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Alcohol Use and Cardiovascular Disease Risk in Patients with Nonalcoholic Fatty Liver Disease

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Abstract

Background & Aims—Cardiovascular disease (CVD) is the leading cause of death among patients with non-alcoholic fatty liver disease (NAFLD). Moderate drinking (vs abstinence) is associated with lower risk of CVD in the general population. We assessed whether alcohol use is associated with CVD risk in patients with NAFLD.

Methods—We analyzed data from participants in the Coronary Artery Risk Development in Young Adults longitudinal cohort study of 5115 black and white young adults, 18–30 years old, recruited from 4 cities in the United States from 1985 through 1986. Participants self-reported alcohol use at study entry and then again after 15, 20, and 25 years. At year 25 (2010–2011),

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Disclosures

The authors have no conflicts of interest pertinent to this study. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Institutes of Health; or the U.S. Department of Health and Human Services.

Author Contributions

Lisa B. VanWagner MD MSc: study design, analysis, interpretation of results, drafting of manuscript
Hongyan Ning MS: study design, statistical analysis, interpretation of results, manuscript editing
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participants underwent computed tomography examination of the thorax and abdomen and tissue Doppler echocardiography with myocardial strain measured by speckle tracking. Coronary artery calcification was defined as an Agatston score above 0. NAFLD was defined as liver attenuation less than 51 Hounsfield Units after exclusions. Drinkers reported 1–21 (men) or 1–14 (women) standard drinks/week at years 15, 20, or 25. Nondrinkers reported no alcohol use at years 15, 20, and 25.

Results—Of the 570 participants with NAFLD (mean age 50 years; 54% black; 46% female), 332 (58%) were drinkers; significantly higher proportions of drinkers were white, male, and with higher levels of education compared with nondrinkers ($P<.05$ for all). Higher proportions of drinkers had obesity, diabetes, and the metabolic syndrome compared with nondrinkers ($P<.01$). There was no difference in liver attenuation between groups ($P=.12$). After multivariable adjustment, there was no association between alcohol use and CVD risk factors (diabetes, hypertension, hyperlipidemia) or subclinical CVD measures (coronary artery calcification, E/A ratio, global longitudinal strain).

Conclusions—In a population-based sample of individuals with NAFLD in midlife, prospectively assessed alcohol use is not associated with significant differences in risk factors for CVD or markers of subclinical CVD. In contrast to general population findings, alcohol use may not reduce risk of CVD in patients with NAFLD.

Keywords

CARDIA study; NASH; heart disease; NAFLD

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease affecting up to 35% of the U.S. population and is associated with high cardiovascular disease (CVD) morbidity and mortality.[1, 2] The disease is defined as abnormal accumulation of fat in the liver in the absence of heavy alcohol consumption (typically defined as average of > 21 drinks per week for men and > 14 drinks per week for women) and other causes of secondary hepatic steatosis.[3]

According to the 2015 National Survey on Drug Use and Health (NSDUH), 87.1% of people ages 26 or older reported that they drank alcohol at some point in their lifetime, the vast majority of whom drank in moderation.[4] The United States Department of Agriculture dietary guidelines define moderate alcohol use as up to one drink per day for women and up to two drinks per day for men, but definitions vary widely across studies.[5] In most Western countries where chronic diseases such as coronary heart disease, cancer, stroke, and diabetes are the primary causes of death, results from large epidemiological studies consistently show that moderate alcohol use (compared to abstinence) is associated with lower mortality, especially among middle-aged and older men and women—an association which may reflect salutary effects of moderate alcohol consumption on coronary heart disease, diabetes, and ischemic stroke.[6] Identification of CVD as the leading cause of death in NAFLD raises the question of whether persons with NAFLD may benefit from moderate alcohol use.

Despite the association of moderate alcohol use with improved insulin sensitivity and lower cardiovascular mortality in the general population,[6] whether similar benefits are seen in

persons with NAFLD is largely unstudied. Thus, the primary objective of the current study was to examine whether alcohol use (compared to no alcohol use) is associated with prevalence of adverse CVD risk factors and of subclinical CVD among persons with NAFLD in midlife. We hypothesized that alcohol use would be inversely associated with adverse CVD risk factors and markers of subclinical CVD, similar to observations in the general population.

METHODS

Study Sample

The Coronary Artery Risk Development in Young Adults (CARDIA) study is an ongoing longitudinal cohort study of the development and determinants of CVD in 5,115 black and white young adults recruited in 1985 and 1986 at 18–30 years of age across 4 U.S. cities (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). The study design has been published previously.[7] Participants have been followed at 9 examinations for more than 30 years with collection of detailed clinical data, including self-reported alcohol use at each exam and non-contrast CT measurement of liver fat, coronary artery calcification (CAC) score and comprehensive echocardiography at the year 25 (Y25) exam. Retention rates among survivors for the in-person examinations have been high throughout the study (Y2, 90%; Y5, 86%; Y7, 81%; Y10, 77%; Y15, 74%; Y20, 72%; Y25, 72%; Y30, 71%) with > 90% of the surviving cohort maintaining contact in the last two years.[7] Participants provided written informed consent at each examination, and institutional review boards from each field center and the coordinating center approved the study annually.

There were 3,498 participants (45.5% men, 50.5% black) who attended the CARDIA Y25 Exam (2010–2011). Participants were excluded from the CT exam if they were pregnant, weighed more than 450lbs or were unable to fit within the CT gantry (n=3). We excluded those missing measurements for liver fat (n=316). We also excluded participants with self-reported hepatitis or cirrhosis (n=55), a risk factor for chronic liver disease (i.e. intravenous drug use) or with a potential cause of secondary hepatic steatosis (n=645): heavy alcohol consumption > 14 drinks/week in women and > 21 drinks/week in men[1, 3] (n=530), self-reported HIV (n=21), prior intravenous drug use (n=67), and medications known to cause hepatic steatosis (e.g. valproic acid, methotrexate, tamoxifen or amiodarone) (n=27). Of the remaining 2,479 NAFLD-eligible participants we excluded an additional 21 participants with a medically verified history of acute myocardial infarction, angina or congestive heart failure in analyses of subclinical CVD (Figure 1).

