposes.²⁹ Subjects were genotyped using an Illumina HumanCoreExome v.12.1 array. Among these patients, we compared the distribution of *PNPLA3*-rs738409 genotype (defined as 0, 1, or 2 copies of the risk allele *PNPLA3*-rs738409-G). The chi-square test was used to compare the genotype distribution among NAFLD patients based on BMI category.

Statistical Analyses

Baseline characteristics were compared between groups by the Chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. For descriptive statistics, the baseline characteristics were reported by number and percentages for categorical variables and median and interquartile range (IQR) for continuous variables. We used multivariable logistic regression analyses to determine the independent associations between

the prevalence of diseases and NAFLD after adjusting for confounders including age, sex, race, smoking status, alcohol consumption, type 2 DM, hypertension, dyslipidemia, and use of aspirin or statin.

The cumulative incidence of death by BMI category was calculated using Kaplan-Meier estimates. For evaluation of incident events, we required >1 year of follow-up. Time at risk was defined as the time from the index date to the date of recorded death or last visit. The log-rank test was applied to compare differences in the cumulative incidence of death between groups. For the outcome of mortality, we evaluated the effect of the BMI category using a Cox proportional hazards model. For all other outcomes (CVD, cirrhosis, etc.), we evaluated the cumulative incidence and the effects of the BMI category using a Fine-Gray competing risk model, with death without the outcome of interest as a competing event. For both model types, we adjusted for the same covariates as in the prevalent disease analyses. We performed additional analysis to assess association between *PNPLA3-rs738409* genotype and risk of mortality and incidences of diseases among NAFLD patients stratified by BMI category adjusted for the same covariates with genetic principal components to account for race and ethnicity. We also performed sensitivity analysis among NAFLD patients with no change in BMI category throughout follow-up and separate analysis for smokers and non-smokers. For cause of death analysis, *F*-test was used to compare the differences between the lean and non-lean groups.

All analyses were performed in RStudio with R version 4.1.2. A two-tailed $P \leq 0.05$ was considered statistically significant.

Results

Cross-sectional analysis

A total of 18,594 patients with NAFLD were included in the cross-sectional analysis: 2,137 lean, 4,692 overweight, 5,234 with class 1 obesity, and 6,531 with class 2-3 obesity. As shown in **Table 1**, lean individuals were more often female, more likely to have active tobacco use and prior CVA, and had lower prevalence of metabolic abnormalities including DM, hypertension, dyslipidemia, CKD stage 3-5 and CAD than non-lean individuals. The lean individuals also had lower levels of liver enzymes, total cholesterol, low-density lipoprotein, and triglycerides and higher level of high-density lipoprotein compared with non-lean individuals ($p < 0.05$ for all). There was no significant difference in race distribution between lean and overweight/obese groups, though our cohort was predominantly Caucasian.

Multivariate logistic regression analysis demonstrated that the overweight group had a significantly lower prevalence of CVA and PAD with adjusted odds ratio (OR) and 95% confidence interval (CI) of 0.68 (95% CI 0.54–0.86, $P = 0.001$) and 0.73 (95% CI 0.58–0.93, $P = 0.01$), respectively, and the obese groups (class 1 and class 2-3) had significantly lower prevalence of CAD, CVA, PAD and any CVD (all P values < 0.001), compared to the lean group (**Table 2**). The prevalence of cirrhosis and CKD stage 3-5 was significantly higher in the obesity class 2-3 group compared with the lean group, with an adjusted OR 1.66 (95% CI 1.11–2.58, $P = 0.019$) and 1.22 (95% CI 1.03–1.44, $P = 0.02$), respectively (**Table 2**).

Subgroup analysis of CVD prevalence among smokers and non-smokers

Since lean persons with NAFLD were more likely to be current smokers than non-lean persons with NAFLD ($P < 0.0001$), we performed a subgroup analysis to compare the prevalence of CVD across BMI categories separately for never smokers ($n = 12,846$), former smokers ($n = 3,993$), and current smokers ($n = 1,755$) (**Supplementary Table 2**). Among never smokers, multivariate logistic regression analysis demonstrated that the odds of CVD prevalence were significantly lower in non-lean than lean persons, with adjusted OR of 0.82 (95% CI 0.68–0.99, $P = 0.04$) for overweight individuals, 0.72 (95% CI 0.60–0.87, $P < 0.001$) for obesity class 1, and 0.78 (95% CI 0.65–0.94, $P = 0.007$) for obesity class 2-3 vs. lean persons. Among former smokers and current smokers, there were no significant differences in CVD prevalence between lean and non-lean individuals (all P values > 0.05). Overall, the higher prevalence of CVD among lean subjects with NAFLD compared to non-lean subjects was mainly attributed to never smokers.

Longitudinal analysis

A total of 13,420 patients with NAFLD were included in the longitudinal analysis: 1,454 lean, 3,373 overweight, 3,830 class 1 obesity, and 4,763 class 2-3 obesity. Median (IQR) follow-up time was 49.3 (29.2–79.8) months and total follow-up of 64,149 person-years. Roughly half (54.6%) of the patients were female, 80.7% were Caucasian, 8.6% African American, 4.9% Asian, and 5.8% other/mixed races.

Risk of overall mortality and causes of death

During follow-up, a total of 616 patients died, including 111 lean, 162 overweight, 136 obesity class 1, and 207 obesity class 2-3 individuals, with incidence per 1,000 person-years of

16.67, 10.11, 7.37, and 8.99, respectively ($p < 0.0001$). Cumulative incidence of mortality is shown in **Figure 2A**. Compared to lean individuals, overweight (adjusted HR 0.54, 95% CI 0.42–0.69, $P < 0.001$), obesity class 1 (adjusted HR 0.40, 95% CI 0.31–0.52, $P < 0.001$), and obesity class 2-3 (adjusted HR 0.52, 95% CI 0.41–0.66, $P < 0.001$) individuals had significantly lower mortality after adjusting for confounders (**Table 3**). After adjusting for Charlson Comorbidity Index, overweight (adjusted HR 0.44, 95% CI 0.27–0.71, $P < 0.001$), obesity class 1 (adjusted HR 0.34, 95% CI 0.21–0.56, $P < 0.001$), and obesity class 2-3 (adjusted HR 0.30, 95% CI 0.19–0.49, $P < 0.001$) individuals still had significantly lower mortality. The causes of death were mainly CVD (190, 30.8%), neoplasms (103, 16.7%), and respiratory diseases (75, 12.2%) with no statistically significant differences in causes of death between lean and non-lean groups (**Table 4**). CVD-related deaths were reported in 26.1%, 28.4%, 33.1%, and 33.8% of all deaths in lean, overweight, obesity class 1, and obesity class 2-3 groups, respectively. Compared with the non-lean group, the lean group tended to die more often from respiratory (15.3% vs 11.5%), metabolic (8.1% vs 5.3%), liver (7.2% vs 5.0%), mental-neurological (8.1% vs 6.1%), and infectious (5.4% vs 4.2%) diseases, though the differences were not statistically significant. None of the lean persons with NAFLD died from DM related causes in this cohort.

We also performed subgroup analysis to compare mortality between non-obese (lean and overweight) versus obese patients with NAFLD. Compared to non-obese patients, obese individuals had a significantly lower mortality after adjusting for confounders (adjusted HR 0.71, 95% CI 0.60–0.83, $P < 0.001$) (**Supplementary Figure 1**).

