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Is Moderate Alcohol Use in Non-Alcoholic Fatty Liver Disease Good or Bad? A Critical Review

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Abstract

Moderate alcohol consumption in patients with nonalcoholic fatty liver disease (NAFLD) is common, yet the effects on cardiovascular and liver health are unclear. Moderate alcohol use is associated with improved insulin sensitivity and decreased cardiovascular mortality in the general population but whether similar benefits are seen in persons with NAFLD is largely unstudied. There is significant overlap in the pathogenesis of alcoholic liver disease (ALD) and NAFLD although studies of ALD have focused on pathologic alcohol intake and few mechanistic studies of moderate alcohol use in NAFLD exist. We undertook a critical review of the effect of moderate alcohol use on cardiovascular and liver disease in patients with NAFLD. A total of 7 observational studies met criteria for inclusion (one for cardiovascular endpoints and 6 for liver endpoints). There were insufficient studies to assess the association with cardiovascular outcomes. There was a positive association between moderate alcohol use and decreased NASH and fibrosis, however heavy episodic drinking may accelerate fibrosis progression and in patients with advanced fibrosis moderate alcohol use may increase the risk of hepatocellular carcinoma. Significant methodologic limitations were present including incomplete adjustment for confounders and failure to measure lifetime use or the pattern of alcohol intake. Thus, a strong recommendation of benefit of moderate alcohol use in NAFLD cannot be made. There remains a need for additional high quality longitudinal studies that evaluate both cardiovascular and liver outcomes among NAFLD patients with moderate or lesser degrees of alcohol use.

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INTRODUCTION

More than a third of the adult population in the United States is affected by NAFLD and approximately two-thirds drink alcohol, the vast majority of whom drink in moderation (1–3) The beneficial effects of moderate alcohol use on mortality have long been recognized and are largely mediated by a decrease in cardiovascular disease.(4, 5) The identification of cardiovascular mortality as the most common cause of death among patients with NAFLD raises the question of whether patients with NAFLD-associated liver disease may benefit from moderate alcohol use. At present, no clear guidelines exist on how to counsel patients with NAFLD regarding alcohol use. Indeed, alcohol use is generally discouraged in patients with concomitant liver disease due to concern for potential synergistic hepatic injury based primarily on work from animal models and studies of patients with chronic viral hepatitis. Moreover, there is significant overlap in the pathogenesis of alcoholic liver disease (ALD) and NAFLD and the concern that moderate alcohol use in patients with NAFLD can exacerbate or accelerate liver disease progression remains. This review will highlight the overlap in pathogenesis of NAFLD and ALD, critically appraises the published studies on the impact of moderate alcohol use on NAFLD including the methodological challenges in studying moderate alcohol use in persons with NAFLD and finally, examines the future research needed to bring greater clarity to this important issue.

OVERLAP IN PATHOGENESIS OF NAFLD AND ALD

Both NAFLD and ALD cause a histologic spectrum of disease ranging from isolated steatosis to steatohepatitis, which can lead to progressive fibrosis, cirrhosis and the development of hepatocellular carcinoma (HCC) and there is significant overlap in the pathogenesis underlying these two diseases (Figure 1). However, since the level of alcohol consumption leading to ALD is generally not “moderate” alcohol use, extrapolating findings from the pathogenesis of ALD to that of NAFLD with moderate alcohol use may not be appropriate. The development of hepatic steatosis is a result of increased free fatty acid (FFA) influx from dietary sources or adipocytes, increased de novo lipogenesis in the liver, or decreased FFA oxidation and triacylglycerol export.(6) Transcription factors that affect lipogenesis have been implicated in the pathogenesis of NAFLD and ALD including sterol regulatory element-binding protein 1c (SREBP-1c) and peroxisome proliferator-activated receptor alpha (PPAR-α) (6–10). In both NAFLD and ALD, the innate immune system is activated through adipocytokines that shift macrophages to an activated state.(7–9) Studies have demonstrated synergism between heavy alcohol use and obesity with increased macrophage activation, adiponectin resistance, and endoplasmic reticulum and mitochondrial stress in murine models (10) and in humans (11). However, while chronic ethanol at high doses leads to insulin resistance and macrophage infiltration into adipose tissue (8), moderate alcohol use has been associated with beneficial effects on insulin sensitivity and plasma adiponectin in observational studies (12–15) a clinical trial of post-menopausal women (16) as well as limited animal models. (17)