Measurements

Standardized protocols for data collection were used across study centers and measurements have previously been described.[7] Participants were asked to fast for at least 12h and to avoid smoking and heavy physical activity for at least 2h before each examination. Demographics, alcohol and smoking habits were ascertained through questionnaires. At each CARDIA Study examination, participants were asked, “Did you drink any alcoholic beverages in the past year?” and, with the use of visual aids to demonstrate a typical drink, were asked 3 follow-up questions to assess the number of drinks of wine, beer, and liquor typically

consumed in a week. Assuming that 1 drink of beer, wine, or liquor contains 16.7 mL, 17.0 mL, or 19.2 mL of ethanol, respectively (per CARDIA Study protocol), we estimated total ethanol consumption/week in milliliters of ethanol. The result was divided by 17.2 mL of ethanol/average drink to estimate the usual number of standard drinks/week.[8] We used this combined alcohol variable because there were not sufficient numbers of individuals, especially women, to conduct the analyses stratified by type of alcohol. Heavy alcohol use was defined as > 14 standard drinks/week in women and > 21 standard drinks/week in men.[1] Binge drinking was defined as ≥ 5 drinks on a single occasion and was assessed at exam Y15, Y20 and Y25 with the question "During the past 30 days, that is since ____ / _____ / _____ (fill in date), on how many days did you have five or more drinks on the same occasion? By "occasion," we mean at the same time or within a couple of hours of each other." Alcohol use was defined as ≤ 14 standards drinks per week for women and ≤ 21 standard drinks per week for men at exam years 15 or 20 or 25 by adapting the definition of moderate or light drinking set by the National Institute on Alcohol Abuse and Alcoholism (NIAAA).[9] Binge drinkers were included in the primary analysis only if they met moderate or light drinking thresholds (women ≤ 14; men ≤ 21 standard drinks/week). Nondrinkers were defined as no reported alcohol use at exam years 15 and 20 and 25 (Figure 2). Primary analyses were restricted to alcohol exposure data ascertained within the 10 years prior to CT scan assessment of NAFLD (e.g., exam years 15, 20 and 25) since the potential effect of alcohol use on CVD benefit (or harm) is most likely to occur with more proximal use, and that moderate or heavy drinking in early adulthood (baseline mean CARDIA participant age was 26.2 years) tends not to continue into later life.[10] Medication use was self-reported and participants brought in medications for verification. Blood was drawn in the seated position, separated and plasma frozen to −70°C prior to analysis in a central laboratory. [7] Glucose was assayed using the hexokinase method and insulin by the Elecsys sandwich immunoassay. Total cholesterol, HDL cholesterol and triglycerides were measured enzymatically by the Northwest Lipid Laboratory.[11] LDL cholesterol was calculated using the Friedewald equation.[12] Body weight was measured to the nearest 0.2 kg with a calibrated balance-beam scale. Height was measured with a vertical ruler to the nearest 0.5 cm. Seated blood pressure was measured three times at 1-min intervals after 5-min resting and the second and third measures averaged. Hypertension was defined as antihypertensive medications use and/or systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg. Diabetes was defined as fasting plasma glucose ≥126 mg/dl, treatment with insulin or hypoglycemic agent, 2-hour post-challenge glucose ≥200 mg/dl and/or HbA_{1c} ≥6.5%. Impaired fasting glucose was defined as a fasting plasma glucose ≥ 100 and <126 mg/dl. Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2 and modified National Cholesterol Education Program Adult Treatment Panel III criteria were used to define dyslipidemia and the metabolic syndrome.[13]

The CT protocol included the heart and abdomen using a non-contrast CT scan performed using GE (GE 750HD 64 and GE LightSpeed VCT 64 Birmingham and Oakland Centers, respectively; GE Healthcare, Waukesha, WI) or Siemens (Sensation 64, Chicago and Minneapolis Centers; Siemens Medical Solutions, Erlangen, Germany) multi-detector CT scanners and has been described previously.[14] Quality control and image analysis were performed at a core reading center (Wake Forest University Health Sciences, Winston-Salem, NC). NAFLD was defined as CT liver attenuation (LA) < 51 Hounsfield Units

(equivalent to a liver/spleen ratio<1; at least mild NAFLD)[15] after exclusion of other causes of liver fat (Figure 1).[14, 16] LA was measured in the right lobe of the liver and was reported as the average of nine measurements on three CT slices using circular regions of interest of 2.6 cm^2. The intraclass correlation coefficient between different readers on a random selected sample of 156 participants was 0.975 for LA, indicating high reproducibility of CT measured LA in this study. CT assessed CAC was reported as present or absent based on CAC score > 0 using a modified Agatston method (Aquarius Workstation, TerraRecon, Foster City, CA).[17] The interclass correlation coefficient for inter-reader comparisons was 0.999 for CAC, and intra- and inter-reader error were 5.6% and 7.0%, respectively, in 156 scans that were blinded and reevaluated.[18–21]

Comprehensive echocardiography, including Doppler and tissue Doppler imaging, was performed using an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Otawara, Japan) by trained sonographers using a standardized protocol. Experienced sonographers made measurements from digitized images using a standard software offline image analysis system (Digisonics, TX, USA). The Y25 echocardiography protocol has been previously published and followed American Society of Echocardiography guidelines.[22, 23] Quality control and image analysis was performed at a core reading center (Johns Hopkins University, Baltimore, MD). The protocol for speckle tracking echocardiography images for myocardial strain and strain rate measurements has been previously described.[16] Abnormal left ventricular (LV) relaxation was defined as lateral tissue Doppler e' velocity < 10 cm/s.[24] Increased LV filling pressure was defined as E/e' ratio ≥ 12 alone or the combination of E/e' ratio 8–12 and left atrial volume index ≥ 34 ml/m^2.[24] LV mass was indexed to height$^{2.7}$ and left atrial volume indexed to height.

Statistical Analysis

Characteristics were compared by alcohol use status (nondrinker vs. drinker) using linear models for continuous variables and chi-square or Fisher exact test for categorical variables. Logistic regression models were used to quantify cross-sectional associations between the exposure, alcohol use (drinker vs. nondrinker), and the outcome variables, presence of CAC (score>0), diastolic dysfunction, diabetes, hypertension or hyperlipidemia, in separate analyses. Linear regression models were used to quantify cross-sectional associations between alcohol use (drinker vs. nondrinker) and continuous markers of subclinical abnormalities in cardiac structure, function and hemodynamics. Covariates in the multivariable models were chosen *a priori* for clinical importance. Continuous variables were standardized to a mean of 0 and a standard deviation of 1 prior to model entry. Cumulative exposure to potential confounders was assessed with baseline set at the Y15 exam (10-year exposure prior to NAFLD assessment). Two models were fitted: The base model was adjusted for center, age, race, sex, education, income level, pack-years of smoking exposure, and cumulative physical activity score. The multivariable model was adjusted additionally for cumulative BMI (diabetes, hypertension, and hyperlipidemia models) and cumulative glomerular filtration rate (GFR, hypertension model only). In multivariable models that assessed markers of subclinical CVD we performed additional adjustment for cumulative CVD risk factors (cumulative systolic blood pressure (mmHg-years), number of years with blood pressure medications, cumulative total cholesterol