Risk of type 2 DM

There were 846 incident cases of type 2 DM, of which 45 were in lean, 254 in overweight, 393 in obesity class 1, and 154 in obesity class 2-3 individuals, with the incidence per 1,000 person-years of 8.62, 12.50, 18.89, and 27.05, respectively ($p < 0.0001$). The cumulative incidence of type 2 DM among the 4 groups is displayed in **Figure 2B**. The risks of incident DM among patients in obesity class 1 and obesity class 2-3 were significantly higher than the lean patients, with adjusted HR 1.78 (95% CI 1.29–2.45, $P < 0.001$) and 2.85 (95% CI 2.08–3.91, $P < 0.001$) (**Table 3**).

Risk of CVD

There were 719 events of any CVD during the study, with 43 in lean, 195 in overweight, 286 in obesity class 1, and 195 in obesity class 2-3 patients. The incidence per 1,000 person-years of CVD in each weight category was 8.67, 15.95, 13.85, and 16.22, respectively ($p < 0.001$). The cumulative incidence of any CVD is displayed in **Figure 2C**. In the competing risk analysis, compared to lean individuals with NAFLD, there was a marginally significant increased risk of any CVD in overweight (adjusted HR 1.40, 95% CI 1.00–1.95, $P = 0.051$) but not in obese individuals (**Table 3**). We stratified by smoking status and found no difference in CVD incidence in lean vs. non-lean persons among never smokers, ever smokers, or current smokers (**Supplementary Table 3**).

Risk of cirrhosis and LREs

Of the 12,646 NAFLD individuals with no cirrhosis at study entry, 254 developed cirrhosis during follow-up, with the incidence per 1,000 person-years of 1.97, 3.35, 3.62, and 5.81 in lean,

overweight, obesity class 1, and obesity class 2-3 groups, respectively ($p < 0.0001$). The cumulative incidence of cirrhosis based on the competing risk analysis is displayed in **Figure 2D**. Compared with lean individuals, obesity class 2-3 individuals were more likely to develop cirrhosis with adjusted HR 2.19 (95% CI 1.20–4.01, $P = 0.01$) (**Table 3**). In FIB-4 category 1.3-2.67, the incidence of cirrhosis was significantly higher among patients with obesity class 2-3 compared to lean patients only as well as to non-obese (lean + overweight) patients (**Supplementary Table 4**). Patients with obesity class 2-3 also had higher incidence of cirrhosis compared with overweight patients in those with FIB-4 > 2.67. There was no significant difference in LREs between lean and non-lean persons with NAFLD (**Table 3**) regardless of FIB-4 category (**Supplementary Table 4**).

Risk of any cancer and obesity-related cancer

For any cancer, there were 556 total events with incidence per 1,000 person-years of 9.10, 10.82, 9.05, 8.93, and 8.80 in lean, overweight, obesity class 1, and obesity class 2-3 groups, respectively ($p = 0.51$). The cumulative incidence of any cancer is shown in **Figure 2E** and the competing risk analysis of any cancer displayed in **Table 3** shows no significant difference across the groups.

There were 243 obesity-related cancer, with 24 in lean, 71 in overweight, 94 in obesity class 1, and 54 in obesity class 2-3 groups, and incidence per 1,000 person-years of 3.94, 3.54, 4.01, and 4.29 events, respectively ($p = 0.73$). The cumulative incidence of obesity-related cancers among the 4 groups is illustrated in **Figure 2F**. There was no statistically significant difference in risk of obesity-related cancers among overweight (adjusted HR 0.87, $P = 0.58$), obesity class 1 (adjusted HR 0.97, $P = 0.90$), and obesity class 2-3 (adjusted HR 1.02, $P = 0.93$) individuals compared to lean individuals (**Table 3**).

Sensitivity analysis among patients with no change in BMI category during the follow-up period

We conducted a sensitivity analysis of subjects whose BMI category did not change throughout the follow-up period of this study. A total of 3,773 (28.1%) patients were included (370 lean, 680 overweight, 538 obesity class 1, and 2,185 obesity class 2-3). The cumulative incidence of any CVD, CAD, type 2 DM, obesity-related cancer, and all cancer using the competing risk model are shown in **Supplementary Figure 2**. Among the patients who stayed in the same BMI category, cumulative incidences of any CVD ($P = 0.03$), cirrhosis ($P < 0.001$), and type 2 DM ($P < 0.001$) were significantly different among different BMI categories with the persistently lean group having lower incidences of these outcomes. However, the mortality in the persistently lean group remained significantly higher than in the non-lean groups (**Supplementary Table 5**).

Sensitivity analysis among smokers versus non-smokers during the follow-up period

A total of 13,420 patients were included—9,113 never smokers, 1,275 current smokers, and 3,032 former smokers. Among never and former smokers, the lean subgroups had significantly higher cumulative incidence of death compared with the non-lean subgroups (both $P < 0.05$), and a trend toward a higher cumulative incidence of death in lean vs non-lean subgroups among current smokers ($P = 0.057$) (**Supplementary Figure 3**).

Sensitivity analysis among patients with available PNPLA3-rs738409 genotype

A total of 3,039 patients with NAFLD: 259 lean, 652 overweight, and 2,128 obese, followed for a median (IQR) of 54.7 (28.0-86.6) months and total follow up of 15,311 person-years were studied. 84.1% were Caucasian, 6.4% African American, and 3.3% Asian. PNPLA3 genotype was CC, CG, and GG in 52.7%, 38.1%, and 9.2% of patients overall; 43.2%, 38.0%, and 8.7% of obese

patients; and 51.4%, 38.3%, and 10.3% of lean/overweight patients ($p>0.05$). NAFLD patients with PNPLA3 GG, but not those with CG genotype, had higher incidence of cirrhosis with adjusted HR 2.23 (95% CI 1.25-4.00, p -value=0.007) compared to patients with CC genotype (**Supplementary Table 6**). This was true in both obese and non-obese patients. PNPLA3 GG was significantly associated with LREs in the overall cohort with adjusted HR 1.87 (95%CI 1.04-3.34, p -value=0.04), and in obese patients with adjusted HR 6.26 (95%CI 1.81-21.65, p -value=0.004) but not in the non-obese (lean/overweight) patients, compared to patients with CC genotype. PNPLA3 genetic variants were not associated with all-cause mortality or incidence of CVD, DM, or cancer (**Supplementary Table 6**).