People at risk for NAFLD are also at risk for ALD based on overlapping genetic factors that contribute to NAFLD and ALD pathogenesis. A genetic variant in patatin-like phospholipase domain-containing 3 (PNPLA3) is associated with increased risk of steatosis, fibrosis and

HCC in both NAFLD and ALD (18–24) and a coding variant in transmembrane 6 superfamily member 2 (TM6SF2) is associated with increased risk of steatosis and fibrosis in NAFLD (25, 26) and ALD (27), but is protective against cardiovascular disease in NAFLD.(28) Epigenetic changes in DNA methylation and expression of microRNA also overlap in NAFLD and ALD.(33–39) However, these similarities may be related to the stage of fibrosis rather than similarities in pathogenesis and further studies corroborating these findings are warranted

The intestinal microbiome is also implicated in the pathogenesis of both ALD and NAFLD. In fact patients with NASH have increased microbiome mediated endogenous alcohol production compared to obese and healthy controls(29). Moderate alcohol use is associated with small intestinal bacterial overgrowth compared to teetotalers.(30) In addition, both NAFLD- and ALD-mediated dysbiosis may impact enterohepatic circulation of bile acids. Intestinal bacteria can deconjugate and dehydroxylate bile acids creating secondary bile acids. Studies of patients with both diseases reveal increased serum (31) and stool levels (32) of total and secondary bile acids, which may be more potent activators of inflammatory pathways.(33, 34) Thus, the pathogenesis of both NAFLD and ALD involve intestinal dysbiosis with resultant inflammation, activation of the innate immune system and disruption of the intestinal barrier with likely concomitant changes in bile acid metabolism.

In summary, there is significant overlap in the pathways by which NAFLD and ALD cause disease. However, as previously highlighted, the studies of these different pathways largely stem from evaluation of pathologic alcohol intake. Moderate alcohol use clearly mitigates insulin resistance, which is a driving factor in NAFLD. However, the severity of NAFLD may impact the effect of moderate alcohol intake and trigger different pathogenic pathways. Subsequently, our ability to derive a hypothesis regarding the impact of moderate alcohol use on NAFLD based on these mechanistic data are limited.

METHODOLOGICAL CONSIDERATIONS FOR CLINICAL STUDIES OF MODERATE ALCOHOL USE

No prospective randomized trials on moderate alcohol use in NAFLD exist. At present, the highest quality data on the relationship between moderate alcohol use and clinical outcomes in patients with NAFLD are derived from observational studies. There are several challenges in studying alcohol use in observational studies. **First**, since moderate alcohol use is not randomly distributed among patients with NAFLD, numerous factors differ between NAFLD patients who consume moderate amounts of alcohol and those who abstain. These factors may not only affect the pattern of alcohol use but also affect the severity of underlying liver disease thereby confounding the association between alcohol use and NAFLD. 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.(35, 36) **Second**, alcohol use is obtained by history taking, and thus subject to recall bias. Many studies of moderate alcohol use in NAFLD evaluated current drinking patterns but failed to obtain lifetime drinking histories to evaluate for prior heavy alcohol use. The

population abstaining from alcohol use may be enriched for former heavy drinkers, which could lead to selection bias and more severe liver disease or the disease may actually represent ALD.(37) Furthermore, patients with other chronic illnesses often abstain from alcohol use, which would enrich the group of abstainers with comorbid diseases.(38) **Finally**, race and sex may influence the likelihood of abstaining from alcohol and the severity of NAFLD leading to confounding. In addition, thresholds for moderate alcohol use in women are lower than in men, and use of a single cutoff can lead to misclassification. Studies of the impact of moderate alcohol use have often failed to consider these potential sources of bias and error, and thus confidence in the findings is diminished.

