# Effects of Alcohol Consumption and Metabolic Syndrome on Mortality in Patients With Nonalcoholic and Alcohol-Related Fatty Liver Disease

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**BACKGROUND & AIMS:** **Non-alcoholic and alcohol-related fatty liver disease are overlapping diseases in which metabolic syndrome and alcohol consumption each contribute to progressive liver disease. We aimed to assess the effects of alcohol consumption and metabolic syndrome on mortality in individuals with fatty liver.**

**METHODS:** **We searched the National Health and Nutrition and Examination Survey III for adults (20–74 years old) with hepatic steatosis, detected by ultrasound, for whom mortality and follow-up data were available. We collected data from the alcohol use questionnaire (self-reported number of days a participant drank alcohol; the number of drinks [10 g alcohol] per day on a drinking day; the number of days the participant had 5 or more drinks) and calculated the average amount of alcohol consumption in drinks/day for each participant during the year preceding enrollment. Excessive alcohol consumption for men was >3 drinks/day and for women was >1.5 drinks/day. We also collected clinical data, and mortality data were obtained from the National Death Index. Demographic and clinical parameters were compared among consumption groups using the $\chi^2$ test for independence or survey regression models. We used Cox proportional hazard models to identify independent predictors of all-cause and cause-specific mortality.**

*Abbreviations used in this paper:* AFLD, alcohol-related fatty liver disease; aHR, adjusted hazard ratio; CI, confidence interval; DM, type 2 diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey.


1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2018.11.033

Most current article

**RESULTS:** **The study cohort included 4264 individuals with hepatic steatosis (mean age, 45.9 years; 51% male; 76% white; 46% with metabolic syndrome; 6.2% with excessive alcohol use). There was no significant difference in mean age between individuals with vs without excessive alcohol consumption ($P$=.65). However, overall mortality was significantly higher among participants with excessive alcohol consumption (32.2%) vs participants with non-excessive alcohol use (22.2%) after mean 20 years of follow up ($P$=.003), as well as after 5 years of follow up. In multivariate analysis, the presence of metabolic syndrome (adjusted hazard ratio [aHR], 1.43; 95% CI, 1.12–1.83) and excessive alcohol consumption (aHR, 1.79; 95% CI, 1.21–2.66) were independently associated with an increased risk of death in individuals with hepatic steatosis; any lower average amount of alcohol consumption was not associated with mortality (all $P$>.60). In a subgroup analysis, the association of excessive alcohol use with mortality was significant in individuals with metabolic syndrome (aHR, 2.46; 95% CI, 1.40–4.32) but not without it ($P$=.74).**

**CONCLUSION:** **In review of data from the National Health and Nutrition and Examination Survey III, we associated alcohol consumption with increased mortality in participants with fatty liver and metabolic syndrome. These findings indicate an overlap between non-alcoholic and alcohol-related fatty liver disease.**

*Keywords:* Outcomes; Alcohol Abuse; Diabetes; NASH; Chronic Liver Disease.

Nonalcoholic fatty liver disease (NAFLD) is among the most common causes of chronic liver disease worldwide, with a global prevalence of 25%.[1] Given the epidemic of obesity and diabetes, it is estimated that by 2030, the prevalence of nonalcoholic steatohepatitis will increase by 60%–65% promoting development of nonalcoholic steatohepatitis–related advanced fibrosis, hepatocellular carcinoma, and liver-related deaths.[2] In the United States, NAFLD is already among the top causes of hepatocellular carcinoma and most common indications for liver transplantation.[3–5] In addition to those adverse clinical consequences, NAFLD is associated with a tremendous economic burden[6] and can cause substantial negative impact on patient-reported outcomes.[7]

Alcohol-related fatty liver disease (AFLD) is another important cause of chronic liver disease with a prevalence of 2.0%–2.5% in the U.S. population.[8] The population-based data from the United States suggest that the prevalence of alcohol-related liver disease increased from the early 1990's and remained stable over the 2000s.[9] The reported rates of progression to cirrhosis for patients with alcohol-related hepatitis and AFLD can range from 3% to 12% per year.[10–12] In turn, this progression to cirrhosis is associated with increased mortality; in a longitudinal study of Danish individuals with AFLD (1999–2008), 5-year and 10-year overall mortality rates were 56% and 72% and were significantly increased in patients with cirrhosis.[13]

In the modern diagnostic criteria, the difference between AFLD and NAFLD is determined exclusively by the amount of alcohol consumption considered excessive to the point that it would affect patients' prognosis. As a result, patients may get different diagnoses and end up being treated differently based solely on the alcohol use. In this context, the amount of alcohol consumption which would be detrimental for patients with fatty liver disease is not well described. Indeed, while some studies have suggested protective effects of moderate alcohol use,[14–16] others reported increased risks of moderate or excessive use in the presence or regardless of the presence of metabolic syndrome.[17,18] Our aim was to assess the impact of both alcohol consumption and metabolic syndrome to mortality of individuals with fatty liver disease enrolled in a population-based cohort with 2 decades of mortality follow-up.

## Materials and Methods

### Data Source

For this study, we used the National Health and Nutrition Examination Survey III (NHANES III) data which is a publicly available data collection. The NHANES III is a nationwide survey, spanning the period from 1988 to 1994, originally designed to obtain information regarding the health and nutritional status of the U.S. population. The survey consisted of interviews regarding participants' demographics, socioeconomic status, personal history, diet, and health, standardized physical examinations, the data from blood and urine samples, and other specific tests such as hepatic ultrasound.[19] After applying sampling weights calculated for each NHANES participant, the sample is representative of the U.S. population.

### Study Definitions

The presence of hepatic steatosis was ascertained using the data from hepatobiliary ultrasound tests conducted in a majority of NHANES III participants of 20–74 years of age. Only participants with fatty liver

disease (at least mild steatosis on an ultrasound) were included in this study. Participants who had evidence of other causes of chronic liver disease (positive hepatitis B surface antigen or hepatitis C antibody, transferrin saturation of 50% of greater, the use of steatogenic drugs such as corticosteroids or anabolic steroids) were excluded.