Discussion

In this study of more than 10,000 patients with NAFLD including nearly 1,500 lean persons followed for up to 10 years, we found that lean persons with NAFLD had a lower incidence of cirrhosis and DM and a similar incidence of CVD than overweight/obese persons with NAFLD. Despite similar or lower incidence of cirrhosis, DM and CVD and a lower prevalence of metabolic diseases at initial diagnosis, lean persons with NAFLD had significantly higher overall mortality. The finding of a significantly higher mortality among lean persons with NAFLD compared to overweight/obese persons with NAFLD remained true in a sensitivity analysis of the subgroup who stayed in the same weight category throughout the duration of follow-up and among the subgroups of smokers and non-smokers. This finding is relevant to a large proportion of patients with NAFLD, as 27% patients with NAFLD are lean and this proportion is even higher in Asian (27%-36%) than Western populations (10%-23%).³⁰

We found that lean individuals in our cohort were more likely to be smokers than overweight/obese individuals. However, prevalence of CVD in particular, PAD and CVA, and to a lesser extent CAD were significantly higher in lean individuals, even after adjusting for smoking status. The explanation for the higher prevalence of CVD among lean individuals with NAFLD is not clear. One study found that lean Caucasians with NAFLD showed distinct metabolomics profiles compared to overweight/obese individuals with NAFLD.³¹ Another hypothesis that has been proposed is that lean persons with NAFLD are more prone to have sarcopenia and expansion of visceral adipose tissue may play a role not only in the pathogenesis of NAFLD but also atherosclerosis and CVD.^{32,33}

In our longitudinal analysis, we found a lower incidence of cirrhosis and DM among lean individuals with NAFLD compared to overweight/obese individuals with NAFLD with no significant differences in incident CVD, all cancers or obesity-related cancers. A prospective cohort study from US with 394 NAFLD patients (diagnosed with ultrasound or histology) with median follow-up of 5.7 years also found no significant difference in incidence of CVD between obese versus non-obese patients with NAFLD.³⁴ In contrast, a recent study from the Olmsted county database and a multicenter-study from four countries (Italy, United Kingdom, Spain, and Australia) showed no significant differences in the incidence of both liver and non-liver events: cirrhosis, liver-related events/decompensation, DM, and CVD between lean and obese subjects with NAFLD.^{5,12} Non-invasive fibrosis scores such as FIB-4 has been proposed to risk stratify patients with NAFLD for liver-related outcomes.³⁵ We found that patients with obesity class 2-3 had significantly higher incident cirrhosis than lean and non-obese (lean + overweight) patients among those with intermediate FIB-4 score 1.3-2.67. In addition, among patients with FIB-4

score >2.67, obesity class 2-3 subjects had significantly higher risk of cirrhosis than overweight persons indicating an urgency in weight control among patients with intermediate or high FIB-4 scores.

An intriguing finding from this study is a significantly higher mortality among lean individuals with NAFLD compared with non-lean individuals, though we did not find significant differences in the distribution of causes of death between the two groups. We also found a significantly higher mortality among non-obese (lean and overweight) individuals compared with obese individuals. A nationwide study of 646 patients with biopsy-confirmed NAFLD in Sweden followed for a mean of 20 years demonstrated that patients with normal BMI had significantly higher liver-related death than overweight and obese patients (8.1% vs 3.0% and 8.1% vs 4.3%, respectively, p-value <0.001), and a higher incidence of severe liver disease defined as a diagnosis of cirrhosis, decompensated liver disease, hepatocellular carcinoma, or liver failure, compared with overweight patients (15.5% vs 9.3%, p-value <0.001).³⁶ A population-based study from Olmsted County with 4,834 NAFLD individuals identified by ICD-code with/without imaging diagnosis also demonstrated a higher all-cause mortality in lean individuals compared with obese individuals with HR 1.96 (95% 1.52-2.51) and no significant difference in distribution of deaths.¹² A multicenter study from Europe and Australia of 1,339 patients biopsy-confirmed NAFLD found no significant difference in overall mortality between lean versus non-lean patients but obese patients had significantly higher overall mortality compared to non-obese patients.⁵ A longitudinal U.S. population based study using National Health and Nutrition Examination Survey with 4,711 persons identified as having NAFLD based on US fatty liver index (3,183 obese, 1,299 overweight, and 229 lean) ≥ 30 , found that lean individuals had significantly higher 15-year

cumulative all cause-mortality (76.3% vs 27.2%, p-value <0.001) and CVD-related mortality (16.9% vs 5.6%, p<0.05) than obese individuals.³⁷ The discrepancies in mortality among these studies may be due to differences in definition of NAFLD, i.e. liver histology^{5,36} versus USFLI³⁷ versus ICD codes¹², prevalence of metabolic and CV diseases and severity of liver disease at baseline, and average duration of follow-up (5.7-20 years). A recently published systematic review and meta-analysis including 10 cohort studies with 109,151 NAFLD patients found no difference in overall mortality between lean patients and non-lean patients (relative risk 1.09, 95% CI 0.66-1.90), though there was marked heterogeneity ($I^2 = 97\%$).³⁸ The difference in the mortality finding between our study and the meta-analysis is likely due to differences in patient population, race (our study included mainly Caucasians while 3 studies³⁹⁻⁴¹ in the meta-analysis were conducted in Asia and likely included exclusively Asian), age of the lean patients (median 51 years in our study vs 41-48 years), sex (58.8% female in the lean group vs 24.6% to 45.2%), definition of lean (race-specific BMI cutoff for lean in our study vs. a mix of race-specific and standard BMI cutoff), and methods of NAFLD diagnosis (predominantly imaging in our study vs. a mix of predominantly biopsy, imaging or transient elastography). Of note, the meta-analysis found significantly increased liver-related mortality in lean patients³⁸ and we found a trend toward higher liver-related mortality in lean patients.

Mechanisms underlying potential increased mortality in lean persons with NAFLD remain unclear. We speculate that sarcopenia which has been demonstrated to be more common in lean persons with NAFLD and an inactive lifestyle may partially explain the higher mortality in this group.^{33,42-44} Our results support the recent clinical practice update from the American Gastroenterology Association stating that lean persons with NAFLD should be evaluated and

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treated for modifiable CVD risk factors including DM, hypertension, and dyslipidemia similar to overweight and obese persons with NAFLD.⁴⁵

PNPLA3 genetic variant is associated with hepatic steatosis, cirrhosis, and HCC.⁴⁶ However, the data on prevalence of PNPLA3 genetic variant in obese vs. non-obese persons with NAFLD are limited and it is not clear if the association between PNPLA3 variant and liver-related outcomes is true in both obese and non-obese persons and if PNPLA3 is also associated with non-liver outcomes. Similar to a previous study, we found no difference in *PNPLA3-rs738409* genotype distribution between lean and overweight/obese subjects with NAFLD.⁵ However, majority of NAFLD population in our study and all NAFLD patients in the study cited above⁵ were Caucasian in whom prevalence of PNPLA3 GG genotype is lower, whether there is a difference in *PNPLA3-rs738409* genotype distribution among lean vs. overweight/obese Asian and Hispanic patients with NAFLD remain to be determined.^{46,47} Our study showed that PNPLA3 GG genotype was associated with a higher incidence of liver cirrhosis, but not overall mortality or non-liver outcomes, in both obese and non-obese individuals. In addition, we found that PNPLA3 GG genotype was associated with a higher incidence of LREs in obese patients with NAFLD; the lack of association in non-obese patients may be related to the small number of events in lean NAFLD patients. A recent study from Sweden with 20 years follow-up also found that PNPLA3 GG genotype was associated with an increased risk of cirrhosis, but not mortality, compared with CC genotype among 546 imaging/biopsy-proven NAFLD patients (data for obese vs. non-obese patients was not provided).⁴⁸ Our study found that increasing BMI amplified the risk of PNPLA3 GG genotype (versus CC genotype), with the odds of cirrhosis of 3.2 among non-obese subjects, and 6.3 in obese NAFLD patients compared to lean patients, similar to findings from a study in

Denmark.⁴⁹ Our data suggest that future NAFLD treatment interventions should stratify for PNPLA3 genotype and therapies targeting PNPLA3 variant induced pathophysiology are needed particularly among obese patients who are at higher baseline risk.