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.(39) Studies of alcohol use and the all cause mortality benefit of moderate alcohol use support this cutoff. (40, 41) However, the pattern of alcohol use may be relevant in assessing harm versus benefit. Measurement of alcohol consumption per week or per month without attention to daily alcohol intake may fail to exclude heavy episodic drinking. For example, the individual drinking 5 drinks/week on average, but drinking all five drinks on one day of the week may have different health outcomes from the individual drinking 1 drink on 5 of 7 days per week. At a minimum the number of days per week on which alcohol is consumed, the typical number of drinks per day and evaluation for the presence of episodic heavy drinking should be performed to more fully characterize the moderate alcohol user. Measurement of alcohol use with standardized and validated questionnaires (42, 43) brings a higher level of rigor to the measurement and facilitates comparisons across studies. As the association between liver disease and alcohol use is well known, data collected in a liver clinic or study of liver disease may lead to underreporting of alcohol use by subjects. Even if misclassification of alcohol use is non-differential (ie. all underreport use) and equally distributed among moderate users, there would be a bias towards a null association between moderate alcohol use and disease severity. If patients were aware of their disease status and those with more severe liver disease were more likely to falsely report abstaining from alcohol, a study would be biased to potentially find a protective effect of moderate alcohol use.

Study design is an additional factor affecting the assessment of associations between moderate alcohol use and disease severity in NAFLD. The vast majority of studies have been cross-sectional; meaning the outcome and predictor are measured at the same time and thereby, limiting the ability to assess temporal associations. The direction of causality cannot be determined from a cross-sectional study as patients with more severe liver disease may choose to abstain from alcohol. The optimal observational study design would adjust for confounding factors, use validated tools to measure lifetime alcohol use and pattern of use and follow patients longitudinally.

CLINICAL STUDIES OF MODERATE ALCOHOL USE IN PATIENTS WITH NAFLD

With these epidemiologic considerations in mind, we performed a critical review of the literature on alcohol use in patients with NAFLD with the goal of identifying areas of

consensus regarding moderate alcohol use in this patient group, as well as areas of uncertainty that require more research. A search of MEDLINE using overlapping MESH terms of “Non-alcoholic Fatty Liver Disease” and “Alcohol Drinking” yielded 43 results. Experts in the field were consulted for additional relevant studies (n=11). These 54 articles and their references were reviewed for the effect of moderate alcohol use on cardiovascular disease, NAFLD histology, HCC and mortality in patients with NAFLD. Guidelines, editorials, review articles (n=13) and non-English articles (n=5) were excluded. Studies with inadequate alcohol use data available as a covariate (n=4) were excluded. To be included, NAFLD was defined as the presence of steatosis on imaging or histology and studies that did not use the aforementioned definition of NAFLD (e.g. lab definition of NAFLD) were excluded (n=3). Studies that did not have data on the specified outcomes were also excluded (n=22). This strategy yielded 7 studies (Figure 2), however no studies with mortality data were available.

Cardiovascular Outcomes

Numerous studies have demonstrated the beneficial impact of moderate alcohol use on cardiovascular disease in the general population, (59–60) but only one study has specifically examined the impact of moderate alcohol use on cardiovascular outcomes in patients with NAFLD. In a cross-sectional study, Sinn et al. evaluated the association between moderate alcohol use, defined as <20 g/day, and carotid plaque or stenosis on duplex ultrasonography, as a surrogate for primary cardiovascular disease, in men with NAFLD (Table 1). Moderate alcohol use was associated with a decreased odds of carotid plaque (OR 0.74, 95% CI: 0.60–0.92) and carotid stenosis (OR 0.62, 95% CI: 0.43–0.90), compared to non-drinkers in patients with NAFLD after adjusting for age, smoking and metabolic syndrome.(44)