Using the data from the universally administered alcohol use questionnaire (self-reported number of days a participant drank alcohol; the number of drinks/d on a drinking day; the number of days the participant had 5 or more drinks; recall period 12 months), we calculated the average amount of alcohol consumption in drinks/day for each participant during the year preceding enrollment to NHANES; a drink was equivalent to 10 g of alcohol (or, per NHANES guidelines for participants, a 12-oz beer, a 4-oz glass of wine, or an ounce of liquor).[20] That average amount was used to group participants into 5 mutually exclusive groups: zero alcohol consumption, minimal alcohol consumption (>0 but <3 drinks/wk for men), moderate alcohol consumption (>3 drinks/wk but <2 drinks/d for men), substantial alcohol consumption (>2 but <3 drinks/d for men), and excessive alcohol consumption (more than >3 drinks/d for men); the respective amounts for women were half as much. The definition of excessive alcohol use was based on the recent exclusionary criteria for NAFLD.[21] In addition, we separately assessed the impact of the number of binge drinking days, which was the number of days a participant reported having had 5 or more drinks.

In addition, obesity was defined as a body mass index of 30 kg/m$^2$ or greater; visceral obesity was defined as waist circumference of 102 cm or greater in men, 88 cm or greater in women. Type 2 diabetes mellitus (DM) was defined as fasting glucose level of 126 mg/dL or higher or the use of oral hypoglycemics or insulin. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher, or having a history of the diagnosis and being on oral antihypertensive medications. Similarly, hypercholesterolemia was defined as total cholesterol level of 200 mg/dL or higher, low-density lipoprotein of 130 mg/dL or higher, or high-density lipoprotein lower than 40 mg/dL in men and 50 mg/dL in women. Criteria for metabolic syndrome were as defined by the National Cholesterol Education Program Adult Treatment Panel III.[22] Elevated liver enzymes were defined as alanine aminotransferase higher than 40 U/L or aspartate aminotransferase higher than 37 U/L in men and alanine aminotransferase or aspartate aminotransferase higher than 31 U/L in women. The presence of fibrosis was estimated using Fibrosis-4 scheme[23]; those with Fibrosis-4 score ≥2.67 were considered to have significant hepatic fibrosis.

Mortality status of NHANES III participants was obtained from the National Death Index–linked data file which was updated through December 31, 2011.

## What You Need to Know

### Background

In patients with hepatic steatosis, metabolic disorder and alcohol use could contribute to adverse outcomes. The exact amount of safe alcohol use, if any, is not known.

### Findings

In participants with fatty liver disease detected by ultrasound, excessive alcohol use was associated with increased overall and cause-specific mortality. The cutoff for harmful excessive use was lower in individuals with metabolic syndrome, increased levels of liver enzymes, and in female patients.

### Implications for patient care

Patients with fatty liver should abstain from excessive alcohol use—especially if they have developed metabolic syndrome or liver dysfunction.

### *Statistical Analysis*

Demographic and clinical parameters of NHANES III participants with fatty liver disease were compared between the 5 alcohol consumption groups using Rao-Scott (design-adjusted) chi-square test for independence or survey regression models. The survey Cox proportional hazard models were used to identify independent predictors of all-cause and cause-specific mortality; potential predictors included age, sex, ethnicity, smoking status, education, income, metabolic syndrome or its components, and the average amount of alcohol consumption. In addition, the number of binge drinking days in the year preceding enrollment was tested as a predictor of mortality with adjustment for the average amount of alcohol consumption; the aim was to find the minimal number of binge drinking days that would return a significant association with increased mortality ($P < .05$).

Provided examination sampling weights were applied to adjust for enrollment and nonresponse bias, and stratum and sampling units were used to account for the survey design. All analyses were run using SAS 9.4 (SAS Institute, Cary, NC). The study was approved by Inova Institutional Review Board.

## Results

### *Patient Population*

A total of 20,500 adult subjects were included in NHANES III; of those, 13,852 had hepatobiliary ultrasound, and 4800 had mild, moderate, or severe steatosis on it. After exclusion of those with other causes of chronic liver disease, 4264 individuals with fatty liver disease (weighted proportion 29.2% of all who had