This study has several strengths. First, we included a large number of patients with NAFLD, nearly 20,000 patients in the cross-sectional analysis and more than 13,000 in the longitudinal analysis. We applied minimal exclusion criteria to capture a largely unselected cohort with hepatic steatosis seen in our health system for a variety of reasons and did not limit the cohort to patients seen in specialist clinics or were selected for liver biopsy. Second, diagnosis of NAFLD used a validated natural language processing algorithm that relied primarily on imaging, rather than ICD codes or histology to minimize disease-spectrum bias. Third, access to medical history, laboratory, imaging, and histological data from medical records provided more in-depth clinical information that is not available in large insurance claims databases or national epidemiological databases. These detailed data also allowed us to adjust prevalence and incidence of outcomes for multiple confounding factors including host factors (age, sex, and race), behavioral risk factors (smoking and alcohol consumption), genetic risk factors, and metabolic risk factors (DM, hypertension, and dyslipidemia). Fourth, *PNPLA3* genotype data was available in a large number (3,039) patients allowing us to examine the effect of the GG variant on outcomes in obese vs. non-obese patients.

The current study also has limitations. First, this is a single tertiary referral center study in the U.S. with predominantly Caucasians and the data may not be generalized to other NAFLD populations. Of note, multiple epidemiological studies^{50,51} demonstrated that obese adults had worse survival than those with normal BMI. The finding of higher mortality in lean patients with

NAFLD in our study should be cautiously interpreted because it is a single-center study with potential for referral bias. Second, diagnosis of metabolic and cardiovascular diseases and causes of death were mainly based on ICD codes which may not be accurate though this approach is widely used in large cohort studies and population studies. Although we found 95% accuracy of causes of death, only 20 medical records were manually reviewed and the possibility of misclassification or misdiagnosis based on ICD codes cannot be excluded. We acknowledge that onset or severity of disease cannot be gleaned from ICD codes and that even though we adjusted for multiple major confounders that may affect the outcomes of interest, unmeasured confounders such as diet, body composition and physical activity were not available in this retrospective study. Third, most of our patients had initial diagnosis of NAFLD based on imaging suggesting that the diagnosis of NAFLD was incidental and their outcomes may be different from those who present with liver disease. Fourth, it is possible that some lean patients with NAFLD may have been previously overweight or obese but lost weight due to illnesses which led to worse outcomes (reverse causation) though we excluded patients with comorbidities that might cause significant weight changes such as baseline cancer or prior bariatric surgery. In addition, we performed sensitivity analyses for mortality adjusted for Charlson Comorbidity Index and still found significantly higher mortality in the lean group.

In conclusion, this study found that lean individuals with NAFLD in the U.S. had significantly higher mortality and higher prevalence of CVD and a trend toward a higher incidence of cancers compared with overweight or obese individuals with NAFLD despite a lower incidence of DM and cirrhosis. These findings emphasize that lean individuals with NAFLD merit the same attention in clinical practice as their overweight/obese counterparts. Further studies are

warranted to understand the pathogenic mechanisms of NAFLD in lean persons (such as genetic variants, distinct metabolomic profiles, body fat distribution, and sarcopenia) and the cause of increased mortality in these persons to design specific interventions to reverse the course and improve clinical outcomes.

Funding:

This research was supported by the American Association for the Study of Liver Diseases (AASLD) Advanced/Transplant Hepatology Fellowship Award, AASLD Clinical, Translational and Outcomes Research Award and an NIDDK K08 DK132312.

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Figure legends

Figure 1 Study flowchart

Figure 2 Cumulative incidence of death and diseases among NAFLD by BMI category

Figure 2A Cumulative incidence of death by BMI category

Figure 2B Cumulative incidence of type 2 diabetes mellitus by BMI category

Figure 2C Cumulative incidence of any cardiovascular disease by BMI category

Figure 2D Cumulative incidence of cirrhosis by BMI category

Figure 2E Cumulative incidence of any cancer by BMI category

Figure 2F Cumulative incidence of obesity-related cancer by BMI category

*Figure 2B-2F used competing risk analysis

Supplementary figure 1 Cumulative incidence of death in non-obese and obese patients with NAFLD

Supplementary figure 2 Cumulative incidence of death and diseases among NAFLD subgroup with no change in BMI category throughout the study period

Supplementary figure 2A Cumulative incidence of death by BMI category

Supplementary figure 2B Cumulative incidence of type 2 diabetes mellitus by BMI category

Supplementary figure 2C Cumulative incidence of any cardiovascular disease by BMI category

Supplementary figure 2D Cumulative incidence of cirrhosis by BMI category

Supplementary figure 2E Cumulative incidence of any cancer by BMI category

Supplementary figure 2F Cumulative incidence of obesity-related cancer by BMI category

*Supplementary figure 2B-2F used competing risk analysis

Supplementary figure 3 Cumulative incidence of death among never, former, and current

smokers by BMI category

Supplementary figure 3A Cumulative incidence of death among never smokers by BMI category

Supplementary figure 3B Cumulative incidence of death among former smokers by BMI category

Supplementary figure 3C Cumulative incidence of death among current smokers by BMI category

Table 1 Baseline characteristics, laboratory values, and prevalence of diseases among 18,594 patients with NAFLD^a

Characteristics	Lean (n = 2,137)	Non-lean (n = 16,457)			p Value (Lean vs non-lean)
		Overweight (n = 4,692)	Obesity class 1 (n = 5,234)	Obesity class 2-3 (n = 6,531)	
Age, years	51.0 (36, 63)	52.5 (41, 63)	52.0 (40, 61)	48.0 (37, 58)	0.70
Sex (male, %)	881 (41.2%)	2,574 (54.9%)	2,761 (52.8%)	2,551 (39.1%)	< 0.0001
Ethnicity, %					0.89
Asian	106 (5.0%)	375 (8.0%)	270 (5.2%)	161 (2.5%)	
African American	178 (8.3%)	323 (6.9%)	410 (7.8%)	664 (10.2%)	
Caucasian	1,724 (80.7%)	3,661 (78.0%)	4,227 (80.8%)	5,305 (81.2%)	
Other/Unknown	129 (6.0%)	333 (7.1%)	327 (6.3%)	401 (6.1%)	
Smoking, %					

Level	1,475 (69.0%)	3,283 (70.0%)	3,580 (68.4%)	4,508 (69.0%)	< 0.0001
Former	376 (17.6%)	1,016 (21.7%)	1,181 (22.6%)	1,420 (21.7%)	
Current	286 (13.4%)	393 (8.4%)	473 (9.0%)	603 (9.2%)	
T (U/L)	27 (18, 49)	36 (24, 59)	39 (26, 62)	38 (25, 61)	< 0.0001
T (U/L)	28 (22, 44)	30 (23, 42)	31 (24, 43)	30 (23, 44)	< 0.0001
Platelet (K/μL)	239 (192, 291)	236 (195, 283)	239 (197, 286) &	251 (206, 299)	0.01
A1c (%)	5.8 (5.4, 6.7)	5.8 (5.5, 6.5)	5.9 (5.5, 6.7)	6.1 (5.6, 7.2)	< 0.0001
Total Cholesterol (mg/dL)	173 (143, 210)	184 (155, 213)	180 (150, 212)	176 (148, 206)	0.003
LDL (mg/dL)	51 (38, 66)	45 (38, 55)	43 (36, 52)	42 (36, 50)	< 0.0001
HDL (mg/dL)	91 (66, 116)	101 (76, 125)	99 (75, 123)	95 (72, 119)	< 0.0001
Triglyceride (mg/dL)	125 (88, 189)	153 (107, 226)	163 (115, 240)	164 (119, 240)	< 0.0001
Rheiosis	27 (1.3%)	61 (1.3%)	77 (1.5%)	165 (2.5%)	0.07
Cardiovascular diseases					
Coronary artery disease	206 (9.6%)	562 (12.0%)	607 (11.6%)	660 (10.1%)	0.04
Chronic congestive heart failure	73 (3.4%)	158 (3.4%)	195 (3.7%)	268 (4.1%)	0.45
Cerebrovascular accident	135 (6.3%)	243 (5.2%)	266 (5.1%)	279 (4.3%)	0.003
Peripheral arterial disease	124 (5.8%)	249 (5.3%)	283 (5.4%)	267 (4.1%)	0.07
Any cardiovascular disease	370 (17.3%)	855 (18.2%)	965 (18.4%)	1,099 (16.8%)	0.65