Liver-Related Outcomes: Severity of NAFLD and HCC

Six studies examined the association between moderate alcohol use and liver-related outcomes, specifically severity of disease including fibrosis; one study focused on HCC. Dunn et al. performed a cross-sectional evaluation of moderate alcohol use among patients from the NASH Clinical Research Network, excluding those who drank >20 g/day, binge drinkers, and non-drinkers with a history of alcohol use, and focusing on NASH on liver biopsy as the primary outcome and with secondary outcomes including fibrosis stage and characteristics of the NAFLD activity score (NAS) (45) (Table 1). The odds of NASH among moderate alcohol users was reduced compared to abstainers (OR=0.52, 95% CI: 0.36–0.76, P=0.0006) after adjustment for sex, race, age, income, education, BMI, physical activity, smoking, total calories and percent calories from fat. In addition, the adjusted OR for a one-unit increase in fibrosis stage (0–4) among moderate drinkers was 0.56 (95% CI: 0.41–0.78, P=0.0005). Kwon et al. performed a cross-sectional study of 77 patients with suspected NAFLD and moderate alcohol use defined by ≥24 gram-years and liver fibrosis using liver biopsy. Patients who reported >40g/week or a history of alcohol dependence or abuse in the past were excluded. The odds of severe fibrosis (F3 or 4) were significantly lower (OR=0.26, 95%CI: 0.07–0.97, p=0.046) in those drinkers of ≥ 24 gram-years of alcohol compared to those drinking <24 gram-years, after adjusting for age, sex, BMI, insulin resistance and percent total body fat. There was a similar protective effect in those consuming 10–24 gram-years of alcohol but none in those with > 40 gram-years. The study

was unable to adjust for the possibility that participants with severe liver disease may have not consumed alcohol as a result of their liver disease.(46) Collectively, these studies in persons with NAFLD suggest a significant association between moderate alcohol consumption and less severe histological liver disease. Strengths of the studies include the use of a standardized questionnaire of lifetime drinking to capture the exposure of interest and use of liver biopsy to define the outcome of interest. Limitations relate to study design and the inability to establish a causal relationship between alcohol use and subsequent liver disease severity.

Other studies have focused on more select populations, specifically those with morbid obesity. A cross-sectional study from Dixon et al. of 108 bariatric surgery patients (BMI >35 mg/m^2), found that moderate alcohol consumption was associated with decreased odds of diabetes and NASH on unadjusted analysis compared to those who did not consume alcohol. The study excluded those with a history of alcoholism or consumption of >200 g/week. After adjustment for diabetes or insulin resistance the association between moderate alcohol use and NASH was no longer statistically significant.(47) (Table 1) In this case, adjusting for insulin resistance may represent adjusting for a mediator of the beneficial impact of moderate alcohol on NASH, thereby eliminating the association. Cotrim et al. evaluated the association between alcohol use and histology in another cross-sectional study of 132 morbidly obese patients undergoing bariatric surgery (body mass index above 40 kg/m^2, or above 35 kg/m^2 associated with other conditions) (Table 1). Patients who drank > 280 g/ week were excluded. There was no adjustment for covariates and liver histology was split into four categories of NAFLD; isolated steatosis, steatosis with inflammation, steatohepatitis (steatosis and ballooning) and steatohepatitis with fibrosis. The OR for steatohepatitis with or without fibrosis compared to isolated steatosis or steatosis plus inflammation among moderate alcohol users compared to non-drinkers was 2.69 (95% CI: 0.14 – 161.3, p=0.41). Only three patients had NAFLD without steatohepatitis which limited the precision of the study to evaluate the effect of moderate alcohol on NAFLD histology. (48) Thus, these studies in bariatric surgery patients report conflicting associations between moderate alcohol use and NASH but are limited by small sample sizes and inadequate adjustment for potential confounders.

A more ideal study design would be a prospective study with repeat assessments of alcohol use and liver histology that can better establish a causal association than cross-sectional studies. In the 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 heavy episodic drinking was associated with fibrosis progression. Alcohol use was assessed at follow up biopsy using the AUDIT-C questionnaire plus an additional question to assess for changes in drinking habits since the first liver biopsy. Only 68 repeat biopsies were available to assess for the outcome and 25 patients that died during follow up were excluded. Information on heavy episodic drinking defined as more than 60g/day in males and 48g/day in females was ascertained. Median alcohol consumption was higher in patients who progressed than those who did not, 38 g/week vs 17 g/week p=0.061, however only six patients were non-drinkers, which limited analysis of modest alcohol use versus abstention. Heavy episodic drinking, without exceeding 140 g/week had a strong association with fibrosis progression with an unadjusted OR of 7.11 (95% CI: 1.99–25.5 p=0.003).(49) This

highlights the importance of characterizing patterns of alcohol use as well as average daily use, since patients who attest to heavy episodic drinking are at increased risk of disease progression even if the total amount of alcohol consumed weekly falls within current definitions of moderate use.