**Table 1.** NHANES Participants With Hepatic Steatosis by Their Average Alcohol Consumption

| | Zero alcohol use | Minimal use (>0 and ≤3 drinks/wk for men) | Moderate use (>3 drinks/wk and ≤2 drinks/d for men) | Substantial use (>2 and ≤3 drinks/d for men) | Excessive use (>3 drinks/d for men) | *P* | All steatosis |
|---|---|---|---|---|---|---|---|
| Sample | 2369 (47.0) | 790 (22.8) | 717 (20.1) | 158 (3.9) | 230 (6.2) | | 4264 |
| Drinks/d | 0.00 ± 0.00 | 0.15 ± 0.01 | 0.89 ± 0.03 | 2.21 ± 0.08 | 4.28 ± 0.17 | 0 | 0.56 ± 0.05 |
| Age, *y* | 48.53 ± 0.55 | 43.09 ± 0.76 | 43.36 ± 1.05 | 43.63 ± 1.41 | 45.14 ± 1.34 | .0018 | 45.85 ± 0.42 |
| Male | 38.5 | 61.2 | 62.0 | 70.6 | 62.3 | <.0001 | 51.1 |
| White | 71.0 | 79.1 | 81.3 | 77.6 | 83.2 | <.0001 | 75.9 |
| Black | 11.1 | 6.6 | 7.4 | 7.1 | 7.4 | <.0001 | 8.9 |
| Hispanic | 7.4 | 6.2 | 5.7 | 6.0 | 6.0 | .1526 | 6.6 |
| BMI, $kg/m^2$ | 30.00 ± 0.35 | 29.16 ± 0.28 | 27.26 ± 0.35 | 27.66 ± 0.66 | 28.08 ± 0.41 | <.0001 | 29.05 ± 0.25 |
| Waist circumference, *cm* | 100.23 ± 0.84 | 98.26 ± 0.69 | 94.34 ± 0.93 | 95.54 ± 1.95 | 96.98 ± 1.10 | <.0001 | 98.21 ± 0.62 |
| Obesity | 45.7 | 41.1 | 25.2 | 29.3 | 33.4 | <.0001 | 39.1 |
| Visceral obesity | 65.4 | 56.2 | 40.1 | 35.4 | 50.3 | <.0001 | 56.1 |
| Type 2 diabetes | 18.0 | 8.5 | 5.1 | 6.0 | 9.6 | <.0001 | 12.2 |
| Hypercholesterolemia | 83.7 | 77.5 | 65.8 | 79.3 | 67.3 | <.0001 | 77.5 |
| Hypertension | 35.1 | 24.1 | 26.9 | 46.5 | 38.1 | <.0001 | 31.6 |
| Metabolic syndrome | 54.4 | 45.1 | 32.5 | 40.3 | 34.2 | <.0001 | 46.0 |
| History of congestive heart failure | 3.5 | 1.3 | 2.2 | 2.4 | 0.1 | .0055 | 2.5 |
| History of stroke | 3.1 | 0.7 | 1.2 | 0.0 | 0.5 | 1.00 | 1.9 |
| Current smoker | 19.3 | 25.1 | 33.6 | 36.0 | 43.3 | <.0001 | 25.6 |
| High school graduate | 66.7 | 82.9 | 78.9 | 82.1 | 72.8 | <.0001 | 73.8 |
| Family income <$20,000 | 39.9 | 21.1 | 25.6 | 29.8 | 38.1 | <.0001 | 32.2 |
| Fibrosis by FIB-4 score | 1.3 | 0.8 | 1.2 | 3.8 | 6.2 | .0004 | 1.5 |
| Elevated liver enzymes | 12.6 | 11.6 | 10.1 | 22.3 | 23.9 | .005 | 12.9 |
| Died in follow-up | 27.0 | 16.6 | 18.1 | 19.2 | 32.2 | <.0001 | 22.8 |
| Died of cardiovascular causes | 6.4 | 3.0 | 3.5 | 7.9 | 7.4 | .0305 | 5.2 |
| Died of cancer | 7.1 | 3.7 | 4.3 | 2.6 | 12.1 | <.0001 | 5.9 |
| Died of cerebrovascular causes | 1.3 | 0.6 | 0.8 | 0.4 | 2.8 | .24 | 1.1 |
| 5-y mortality | 4.3 | 1.9 | 2.5 | 2.7 | 2.9 | .09 | 3.2 |
| 10-y mortality | 10.5 | 5.8 | 4.7 | 8.2 | 13.0 | .0015 | 8.3 |
| 15-y mortality | 17.3 | 11.1 | 11.2 | 10.1 | 24.9 | <.0001 | 14.9 |

NOTE. Values are n (%), mean ± SE, or %. For women, the thresholds were half of those for men.
BMI, body mass index; FIB-4, Fibrosis-4; NHANES, National Health and Nutrition Examination Survey.

hepatic ultrasound) comprised the study cohort (Supplementary Figure 1).

### Demographic and Clinical Data

Subjects with fatty liver disease were, on average, 46 years of age, and 51% were men, 76% were white, 9% were black, 39% were with obesity, 56% were with visceral obesity, 12% were had DM, 46% had metabolic syndrome, and 1.5% had fibrosis. In addition, 47.0% reported zero alcohol use, and 22.8% reported minimal, 20.1% moderate, 3.9% substantial, and 6.2% excessive alcohol use. Participants who reported zero alcohol use were, on average, older, predominantly female, less likely to be white, reported less smoking, and had more metabolic syndrome (54%) and some of its components such as obesity and DM ($P < .01$) (Table 1). In contrast, participants who reported excessive alcohol use were more likely men, reported the highest rate of smoking and the highest prevalence of elevated liver enzymes and fibrosis ($P < .05$) (Table 1).

### Mortality Follow-Up

In follow-up (mean cohort duration 20 years), 22.8% of the study participants died, with the highest crude mortality rate observed in the group who consumed excessive amounts of alcohol (32.2% vs mean 22.2% in the rest of the sample; $P = .0029$) (Table 1). The rate remained the highest after adjustment for age (using U.S. Census 2000 data),[24] especially after 5 years of follow-up (Figure 1).

In multivariate analysis, in addition to older age, male sex, and smoking, both the presence of metabolic syndrome (adjusted hazard ratio [aHR], 1.43; 95% confidence interval, 1.12–1.83) and excessive alcohol consumption (aHR, 1.79; 95% confidence interval, 1.21–2.66) were independently associated with increased mortality in individuals with fatty liver disease (both $P < .005$). In contrast, any lower threshold for alcohol consumption did not show such association (all $P > .60$) (Table 2). There was also no association with the severity of steatosis ($P > .20$ for both moderate and severe steatosis parameters).

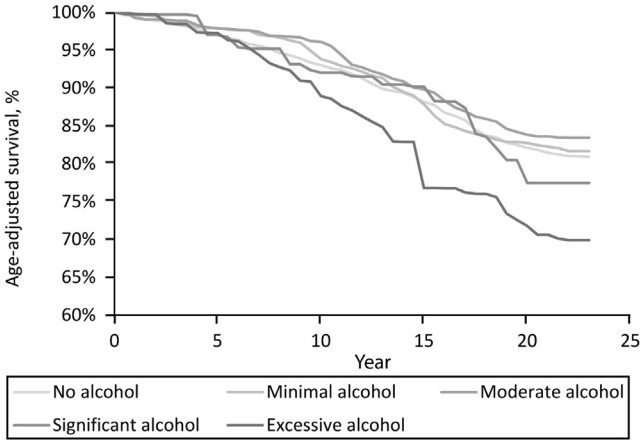


**Figure 1.** Survival of National Health and Nutrition Examination Survey participants with steatosis by their alcohol use (adjusted for age using U.S. Census 2000 data).

