

Alcohol consumption in patients with nonalcoholic fatty liver disease: yes, or no?

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Abstract

Excessive alcohol intake is an established risk factor for chronic liver disease. At the same time, moderate alcohol intake appears to reduce cardiovascular morbidity. Accordingly, recommendations for alcohol intake in patients with nonalcoholic fatty liver disease (NAFLD), who are at increased risk for liver-related and cardiovascular events, are a point of debate. Some studies have shown beneficial effects of alcohol on cardiovascular and overall mortality in this specific subset of patients. Nonetheless, even light alcohol intake appears to aggravate liver disease and increase the risk of hepatocellular cancer. Therefore, patients with nonalcoholic steatohepatitis or advanced fibrosis should be advised against consuming alcohol. On the other hand, only light alcohol consumption (<10 g/day) might be permitted in patients without significant hepatic fibrosis, provided that they are carefully followed-up. As the research field focusing on NAFLD keeps widening, more prospective studies regarding this specific subject are expected, and may provide a basis for less ambiguous recommendations.

Keywords Nonalcoholic fatty liver disease, alcohol, cardiovascular disease, hepatocellular cancer, fibrosis

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease. It affects as many as one-fourth of the general population worldwide, being more frequent in patients with metabolic syndrome (MetS) or its components than in the general population [1]. NAFLD diagnosis requires that the patient does not exhibit daily alcohol consumption of ≥ 30 g for men or ≥ 20 g for women [2]. NAFLD can progress from isolated steatosis to nonalcoholic steatohepatitis (NASH), which encompasses, besides steatosis, ballooning hepatocellular injury, inflammation and liver fibrosis, and might evolve to

cirrhosis or even to hepatocellular carcinoma (HCC) [3,4]. Patients with NAFLD are at high risk for cardiovascular disease and are more likely to die from coronary heart disease than hepatic disease; indeed, cardiovascular disease is the most common cause of death in this population [5-7]. Modification of cardiovascular risk factors includes lifestyle interventions, such as regular physical exercise, and weight loss [8]. In addition, moderate alcohol consumption also appears to reduce the risk of coronary heart disease [9]. On the other hand, excessive alcohol consumption is an established risk factor for liver disease, with various cofactors influencing liver disease development in patients with excessive alcohol use (Fig. 1) [10-23]. However, accumulating data suggest that moderate alcohol intake might reduce NAFLD incidence [24]; the mechanisms possibly involved (studied in both animal and human models) are illustrated in Fig. 2 [25-31]. Taking these conflicting effects of alcohol into account, it is of great interest to elucidate the role of light and moderate alcohol consumption in NAFLD, in order to counsel these patients regarding alcohol use. There have been relatively recent reviews regarding the subject in question [32,33], but because of the constant publication of new studies on the subject, many critical studies are not included in these reviews, which significantly alter prior beliefs regarding alcohol use in NAFLD. This narrative review aims to summarize recent developments in this field and encapsulate how these developments affect recommendations regarding alcohol consumption in NAFLD.

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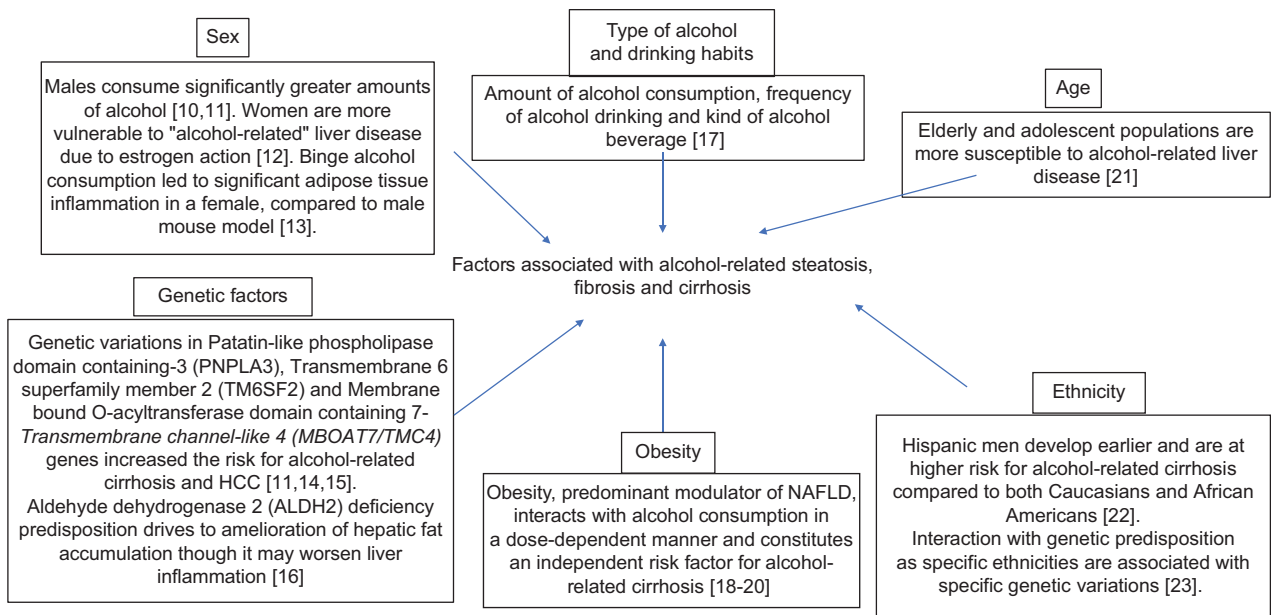


Figure 1 Individual phenotypic and genetic factors associated with alcohol-induced liver steatosis, fibrosis and cirrhosis
NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma

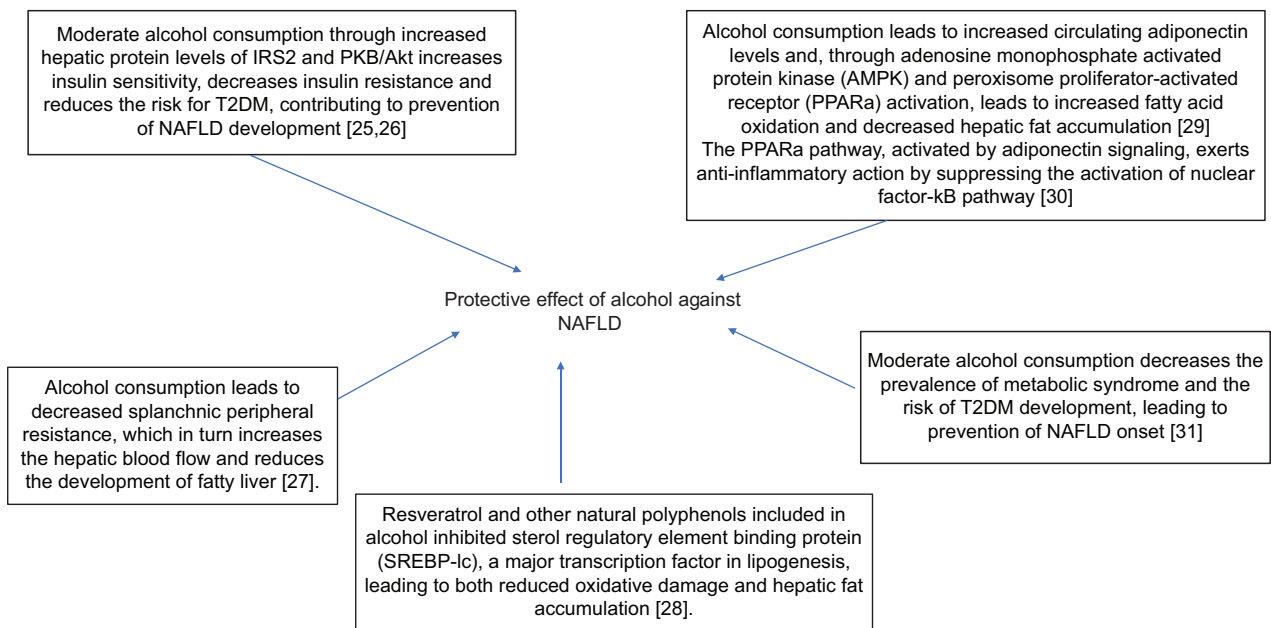


Figure 2 Mechanisms of the beneficial impact of moderate alcohol consumption on NAFLD development
NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus

Literature search

To find relevant studies, we conducted a thorough search in the PubMed, Google Scholar and Cochrane Library databases through December 2020. Search terms included "NAFLD", "non-alcoholic fatty liver disease", "hepatic steatosis", "fatty liver", "alcohol", and "ethanol". We also searched the references of selected studies and relevant reviews for unidentified studies. The studies that were included analyzed outcomes in patients

with NAFLD (or NAFLD incidence) with regard to levels of alcohol consumption.

Does alcohol prevent the development of fatty liver?

The common histopathological features shared between NAFLD and alcoholic liver disease (ALD) [34], as well as the

fact that one is frequently misclassified as the other [35], can be partially explained by the shared mechanisms contributing to the emergence of both diseases [36,37]. However, only one study showed that alcohol consumption increases the risk of NAFLD. Long *et al* evaluated the correlation between the presence of hepatic steatosis (assessed by computed tomography) and alcohol consumption in 2475 participants of the Framingham study [38], after excluding heavy drinkers. The number of alcoholic drinks consumed per week was an independent predictor of steatosis (odds ratio [OR] 1.15, 95% confidence interval [CI] 1.02-1.29).

In contrast, several studies support the notion that moderate alcohol consumption can have a protective effect against NAFLD development. In a large study, Hashimoto *et al* evaluated 5437 healthy Japanese individuals on a regular checkup program for over a decade [39]. The hazard ratios (HR) for newly diagnosed fatty liver in subjects with light (40-140 g/week) and moderate (140-280 g/week) alcohol consumption compared with those with no or minimal alcohol consumption (<40 g/week) were 0.72, 95%CI 0.60-0.86, and 0.69, 95%CI 0.57-0.84 ($P<0.001$), respectively, in men. In women, alcohol consumption was not associated with the incidence of NAFLD. Another study in Japanese men reported similar findings; light (40-140 g/week) and moderate alcohol intake (140-280 g/week) were associated with a reduced risk for fatty liver development, compared to null drinking consumption (OR 0.82, 95%CI 0.68-0.99 and 0.75, 95%CI 0.61-0.93, respectively) [40]. Interestingly, Hiramine *et al* showed that not only light (<20 g/day, OR 0.71, 95%CI 0.59-0.86) and moderate (20-60 g/day, OR 0.55, 95%CI 0.45-0.67), but also heavy (>60 g/day, OR 0.44, 95%CI 0.32-0.62) alcohol drinking was associated with decreased odds for fatty liver compared to non-drinkers in Japanese men [41], confirmed by another study from Asia [42]. In accordance with the studies mentioned above, Hamaguchi *et al* performed a cross-sectional study on 18,571 Japanese individuals. They reported that any level of alcohol consumption—light (40-140 g/week, OR 0.69, 95%CI 0.6-0.79), moderate (140-280 g/week, OR 0.72, 95%CI 0.63-0.83) and excessive (>280 g/week, OR 0.74, 95%CI 0.64-0.85) compared with no or minimal (<40 g/week) was associated with decreased odds for fatty liver in men. In contrast, in women, light (OR 0.54, 95%CI 0.34-0.88) and moderate (OR 0.43, 95%CI 0.21-0.88) alcohol intake decreased the likelihood of the presence of fatty liver [43]. Finally, a recent study by Chang *et al* showed that light (<10 g/day) and moderate (10-20 g/day) drinking were independently associated with a lower incidence of NAFLD compared to non-drinkers (HR 0.93, 95%CI 0.90-0.95, and HR 0.90, 95%CI 0.87-0.92, respectively) [44]. However, light and moderate drinkers were more susceptible to developing NAFLD with significant fibrosis (FIB-4 >1.3) compared to non-drinkers (HR 1.15, 95%CI 1.04-1.27, and HR 1.49, 95%CI 1.33-1.66, respectively).