Finally, in addressing one of the most serious liver-related outcomes of NAFLD, Ascha and colleagues examined the association between moderate alcohol use and HCC. Among patients with NASH cirrhosis followed prospectively, moderate alcohol use was associated with an increased risk of HCC, HR 3.8 (95% CI: 1.6–8.9; p=0.002).(50) This study was limited to patients with established cirrhosis and evaluation of the impact of moderate alcohol use in patients with less severe disease is limited by a low incidence rate of HCC and the long latent period between development of NAFLD and development of HCC.

Summary of Clinical Studies

Currently, data suggests a possible association between moderate alcohol use and decreased NASH and fibrosis, however, the limitations of these studies are well-appreciated. A single study evaluating the relationship between cardiovascular disease and moderate alcohol use in a population with NAFLD demonstrated a benefit. Exceeding the bounds of moderate alcohol use through heavy episodic drinking is associated with fibrosis progression in a single study and moderate alcohol use is associated with an increased risk of HCC in patients with NAFLD cirrhosis.

FUTURE DIRECTIONS

Studies of the effect of moderate alcohol use on cardiovascular disease, NASH histology, fibrosis and HCC have yielded mixed results, and support the need for additional, high quality studies to be conducted. While many studies have examined moderate alcohol and its association with cardiovascular outcome, very few have been done in persons *with* NAFLD. Ideally, such studies in patients with NAFLD would be longitudinal, evaluate the interrelationships between moderate alcohol, serum lipids and insulin resistance, and how they are associated with cardiovascular endpoints. Furthermore, the effect of genetic factors should be considered, particularly TM6SF2, in which a coding variant is associated with less cardiovascular disease at the expense of an increased risk of liver disease. Additional evaluation of the impact of moderate alcohol on liver related outcomes is also needed. Again, genetic factors including PNPLA3 status should be considered as well as the severity of NAFLD as patients with isolated steatosis may respond differently than those with NASH with fibrosis. Longitudinal studies should be performed with attention to appropriate measurement of the type and pattern of alcohol use, adjustment for confounding factors, and patient selection. Changes in alcohol use patterns over time may be informative in longitudinal studies and a more detailed dose-response relationship should be explored among moderate users. In addition, the type of alcohol may be relevant and should be measured. In particular polyphenols in red wine, including resveratrol, may have beneficial effects on lipids and antioxidant properties and previous studies have suggested that modest red wine may be protective against NAFLD (51). Effect modification by degree of obesity, race and sex should also be explored.

CONCLUSIONS

There is insufficient evidence for or against moderate alcohol consumption in NAFLD. Key to future studies is the recognition of possible variable impact of moderate alcohol use across the different stages of NAFLD and the inclusion of both cardiovascular and liver-related outcomes. Certainly, the cross-sectional association between moderate alcohol use and decreased disease severity warrants further longitudinal study. With NASH and advanced fibrosis, concerns for liver related harm including an increase in the risk of HCC will be a barrier to further study of moderate alcohol use. Conversely, in patients with NAFLD without NASH, the cardiovascular benefits of moderate alcohol use may outweigh theoretical liver related harms and is a priority for future research. In conclusion, alcohol use and NAFLD have the potential to influence cardiovascular and liver health and therefore, there is high need to better understand the risk versus harm of moderate alcohol use across the spectrum of NAFLD patients.