(mg/dl-years), cumulative years with diabetes, cumulative GFR). Interaction terms were generated between race and sex in terms of CAC, E/A ratio, global longitudinal strain, LV mass index, diabetes, hypertension or hyperlipidemia status. Because no interactions by race or sex were noted, all models include only main effects for race and sex. Sensitivity analyses were also performed 1) excluding participants who reported any prior heavy alcohol use at exam years 0,2,5,7 and 10 (e.g., former drinkers) in order to account for lifetime drinking history, and 2) excluding participants who reported prior binge drinking behavior (e.g., possible alcoholic liver disease) during the exam years in which binge drinking was assessed (Figure 2). As a sensitivity analysis looking at the dose-response effect of alcohol intake, we entered alcohol intake as a continuous variable (average standard drinks per week at Y15, Y20 and Y25) in all logistic and linear regression models. To take into account differential effects of alcohol intake by sex, these models also included a sex by drinks per week interaction term. As a sensitivity analyses looking at the effect of alcohol use on prevalent cardiovascular events among NAFLD participants we included the 21 NAFLD participants who had a medically verified history of acute myocardial infarction, angina or congestive heart failure prior to the Y25 exam in our models predicting global longitudinal strain, LV mass index, E/A ratio, E/e' ratio, and CAC score > 0. Finally, as a comparator group we also assessed the effect of alcohol use on subclinical CVD and CVD risk factors among the 1902 NAFLD-eligible participants with CT liver attenuation > 51 HU (e.g., non-NAFLD) in CARDIA (Figure 1). A p value < 0.05 was considered statistically significant. Analyses were performed using SAS 9.2 (SAS institute, Cary, NC).

RESULTS

A total of 2,479 participants (54% men, 46% black) met the inclusion criteria and of these, 570 (23%) had CT-diagnosed NAFLD (Figure 1). Of the 570 NAFLD participants, 332 (58.2%) were classified as drinkers and 238 were nondrinkers (Figure 2). In general, most participants who reported moderate alcohol use continued to report moderate alcohol use over time in CARDIA. Compared to reports at the Y15 exam (mean age 40.1 years), 74% of non-drinkers remained non-drinkers, and only 25% of modest drinkers had stopped drinking at follow up (mean age 50.4 years). Table 1 compares the characteristics of the Y25 NAFLD participants who reported any drinking behavior compared to those who denied any alcohol use within 10 years of CT assessment of NAFLD. Mean age of the NAFLD population was 50.4 years, 54% were men and 45.6% were black. At Y25 drinkers were more often white (59.6% vs. 47.1%), male (61.5% vs. 43.7%), highly educated (15.2 vs. 14.6 years), and had higher physical activity (332.6 vs. 243.1 exercise units/week) than nondrinkers ($p<0.01$ for all). Nondrinkers had higher BMI (37.3 vs. 34.3 kg/m^2), c-reactive protein (6.1 vs. 4.2 mg/L), diabetes (37.4% vs. 22.6%), obesity (82.5% vs. 74.5%) and metabolic syndrome prevalence than drinkers (66.0% vs. 55.1%, $p<0.05$ for all). There was no difference in mean liver attenuation between groups ($p=0.12$). There was also no difference in measured systolic or diastolic blood pressure or prevalence of hypertension though more nondrinkers were using antihypertensive medications than drinkers (46.2% vs. 34.6%, $P=0.005$). There was no difference in multiple lipid parameters or use of lipid-lowering medications between groups. Notably, there was a trend towards increased CAC prevalence in drinkers compared to nondrinkers (42.2% vs. 34.3%, $p=0.052$). In univariate analysis, alcohol use was

associated with a slightly higher e' velocity, which is a marker of impaired LV relaxation (8.9 vs. 8.5 cm/s, p=0.04). There were no other statistically significant different differences in markers of cardiac structure or function in univariate analysis (Table 1 and Supplemental Table 1).

In unadjusted and adjusted linear regression analyses there were no significant associations between alcohol use and markers of subclinical abnormalities in cardiac structure (e.g., LV mass index, LV end diastolic volume, left atrial volume index), function (e.g., global longitudinal strain, E/A ratio, E/e' ratio) or hemodynamics (e.g., cardiac output)(Table 2). In multivariable logistic regression analyses adjusted for demographics and cumulative CVD risk factors there was also no association between alcohol use and abnormal LV relaxation or increased LV filling pressures (Table 3). Despite a trend towards increased CAC among drinkers, in multivariable logistic regression analyses adjusted for demographics and cumulative CVD risk factors there was no statistical association between alcohol use and prevalent CAC (OR, 95% CI: 1.46, 0.94–2.28; p=0.09, Table 4) or continuous logCAC (β (SE): 0.26 (0.18); p=0.14, Supplemental Table 2). Similarly, there was no association between alcohol use and either prevalent hypertension or hyperlipidemia (Table 5) or in continuous markers of hypertension or dyslipidemia (Supplemental Table 2) at Y25 in CARDIA. However, in unadjusted analyses alcohol use was associated with a 51% lower odds of prevalent diabetes (OR, 95% CI: 0.49, 0.34–0.71; p=0.0001). This association was attenuated and no longer significant when adjusted for demographics and cumulative BMI (OR, 95% CI: 0.73, 0.46–1.15; p=0.17). Alcohol use was also inversely associated with continuous HbA1c level when adjusted for demographics and health behaviors (β (SE): −0.27 (0.09); p=0.004). This association was attenuated, but remained significant when adjusted additionally for cumulative BMI and years with treatment for diabetes (β (SE): −0.21 (0.09); p=0.02, Supplemental Table 2). There was no association between alcohol use and continuous HOMA-IR (Supplemental Table 2). Findings remained unchanged in sensitivity analyses that used continuous alcohol (average standard drinks/week) as the exposure variable (see Tables 2–5). Findings were also unchanged in sensitivity analyses that excluded NAFLD participants with any prior heavy alcohol use (e.g., former drinkers) and binge drinkers, and in analyses that included the 21 participants with cardiovascular events (e.g., acute myocardial infarction, angina or congestive heart failure) prior to the Y25 exam (data not shown).

In contrast, there were significant differences seen in drinkers versus nondrinkers in unadjusted analyses among non-NAFLD participants in CARDIA who were excluded from analyses (n=1902, Figure 1). Drinkers had lower LV mass index, left atrial volume index, E/e' ratio, LV filling pressures, absolute global longitudinal strain and lower odds of hypertension than nondrinkers ($p<0.05$ for all; Supplemental Table 3). However, these associations were attenuated and no longer significant when controlled for demographics and cumulative cardiometabolic risk factors. Similar to NAFLD CARDIA participants, there were no significant differences between drinkers and nondrinkers in terms of CAC, diabetes or hyperlipidemia prevalence (Supplemental Table 3).