Metabolic diseases					
Diabetes mellitus	288 (13.5%)	828 (17.7%)	1,138 (21.7%)	1,972 (30.2%)	< 0.0001
Hypertension	608 (28.5%)	1,689 (36.0%)	2,187 (41.8%)	3,042 (46.6%)	< 0.0001
Dyslipidemia	473 (22.1%)	1,626 (34.7%)	1,928 (36.8%)	2,195 (33.6%)	< 0.0001
Any metabolic disease	845 (39.5%)	2,467 (52.6%)	2,995 (57.2%)	3,933 (60.2%)	< 0.0001
CKD (stage 3-5)	261 (12.3%)	754 (16.3%)	867 (16.7%)	953 (14.7%)	< 0.0001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

^aData are expressed as median (interquartile range) for continuous variables or number (percentage) for categorical variables.

Table 2 Logistic regression analysis of factors associated with the prevalence of cardiovascular disease, cirrhosis, and chronic kidney disease

Any cardiovascular disease		Coronary artery disease		Peripheral artery disease		Cerebrovascular accident		Congestive heart failure		Cirrhosis		Chronic kidney disease
OR (95% CI) ^a	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)
Referent		Referent		Referent		Referent		Referent		Referent		Referent
0.88 (0.75-1.02)	0.08	0.91 (0.75-1.12)	0.38	0.73 (0.58-0.93)	0.01	0.68 (0.54-0.86)	0.001	0.76 (0.56-1.02)	0.07	0.96 (0.61-1.55)	0.87	1.09 (0.92-1.28)
0.75 (0.65-0.88)	<0.001	0.77 (0.63-0.94)	0.009	0.70 (0.56-0.89)	0.003	0.61 (0.48-0.77)	<0.001	0.76 (0.57-1.02)	0.06	1.04 (0.67-1.66)	0.86	1.13 (0.96-1.34)
0.77 (0.66-0.89)	<0.001	0.72 (0.59-0.87)	<0.001	0.58 (0.46-0.74)	<0.001	0.51 (0.40-0.64)	<0.001	0.88 (0.66-1.17)	0.36	1.66 (1.11-2.58)	0.02	1.22 (1.03-1.44)

Abbreviations: CI, confidence interval; OR, odds ratio.

^aOR was adjusted for age, sex, race, smoking status, type 2 diabetes, alcohol consumption, hypertension, dyslipidemia, and use of aspirin and statin.

Table 3 Competing risk analysis for death and incidence of diseases by BMI category^a

Weight category	Death ^b		Any cardiovascular diseases		Cirrhosis		Liver-related events		Type 2 Diabetes Mellitus ^c		Obesity-related cancer		Any Cancer	
	HR (95% CI)	<i>p</i> Value	HR (95% CI)	<i>p</i> Value	HR (95% CI)	<i>p</i> Value	HR (95% CI)	<i>p</i> Value	HR (95% CI)	<i>p</i> Value	HR (95% CI)	<i>p</i> Value	HR (95% CI)	<i>p</i> Value
Lean	Referent		Referent		Referent		Referent		Referent		Referent		Referent	
Overweight	0.54 (0.42-0.69)	< 0.001	1.40 (1.00-1.95)	0.051	1.53 (0.81-2.88)	0.19	1.08 (0.42-2.78)	0.88	1.22 (0.87-1.71)	0.25	0.87 (0.53-1.42)	0.58	0.76 (0.56-1.02)	0.07
Obesity class 1	0.40 (0.31-0.52)	< 0.001	1.08 (0.77-1.50)	0.66	1.50 (0.80-2.81)	0.20	0.77 (0.30-2.01)	0.60	1.78 (1.29-2.45)	< 0.001	0.97 (0.60-1.56)	0.90	0.75 (0.56-1.00)	0.049
Obesity class 2-3	0.52 (0.41-0.66)	< 0.001	1.27 (0.91-1.76)	0.15	2.19 (1.20-4.01)	0.011	1.15 (0.48-2.76)	0.76	2.85 (2.08-3.91)	< 0.001	1.02 (0.64-1.62)	0.93	0.78 (0.59-1.04)	0.09

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aHR was adjusted for age, sex, race, smoking status, alcohol consumption, type 2 diabetes mellitus, hypertension, dyslipidemia, and use of aspirin and statin.

^bCox proportional hazards model was performed for death analysis.

^cFor type 2 diabetes mellitus, HR was adjusted with the same confounders^a excluding type 2 diabetes mellitus.

Table 4 Causes of death of all deceased patients in each BMI group

Causes of death	Total (n = 616)	Lean (n = 111)	Non-lean (n = 505)			p Value (Lean vs non-lean)
			Overweight (n = 162)	Obesity 1 (n = 136)	Obesity 2-3 (n = 207)	
All death	616/13,420 (4.6%)	111/1,454 (7.6%)	162/3,373 (4.8%)	136/3,830 (3.6%)	207/4,763 (4.3%)	< 0.0001
Cardiovascular diseases	190 (30.8%)	29 (26.1%)	46 (28.4%)	45 (33.1%)	70 (33.8%)	0.24
Diabetes	103 (16.7%)	14 (12.6%)	31 (19.1%)	21 (15.4%)	37 (17.9%)	0.20
Gastrointestinal and liver cancers	33 (5.4%)	3 (2.7%)	7 (4.3%)	12 (8.8%)	11 (5.3%)	0.17
Other neoplasms^a	70 (11.3%)	11 (9.9%)	24 (14.8%)	9 (6.6%)	26 (12.6%)	0.59
Respiratory diseases	75 (12.2%)	17 (15.3%)	15 (9.3%)	18 (13.2%)	25 (12.1%)	0.26
Infective diseases	48 (7.8%)	11 (9.9%)	13 (8.0%)	8 (5.9%)	16 (7.7%)	0.36
Other diseases	33 (5.4%)	8 (7.2%)	8 (4.9%)	6 (4.4%)	11 (5.3%)	0.34
Gastrointestinal diseases other than cancers	15 (2.4%)	3 (2.7%)	5 (3.1%)	2 (1.5%)	5 (2.4%)	0.84
Unknown cause^b	45 (7.3%)	6 (5.4%)	19 (11.7%)	12 (8.8%)	8 (3.9%)	0.40

tal-neurological diseases	40 (6.5%)	9 (8.1%)	13 (8.0%)	8 (5.9%)	10 (4.8%)	0.45
abolic diseases ^c	36 (5.8%)	9 (8.1%)	6 (3.7%)	6 (4.4%)	15 (7.3%)	0.26
betes mellitus	7 (1.1%)	0 (0.0%)	2 (1.2%)	1 (0.7%)	4 (1.9%)	0.22
tious diseases	27 (4.4%)	6 (5.4%)	8 (4.9%)	3 (2.2%)	10 (4.8%)	0.56
tourinary diseases	25 (4.1%)	1 (0.9%)	4 (2.5%)	9 (6.62%)	11 (5.3%)	0.06
culoskeletal and connective e diseases	9 (1.5%)	3 (2.7%)	2 (1.2%)	3 (2.2%)	1 (1.5%)	0.23
r ^d	18 (2.9%)	6 (5.4%)	5 (3.1%)	3 (2.2%)	4 (1.9%)	0.09

Note: The cause of death was categorized based on the ICD-10-CM codes.