**Table 2.** Independent Predictors of Mortality in NHANES Participants With Steatosis With Metabolic Syndrome, Components of Metabolic Syndrome, and Metabolic Syndrome Interacted With the Amount of Alcohol Consumption

| Predictor | aHR (95% CI) | *P* |
|---|---|---|
| Metabolic syndrome | | |
| Metabolic syndrome | 1.43 (1.12–1.83) | .0049 |
| Minimal alcohol use[a] | 0.94 (0.70–1.27) | .69 |
| Moderate alcohol use | 0.91 (0.63–1.31) | .60 |
| Substantial alcohol use | 0.95 (0.43–2.11) | .89 |
| Excessive alcohol use | 1.79 (1.21–2.66) | .0046 |
| Age, per year | 1.09 (1.08–1.10) | <.0001 |
| Male | 1.37 (1.16–1.63) | .0005 |
| Black | 1.04 (0.83–1.32) | .71 |
| Hispanic | 0.76 (0.61–0.93) | .01 |
| Current smoking | 2.05 (1.58–2.66) | <.0001 |
| High school graduate | 0.84 (0.66–1.06) | .14 |
| Family income <$20,000 | 1.39 (1.11–1.74) | .0048 |
| Components of metabolic syndrome | | |
| Minimal alcohol use[a] | 0.92 (0.71–1.18) | .50 |
| Moderate alcohol use | 0.92 (0.67–1.25) | .57 |
| Substantial alcohol use | 0.91 (0.44–1.90) | .81 |
| Excessive alcohol use | 1.64 (1.18–2.27) | .0040 |
| Age, per year | 1.09 (1.08–1.10) | <.0001 |
| Male | 1.37 (1.19–1.58) | <.0001 |
| Black | 1.02 (0.82–1.26) | .86 |
| Hispanic | 0.73 (0.59–0.89) | .0028 |
| Obesity | 1.07 (0.89–1.28) | .46 |
| Type 2 diabetes | 2.11 (1.74–2.57) | <.0001 |
| Hypercholesterolemia | 0.98 (0.76–1.28) | .90 |
| Hypertension | 1.35 (0.99–1.82) | .05 |
| Current smoking | 2.11 (1.68–2.64) | <.0001 |
| High school graduate | 0.90 (0.72–1.12) | .34 |
| Family income <$20,000 | 1.46 (1.17–1.82) | .0014 |
| Metabolic syndrome interacted with alcohol consumption amount | | |
| Metabolic syndrome | 1.31 (0.94–1.84) | .11 |
| Minimal alcohol use[a] | 1.17 (0.70–1.95) | .53 |
| Moderate alcohol use | 0.73 (0.45–1.19) | .20 |
| Substantial alcohol use | 0.90 (0.41–1.97) | .79 |
| Excessive alcohol use | 1.15 (0.71–1.86) | .56 |
| Minimal alcohol use —interaction with metabolic syndrome | 0.69 (0.39–1.25) | .22 |
| Moderate alcohol use —interaction with metabolic syndrome | 1.46 (0.86–2.47) | .16 |
| Substantial alcohol use —interaction with metabolic syndrome | 1.06 (0.32–3.46) | .92 |
| Excessive alcohol use —interaction with metabolic syndrome | 2.14 (1.02–4.48) | .0436 |
| Age, per year | 1.09 (1.08–1.11) | <.0001 |
| Male | 1.38 (1.17–1.63) | .0003 |
| Black | 1.03 (0.82–1.30) | .78 |
| Hispanic | 0.75 (0.61–0.93) | .0110 |
| Current smoking | 2.07 (1.59–2.69) | <.0001 |
| High school graduate | 0.84 (0.67–1.06) | .14 |
| Family income <$20,000 | 1.37 (1.09–1.72) | .0077 |

aHR, adjusted hazard ratio; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey.
[a]Reference: zero alcohol use.

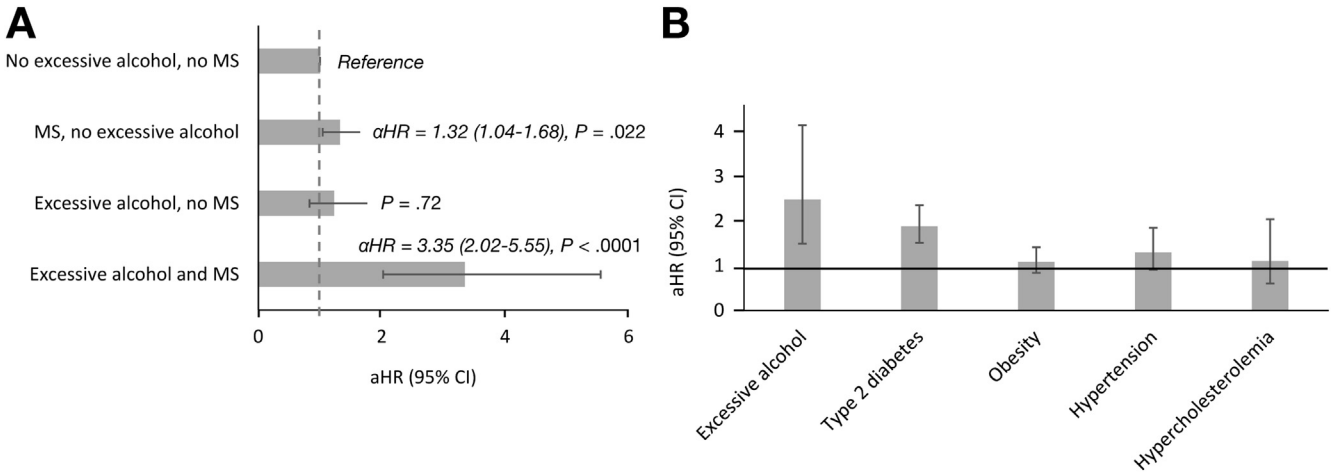


**Figure 2.** (*A*) Adjusted hazard ratios for overall mortality in patients with fatty liver disease; (*B*) independent predictors of mortality in patients with fatty liver disease and metabolic syndrome (MS). aHR, adjusted hazard ratio; CI, confidence interval.