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Abbreviations

NAFLD	non-alcoholic fatty liver disease
ALD	alcoholic liver disease
FFA	free fatty acid
SREBP-1c	sterol regulatory element-binding protein 1c
PPAR-α	peroxisome proliferator-activated receptor alpha
PNPLA3	patatin-like phospholipase domain-containing 3
TM6SF2	transmembrane 6 superfamily member 2
NASH	non-alcoholic steatohepatitis
SIBO	small intestinal bacterial overgrowth
HCC	hepatocellular carcinoma
NAS	NAFLD activity score

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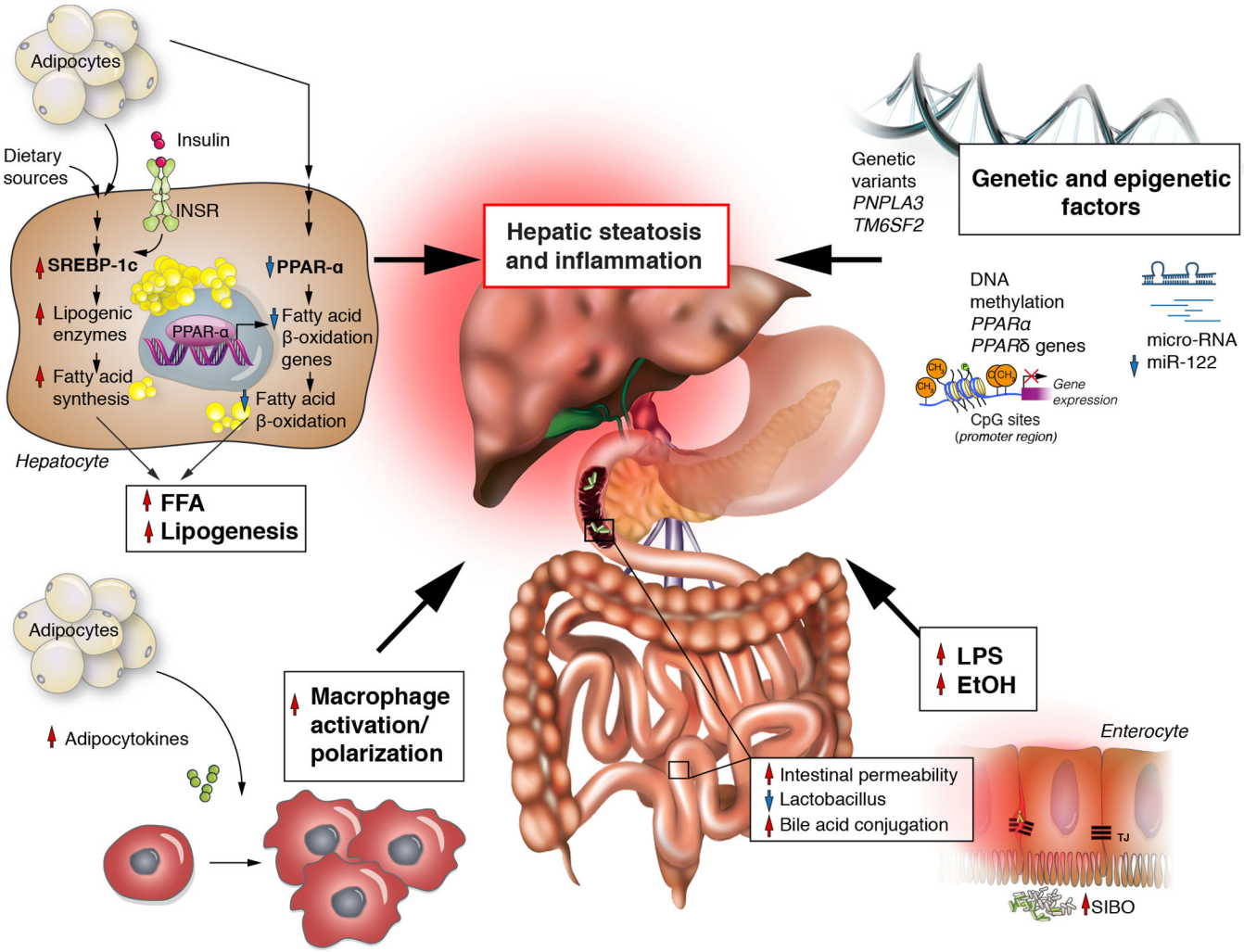