DISCUSSION

In a biracial sample of middle-age adults with CT-defined NAFLD, in whom alcohol use was prospectively assessed, alcohol use was not associated with a beneficial cardiovascular disease profile when adjusted for multiple confounders, nor was alcohol use associated with lower prevalence of subclinical coronary artery disease or markers of myocardial remodeling and dysfunction. These findings were independent of binge drinking behavior. Our findings challenge the belief that alcohol use may reduce CVD risk in persons with NAFLD.

Alcohol use has been consistently found to have a J-shaped association with coronary heart disease, with moderate drinkers exhibiting a lower risk compared to both heavy drinkers and non-drinkers.[25] In the general population, moderate alcohol intake is also associated with higher HDL-cholesterol,[26] lower inflammation,[27] lower fibrinogen,[26] and a lower risk of type 2 diabetes.[28] Similarly, in univariate analyses we found an inverse association between alcohol use and markers of insulin resistance, inflammation and dyslipidemia in CARDIA participants with NAFLD and non-NAFLD. However, when additional confounders were considered, these associations were no longer significant. Since alcohol use is not randomly distributed among persons with NAFLD, numerous factors differ between persons who consume light-to-moderate amounts of alcohol and those who abstain. Multiple studies have shown an association between moderate alcohol use and lifestyle factors associated with better overall health. Moderate alcohol users tend to have higher socioeconomic status, increased education, increased physical activity, and less obesity.[29, 30] We found similar associations among persons with NAFLD and non-NAFLD and in multivariable analyses adjusted for demographics and lifestyle factors any association between alcohol use and reduced CVD risk was no longer statistically significant, suggesting that better overall health may account for the observed “protective” effect of alcohol intake in the NAFLD population. On the other hand, we did observe a relationship between alcohol use and lower risk for prevalent midlife diabetes and lower HbA1c among persons with NAFLD. The apparent inverse association between alcohol use and diabetes prevalence may be explained by an improvement in insulin sensitivity and other metabolic parameters, including improved cytokine profiles and decreased oxidative stress, as has been described in the general population.[31, 32] Mechanisms underlying this observation in persons with NAFLD require further prospective study.

In the general population, there is uncertainty regarding the association between alcohol use and CAC, a well-established risk marker for future cardiovascular events.[33] Reports have included no association,[34–36] a U-shaped association,[37] and a dose-response relationship.[38] We found no significant association between alcohol use and prevalent CAC in midlife in persons with NAFLD and non-NAFLD, and in fact, in univariate analysis, drinkers had a higher prevalence of CAC. Alcohol is also a known cardiac toxin and heavy consumption is associated with impairment in left ventricular function and eventual alcoholic cardiomyopathy with symptomatic heart failure.[39] However, several large epidemiological studies, including the Atherosclerosis Risk in Communities (ARIC) study,[40] the Framingham Heart Study[41] and The Cardiovascular Health Study[42] have consistently observed that moderate alcohol consumption is inversely associated with the risk for incident heart failure, independent of multiple confounders, including coronary heart

disease. The small number of heart failure events in the CARDIA NAFLD sample limits evaluation for the risk of clinical heart failure, but we failed to observe an association between alcohol use and multiple markers of subclinical changes in cardiac structure and function that may be precursors of incident heart failure in NAFLD. The longitudinal effect of moderate alcohol use in NAFLD on CAC progression and changes in myocardial structure and function over time requires further study.

Despite a large body of literature on the association of moderate alcohol use with CVD in the general population, only one additional published study has specifically examined the impact of moderate alcohol use on CVD in patients with NAFLD. In a cross-sectional study of 10,581 Korean men with NAFLD (mean age 51.8 years), Sinn et al. evaluated the association between moderate alcohol use, defined as <20 g/day (equivalent to approximately 1.4 standard U.S. drinks/day[43]), and carotid plaque or stenosis on duplex ultrasonography, as a surrogate for subclinical CVD. Alcohol use (<20g/day) was associated with lower odds of carotid plaque (OR, 95% CI: 0.74, 0.60–0.92) and carotid stenosis (OR, 95% CI: 0.62, 0.43–0.90), compared to nondrinkers after adjusting for age, smoking and metabolic syndrome.[44] Recently, Hajifathalian et al. presented data from the National Health and Nutrition Examination (NHANES) survey, that modest alcohol consumption of less than 1.5 drinks of alcohol per day is associated with decreased risk of overall mortality in persons with biochemically-assessed NAFLD (HR 0.64, CI 0.42–0.97, p=0.035).[45] However, the authors also found that drinking more than 1.5 drinks of alcohol per day was actually linked to an increased hazard of death (HR 1.45, CI 1.01–2.19, p=0.047).[45] Thus, the potential "therapeutic window" for the beneficial effect of alcohol use in NAFLD appears very narrow limiting the safely profile for a clinical recommendation of moderate alcohol use as a preventive measure to reduce morbidity and mortality in NAFLD. Importantly, cause of death was not reported in this study and the authors did not account for interactions between race and sex by alcohol consumption. In the current study, while we were not able to assess for mortality outcomes in CARDIA due to low event rates at this time, alcohol use was not associated with multiple markers of CVD and CVD risk, which is the leading cause of death in NAFLD. In addition, we assessed alcohol exposure using both sex-specific cut-points and continuous alcohol use that included a sex by drinks per week interaction term, further strengthening confidence in our consistent null findings.

Importantly, heavy alcohol use is a well-known risk factor for chronic liver disease and cirrhosis. Moreover, there is significant overlap in the pathogenesis of alcoholic liver disease and NAFLD and the concern that light to moderate alcohol use in patients with NAFLD can exacerbate or accelerate liver disease progression remains. There are six currently published studies on the association between alcohol use and liver-related outcomes in NAFLD, which were recently summarized by Ajmera et al.[46] Five of the six studies were cross-sectional and collectively suggest that individuals that drink light to moderate amounts of alcohol not only have low prevalence of NAFLD but also less severe histological disease.[47–51] In a recent metanalysis of 43,175 individuals, low to moderate amounts of alcohol consumption is associated with a 31% reduction in NAFLD prevalence.[52] However, a recent presentation from the NASH Clinical Research Network (NASH CRN), using a prospective longitudinal cohort study of over 3500 children and adults with biopsy-proven NAFLD, has challenged this paradigm. In the NASH CRN, moderate alcohol use was associated with less

improvement in steatosis on paired liver biopsies and with no statistically significant differences in other histological characteristics of NAFLD including fibrosis.[53] In addition, a recently published Mendelian randomization analysis supports the NASH CRN findings that light to moderate alcohol intake has no beneficial effect on the histological outcomes of NAFLD.[54]