Several studies also suggest that more frequent alcohol consumption might also decrease the risk of NAFLD. Hiramine *et al* [41] reported that the prevalence of fatty liver was negatively correlated with alcohol drinking (OR 0.62, 95%CI 0.53-0.71 for ≥ 21 days/month vs. ≤ 10 days/month). Similarly, in the cross-sectional study by Moriya *et al*, an inverse association

between the prevalence of fatty liver and alcohol consumption frequency was observed in men [45]. In women, drinking <20 g alcohol during 1-3 days/week was also associated with a reduced prevalence of fatty liver [45]. A longitudinal study from the same group in 5297 Japanese individuals showed that the frequency of alcohol consumption was inversely associated with fatty liver in men (OR 0.81, 95%CI 0.71-0.93, OR 0.68, 95%CI 0.58-0.78, and OR 0.64, 95%CI 0.56-0.73, for 1-3 days/week, 4-6 days/week and daily, respectively); in women, daily alcohol consumption was also associated with a lower incidence of fatty liver (OR 0.60, 95%CI 0.40-0.90) [46]. In another study from Japan, Sogabe *et al* assessed 1055 men with MetS and NAFLD and reported that the prevalence of NAFLD was lower in light drinkers (consuming <20 g of alcohol/drinking day) than in non-drinkers [47]. Finally, a meta-analysis by Sookoian *et al* confirmed the findings of previous studies, showing that moderate consumption (<40 g/day) was associated with lower odds of NAFLD (OR 0.68, 95%CI 0.58-0.81) and NASH (OR 0.5, 95%CI 0.34-0.74) development, compared to non-drinkers [48].

It should be emphasized that most of the studies that evaluated the impact of alcohol consumption on the incidence of fatty liver were performed in Asian and mostly Japanese populations. Therefore, the generalizability of their findings in non-Asian subjects is an open question. Also, it should be noted that many of these studies use definitions of moderate alcohol consumption that are nowadays considered to be equivalent to alcohol-related liver disease. Studies investigating the effect of alcohol consumption on the development of NAFLD are summarized in Table 1.

Is alcohol associated with less severe histological lesions in NAFLD patients?

To evaluate the impact of alcohol consumption on the severity of hepatic fibrosis in patients with NAFLD, Hagström *et al* prospectively studied 120 patients with biopsy-proven NAFLD and evaluated their lifetime alcohol use using questionnaires [49]. After adjusting for physical activity, and soft drink and coffee consumption, the odds for severe fibrosis decreased for each additional alcohol unit consumed (i.e., 12 grams of alcohol) for up to a maximum of 13 drinks/week (OR 0.86, 95%CI 0.76-0.97); moreover, subjects in the top quartile of alcohol consumption (3.1-13.3 alcohol units/week) had the lowest risk for severe fibrosis (OR 0.23, 95%CI 0.08-0.66). Furthermore, patients who consumed alcohol more than the median (1.1 units of alcohol/week) had lower levels of markers of subclinical inflammation (tumor necrosis factor and high-sensitivity C-reactive protein) and higher total cholesterol levels compared with those who consumed lower amounts of alcohol [49]. In accordance with these findings, a study from the USA in 77 patients with histologically confirmed NAFLD showed that those with overall lifetime alcohol use ≥ 24 gram-years had less advanced fibrosis, lower percent total body fat and lower total cholesterol levels compared with those who had consumed <24 gram-years of alcohol [50]. Gram-years were

Table 1 Studies investigating the effect of alcohol consumption on the development of NAFLD