Figure 1.
Overlap in Pathogenesis in NAFLD and ALD

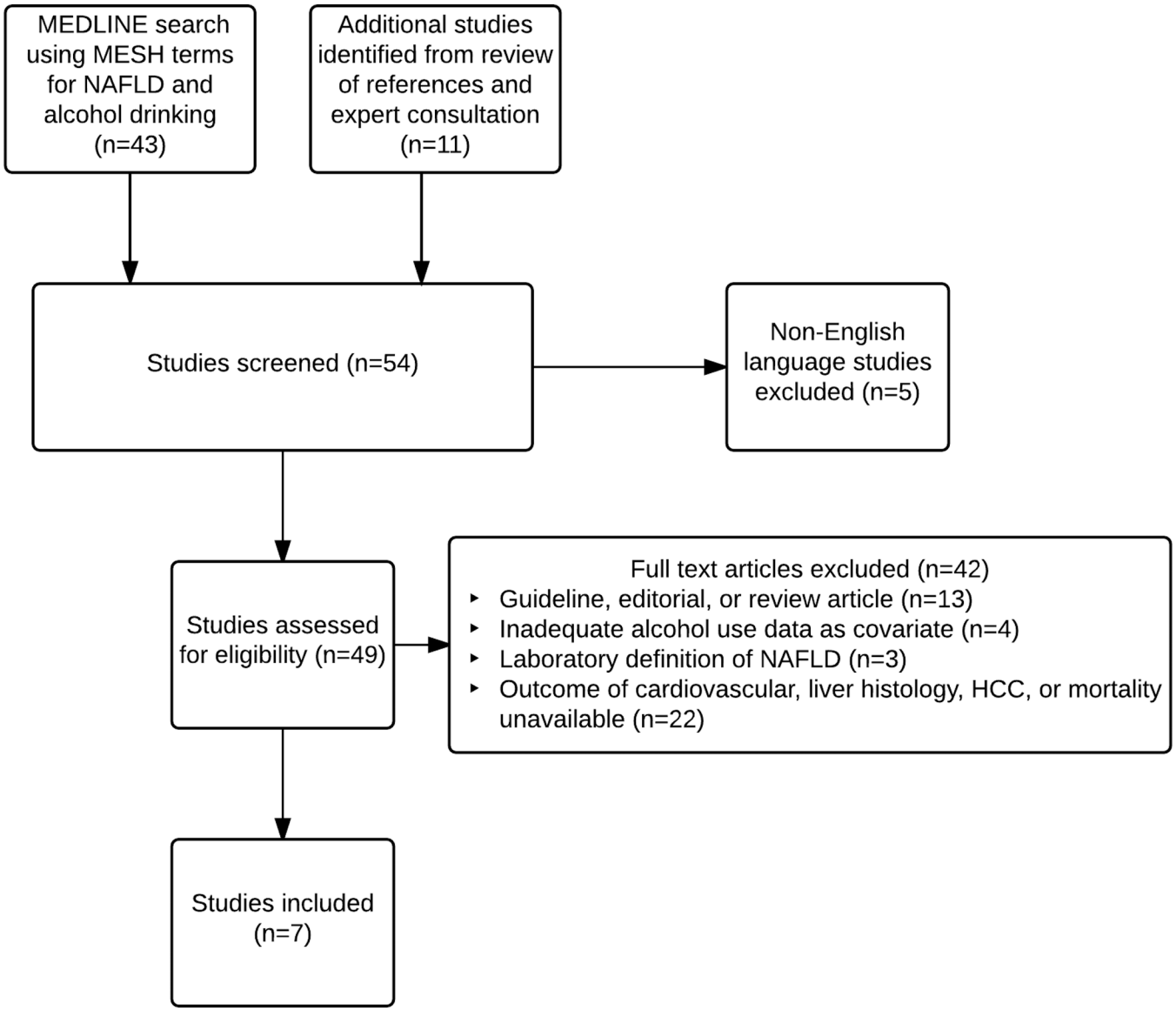

Figure 2.
Flow diagram of studies included from critical review

Table 1

Summary of studies of moderate alcohol use in NAFLD

Author, year	Outcome Measure	Study Design and Population	Sample Size	Criteria for NAFLD	Definition of Moderate Alcohol Use Method of Assessing Alcohol Use	Potential Methodological Concerns	Results
Sinn DH[61], 2014	Carotid plaque & carotid stenosis by ultrasound	Cross-sectional Korean men undergoing routine health check-up	2280 with NAFLD, 1797 with moderate alcohol use	Ultrasound	<20 g/day average Self-administered questionnaire	Limited to Korean men Adjusted for age, smoking, MS but not socioeconomic status and physical activity	Carotid plaque: OR 0.74 (95% CI: 0.60–0.92), Carotid stenosis, OR 0.62 (95% CI: 0.43–0.90) among moderate alcohol users vs non-drinkers
Dunn W[62], 2012	NASH & Increase in fibrosis stage on liver biopsy	Cross-sectional Men and women in the US at risk for NAFLD	582 with NAFLD, 331 moderate alcohol use	Liver Biopsy	< 20 g/day, not a binge drinker and not a former user currently abstaining Lifetime Drinking History (past) and AUDIT (current) questionnaires	Lack of sex-specific modest alcohol use cut-off	NASH: OR 0.52 (95% CI:0.36–0.76, P=0.0006) Higher fibrosis stage: 0.56 (95% CI: 0.41–0.78, P=0.0005) among moderate alcohol users vs lifelong non-drinkers
Cotrim HP[64], 2009	NASH on liver biopsy	Cross-sectional Brazilian men and women undergoing bariatric surgery	132 patients with NAFLD, 75 moderate alcohol use	Liver Biopsy	< 40 g/day & less than 280g/week Physician interview of patient and relatives	Select population: morbidly obese Lack of adjustment for confounders Modest statistical power	NASH: OR 2.69 (95% CI: 0.14 – 161.3, P=0.41) among moderate alcohol users versus non-drinkers
Dixon JB[65], 2011	NASH on liver biopsy	Cross-sectional Australian men and women	108 patients with NAFLD, 57 moderate alcohol use	Liver Biopsy	< 200 g/week Physician interviews and questionnaire	Select population: morbidly obese Lack of adjustment for confounders Modest statistical power	NASH: OR 0.35 (95% CI: 0.12 – 1.0, P=0.04) among alcohol users versus abstainers in univariate; not significant after adjustment for diabetes or IR