The conflicting findings regarding associations between light to moderate alcohol use and liver-related or CVD outcomes may be explained by failure to consider patterns of alcohol use in assessing harm versus benefit. For example, the individual drinking 5 drinks/week on average, but drinking all five drinks on one day of the week (e.g., binge drinking) may have different health outcomes from the individual drinking 1 drink on 5 of 7 days per week.[46] The potential clinical consequence of episodic heavy alcohol use is illustrated in a prospective study by Ekstedt et al, in which 137 patients referred for abnormal liver tests attributed to NAFLD were followed for a mean of 13.8 years.[55] Heavy episodic drinking (defined as more than 60g/day in males and 48g/day in females without exceeding 140 g/week) was associated with NAFLD fibrosis progression.[55] In the current study, we also assessed binge drinking behavior in addition to average weekly use and found consistent null findings for the association of alcohol use and CVD risk factors or subclinical disease. Thus, episodic alcohol use does not seem to differentially effect benefit or harm in terms of CVD risk in persons with NAFLD.

The strengths of our study include our large, well-characterized population-based cohort of both whites and blacks, the ability to analyze sex-specific differences, a NAFLD prevalence that is consistent with published population estimates,[1] the use of tissue Doppler imaging and speckle-tracking analysis to assess subclinical myocardial dysfunction, the use of CAC score to assess for subclinical atherosclerosis, the prospective measurement of a comprehensive set of metabolic and socioeconomic covariates to assess for potential confounding and prospective assessment of alcohol use, including assessment of binge drinking behavior. Several limitations should also be considered when interpreting our study results. First, our findings are cross-sectional and derived from an observational study; therefore, neither temporal nor causal relationships can be inferred. Second, reduced statistical power because of the modest NAFLD sample size in the present study may have played a role in limiting the significance of some of the statistical comparisons conducted. A post hoc power analysis revealed that on the basis of the available 570 NAFLD participants in CARDIA, the minimal detectable between group effect for the outcome of diabetes was 10.5% to obtain statistical power at the recommended .80 level and alpha 0.05. Thus, it is unlikely that our negative findings can be attributed to a limited sample size. In addition, similar findings were observed in the larger (n=1902) non-NAFLD CARDIA sample in fully adjusted analyses. Third, CT is a relatively insensitive measure of hepatic fat when compared with magnetic resonance imaging (e.g., MR-spectroscopy or MR-proton density fat fraction),[15, 56] which may bias our results toward the null. Contemporaneous laboratory data on hepatic function are not available in CARDIA and therefore we cannot assess risk for fibrosis. NAFLD was also not assessed in CARDIA prior to the Y25 follow up examination and thus, we do not know when during adulthood NAFLD may have developed. However, since NAFLD is primarily an asymptomatic disease, detection in midlife mirrors clinical practice when NAFLD is commonly incidentally found on imaging performed for

other reasons.[57] Fourth, as is the case for nearly all large longitudinal cohorts, the study relied on self-reported alcohol intake and did not include biologic measures (which capture only recent use) or indicators of alcohol abuse (e.g., alcohol-related traffic violations or job loss). Although recall bias and minimization are limitations to self-report, we do not have reason to believe that differential misclassification occurred in CARDIA. In fact, most participants who reported moderate alcohol use maintained reported moderate alcohol use over time in CARDIA. Fifth, in CARDIA most participants drank more than one kind of drink, precluding additional interpretation on the association between alcohol intake and CVD risk by type of drink. However, systematic reviews of observational studies in which moderate alcohol consumption was directly compared with individuals' risk of CVD demonstrate that all types of alcoholic drinks confer lower risk, suggesting that the benefit is primarily from the alcohol itself, rather than other, variable components.[58] No consistent difference has been noted between beer and wine in terms of clinical outcomes in several studies.[59, 60] Finally, CARDIA includes only African Americans and European Americans, so findings may not be generalizable to other racial/ethnic groups.

CONCLUSION

In summary, in this population-based sample of individuals with NAFLD assessed in midlife, prospectively assessed alcohol use is not associated with significant differences in prevalent adverse CVD risk factors or markers of subclinical CVD among NAFLD or non-NAFLD participants. Thus, a recommendation of CVD risk benefit of alcohol use in persons with NAFLD cannot be made based on the current findings. Prospective long-term follow-up studies that compare the effects of various alcohol types and doses on hard cardiovascular endpoints among populations of varied racial and ethnic backgrounds would be useful to advance our understanding about the link between alcohol, NAFLD and cardiovascular diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations (in alphabetical order)

A	late (atrial) transmitral velocity
BMI	body mass index

CAC	coronary artery calcification
CARDIA	coronary artery risk development in young adults
CT	computerized tomography
CVD	cardiovascular disease
E	early transmitral velocity
e'	early diastolic tissue velocity
GFR	glomerular filtration rate
GLS	global longitudinal strain
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance
HU	Hounsfield Units
LA	liver attenuation
LDL	low density lipoprotein
NAFLD	nonalcoholic fatty liver disease
NASH CRN	nonalcoholic steatohepatitis clinical research network

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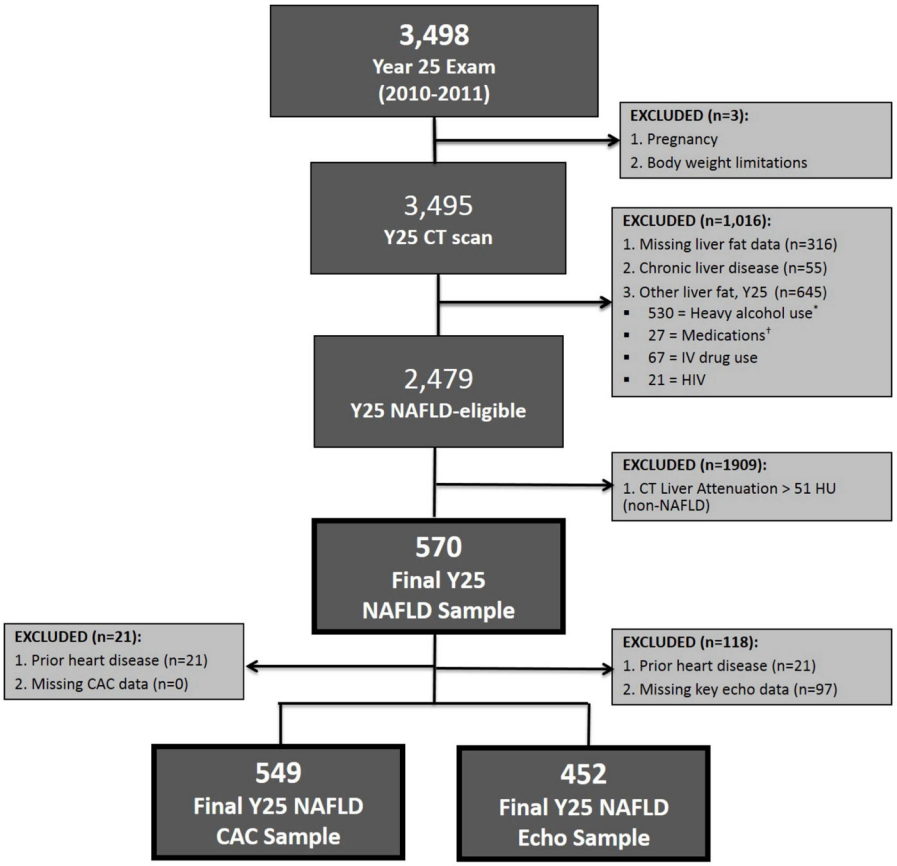

Figure 1.