Study/ year/ country/ type	Study population/ NAFLD diagnosis	Outcome: Development of NAFLD (statistically significant correlations)	Comments
Long <i>et al</i> [38] 2019 / USA Cross-sectional	- 2475 participants of the Framingham study - Computed tomography	- Alcohol consumption (drinks/week) independently correlated with the development of liver steatosis - Binge drinking was independently associated with presence of steatosis - Wine consumption was not associated with steatosis	- Exclusion of heavy drinkers (>14 or >21 drinks/week for women and men respectively)
Hashimoto <i>et al</i> [39] 2015 / Japan Longitudinal	- 5437 healthy subjects undergoing repeated health checkups - Abdominal ultrasound	- Light (40-140 g/week) and moderate (140-280 g/week) alcohol consumption vs. minimal or no (<40 g/week) alcohol consumption (HR 0.72 [95%CI 0.60-0.86] and 0.69 [95%CI 0.57-0.84] respectively)	- High alcohol thresholds for moderate drinkers - Results were significant only for men
Gunji <i>et al</i> [40] 2009 / Japan Cross-sectional	- 5599 men having a health checkup - Abdominal ultrasound	- Light (40-140 g/week) and moderate (140-280 g/week) alcohol intake vs. abstinence (<40 g/week) (OR 0.82 [95%CI 0.68-0.99] and 0.75 [95%CI 0.61-0.93], respectively)	- High alcohol thresholds for moderate drinkers
Hiramine <i>et al</i> [41] 2011 / Japan Cross-sectional	- 9886 men undergoing a health checkup, aged 30-69 years - Abdominal ultrasound	- Light (<20 g/day), moderate (20-60 g/day) and heavy (>60 g/day) vs. non-drinkers (OR 0.71 [95%CI 0.59-0.86], 0.55 [95%CI 0.45-0.67] and 0.44 [95%CI 0.32-0.62], respectively) - Frequent (>21 days/month) vs rare consumption (<10 days/month) (OR 0.62[95%CI 0.54-0.71])	- High alcohol thresholds for moderate drinkers
Yamada <i>et al</i> [42] 2010 / Japan Cross-sectional and longitudinal	- 12453 (5444 male and 4980 female) healthy subjects undergoing health checkups in 2002-2005 - Abdominal ultrasound	- Cross-sectional: moderate (one drink/day) and heavy (≥ 2 drinks/day) alcohol intake vs. non-drinkers (OR 0.58 [95%CI 0.52-0.63]/0.57 [95%CI 0.52-0.63] for men and 0.53 [95%CI 0.43-0.64]/0.85 [95%CI 0.60-1.23] for women) - Longitudinal/ Men: daily moderate and heavy alcohol intake vs. non-drinkers (OR 0.72 [95%CI 0.58-0.89]/0.65 [95%CI 0.50-0.85])	- Longitudinal study: Exclusion of patients who had NAFLD at the first checkup - Non-significant results for women in the longitudinal study
Hamaguchi <i>et al</i> [43] 2012 / Japan Cross-sectional	- 18571 (10982 men and 7589 women) healthy subjects undergoing a health checkup - Abdominal ultrasound	- Light (40-140 g/week) and moderate (140-280 g/week) vs. minimal or no (<40 g/week) alcohol consumption (OR 0.69 [95%CI 0.6-0.79], 0.72 [95%CI 0.63-0.83] for men and 0.54 [95%CI 0.34-0.88], 0.43 [95%CI 0.21-0.88] and for women, respectively) - Men: Heavy vs. minimal or no alcohol consumption (OR 0.74 [95%CI 0.64-0.85])	- High alcohol thresholds for moderate drinkers - Alcohol consumption had no significant effect on the incidence of metabolic syndrome
Chang <i>et al</i> [44] 2020 / S. Korea Retrospective	- 190048 subjects without NAFLD at baseline - Abdominal ultrasound - Median follow up: 4.1 years	- NAFLD: Light (<10 g/day), moderate (10-20 g/day vs. non-drinkers (HR 0.94 [95%CI 0.90-0.95] and 0.90 [95%CI 0.87-0.92], respectively) - Significant fibrosis: Light (<10 g/day), moderate (10-20 g/day vs. non-drinkers (HR 1.15 [95%CI 1.04-1.27] and 1.49 [95%CI 1.33-1.66], respectively)	- Significant fibrosis was assessed with the use of FIB-4 - Low BMI of the study population (mean: 22 kg/m ²)
Moriya <i>et al</i> [45] 2011 / Japan Cross-sectional	- 7112 (4957 men and 2155 women) healthy subjects undergoing a health checkup - Abdominal ultrasound	- Men: Light (<70 g/week), moderate (70-140 g/week), heavy (140-280 g/week) and overt (>280 g/week) vs. no alcohol consumption (OR 0.75 [95%CI 0.60-0.94], 0.62 [95%CI 0.49-0.77], 0.50 [95%CI 0.41-0.61] and 0.40 [95%CI 0.32-0.49], respectively) - Women: Light (<70 g/week) vs no alcohol consumption (OR 0.72 [95%CI 0.53-0.97])	- In men, increasing alcohol consumption was associated with a further decrease in odds for NAFLD, while in women, only light alcohol consumption conferred a benefit
Moriya <i>et al</i> [46] 2015 / Japan Longitudinal	- 5297 (3773 men and 1524 women) healthy subjects undergoing repeated health checkups in 2003-2006 - Abdominal ultrasound	- Men: Light (<70 g/week), moderate (70-140 g/week), heavy (140-280 g/week) and overt (>280 g/week) vs. no alcohol consumption (OR 0.79 [95%CI 0.68-0.90], 0.73 [95%CI 0.63-0.84], 0.69 [95%CI 0.60-0.79] and 0.68 [95%CI 0.58-0.79], respectively)	- In men, increasing consumption was associated with a decrease in odds for NAFLD, while in women, there was no significant difference among all groups
Sogabe <i>et al</i> [47] 2015 / Japan Cross-sectional	- 1055 men with metabolic syndrome - Abdominal ultrasound	- Light (<20 g/day) alcohol consumption vs. non-drinkers (OR 0.65 [95%CI 0.47-0.91])	- Only analyzed patients with light alcohol consumption (<20 g/day)
Sookoian <i>et al</i> [48] 2013 / Meta-Analysis	Research on NAFLD development: 43175 patients Research on NASH development: 822 patients	- Moderate consumption (<40 g/day) was associated with lower odds of NAFLD (OR 0.68 [95%CI 0.58-0.81]) and NASH (OR 0.5 [95%CI 0.34-0.74]) development, compared to non-drinkers	- High alcohol thresholds for moderate drinkers - Significant heterogeneity in NAFLD studies, none in NASH studies

NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; HR, hazard ratio; CI, confidence interval; NASH, nonalcoholic steatohepatitis

calculated by multiplying the amount of alcohol consumed per day and consumption duration in years. Notably, patients still drinking alcohol or abstinent for ≤ 1 year had lower fibrosis scores and total body fat percent than patients who abstained from alcohol for >1 year. Notably, in a cross-sectional study that included 582 patients with biopsy-proven NAFLD—331 modest drinkers (≤ 20 g of alcohol daily) and 251 lifetime non-drinkers—moderate drinkers, compared with non-drinkers, had lower odds of having steatohepatitis, fibrosis, hepatocellular ballooning and Mallory-Denk bodies on liver biopsy (OR 0.52, 95%CI 0.36-0.76, OR 0.56, 95%CI 0.41-0.78, OR 0.62, 95%CI 0.45-0.87, and OR 0.65, 95%CI 0.43-0.98, respectively) [51]. Consistently, a cross-sectional study from Australia reported that low (<20 g/week) and moderate (20-100 g/week) consumption was associated with a lower risk for diabetes mellitus (OR 0.18, 95%CI 0.05-0.67), NASH (OR 0.35, 95%CI 0.12-1) and Mallory bodies in liver biopsy (OR 0.16, 95%CI 0.03-0.76) compared to no consumption. However, after adjustment for diabetes or insulin resistance index, alcohol consumption's beneficial effect on NASH severity was not confirmed [52]. Finally, Mitchell *et al* reported that patients with NAFLD who consumed modest (<70 g/week) and moderate (≥ 70 g/week) amounts of alcohol, compared to lifetime non-drinkers, had lower ballooning and fibrosis scores [53]. Notably, only modest alcohol consumption was associated with lower odds for advanced fibrosis (OR 0.33, 95%CI 0.14-0.78) after adjusting for age, diabetes, body mass index (BMI), homeostatic model assessment, sex, and overall lifetime alcohol consumption, whereas binge alcohol drinking was not associated with a lower fibrosis stage [53]. It should be mentioned that patients who consumed only wine, compared to lifetime non-consumers, had a lower fibrosis stage and risk for severe fibrosis (OR 0.20, 95%CI 0.06-0.69), whereas this protective effect was not observed in exclusive beer drinkers.