### *Mortality and Metabolic Syndrome*

Among individual components of metabolic syndrome, only DM was found to be significantly associated with increased mortality (aHR, 2.11; 95% confidence interval, 1.74–2.57; $P < .0001$). Although the presence of hypertension trended to be associated with mortality, it did not reach statistical significance in this study (aHR, 1.35; 95% confidence interval, 0.99–1.82; $P = .055$) (Table 2).

With the addition of metabolic syndrome vs alcohol consumption interaction terms, only interaction of metabolic syndrome with excessive alcohol consumption was statistically significant (aHR, 2.14; 95% confidence interval, 1.02–4.48; $P = .044$) (Table 2).

This observation suggests that the effect of excessive alcohol consumption might vary significantly based on the presence of metabolic syndrome. To further assess this relationship, we conducted 2 subgroup analyses to predict mortality in participants with and without metabolic syndrome separately. In participants with fatty liver disease and metabolic syndrome, only excessive alcohol consumption (aHR, 2.46; 95% confidence interval, 1.40–4.32; $P = .0023$) (Figure 2B) but not any lower amount (all $P > .30$) was associated with increased mortality (Table 3). In contrast, in participants with fatty liver disease who did not have metabolic syndrome, even excessive alcohol consumption as defined in this study was not predictive of mortality (all $P > .10$) (Table 3B). This translated into the aHR for having both metabolic syndrome and excessive alcohol consumption vs having neither being 3.35 (95% confidence interval, 2.02–5.55; $P < .0001$) (Figure 2A). In this context, the effect of metabolic syndrome on mortality (aHR) was also stronger in patients with substantial or excessive alcohol use than in other patients: 2.25 (95% CI, 1.27–4.00) vs 1.31 (95% CI, 1.03–1.67) (both $P < .05$).

For the purpose of comprehensive understanding of the effect of metabolic syndrome and alcohol use and their interaction on mortality, we attempted to search for a potentially higher threshold for alcohol use which would be associated with mortality in patients with fatty liver even in the absence of metabolic syndrome. In this context, we found a borderline significant evidence of such association starting at 6 and 3 drinks/d for men and women, respectively (aHR, 2.64; 95% confidence interval, 0.99–7.06; $P = .054$), although accompanied by a limited sample size: the proportion of participants meeting this threshold of alcohol consumption was only 0.6%.

### *Mortality in Individuals With Nonzero Alcohol Use*

As the group of participants who report zero alcohol use might be biased because it likely included patients who had chosen or been advised to abstain from alcohol owing to pre-existing health conditions (as supported by higher rates of comorbidities in that group) (Table 1), we also ran the regression models reported above with the minimal alcohol use group used as a reference. All reported associations of excessive alcohol use with mortality were reproduced with greater effect magnitudes (aHR, 1.95; 95% confidence interval, 1.30–2.93; $P = .0018$ with adjustment for metabolic syndrome [Table 2]; aHR, 1.83; 95% confidence interval, 1.29–2.60; $P = .0011$ with adjustment for metabolic syndrome components [Table 2]; aHR, 3.13; 95% confidence interval, 1.44–6.80; $P = .0047$ for interaction of metabolic syndrome with excessive alcohol consumption [Table 2]; aHR, 3.30; 95% confidence interval, 1.81–6.02; $P = .0002$ for patients with metabolic syndrome [Table 3] and $P = .60$ for patients without metabolic syndrome [Table 3]).

### *Mortality and Alcohol Use in Clinical Subgroups*

Subgroups analyses of individuals of different sex with and without elevated liver enzymes or fibrosis suggested that in women and those with abnormal liver tests, the association of alcohol use with mortality may

**Table 3.** Independent Association of Alcohol Consumptions in NHANES Participants With and Without Metabolic Syndrome

| Predictor | aHR (95% CI) | *P* |
|---|---|---|
| Subjects with metabolic syndrome | | |
| Minimal alcohol use[a] | 0.85 (0.62–1.17) | .31 |
| Moderate alcohol use | 1.13 (0.75–1.70) | .55 |
| Substantial alcohol use | 1.06 (0.37–3.04) | .91 |
| Excessive alcohol use | 2.46 (1.40–4.32) | .0023 |
| Age, per year | 1.08 (1.06–1.11) | <.0001 |
| Male | 1.32 (1.04–1.68) | .0246 |
| Black | 0.87 (0.66–1.15) | .33 |
| Hispanic | 0.81 (0.62–1.07) | .13 |
| Obesity | 1.11 (0.85–1.43) | .44 |
| Type 2 diabetes | 1.89 (1.51–2.37) | <.0001 |
| Hypercholesterolemia | 1.11 (0.60–2.07) | .74 |
| Hypertension | 1.27 (0.91–1.78) | .15 |
| Current smoking | 2.09 (1.47–2.99) | .0001 |
| High school graduate | 0.86 (0.66–1.11) | .23 |
| Family income <$20,000 | 1.32 (1.02–1.71) | .0330 |
| Subjects without metabolic syndrome | | |
| Minimal alcohol use[a] | 1.22 (0.74–2.03) | .43 |
| Moderate alcohol use | 0.72 (0.45–1.13) | .15 |
| Substantial alcohol use | 0.83 (0.36–1.92) | .66 |
| Excessive alcohol use | 1.09 (0.66–1.80) | .74 |
| Age, per year | 1.09 (1.07–1.11) | <.0001 |
| Male | 1.44 (0.99–2.09) | .06 |
| Black | 1.07 (0.69–1.65) | .77 |
| Hispanic | 0.59 (0.38–0.91) | .0182 |
| Obesity | 0.76 (0.46–1.26) | .28 |
| Type 2 diabetes | 1.55 (0.81–2.97) | .18 |
| Hypercholesterolemia | 0.84 (0.59–1.21) | .35 |
| Hypertension | 1.26 (0.81–1.98) | .30 |
| Current smoking | 2.19 (1.50–3.21) | .0001 |
| High school graduate | 0.92 (0.60–1.40) | .70 |
| Family income <$20,000 | 1.57 (1.18–2.09) | .0023 |

aHR, adjusted hazard ratio; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey.
[a]Reference: zero alcohol use.

start at lower thresholds such as substantial non-excessive use; those trends, however, did not reach the statistical significance threshold in either group ($P$ = .05–.10) (Supplementary Table 1).