^aOther neoplasms refer to neoplasms that are other than digestive cancers, mainly including (1) C15-C26 Malignant neoplasms of digestive organs; (2) C30-C39 Malignant neoplasms of respiratory and intrathoracic organs; (3) C50-C50 Malignant neoplasms of breast; (4) C69-C72 Malignant neoplasms of eye, brain and other parts of central nervous system; (5) C81-C96 Malignant neoplasms of lymphoid, hematopoietic and related tissue; (6) D10-D36 Benign neoplasms, except benign neuroendocrine tumors; and (7) D37-D48 Neoplasms of uncertain behavior, polycythemia vera and myelodysplastic syndromes.

^bExternal cause comprises (1) S00-T88 Injury, poisoning and certain other consequences of external causes and (2) V00-Y99 External causes of morbidity.

^cMetabolic diseases refers to E00-E89 Endocrine, nutritional and metabolic diseases.

^dOther includes (1) D50-D89 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism; (2) Q00-Q99 Congenital malformations, deformations and chromosomal abnormalities and (3) R263 unknown.

Patients diagnosed with fatty liver disease from the University of Michigan Hospital between January 2012 and December 2021 (N = 52,556)

Exclusions (n = 33,962):

- Age < 18 or age > 80 yrs (n = 1,627)
- BMI < 18.5 kg/m² (n = 199)
- Cancer (other than non-melanoma skin cancer) diagnosed up to 1 year after first diagnosis of NAFLD (n = 8,535)
- Decompensated cirrhosis, including with ascites, esophageal varices, or hepatic encephalopathy (n = 1,247)
- Missingness of important information, including without race, BMI, AST, ALT, or PLT (n = 17,087)
- Other causes of liver disease (n = 4,577)
- Previous history of bariatric surgery (n = 550)
- Significant alcohol consumption (n = 690)

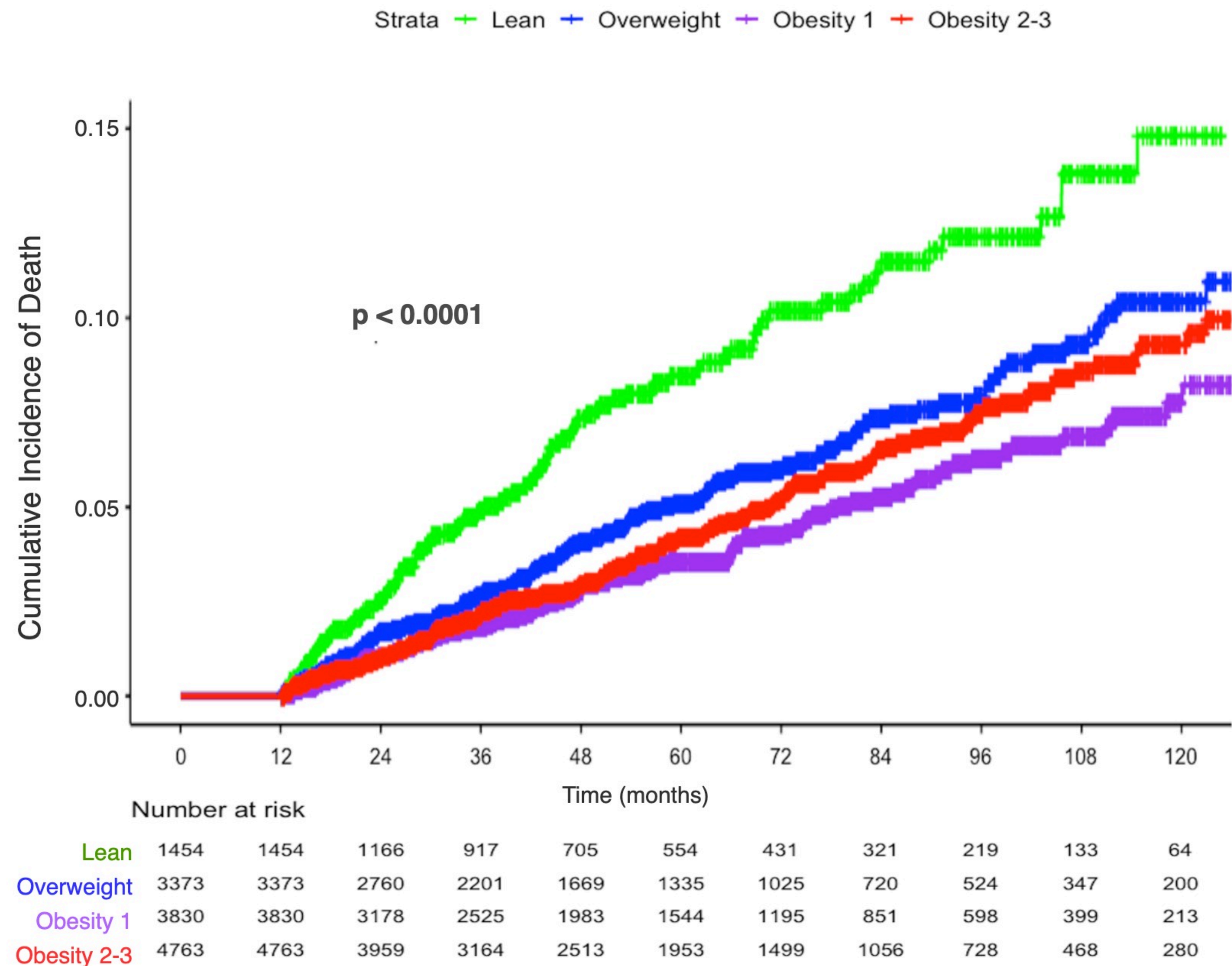
NAFLD participants included for ***the cross-sectional study*** (n = 18,594)

Exclusion:

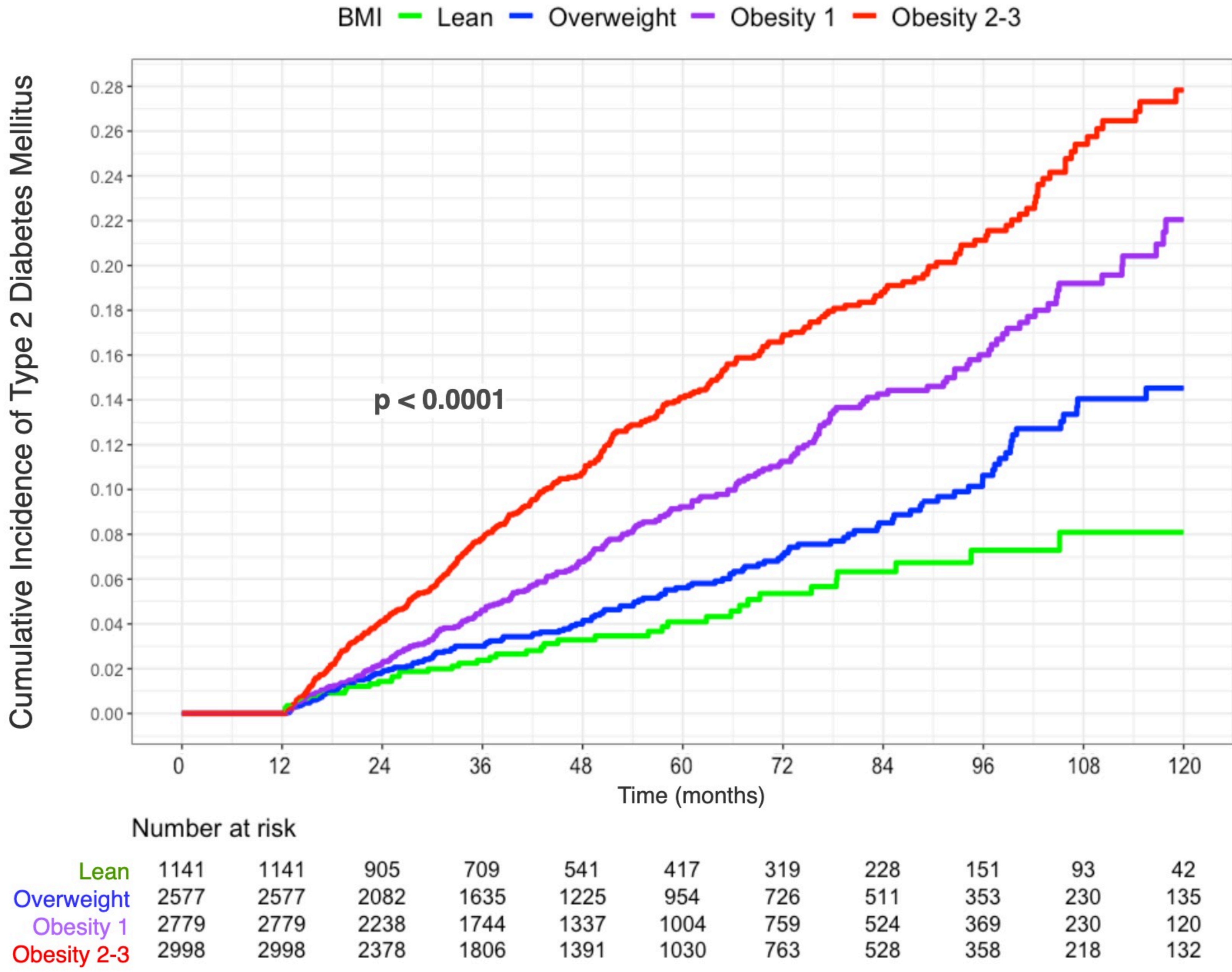
- Follow-up (from the first diagnosis of NAFLD to the last visit, or death, or study end date) < 365 days (n = 5,174)

NAFLD participants included for ***the longitudinal study*** (n = 13,420)

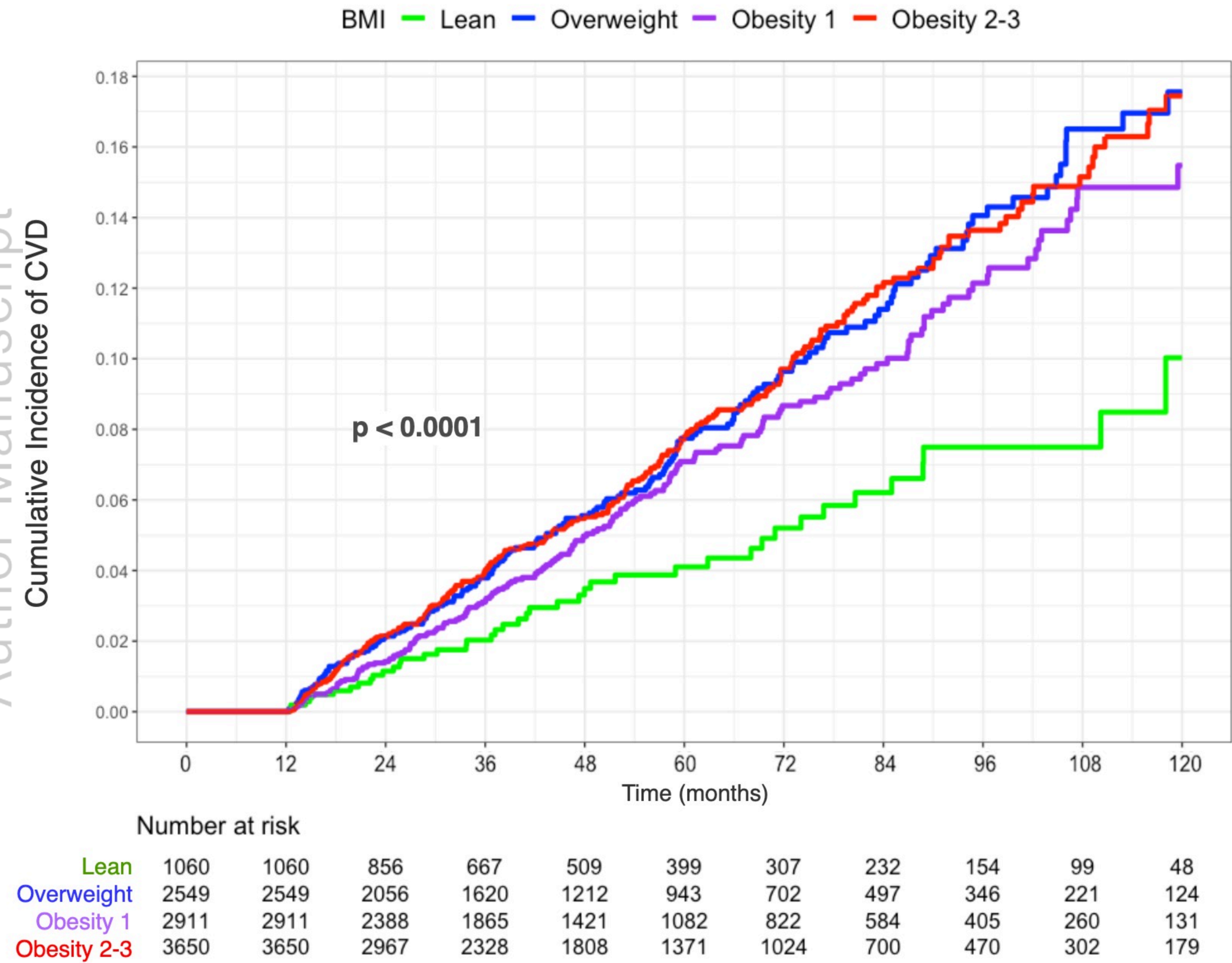
A. Survival Analysis of Overall Mortality by BMI Category