Given the limitations of self-reported alcohol consumption, Sookoian *et al* used a genetic variant (rs1229984 A;G) in the alcohol dehydrogenase (*ADH1B*) gene as a proxy of long-term alcohol exposure and evaluated its association with the severity of histological lesions in patients with NAFLD [54]. Carriers of this polymorphism were found to consume lower amounts of alcohol than non-carriers. In contrast to the aforementioned studies' findings, carriers of this polymorphism had less severe steatosis and inflammation than non-carriers, whereas the fibrosis stage did not differ between the 2 groups. Moreover, several studies reported that increased alcohol consumption is associated with liver disease progression in patients with NAFLD. Ekstedt *et al* evaluated 71 patients with NAFLD diagnosed by liver biopsy [55]. The authors divided the patients according to disease progression as having insignificant or significant changes in liver biopsy (significant defined as worsening of ≥ 2 stages of fibrosis). After a mean follow up of 13.8 years, reported heavy episodic drinking was independently associated with significant liver biopsy changes. In another study, which included 285 patients with NASH diagnosed by liver biopsy, those who abstained from alcohol at baseline experienced more significant reductions in steatosis grade and aspartate aminotransferase (AST) levels compared to modest drinkers (1 or 2 drinks on a typical drinking day) after a

mean follow up of 47 months, while modest drinkers also had lower odds of NASH resolution (OR 0.32, 95%CI 0.11-0.92). Interestingly, when considering changes in drinking habits, consistent non-drinkers had a more pronounced reduction in steatosis grade and higher odds of NASH resolution compared to consistent modest drinkers [56]. In a large study in 58,927 Korean patients with NAFLD and low fibrosis scores—NAFLD fibrosis score (NFS), FIB-4 and AST-to-platelet ratio index (APRI)—followed-up for a median of 8.3 years, modest alcohol drinking (10-20 g/day) was independently associated with worsening of all noninvasive fibrosis scores (HR 1.29, 95%CI 1.18-1.40, HR 1.31, 95%CI 1.23-1.40, and HR 1.09, 95%CI 1.01-1.19 for FIB-4, NFS and APRI, respectively). In addition, light alcohol consumption (0-10 g/day) was also independently associated with worsening of NFS (HR 1.09, 95%CI 1.02-1.16) [57]. Finally, a study by Aberg *et al* evaluated the risk of advanced liver disease in 8345 Finnish patients with NAFLD diagnosed with the Fatty Liver Index with respect to their drinking habits. Patients with alcohol consumption >10 g/day were more susceptible to developing advanced liver disease and the HR was dose-dependent (10-19 g, HR 2.18, 95%CI 1.05-4.53; 20-29 g, HR 3.62, 95%CI 1.69-7.76) [58]. Interestingly, this correlation was not significant in patients drinking mainly wine in amounts <25 g/day.

Studies in this section are divided into 2 groups: studies investigating the effect of alcohol consumption on NAFLD severity at diagnosis, and studies investigating alcohol consumption on NAFLD progression. The latter studies provide more trust-worthy data because of the patients' follow up and share an identical conclusion: even modest consumption (>10 g/day) is tied to worse liver-related outcomes. However, light consumption (<10 g/day) was not associated with worse liver-related outcomes in most studies and was associated with lower odds for significant fibrosis in most studies investigating disease severity at diagnosis. Studies evaluating the effect of alcohol on the severity of hepatic disease in NAFLD are outlined in Table 2.

Does alcohol consumption increase the incidence of cancer in patients with NAFLD?

In the study mentioned above by Alberg *et al*, the association between alcohol intake and cancer was also evaluated [58]. Patients with high alcohol consumption (>30 g/day) were more likely to be diagnosed with any malignancy, whereas those with low or moderate alcohol consumption (<30 g/day) showed no increased risk for malignancies. Others assessed whether alcohol affects the risk of HCC in patients with NAFLD. Ascha *et al* evaluated the risk of HCC in 195 patients with NASH-related cirrhosis [59]. During a median follow up of 3.2 years, any alcohol use and even social alcohol intake were independently associated with an increased risk of HCC compared with non-drinkers. These results were reinforced by a study by Kimura *et al*, which evaluated the occurrence of HCC in 301 patients with biopsy-proven NAFLD [60]. During a follow up of 6

Table 2 Studies investigating the effect of alcohol consumption on the severity of hepatic disease in NAFLD