Study sample—Abbreviations: CAC, coronary artery calcification; CT, computed tomography; HIV, human immunodeficiency virus; IV, intravenous; NAFLD, nonalcoholic fatty liver disease; Y25, year 25 *Heavy alcohol use was defined as > 14 standard drinks/ week in women, > standard 21 drinks/week in men at Y25

†Medications = valproic acid, methotrexate, tamoxifen and amiodarone.

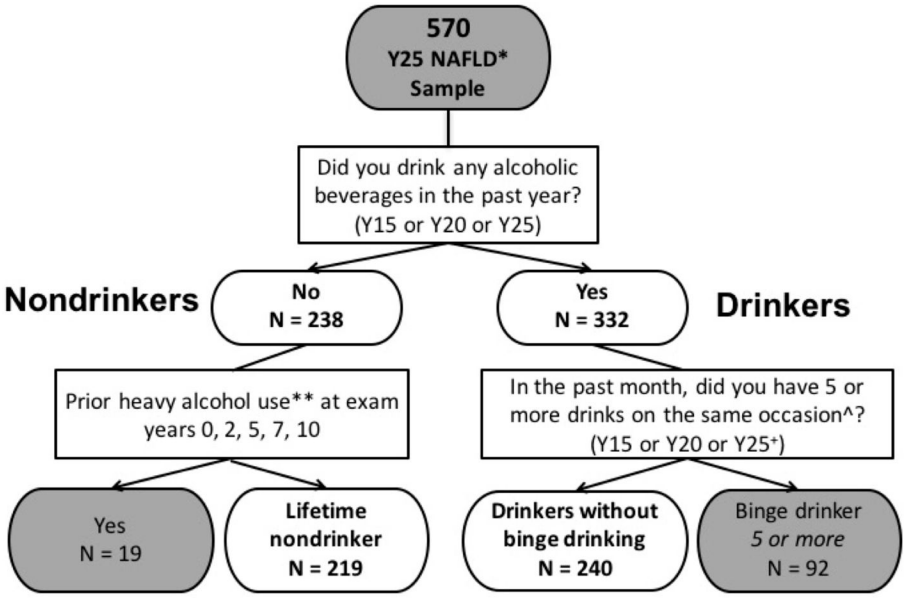

Figure 2. Alcohol exposure assessment

Primary analyses included 332 drinkers compared with 238 nondrinkers. Binge drinkers were included in the primary analysis only if they met moderate drinking thresholds (women ≤ 14; men ≤ 21 standard drinks/week). In sensitivity analysis, those participants with heavy alcohol use at any prior exam (n=19) or reported binge drinking behavior during the 10 years prior to liver fat assessment (n=92) were excluded. Thus, sensitivity analysis included comparisons between lifetime never-drinkers and drinkers without binge drinking behavior.

*NAFLD was defined as CT liver attenuation < 51 Hounsfield units after exclusions for secondary causes of liver fat (heavy alcohol/medications/HIV/hepatitis/cirrhosis).

**Heavy alcohol use was defined as > 14 standard drinks/week in women, > 21 standard drinks/week in men ^By “occasion” we mean at the same time or within a couple of hours of each other

Table 1

Comparison of year 25 characteristics between the overall study sample and NAFLD participants by alcohol use status, The CARDIA study

Year 25 covariates	NAFLD Study Sample (n=570)	Nondrinkers (n=238)	Drinkers[a] (n=332)	P value[b]
Age, mean, years	50.4 ± 3.6	50.5 ± 3.7	50.2 ± 3.6	0.28
Women, No (%)	262 (46.0)	134 (56.3)	128 (38.6)	**<0.0001**
Menopause status	120 (46.3)	66 (48.1)	56 (44.4)	0.55
Black	260 (45.6)	126 (52.9)	134 (40.4)	**0.003**
Grade of School completed	15.0 ± 2.5	14.6 ± 2.6	15.2 ± 2.5	**0.004**
Income < $50,000/year	209 (37.1)	108 (46.2)	101 (30.6)	**0.0002**
BMI (kg/m^2)	35.5 ± 7.3	37.3 ± 8.1	34.3 ± 6.4	**<0.0001**
BMI ≥ 30	459 (77.8)	202 (82.5)	257 (74.5)	**0.02**
Weight (lbs)	231.7 ± 49.8	238.1 ± 55.9	227.1 ± 44.5	**0.009**
Height (cm)	172.3 ± 9.9	170.4 ± 9.9	173.6 ± 9.7	**<0.0001**
Waist circumference (cm)	108.8 ± 14.5	110.9 ± 15.4	107.3 ± 13.7	**0.004**
Waist-to-hip ratio	0.91 ± 0.08	0.90 ± 0.08	0.92 ± 0.08	**0.03**
Body surface area (m^2)	2.2 ± 0.27	2.2 ± 0.29	2.2 ± 0.25	0.22
Smoking status				**0.02**
Current	81 (14.4)	26 (11.1)	55 (16.8)	
Former	130 (23.0)	47 (20.0)	83 (25.3)	
Never	352 (62.5)	162 (68.9)	190 (57.9)	
Binge drinking[c]	92 (16.1)	0	92 (27.7)	NA
Average alcohol use (standard drinks/week)	2.2 ± 3.6	0	3.8 ± 4.0	NA
Physical activity (exercise units/week)	295.3 ± 243.9	243.1 ± 226.1	332.6 ± 249.6	**<0.0001**
Y25 Comorbidities				
Hyperlipidemia	181 (32.0)	80 (33.9)	101 (30.7)	0.42
Hypertension	279 (50.0)	128 (53.8)	151 (45.5)	0.05
Diabetes Mellitus	164 (28.8)	89 (37.4)	75 (22.6)	**<0.0001**
Impaired glucose tolerance	261 (45.8)	99 (41.6)	162 (48.8)	**0.0005**
Peripheral vascular disease	9 (1.6)	2 (0.84)	7 (2.1)	0.82
Stroke	6 (1.1)	4 (1.7)	2 (0.61)	0.24
Obstructive sleep apnea	115 (20.3)	50 (21.0)	65 (19.7)	0.68
Metabolic syndrome[d]	340 (60.0)	157 (66.0)	183 (55.1)	**0.009**
Laboratory Values				
HOMA-IR score	5.2 ± 3.9	5.5 ± 4.1	4.9 ± 3.6	0.051
Hemoglobin A1c (%)	6.2 ± 1.3	6.5 ± 1.6	6.0 ± 1.0	**<0.0001**
Total Cholesterol (mg/dL)	191.0 ± 38.9	188.8 ± 42.1	192.4 ± 36.3	0.27
LDL cholesterol (mg/dL)	112.5 ± 33.7	112.6 ± 36.8	112.5 ± 31.3	0.96
HDL cholesterol (mg/dL)	48.5 ± 13.5	47.6 ± 11.5	49.2 ± 14.7	0.18
Triglycerides (mg/dL)	157.2 ± 133.1	149.2 ± 102.0	162.9 ± 154.5	0.23
Creatinine (mg/dL)	0.89 ± 0.25	0.87 ± 0.31	0.90 ± 0.20	0.20
Log c-reactive protein (mg/L)	1.0 ± 1.1	1.2 ± 1.1	0.92 ± 1.0	**0.002**