### *Cause-Specific Mortality and Alcohol*

In a separate round of survival analysis, we have studied cause-specific mortality, in particular, cardiovascular, cancer-related, and cerebrovascular diseases (other causes of death returned less than 50 events in the sample). Of these, only cancer mortality was found to be associated with excessive alcohol consumption (aHR, 2.13; 95% confidence interval, 1.26–3.62; $P$ = .0060 with adjustment for metabolic syndrome; aHR, 3.04; 95% confidence interval, 1.24–7.46; $P$ = .0163 in patients with metabolic syndrome, $P$ = .28 in patients without metabolic syndrome). Similar associations with cardiovascular mortality suggested a trend in the entire sample ($P$ = .15) and was significant in patients with metabolic syndrome (aHR, 2.41; 95% confidence interval, 1.10–5.29; $P$ = .029). Similarly to overall mortality, no such associations were found with lower amounts of alcohol use (all $P$ > .10).

### *Mortality and Binge Drinking*

Finally, we also assessed the minimum number of binge drinking days per year that would be significantly associated with increased mortality. For this purpose, we ran a series of survival models which included adjustment for age, sex, ethnicity, smoking, the presence of metabolic syndrome and the average amount of daily alcohol use. In this case, subjects with fatty liver disease who had binge drinking for at least 13 days/y had a significantly increased risk of mortality (aHR, 1.49; 95% confidence interval, 1.01–2.21; $P$ = .046) (Figure 3). Notably, the adjusted hazard ratio additionally increased to ≥1.70 if binge drinking increased to more than 20 days/y (Figure 3). There was no evidence of association of this relationship with metabolic syndrome ($P$ = .30 for the interaction term).

## Discussion

Fatty liver disease is a highly prevalent condition affecting about one-third of the U.S. population. Although fatty liver can be caused by a number of underlying etiologies, the predominant cause of fatty liver are metabolic syndrome or alcohol consumption. In this study, we attempted to investigate the effect of alcohol consumption and components of metabolic syndrome, as well as and their overlap, on the long-term outcomes of patients with fatty liver disease in the United States.

Our data show that in subjects with fatty liver, excessive alcohol consumption is associated with increased mortality, both crude and age-adjusted rates. Notably, while the accepted definition of NAFLD requires that daily alcohol consumption should be less than 20 g/d for men

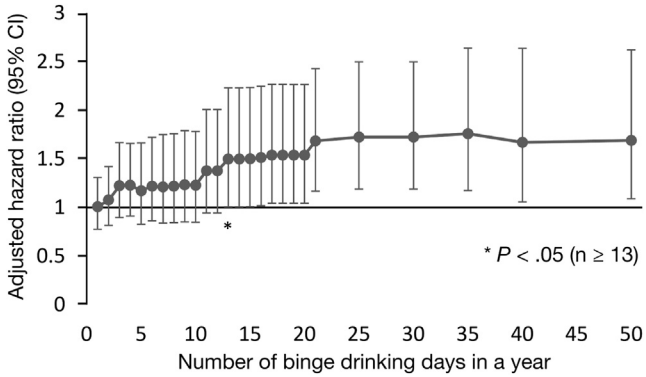


**Figure 3.** Independent association of the number of binge drinking days per year with mortality in National Health and Nutrition Examination Survey participants with steatosis (adjusted for age, sex, race, smoking, metabolic syndrome components and mean daily amount of alcohol use; a binge drinking day is a day with consumption of 5 or more drinks).

and less than 10 g/d for women, there is still some controversy regarding this particular threshold. In this study, the association of alcohol consumption with mortality in patients with fatty liver was not observed below 30 g/d of alcohol consumption for men, half as much for women. Other predictors of mortality in individuals with fatty liver disease included older age, male sex, smoking, and DM, all consistent with prior reports for this patient population.[25,26]

In addition, our results suggest that the harmful impact of excessive alcohol consumption defined at the level of 3 drinks/d is manifested primarily in the presence of metabolic syndrome while in the absence of metabolic syndrome, a similar association is not observed until the consumption of alcohol increases to at least 6 drinks/d for men, 3 drinks/d for women. Although it is likely that our sample was not large enough to capture milder effects which could still exist for lower amounts of alcohol in both patient groups, significant interaction between the amount of alcohol use and the presence of metabolic syndrome provides evidence for substantial overlap between the AFLD and NAFLD patient populations. It is also important to note that that interaction seems to go both ways (ie, not only did a lower amount of alcohol become harmful in the presence of metabolic syndrome, but also the risk associated with having metabolic syndrome was higher in the setting of substantial or excessive alcohol use).

In addition to harmful effects of chronic excessive alcohol use, our data show that binge drinking is additionally associated with mortality even with adjustment for average daily consumption. In this study, the association became significant at 13 days of binge drinking per year. It is, however, important to note that the particular threshold of significance is, to a large extent, determined by the sample size while the point estimates exceeding 1.0 for aHRs observed for lower numbers suggest that a similar association may exists there even though the respective statistical tests happened to be underpowered in this study. On the other hand, there was a steady increasing trend supporting the hypothesis; in particular, increasing the number of binge drinking days per year to approximately 20 days further increased the risk of mortality.

The limitations of this study include the use of self-reported rather than formally recorded, and also 1 time rather than longitudinally collected alcohol consumption data, which is likely an imperfect proxy for the lifetime use. Another limitation is the use of ultrasound findings for determining the fatty liver cohort —a method with its own shortcomings, which was accompanied by our inability to rule out not only the most common (eg, viral hepatitis) but also other potential causes of chronic liver disease. As clinical data were collected only once, we were unable to track morbidity in the cohort while 20 years of follow-up might have been insufficient for that to translate to mortality. In addition, the study cohort was enrolled nearly 3 decades ago so it may be not exactly reflective of the current fatty liver population. Finally, owing to the survey design of NHANES which resulted in a limited number of degrees of freedom for statistical tests, this study might be underpowered to detect mild associations that may still exist and would probably manifest in larger or less clustered samples, such as association of mild or moderate alcohol use with mortality, which we were unable to confirm in this study.