Study/ year/ country / type	Study population	Liver-related outcomes	Comments
Hagstrom <i>et al</i> [49] 2017 / Sweden Cross-sectional	- 120 patients with biopsy-proven NAFLD	- Lifetime alcohol consumption (up to 13 units/week) independently correlated with lower odds for severe fibrosis (OR 0.86 [95%CI 0.76-0.97] for each unit added) - Consumption of 3.1-13.3 units/week had lower odds for severe fibrosis compared to minimal or no consumption (0-0.3 units/week) (OR 0.23 [95%CI 0.08-0.66]) - Lower levels of tumor necrosis factor and high-sensitivity C-reactive protein in patients that consumed >1.1 units/week	- The biomarker phosphatidyl ethanol (PEth) was used to avoid underreporting of alcohol intake. Patients with PEth >0.3 μmol/L were classified as consuming more than moderate amounts of alcohol and were excluded from the primary analysis - Exclusion of heavy drinkers (>14 units/week)
Kwon <i>et al</i> [50] 2014 / USA Cross-sectional	- 77 patients with biopsy-proven NAFLD	- Lifetime alcohol consumption ≥24 gram-years associated with less advanced fibrosis (OR 0.26 [95%CI 0.07-0.97]) compared to consumption <24 gram-years - Patients with abstinence >1 year had significantly higher fibrosis score compared to patients with no or <1-year abstinence (P=0.04)	- Exclusion of even moderate drinkers (>40 g/week) - Gram-years: grams of alcohol consumed per day multiplied by years of consumption
Dunn <i>et al</i> [51] 2012 / USA Cross-sectional	- 582 patients with biopsy-proven NAFLD	- Lifetime modest drinkers (≤20 g/day) had lower odds of having steatohepatitis, fibrosis, hepatocellular ballooning and Mallory–Denk bodies in liver biopsy (OR 0.52 [95%CI 0.36-0.76], 0.56 [95%CI 0.41-0.78], 0.62 [95%CI 0.45-0.87] and 0.65 [95%CI 0.43-0.97], respectively) compared to non-drinkers	- Exclusion of heavy drinkers (>20 g/day), binge drinkers (≥6 drinks on one occasion ≥ once monthly) and current non-drinkers with a history of alcohol consumption
Dixon <i>et al</i> [52] 2001 / Australia Cross-sectional	- 105 patients with severe obesity - Liver biopsy during laparoscopy	- Moderate (20-100 g/week) and low (<20 g/week) alcohol consumption was associated with a lower incidence of diabetes, NASH and presence of Mallory-Denk bodies in liver biopsy (OR 0.18 [95%CI 0.05-0.67], 0.35 [95%CI 0.12-1] and 0.16 [95%CI 0.03-0.76], respectively) - However, the effect on NASH severity was not significant when adjusting for diabetes and insulin resistance	- Patients with BMI >35 kg/m ² - Exclusion of heavy drinkers (>200 g/week)
Mitchell <i>et al</i> [53] 2018 / Australia Cross-sectional	- 187 patients with biopsy-proven NAFLD	- Modest consumption (<70 g/week) was associated with a decreased risk of advanced fibrosis (OR 0.33 [95%CI 0.14-0.78]) compared to lifetime abstainers - Exclusive wine drinkers had lower odds of advanced fibrosis (OR 0.20 [95%CI 0.06-0.69]) compared to lifetime abstainers	- Exclusion of heavy drinkers (>210 and 140 g/week for men and women, respectively) - Benefits are mainly associated with wine drinking, not beer
Sookoian <i>et al</i> [54] 2016 / Argentina Cross-sectional	- 266 patients with biopsy-proven NAFLD	- Validation and use of a genetic variant in the alcohol dehydrogenase gene, indicative of less long-term alcohol-exposure (P=0.04) - Carriers of the genetic variant had less severe steatosis and inflammation (P=0.04 and 0.015, respectively)	- Exclusion of heavy drinkers (>210 and 140 g/week for men and women, respectively) - Non-significant results regarding liver fibrosis
Ekstedt <i>et al</i> [55] 2009 / Sweden Longitudinal	- 71 patients with biopsy-proven NAFLD - Median follow up: 13.8 years	- Patients with heavy episodic drinking (more than 60 g ethanol in males and 48 g in females on one occasion/month) had significantly higher odds of disease progression (worsening of ≥2 stages of fibrosis) (OR 42 [95%CI 5.39-329]) - No association between average alcohol consumption and disease progression	- Exclusion of heavy drinkers (>140 g/week), either at baseline or at follow up - Higher alcohol consumption was borderline insignificant regarding fibrosis progression (P=0.55 OR 1.01 [95%CI 1-1.03] at the multivariate model)
Ajmera <i>et al</i> [56] 2018 / USA Longitudinal	- 285 patients with 2 or more liver biopsies - Median follow up: 47 months	- Modest alcohol use (≤2 drinks/day) was associated with lower odds of NASH resolution (OR 0.32 [95%CI 0.11-0.92]) compared to non-drinkers.	- Exclusion of moderate drinkers (≥20g/day for men and 10g/day for women), binge drinkers (≥6 drinks on one occasion ≥ once monthly) and non-drinkers with a history of alcohol consumption
Chang <i>et al</i> [57] 2019 / S. Korea Longitudinal	- 58927 patients with an ultrasound diagnosis of NAFLD - Median follow up: 8.3 years	- Modest alcohol consumption (10-20 g/day) was associated with worsening of noninvasive fibrosis score FIB-4, NFS and APRI (HR 1.29 [95%CI 1.18-1.40], 1.31 [95%CI 1.23-1.40] and 1.09 [95%CI 1.01-1.19], respectively) - Light alcohol consumption (<10 g/day) was associated with worsening of NFS (HR 1.09 [95%CI 1.02-1.16])	- Exclusion of patients with cirrhosis or intermediate/high noninvasive risks score

(Contd...)

Table 2 (Continued)

Study/ year/ country / type	Study population	Liver-related outcomes	Comments
Aberg <i>et al</i> [58] 2020 / Finland Longitudinal	- 8435 patients with NAFLD diagnosis based on Fatty Liver Index >60 - Median follow up: 11.1 years	- Progressive increase in odds for liver-related outcomes for patients with moderate to excessive alcohol consumption compared to non-drinkers (HR 2.18 [95%CI 1.05-4.53] for 10-19 g/day, 3.62 [95%CI 1.69-7.76] for 20-29 g/day, 3.53 [95%CI 1.53-8.14] for 30-39 g/day, 8.79 [95%CI 3.95-19.6] for 40-49 g/day) - Alcohol consumption <25 g with light preferential wine consumption was not associated with increased odds for liver-related outcomes compared to abstainers	- Exclusion of excessive drinkers (>50 g/day) - Non-significant difference between light (<10 g/day) drinkers and abstainers - Liver related outcomes included the development of hepatocellular carcinoma

NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; HR, hazard ratio; CI, confidence interval; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score

years, more patients who reported mild alcohol consumption (<20 g/day) developed HCC than patients abstaining from alcohol (6.5% vs. 1.4%). This detrimental effect of alcohol was more pronounced in patients with advanced fibrosis; in this group, mild alcohol use was independently associated with the development of HCC (risk ratio 4.83, 95%CI 1.01-23). Loomba *et al* evaluated the synergistic effects of alcohol and obesity on the incidence of HCC on 23,712 participants and reported similar results [61]. After a median follow up of 11.6 years, patients who consumed alcohol regularly and had BMI >30 kg/m² had a higher incidence of HCC (HR 3.82, 95%CI 1.94-7.52) compared with patients with neither of these factors (reference population), while patients who had BMI >30 kg/m² and did not consume alcohol regularly had a similar incidence of HCC with the reference population.

While there are only a small number of studies investigating cancer incidence in patients with NAFLD in relation to alcohol consumption, all arrive at the same conclusion: alcohol consumption in patients with NAFLD is associated with higher odds of incident cancer, with the odds increasing in parallel with alcohol consumption. Nevertheless, the lower the consumption, the weaker the association, and more studies are needed to provide data regarding light or modest alcohol consumption to justify this association. Studies investigating the effect of alcohol consumption on cancer development in patients with NAFLD are outlined in Table 3.

Is alcohol associated with better cardiovascular outcomes in patients with NAFLD?