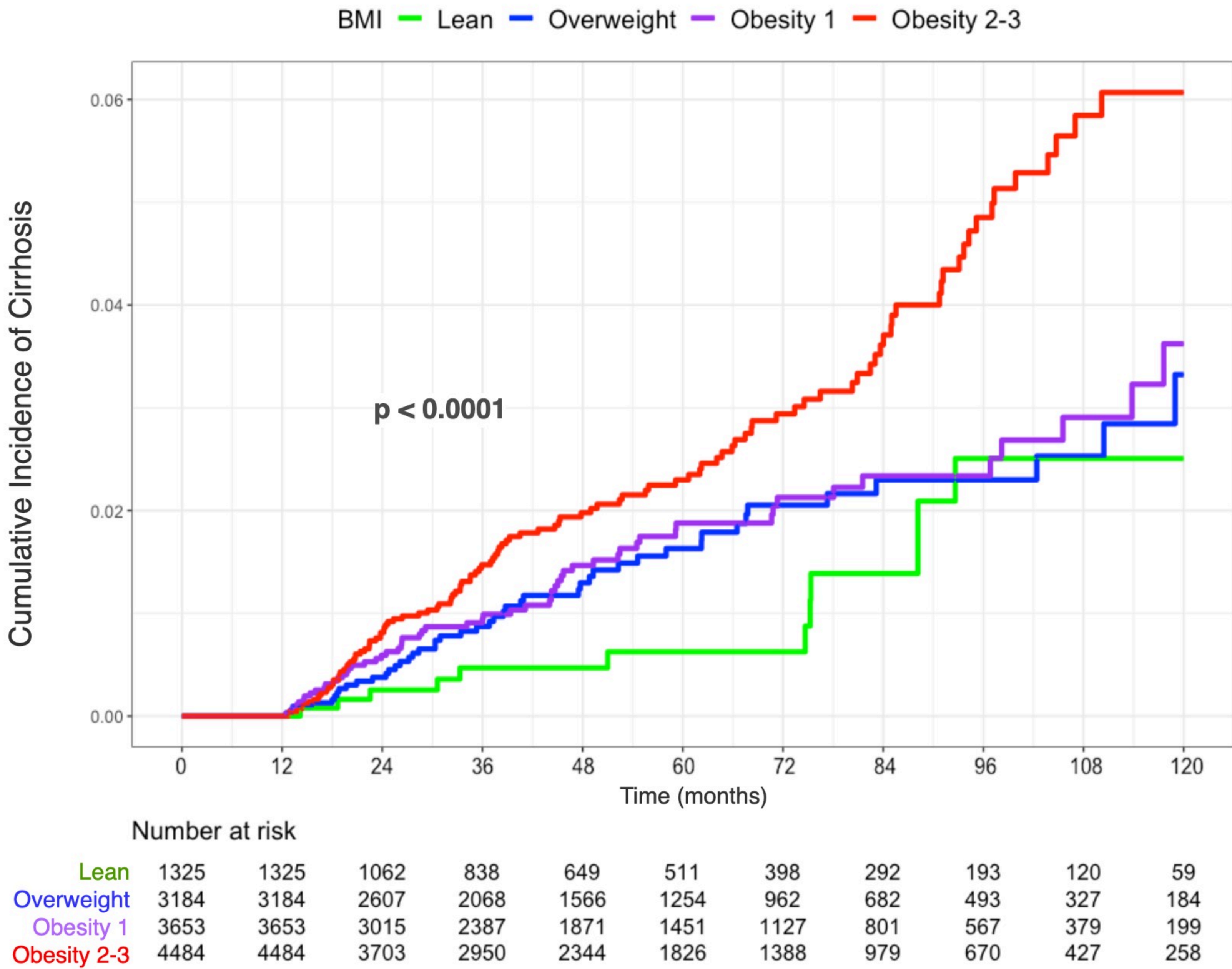
B. Competing Risk Analysis of Type 2 Diabetes Mellitus by BMI Category



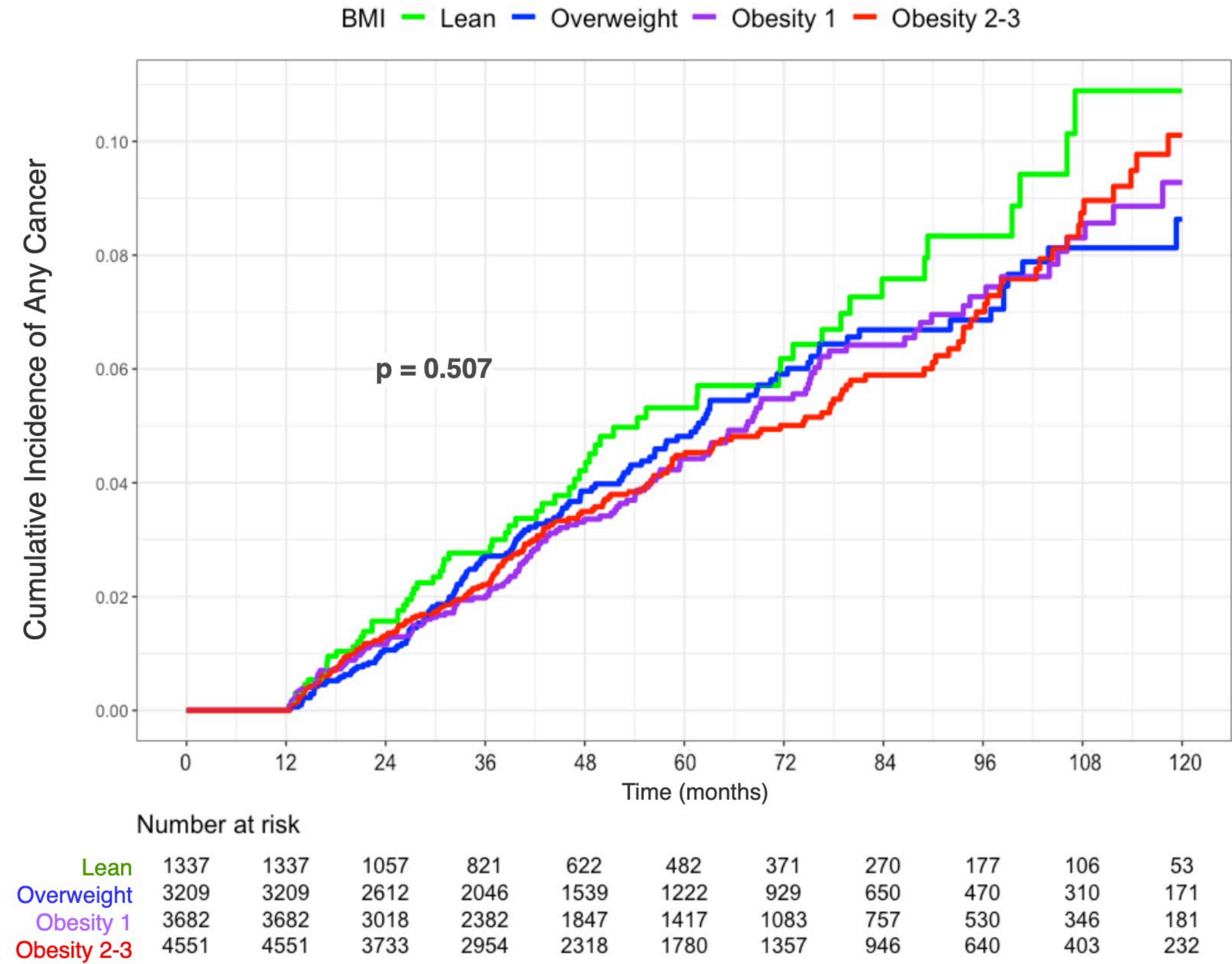
C. Competing Risk Analysis of Any CVD by BMI Category



D. Competing Risk Analysis of Cirrhosis by BMI Category



E. Competing Risk Analysis of Any Cancer by BMI Category



F. Competing Risk Analysis of Obesity-related Cancer by BMI Category