Year 25 covariates	NAFLD Study Sample (n=570)	Nondrinkers (n=238)	Drinkers[a] (n=332)	P value[b]
Medication usage				
Diabetes medication	126 (22.2)	72 (30.1)	54 (16.4)	**<0.0001**
Hypertension medication	223 (39.4)	109 (46.2)	114 (34.6)	**0.005**
Lipid-lowering medication	129 (22.8)	52 (22.0)	77 (23.3)	0.72
CT fat measures				
Total Abdominal Fat Volume (cm^3)	646.7 ± 193.5	689.5 ± 190.0	616.6 ± 190.6	**<0.0001**
SAT (cm^3)	426.0 ± 157.1	468.7 ± 158.0	396.0 ± 149.6	**<0.0001**
VAT (cm^3)	195.6 ± 78.0	194.3 ± 70.9	196.4 ± 82.6	0.75
Liver Attenuation (HU)	39.4 ± 11.1	40.2 ± 9.3	38.8 ± 12.2	0.12
Subclinical Atherosclerosis measure				
Coronary artery calcium score > 0	230 (38.9)	84 (34.3)	146 (42.2)	0.052
Left ventricular systolic function measures				
Left ventricular ejection fraction	69.4 ± 8.6	69.8 ± 8.8	69.2 ± 8.4	0.41
Global longitudinal strain	−14.4 ± 2.3	−14.1 ± 2.4	−14.5 ± 2.2	0.06
Left ventricular diastolic function measures				
E/A ratio	1.2 ± 0.33	1.2 ± 0.31	1.2 ± 0.34	0.41
E/e' ratio	7.6 ± 2.5	7.7 ± 2.7	7.4 ± 2.3	0.17
Septal tissue doppler e' velocity (cm/s)	8.7 ± 2.3	8.5 ± 2.3	8.9 ± 2.2	**0.04**
Cardiac structure measures				
LV mass index ($g/m^{2.7}$)[e]	44.3 ± 11.6	45.0 ± 12.5	43.8 ± 11.0	0.25
Left atrial volume index (ml/m)[f]	31.5 ± 9.0	31.9 ± 10.3	31.2 ± 8.1	0.40

Results are presented as mean ± standard deviation or number (%)

[a] General linear model for continuous variables, chi-square or Fischer exact for categorical variables for the difference between NAFLD and no NAFLD

[b] Drinkers were defined as any reported alcohol use at exam years 15 or 20 or 25 after exclusion for participants with self-reported heavy alcohol use (> 14 standard drinks/week for women; > 21 standard drinks/week for men). Nondrinkers were defined as no reported alcohol use at exam years 15 and 20 and 25.

[c] Binge drinking was defined as ≥ 5 drinks on a single occasion. Binge drinkers were included in the primary analysis only if they met moderate drinking thresholds (women ≤ 14; men ≤ 21 standard drinks/week)

[d] Defined using ATPIII criteria

[e] Indexed to height$^{2.7}$

[f] Indexed to height

NAFLD is defined as CT liver attenuation < 51 HU after exclusion for other causes of liver fat

Abbreviations: SD, standard deviation; No, number; BMI, body mass index; CT, computed tomography; CRP, c-reactive protein; LDL, low density lipoprotein; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; NAFLD, nonalcoholic fatty liver disease; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue

Table 2

Linear regression analysis for the association of alcohol use among NAFLD participants with continuous markers of subclinical abnormalities in cardiac structure, function and hemodynamics

	Measures of Cardiac Structure						Measures of Cardiac Function						Hemodynamics	
Model	**LV mass index[e]**		**LV end diastolic volume**		**Left atrial volume index[f]**		**Absolute GLS**		**E/A ratio**		**E/e' ratio**		**Cardiac output**	
	β (SE)	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**
Unadjusted[a]														
Alcohol use (y/n)	−1.3 (1.1)	0.25	−2.4 (2.8)	0.38	−0.80 (0.78)	0.30	−0.40 (0.22)	0.07	0.02 (0.03)	0.46	−0.28 (0.22)	0.19	−2.2 (1.4)	0.12
Alcohol (drinks/week)[d]	−0.34 (0.18)	0.07	0.63 (0.44)	0.15	0.06 (0.13)	0.96	−0.05 (0.03)	0.14	0.0003 (0.005)	0.94	−0.09 (0.03)	0.01	−32.9 (23.8)	0.17
Base model[b]														
Alcohol use (y/n)	−1.1 (1.2)	0.35	−6.1 (2.8)	0.07	−0.19 (0.85)	0.83	−0.42 (0.24)	0.08	−0.01 (0.03)	0.66	−0.07 (0.23)	0.76	−213.2 (155.4)	0.17
Alcohol (drinks/week)[d]	−0.25 (0.22)	0.24	−0.24 (0.49)	0.62	0.06 (0.15)	0.70	−0.05 (0.04)	0.25	−0.007 (0.005)	0.21	−0.02 (0.04)	0.59	−35.9 (28.3)	0.21
+ CVD risk factors[c]														
Alcohol use (y/n)	0.75 (1.1)	0.51	−2.1 (2.7)	0.44	0.93 (0.81)	0.25	−0.24 (0.25)	0.33	−0.04 (0.03)	0.22	0.20 (0.23)	0.38	−57.3 (152.7)	0.71
Alcohol (drinks/week)[d]	0.008 (0.21)	0.97	0.15 (0.48)	0.76	0.23 (0.15)	0.12	−0.02 (0.04)	0.73	−.001 (0.006)	0.09	0.01 (0.04)	0.73	−22.0 (28.2)	0.44