Given the association of NAFLD with increased cardiovascular risk, a number of studies evaluated the effects of alcohol intake on cardiovascular morbidity. In the above-mentioned study by Aberg *et al*, patients with NAFLD who were consuming alcohol <50 g/day had a lower risk for cardiovascular disease compared with abstainers (HR compared with abstainers ranging from 0.6, 95%CI 0.37-0.96 in patients consuming 40-49 g/day to 0.78, 95%CI 0.64-0.95 in those consuming 0-9 g/day) [58]. This effect was even more pronounced in patients mainly consuming wine. In a study by Sinn *et al* in 2280 men in South Korea diagnosed with

NAFLD using ultrasound, 1797 were modest drinkers (<20 g alcohol/day) and the rest did not consume any alcohol [62]. The prevalence of carotid plaques and carotid artery stenosis, surrogate markers for cardiovascular disease, was lower in the former (OR 0.74, 95%CI 0.6-0.92, and OR 0.62, 95%CI 0.43-0.9, respectively) after adjustment for age, smoking and MetS [62]. In contrast, in a recent study by VanWagner *et al* in 570 patients with NAFLD diagnosed by computed tomography, moderate alcohol consumption (≤14 standard drinks/week for women and ≤21 standard drinks/week for men) was not independently associated with the incidence of hypertension, dyslipidemia and diabetes, or with differences in measurements of coronary artery calcification, E/A ratio and global longitudinal strain after a follow up of 25 years, compared to abstainers [63].

While there is only a small number of studies regarding cardiovascular outcomes, their results imply that patients with NAFLD enjoy the same positive cardiovascular outcomes as the general population regarding moderate alcohol consumption. Notably, wine consumption seems to be the key to positive cardiovascular outcomes. Studies investigating the effect of alcohol consumption on cardiovascular outcomes in patients with NAFLD are summarized in Table 4.

Does alcohol consumption impact all-cause mortality in patients with NAFLD?

Given that alcohol consumption appears to exert different effects on the significant causes of death in patients with NAFLD (i.e., increased risk for liver-related death and lower risk for cardiovascular mortality), a limited number of studies evaluated the overall effect of moderate alcohol consumption on all-cause mortality in this population. Aberg *et al* reported that alcohol consumption <10 g/day was independently associated with lower all-cause mortality compared with non-drinkers during a follow up of 11.1 years (HR 0.79, 95%CI 0.66-0.95) [58]. There was no effect of alcohol consumption between 10-50 g/day. A similar study by Younossi *et al* showed that only excessive alcohol consumption (>3 drinks/day) was independently associated with higher overall mortality (HR 1.79, 95%CI 1.21-2.66) compared to non-excessive consumption after 20 years of mean follow up [64]. Notably, there was no difference in terms of mortality between non-

Table 3 Studies investigating the effect of alcohol consumption on the development of cancer in patients with NAFLD

Study/ year/ country / type	Study population	Cancer-related outcomes	Comments
Aberg <i>et al</i> [58] 2020 / Finland Longitudinal	- 8435 patients with NAFLD diagnosis based on Fatty Liver Index >60 - Median follow up: 11.1 years	- Progressive increase in odds for development of cancer for patients with heavy to excessive alcohol consumption compared to non-drinkers (HR 1.58 [95%CI 1.08-2.32] for 30-39 g/day, 1.75 [95%CI 1.1-2.79] for 40-49 g/day)	- Exclusion of excessive drinkers (>50 g/day) - Non-significant difference between light and moderate (<30 g/day) drinkers and abstainers - HCC was included in liver-related outcomes
Ascha <i>et al</i> [57] 2010 / USA Longitudinal	- 195 patients with decompensated cirrhosis with biopsy-proven NASH or cryptogenic cirrhosis with metabolic syndrome - Median follow up: 3.2 years	- Patients with any lifetime alcohol consumption were more likely to develop (HCC compared to abstainers (HR 3.6 [95%CI 1.5-8.3]) - Social drinkers (≤2 drinks/day) were more likely to develop HCC compared to abstainers (P=0.001)	- Included heavy drinkers and binge drinkers - Social drinker definition was equivalent to moderate and binge drinker - Data from a transplantation clinic - Histologic confirmation on 59% of HCC patients
Kimura <i>et al</i> [59] 2018 / Japan Longitudinal	- 301 patients with biopsy-proven NAFLD - Median follow up: 6 years	- HCC incidence was higher in light drinking group (<20 g/day) compared to the non-drinkers (6.5% vs. 1.4%, P=0.02) - Light drinkers had a marginally non-significant higher risk of developing HCC compared to non-drinkers (RR 4.43 [95%CI 0.88-22.4], P=0.07) - In the severe fibrosis group (F3-F4), light drinkers were at significantly higher risk of developing HCC compared to non-drinkers (RR 4.83 [95%CI 1.01-23], P=0.04)	- Exclusion of moderate drinkers (≥20 g/day)
Loomba <i>et al</i> [60] 2013 / Taiwan Longitudinal	- 23712 participants in a cancer screening program - Median follow up: 11.6 years	- Patients with regular alcohol consumption (≥4 days/week, ≥one year), both BMI >30 kg/m ² and BMI <30 kg/m ² were more likely to develop HCC compared to non-drinkers with BMI <30 kg/m ² (HR 3.82 [95%CI 1.94-7.52] and 1.46 [95%CI 1.07-1.98], respectively) - There was no significant difference between patients with BMI >30 kg/m ² and no alcohol consumption and non-drinkers with BMI <30 kg/m ²	- No exclusion criteria - Alcohol consumption correlated independently with HCC development - Higher BMI was associated with risk of HCC only when paired with regular alcohol consumption

NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; HR, hazard ratio; RR, risk ratio; CI, confidence interval; NASH, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma; BMI, body mass index

Table 4 Studies investigating the effect of alcohol consumption on cardiovascular outcomes in patients with NAFLD

