# Among Patients With Nonalcoholic Fatty Liver Disease, Modest Alcohol Use Is Associated With Less Improvement in Histologic Steatosis and Steatohepatitis

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**BACKGROUND & AIMS:** **Cross-sectional studies of patients with nonalcoholic fatty liver disease (NAFLD) have reported a lower prevalence of severe disease among modest drinkers compared with nondrinkers. We collected data from adult participants in the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network to evaluate the longitudinal association between modest use of alcohol and histology findings in patients with NAFLD, using paired liver biopsies collected more than 1 year apart.**

**METHODS:** **We studied NASH Clinical Research Network participants 21 years or older, not receiving pharmacologic therapy, from whom 2 or more liver biopsies and data on alcohol use within 2 years of the initial biopsy were available. Alcohol consumption was evaluated at study entry using the AUDIT and Skinner Lifetime Drinking History questionnaires. At each follow-up visit participants were asked about alcohol use frequency, number of drinks on a typical day, and frequency of heavy drinking. The association between baseline drinking status and changes in fibrosis stage, NASH histology, and the NAFLD Activity Score and its individual components were evaluated by analysis of covariance. The association between change in drinking status and change in histology was evaluated using adjusted logistic regression.**

**RESULTS:** **Of 285 participants (82% white, 70% female, mean age, 47 y) meeting entry criteria, 168 (59%) were modest alcohol users (≤2 drinks/d) and the remaining 117 were abstinent. At baseline, a higher proportion of modest alcohol users were white (86% vs 76% nonwhite) ($P = .04$) and a lower proportion of modest alcohol users were diagnosed with definite NASH (57% vs 74% without NASH; $P = .01$). During a mean follow-up period of 47 months between biopsies, nondrinkers had a greater mean reduction in steatosis grade (reduction, 0.49) than modest drinkers (reduction, 0.30; $P = .04$) and a greater reduction in mean level of aspartate transaminase (reduction, 7 U/L vs an increase of 2 U/L in modest drinkers; $P = .04$). Modest drinkers had significantly lower odds of NASH resolution compared with nondrinkers (adjusted odds ratio, 0.32; 95% CI, 0.11–0.92; $P = .04$) on adjusted analysis.**

**CONCLUSIONS:** **In a longitudinal analysis of liver biopsies from patients with NAFLD not receiving pharmacologic therapy, modest alcohol use was associated with less improvement in steatosis and level of aspartate transaminase, as well as lower odds of NASH resolution, compared with no use of alcohol.**

*Keywords:* Fatty Liver; Resolution; Cohort Study; Long-Term.

***Abbreviations used in this paper:*** **AST, aspartate aminotransferase; AUDIT, _____; BMI, body mass index; FLINT, Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment; HOMA-IR, homeostasis model assessment of insulin resistance; NAFLD, nonalcoholic fatty liver disease; NASH CRN, Nonalcoholic Steatohepatitis Clinical Research Network; PIVENS, Pioglitazone vs Vitamin E vs Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis.**


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Nonalcoholic fatty liver disease (NAFLD) has emerged as the most prevalent form of liver disease in the United States[1] and cardiovascular mortality is the most common cause of death among patients with NAFLD.[2] The beneficial impact of modest alcohol use on mortality in the general population is largely mediated by a decrease in cardiovascular disease.[3] Although this suggests that many patients with liver disease may benefit from modest alcohol use, even modest alcohol use often is discouraged in patients with concomitant liver disease owing to concern for potential synergistic hepatic injury. More than one third of the adult population in the United States is affected by NAFLD and approximately two-thirds drink alcohol,[4] the vast majority of whom drink in moderation, however, no clear guidelines exist on how to counsel these patients.

There is significant overlap in the pathways by which alcohol and NAFLD cause disease.[5–7] However, these overlapping pathways largely stem from evaluation of pathologic alcohol intake, and modest alcohol use clearly mitigates insulin resistance,[8] which is a driving factor in NAFLD. Multiple studies have shown a lower incidence of NAFLD among modest drinkers, although the beneficial effect may vary based on race and the degree of underlying obesity.[9,10] In addition, previous cross-sectional studies of patients with NAFLD, including a publication by the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN), have suggested that modest alcohol use is associated with less severe histology including less NASH and fibrosis,[11,12] however, modest alcohol users tend to have higher physical activity levels and less obesity, which are potential confounding factors. Furthermore, cross-sectional studies limit the ability to make temporal associations and the direction of causality cannot be determined because patients with more severe disease may be more likely to abstain from alcohol.

Therefore, the longitudinal association between modest alcohol intake and NAFLD remains unclear. In this study, we evaluated the effect of modest alcohol use compared with abstinence on NAFLD histology over time using paired liver biopsy specimens after adjusting for factors associated with alcohol use.

## Methods

### *Study Design and Participants*

This was a longitudinal cohort study of adult participants recruited into the studies conducted by the NASH CRN, a multicenter network sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases. Participants for this study were drawn from 3 groups within the NASH CRN studies, as follows: (1) the adult NAFLD Database study, (2) adults on placebo in the Pioglitazone vs Vitamin E vs Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) trial, and (3) adults on placebo in the Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment (FLINT) Trial. Informed consent was obtained from all participants, and the studies were approved by the Institutional Review Boards at each clinical center and the Data Coordinating Center.

The adult NAFLD Database is a prospective observational study of participants at least 18 years of age with either a histologic diagnosis of NAFLD or cryptogenic cirrhosis, suspected NAFLD based on imaging studies, or clinical evidence of cryptogenic cirrhosis. Exclusion criteria included clinical evidence of alcoholic liver disease or alcohol consumption during the 2 years before entry of more than 20 g/d for men and 10 g/d for women, and evidence of other forms of chronic liver disease.[13] The PIVENS trial was conducted from 2005 to 2008 and included nondiabetic, noncirrhotic adults with definite or possible steatohepatitis.[14,15] The FLINT trial was conducted from 2011 to 2014 and included noncirrhotic adults with NASH.[16] This study included all participants in these 3 studies who did not receive specific pharmacologic therapy for NASH, were aged 21 years or older, and had 2 or more liver biopsies and alcohol use history within 2 years of the initial biopsy. The median time between baseline biopsy and alcohol use history was 63 days, and between biopsy and laboratory data acquisition was 59 days. For the second biopsy, the median number of days between the biopsy and alcohol history was 19 days, and the median number of days between the biopsy and the laboratory data was 22 days. The average number of follow-up visits over the study period was 4.26, and the interval depended on the study cohort from which the patient was recruited. Patients who reported more than 20 g of alcohol in a typical drinking day, 6 or more drinks on 1 occasion at least monthly, or with biopsies less than 1 year apart were excluded at baseline. Patients with no follow-up history were excluded and nondrinkers at baseline with a previous history of alcohol drinking were excluded. Of 530 identified patients, 285 were included in this analysis (Figure 1). A total of 172 patients in this longitudinal study (60%) overlapped with the previous cross-sectional study of modest alcohol use performed by the NASH CRN.[11]

### *Alcohol Consumption*

The primary exposure of interest was modest alcohol consumption compared with abstinence from alcohol. Alcohol consumption was evaluated at study entry using the AUDIT and Skinner Lifetime Drinking History questionnaires. At follow-up visits the abbreviated AUDIT-C questionnaire was administered. At baseline, participants were asked, “How often do you have a drink containing alcohol?” Those who responded “never” were characterized further based on their response to the question from the Skinner Lifetime Drinking Assessment, “Over the course of your lifetime have you ever had at least 1 drink of alcohol, beer, liquor, wine, or wine