Linear regression

NAFLD is defined as CT liver attenuation < 51 HU after exclusion for other causes of liver fat

[a] Adjusted for center only

[b] Base model: center, age, race, sex, education, income level, pack-years of smoking exposure, and cumulative physical activity score

[c] CVD risk factors: cumulative systolic blood pressure (mmHg-years), cumulative total cholesterol (mg/dl-years), cumulative high density lipoprotein (HDL) cholesterol, cumulative years with diabetes, cumulative glomerular filtration rate (GFR), cumulative body mass index and number of years with treatments for hypertension and dyslipidemia

[d] Average alcohol use in standard drinks per week at exam years 15, 20 and 25

[e] Indexed to height$^{2.7}$

[f] Indexed to height

Abbreviations: NAFLD, nonalcoholic fatty liver disease; CI, confidence intervals; OR, odds ratio; CVD, cardiovascular disease; GLS, global longitudinal strain; LV, left ventricle

Table 3

Odds ratios for the association of alcohol use among NAFLD participants with markers of subclinical diastolic myocardial dysfunction

Model	Markers of Diastolic Dysfunction			
	Abnormal LV relaxation		Higher LV filling pressures	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Unadjusted[a]				
Alcohol use (y/n)	0.88 (0.62–1.27)	0.50	0.79 (0.55–1.14)	0.21
Alcohol (drinks/week)[d]	0.95 (0.87–1.02)	0.13	0.95 (0.89–1.01)	0.10
Base model[b]				
Alcohol use (y/n)	1.0 (0.66–1.52)	0.99	0.95 (0.62–1.45)	0.80
Alcohol (drinks/week)[d]	0.98 (0.91–1.06)	0.61	0.99 (0.91–1.07)	0.81
+ CVD risk factors[c]				
Alcohol use (y/n)	1.2 (0.77–1.8)	0.44	1.2 (0.75–1.88)	0.45
Alcohol (drinks/week)[d]	1.0 (0.93–1.1)	0.91	1.03 (0.94–1.12)	0.58

Logistic regression

NAFLD is defined as CT liver attenuation < 51 HU after exclusion for other causes of liver fat

Abnormal LV relaxation was defined as lateral tissue doppler e' velocity < 10. Abnormal LV filling pressures were defined as 8 < E/e' ratio < 12 and left atrial volume index ≥ 34 or E/e' ratio ≥ 12

[a] adjusted for center only

[b] base model: adjusted for center, age, race, sex, education, income level, pack-years of smoking exposure, and cumulative physical activity score

[c] CVD risk factors: cumulative systolic blood pressure (mmHg-years), cumulative total cholesterol (mg/dl-years), cumulative high density lipoprotein (HDL) cholesterol, cumulative years with diabetes, cumulative glomerular filtration rate (GFR), cumulative body mass index and number of years with treatments for hypertension and dyslipidemia

[d] Average alcohol use in standard drinks per week at exam years 15, 20 and 25

Abbreviations: NAFLD, nonalcoholic fatty liver disease; CI, confidence intervals; OR, odds ratio; CVD, cardiovascular disease, LV, left ventricle

Table 4

Odds ratios and 95% Confidence Intervals (CI) for the association of alcohol use among NAFLD participants with coronary artery calcification (CAC) score > 0

	CAC > 0	
	OR (95% CI)	**P value**
Unadjusted[a]		
Alcohol use (y/n)	1.37 (0.97–1.93)	0.08
Alcohol (drinks/week)[d]	0.95 (0.90–1.02)	0.13
Base model[b]		
Alcohol use (y/n)	1.19 (0.79–1.79)	0.41
Alcohol (drinks/week)[d]	1.03 (0.96–1.10)	0.43
+ CVD risk factors[c]		
Alcohol use (y/n)	1.46 (0.94–2.28)	0.09
Alcohol (drinks/week)[d]	1.05 (0.98–1.14)	0.19

Logistic regression

NAFLD is defined as CT liver attenuation < 51 HU after exclusion for other causes of liver fat

[a]Adjusted only for field center

[b]base model: adjusted for center, age, race, sex, education, income level, pack-years of smoking exposure, and cumulative physical activity score

[c]CVD risk factors: cumulative systolic blood pressure (mmHg-years), cumulative total cholesterol (mg/dl-years), cumulative high density lipoprotein (HDL) cholesterol, cumulative years with diabetes, cumulative glomerular filtration rate (GFR), cumulative body mass index and number of years with treatments for hypertension and dyslipidemia

[d]Average alcohol use in standard drinks per week at exam years 15, 20 and 25

Abbreviations: NAFLD, nonalcoholic fatty liver disease; CI, confidence intervals; OR, odds ratio; CAC, coronary artery calcification; CVD, cardiovascular disease

Table 5

Odds ratio and 95% Confidence Intervals (CI) for the association of alcohol use with prevalent CVD risk factors at Y25 among CARDIA participants with CT-defined NAFLD

	Y25 Diabetes		Y25 Hypertension		Y25 Hyperlipidemia	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Unadjusted[d]						
Alcohol use (y/n)	0.49 (0.34–0.71)	**0.0001**	0.72 (0.51–1.00)	0.051	0.86 (0.60–1.24)	0.42
Alcohol (drinks/week)[c]	0.90 (0.84–0.97)	**0.004**	0.97 (0.94–1.03)	0.40	0.98 (0.93–1.04)	0.57
Multivariable model[b]						
Alcohol use (y/n)	0.73 (0.46–1.15)	0.17	1.13 (0.75–1.72)	0.56	0.09 (0.59–1.38)	0.63
Alcohol (drinks/week)[c]	1.09 (0.86–1.05)	0.31	1.05 (0.97–1.13)	0.22	0.99 (0.92–1.06)	0.73

Logistic regression

NAFLD is defined as CT liver attenuation < 51 HU after exclusion for other causes of liver fat

[a]Adjusted only for field center

[b]Multivariable model: Adjusted for age, race, sex, study center, income level, educational level, pack-years of smoking exposure, and cumulative physical activity score, cumulative BMI and cumulative GFR (hypertension model only)

[c]Average alcohol use in standard drinks per week at exam years 15, 20 and 25

Abbreviations: NAFLD, nonalcoholic fatty liver disease; CI, confidence intervals; OR, odds ratio; CVD, cardiovascular disease; Y25, Year 25 exam