Ekstedt M[66], 2009	Fibrosis progression by more than one stage on follow up biopsy or clinical evidence of the development of cirrhosis	Prospective cohort Scandinavian men and women	71 patients with NAFLD, 65 with moderate alcohol use	Liver Biopsy	< 140 g/week AUDIT-C questionnaire plus an additional question to assess for changes in drinking habits	Modest statistical power Lack of adjustment for confounders, Possible selection bias from 25 patient deaths and low study retention	Fibrosis progression: OR of 7.11 (95% CI: 1.99–25.5, P=0.003) for heavy episodic drinkers vs. those without heavy episodic drinking

Author, year	Outcome Measure	Study Design and Population	Sample Size	Criteria for NAFLD	Definition of Moderate Alcohol Use Method of Assessing Alcohol Use	Potential Methodological Concerns	Results
					from time of first biopsy		
Kwon HK[63], 2014	Advanced fibrosis, stage 3–4	Cross-sectional Men and women in the US with suspected NAFLD	77 patients with NAFLD, 52 with moderate alcohol use	Liver Biopsy	< 40 g/week, evaluated Lifetime Drinking History with total gm-years determined by average g/day × years of drinking	Possible reverse causation patients with more advanced disease may have decreased alcohol consumption Limited sample size for multivariate adjustment	Advanced Fibrosis: OR 0.26 (95%CI: 0.07–0.97, p=0.046) among those with lifetime ≥24 gram-years of alcohol compared to <24 gram-years alcohol use
Ascha MS[67], 2010	Hepatocellular Carcinoma (HCC) on imaging	Cohort Men and women in the US	195 NAFLD patients, 58 with moderate alcohol use	Liver Biopsy or cryptogenic cirrhosis + metabolic syndrome without alcohol abuse	< 2 drinks daily or 3–6 drinks daily on weekends Method of ascertainment not stated	No adjustment for confounders, limited to cirrhotic patients, included 10 former heavy drinkers among alcohol users	HCC: HR 3.8 (95% CI: 1.6–8.9; p=0.002) For any alcohol use adjusted for age at cirrhosis diagnosis