In summary, both the presence of metabolic syndrome, especially DM, and excessive alcohol use are the risk factors for mortality in subjects with hepatic steatosis which seem to exacerbate each other. As both are largely modifiable, national effective prevention policies and management strategies for patients at risk are needed to improve their long-term prognosis.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.11.033.

## References


1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.
2. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018; 67:123–133.
3. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015;148:547–555.
4. Younossi Z, Stepanova M, Ong JP, et al; Global NASH Council. Non-alcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol 2018 Jun 14 [E-pub ahead of print].
5. Younossi ZM, Otgonsuren M, Henry L, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology 2015;62:1723–1730.
6. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology 2016;64:1577–1586.
7. Golabi P, Otgonsuren M, Cable R, et al. Non-alcoholic Fatty Liver Disease (NAFLD) is associated with impairment of Health Related Quality of Life (HRQOL). Health Qual Life Outcomes 2016;14:18.
8. Younossi Z, Henry L. Contribution of Alcoholic and Nonalcoholic Fatty Liver Disease to the Burden of Liver-Related Morbidity and Mortality. Gastroenterology 2016;150:1778–1785.
9. Younossi ZM, Stepanova M, Afendy M, et al. Changes in the prevalence of the most common causes of chronic liver

diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol 2011;9:524–530.e1.
10. Mathurin P, Beuzin F, Louvet A, et al. Fibrosis progression occurs in a subgroup of heavy drinkers with typical histological features. Aliment Pharmacol Ther 2007;25:1047–1054.
11. Kwon HK, Greenson JK, Conjeevaram HS. Effect of lifetime alcohol consumption on the histological severity of non-alcoholic fatty liver disease. Liver Int 2014;34:129–135.
12. Chedid A, Mendenhall CL, Gartside P, French SW, Chen T, Rabin L. Prognostic factors in alcoholic liver disease. VA Cooperative Study Group. Am J Gastroenterol 1991; 86:210–216.
13. Dam-Larsen S, Becker U, Franzmann MB, Larsen K, Christoffersen P, Bendtsen F. Final results of a long-term, clinical follow-up in fatty liver patients. Scand J Gastroenterol 2009; 44:1236–1243.
14. Moriya A, Iwasaki Y, Ohguchi S, et al. Roles of alcohol consumption in fatty liver: a longitudinal study. J Hepatol 2015; 62:921–927.
15. Dunn W, Sanyal AJ, Brunt EM, et al. Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with non-alcoholic fatty liver disease (NAFLD). J Hepatol 2012;57:384–391.
16. Hajifathalian K, Torabi Sagvand B, McCullough AJ. Effect of alcohol consumption on survival in non-alcoholic fatty liver disease: a national prospective cohort study. Hepatology 2018 Aug 19 [E-pub ahead of print].
17. Loomba R, Bettencourt R, Barrett-Connor E. Synergistic association between alcohol intake and body mass index with serum alanine and aspartate aminotransferase levels in older adults: the Rancho Bernardo Study. Aliment Pharmacol Ther 2009; 30:1137–1149.
18. Ajmera V, Belt P, Wilson LA, et al. Among patients with nonalcoholic fatty liver disease, modest alcohol use is associated with less improvement in histologic steatosis and steatohepatitis. Clin Gastroenterol Hepatol 2018;16:1511–1520.e5.
19. Centers for Disease Control and Prevention. About the National Health and Nutrition Examination Survey. https://www.cdc.gov/nchs/nhanes/about_nhanes.htm. Accessed September 20, 2018.
20. NHANES guidelines for alcohol use. https://wwwn.cdc.gov/Nchs/Nhanes/2011–2012/ALQ_G.htm. Accessed July 1, 2018.
21. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–357.
22. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education Program–Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. Diabetes Care 2007;30:8–13.
23. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317–1325.
24. U.S. Census 2000. https://www.census.gov/census2000/states/us.html. Accessed July 1, 2018.
25. Younossi ZM, Gramlich T, Matteoni CA, Boparai N, McCullough AJ. Nonalcoholic fatty liver disease in patients with type 2 diabetes. Clin Gastroenterol Hepatol 2004;2:262–265.
26. Golabi P, Fazel S, Otgonsuren M, Sayiner M, Locklear CT, Younossi ZM. Mortality assessment of patients with hepatocellular carcinoma according to underlying disease and treatment modalities. Medicine (Baltimore) 2017;96:e5904.

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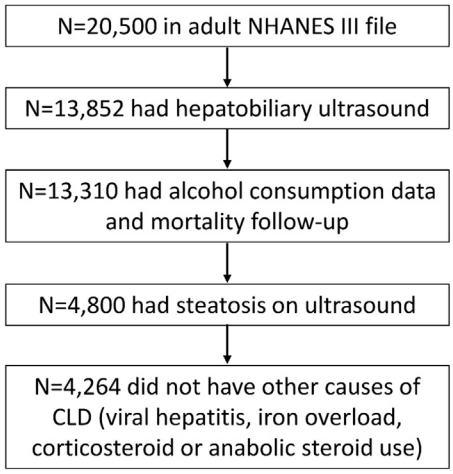
**Conflicts of interest**
These authors disclose the following: Zobair M. Younossi is a consultant or received research funds to BMS, Gilead, AbbVie, Intercept, NovoNordisk, Shionogi, and GSK. Elisabetta Bugianesi is a consultant to Genfit, Intercept, Gilead. Jacob George is a consultant to Gilead, MSD, Abbvie, Pharmaxis, BMS, Eisai. Vincent Wai-Sun Wong is a consultant to AbbVie, Allergan, Echosens, Gilead Sciences, Janssen, Perpectum Diagnostics, Pfizer, and Terns. Ira M. Jacobson is a consultant or received research funds to Gilead, Intercept, Genfit, Novo Nordisk. Aijaz Ahmed is a consultant for Gilead, AbbVie, Intercept, and Shionogi; in addition, he has received research funding from Gilead and Intercept. Robert Wong: Gilead: advisory board, consultant, research grants, speaker's bureau; Abbvie: research grants; Salix, Bayer: speaker's bureau. Georgios Papatheodoridis is advisor/lecturer and or has received research grants from Abbvie, BMS, Gilead, Janssen, MSD, Novo-Nordisk and Roche. The remaining authors disclose no conflicts.