Study/ year/ country / type	Study population	Cardiovascular outcomes	Comments
Aberg <i>et al</i> [58] 2020 / Finland Longitudinal	- 8435 patients with NAFLD diagnosis based on Fatty Liver Index >60 - Median follow up: 11.1 years	- Lower risk for cardiovascular outcomes in patients with low to excessive alcohol consumption compared to non-drinkers (HR 0.78 [95%CI 0.64-0.96] for <9 g/day, 0.78 [95%CI 0.6 2.02] for 10-19 g/day, 0.71 [95%CI 0.53-0.97] for 20-29 g/day, 0.71 [95%CI 0.5-1] for 30-39 g/day, 0.6 [95%CI 0.37-0.96] for 40-49 g/day) - Wine consumption was associated with cardiovascular risk reduction across all categories	- Exclusion of excessive drinkers (>50 g/day) - Beneficial effect observed even in heavy drinkers
Sinn <i>et al</i> [61] 2014 / S. Korea Cross-sectional	- 2280 men with an ultrasound diagnosis of NAFLD	- Lower prevalence of carotid plaque and carotid stenosis among modest drinkers (<20 g/day) compared to non-drinkers (OR 0.74 [95%CI 0.6-0.92] and 0.62 [95%CI 0.43-0.9], respectively)	- Exclusion of moderate drinkers (≥20 g/day) patients with a previous history of alcohol consumption
VanWagner <i>et al</i> [62] 2017/ USA Longitudinal	- 570 patients with CT diagnosis of NAFLD - Median follow up: 25 years	- No significant difference in terms of incident hypertension, dyslipidemia and diabetes or measurements of coronary artery calcification, E/A ratio and global longitudinal strain, according to drinking status	Exclusion of heavy drinkers (>21 and 14 drinks/week for men and women, respectively)

NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; HR, hazard ratio; CI, confidence interval; CT, computed tomography

Table 5 Studies investigating the effect of alcohol consumption on overall mortality in patients with NAFLD

Study/ year/ country / type	Study population	Outcome: overall mortality	Comments
Aberg <i>et al</i> [58] 2020 / Finland Longitudinal	- 8435 patients with NAFLD diagnosis based on Fatty Liver Index >60 - Median follow up: 11.1 years	- Lower risk of all-cause death in patients with low alcohol consumption compared to non-drinkers (HR 0.79 [95%CI 0.66-0.95]) - Alcohol consumption >25 g with no wine consumption was associated with an increased risk of all-cause death compared to abstainers	- Exclusion of excessive drinkers (>50 g/day) - Beneficial effects augmented by wine consumption, while harmful effects observed mainly in patients not consuming wine
Hajifathalian <i>et al</i> [65] 2019 / USA Prospective	- 4568 patients with NAFLD - Diagnosis based on the Hepatic Steatosis Index - Median follow up: 70 months	- Moderate consumption (<1.5 drinks/day) associated with lower all-cause mortality compared to non-drinkers (HR 0.64 [95%CI 0.42-0.97]) - Heavy consumption (>1.5 drinks/day) associated with higher all-cause mortality compared to non-drinkers (HR 1.45 [95%CI 1.01-2.1])	- Exclusion of patients with significant alcohol use (>3 drinks/day for males, and >2 drinks/day for females) - Sub-analysis: benefit of moderate consumption observed only in patients with FIB-4<1.8 (HR 0.46 [95%CI 0.26-0.81])
Younossi <i>et al</i> [63] 2019 / USA Retrospective	- 4264 individuals with ultrasound diagnosis of NAFLD - Mean follow up: 20 years	- Excessive alcohol consumption (>3 drinks/day) associated with higher overall mortality (HR 1.79 [95%CI 1.21-2.66]) compared to non-excessive consumption	- Significant follow-up duration, higher than most studies - No difference with regard to drinking status (non-light-moderate-substantial) of non-excessive drinkers

NAFLD, nonalcoholic fatty liver disease; HR, hazard ratio; RR, risk ratio; CI, confidence interval

drinkers and subjects with minimal (<3 drinks/week), moderate (>3 drinks/week but <2 drinks/day) and substantial (>2 but <3 drinks/day) alcohol use. Finally, a recent study by Hajifathalian *et al* evaluated all-cause mortality in 4568 patients with NAFLD diagnosed with the Hepatic Steatosis Index [65] and reported that moderate consumption of alcohol (<1.5 standard drinks/day) was independently related to lower all-cause mortality (HR 0.64, 95%CI 0.42-0.97), whereas heavy consumption (>1.5 drinks/day) was independently related with higher all-cause mortality (HR 1.45, 95%CI 1.01-2.1), compared to non-drinkers during a median follow up of 70 months [66]. Interestingly the benefit of moderate consumption was limited in patients with a low probability of fibrosis (FIB-4 <1.8, HR 0.46, 95%CI 0.26-0.81) and was not observed in those with a high probability of fibrosis. Studies investigating the effect of alcohol consumption on all-cause mortality in patients with NAFLD are highlighted in Table 5.

Concluding remarks

Alcohol consumption in patients with NAFLD is a relatively novel debate, considering that previous guidelines have consistently discouraged alcohol consumption in patients with (even mild) liver disease. There is currently a relatively small number of studies regarding this topic, with significant differences in terms of conclusions. Additionally, frequent underreporting of alcohol consumption combined with the difficulty of estimating lifetime consumption further complicates these studies [67]. These limitations, combined with the significant variations in terms of methods and outcomes between the studies included in this review, make it difficult to reach definite conclusions. Nevertheless, most

of the studies support the same patterns regarding the effects of alcohol consumption on NAFLD: it appears that moderate alcohol intake is associated with a lower prevalence of NAFLD and reduced cardiovascular risk in patients with NAFLD, while even light alcohol intake appears to aggravate liver disease and increase the risk of HCC. Additionally, there are conflicting reports regarding the effect of alcohol on MetS and type 2 diabetes mellitus. While most studies support a positive effect of alcohol on the development of MetS and diabetes [26,31], a recent study focusing on NAFLD patients showed an increased incidence of diabetes in patients with light-to-moderate alcohol consumption (70-210 g/week) compared to abstainers. Therefore, maintaining a cautious approach, patients with NASH or significant liver fibrosis should be advised against consuming alcohol. On the other hand, taking into account recent data, only light alcohol consumption (<10 g/day) might be permitted in patients without significant hepatic fibrosis, provided that they are carefully followed-up. This recommendation is based on the fact that no study showed significant harm from light alcohol drinking, while many studies showed significant positive effects. Future studies may shed more light on this ongoing debate, possibly challenging traditional views regarding alcohol consumption in patients with liver disease.

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