**Funding**
This research was supported by the Global NASH Council, Center for Outcomes Research in Liver Disease.




**Supplementary Figure 1.** Flowchart of the study sample derived from the National Health and Nutrition Examination Survey III. CLD, chronic liver disease.

**Supplementary Table 1.** Independent Predictors of Mortality in Subgroups of NHANES Participants

| Subgroup/Predictor | aHR (95% CI) | *P* |
|---|---|---|
| Male only (n = 508) | | |
| Metabolic syndrome | 1.41 (1.10-1.81) | .0069 |
| Minimal alcohol use | 1.01 (0.69-1.49) | .94 |
| Moderate alcohol use | 1.04 (0.71-1.51) | .86 |
| Substantial alcohol use | 0.62 (0.31-1.24) | .17 |
| Excessive alcohol use | 2.05 (1.27-3.30) | .004[a] |
| Age, per year | 1.10 (1.08-1.12) | <.0001 |
| Black | 1.01 (0.69-1.48) | .95 |
| Hispanic | 0.72 (0.50-1.03) | .07 |
| Current smoking | 2.02 (1.48-2.74) | <.0001 |
| High school graduate | 0.91 (0.70-1.18) | .45 |
| Family income <$20,000 | 1.56 (1.25-1.96) | .0002 |
| Female only (n = 400) | | |
| Metabolic syndrome | 1.53 (0.99-2.38) | .06 |
| Substantial or excessive alcohol use | 2.04 (0.94-4.41) | .07[a] |
| Age, per year | 1.08 (1.06-1.10) | <.0001 |
| Black | 1.03 (0.81-1.32) | .79 |
| Hispanic | 0.78 (0.60-1.03) | .08 |
| Current smoking | 2.22 (1.52-3.24) | <.0001 |
| High school graduate | 0.76 (0.51-1.13) | .17 |
| Family income <$20,000 | 1.32 (0.90-1.94) | .16 |
| Elevated liver enzymes (n = 107) | | |
| Metabolic syndrome | 2.05 (0.62-6.81) | .23 |
| Minimal alcohol use | 1.61 (0.70-3.70) | .26 |
| Moderate alcohol use | 1.32 (0.60-2.89) | .49 |
| Substantial alcohol use | 4.34 (0.99-19.06) | .05[a] |
| Excessive alcohol use | 1.86 (0.83-4.16) | .13[a] |
| Age, per year | 1.08 (1.05-1.12) | <.0001 |
| Male | 1.13 (0.64-2.01) | .66 |
| Black | 1.32 (0.59-3.00) | .49 |
| Hispanic | 0.56 (0.26-1.23) | .14 |
| Current smoking | 2.92 (1.29-6.60) | .0113 |
| High school graduate | 0.62 (0.34-1.13) | .11 |
| Family income <$20,000 | 1.59 (0.74-3.45) | .23 |
| No elevated liver enzymes (n = 794) | | |
| Metabolic syndrome | 1.38 (1.08-1.77) | .0123 |
| Minimal alcohol use | 0.88 (0.65-1.20) | .41 |
| Moderate alcohol use | 0.86 (0.61-1.22) | .40 |
| Substantial alcohol use | 0.57 (0.28-1.17) | .12 |
| Excessive alcohol use | 1.82 (1.23-2.69) | .0033[a] |
| Age, per year | 1.09 (1.08-1.11) | <.0001 |
| Male | 1.46 (1.21-1.76) | .0002 |
| Black | 1.03 (0.79-1.32) | .85 |
| Hispanic | 0.77 (0.59-0.99) | .0446 |
| Current smoking | 2.06 (1.60-2.66) | <.0001 |
| High school graduate | 0.86 (0.66-1.11) | .24 |
| Family income <$20,000 | 1.37 (1.05-1.80) | .0239 |
| Fibrosis by FIB-4 (n = 51) | | |
| Metabolic syndrome | 1.99 (0.79-4.99) | .13 |
| Minimal alcohol use | 0.84 (0.35-1.99) | .67 |
| Moderate alcohol use | 1.01 (0.17-6.02) | .99 |
| Substantial alcohol use | 0.39 (0.04-3.53) | .38 |
| Excessive alcohol use | 1.10 (0.21-5.88) | .90 |
| Age, per year | 1.04 (0.96-1.12) | .30 |
| Male | 1.12 (0.42-2.93) | .81 |
| Black | 2.75 (0.45-16.68) | .25 |
| Hispanic | 0.72 (0.18-2.88) | .62 |
| Current smoking | 0.58 (0.10-3.26) | .51 |
| High school graduate | 2.81 (1.42-5.57) | .0058 |
| Family income <$20,000 | 0.88 (0.40-1.90) | .72 |
| No fibrosis by FIB-4 (n = 834) | | |
| Metabolic syndrome | 1.41 (1.10-1.82) | .0084 |
| Minimal alcohol use | 0.99 (0.73-1.35) | .95 |
| Moderate alcohol use | 0.96 (0.68-1.37) | .83 |
| Substantial alcohol use | 0.95 (0.40-2.26) | .91 |
| Excessive alcohol use | 2.06 (1.40-3.04) | .0004[a] |
| Age, per year | 1.09 (1.08-1.11) | <.0001 |
| Male | 1.31 (1.09-1.59) | .0056 |
| Black | 1.00 (0.78-1.27) | .97 |
| Hispanic | 0.75 (0.6-0.92) | .008 |
| Current smoking | 2.07 (1.58-2.72) | <.0001 |
| High school graduate | 0.83 (0.64-1.08) | .15 |
| Family income <$20,000 | 1.43 (1.12-1.81) | .0042 |

NOTE. FIB-4, Fibrosis-4; NHANES, National Health and Nutrition Examination Survey.
[a]Independent association of substantial or excessive alcohol use with mortality in the subgroup.