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Drinking and Obesity: Alcoholic Liver Disease/ Nonalcoholic Fatty Liver Disease Interactions

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Abstract

Alcohol and obesity are the main risk factors for alcoholic liver disease and nonalcoholic fatty liver disease (NAFLD), respectively, and they frequently coexist. There are considerable synergistic interaction effects between hazardous alcohol use and obesity-associated metabolic abnormalities in the development and progression of fatty liver disease. Intermittent binge-drinking has been shown to promote steatohepatitis from obesity-related steatosis, and binge-drinking is associated with progression to cirrhosis even when average alcohol intake is within the currently used criteria for a NAFLD diagnosis. Recent longitudinal studies in NAFLD have shown that light-to-moderate alcohol use is associated with fibrosis progression and incident clinical liver disease, suggesting that there is no liver-safe limit of alcohol intake in the presence of NAFLD; a J-shaped association between alcohol and all-cause mortality remains controversial. The interaction effects between alcohol and obesity make the present strict dichotomization of liver disease into alcoholic and NAFLD inappropriate, and require attention in future research, public health policy, individual counseling, and risk stratification.

Keywords
- nonalcoholic fatty liver disease
- alcohol
- fatty liver
- liver cirrhosis
- HCC

Chronic liver disease (CLD) represents a growing health care problem. Globally, liver cirrhosis is the 11th leading cause of death, and hepatocellular carcinoma (HCC) is the 4th leading cause of cancer death.[1] Mortality from liver diseases and HCC has been increasing in many countries.[2,3] Cirrhosis is also one of the top 20 causes of disability-adjusted life years[1] and represents a substantial economic burden.

Nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) are the two main liver diseases worldwide.[1] NAFLD, which is strongly interlinked with obesity and metabolic disorders, affects 25% of individuals in the population, increasing to more than 90% in the morbid obese.[4] One study estimated that the annual direct medical costs from NAFLD alone are US$103 billion in the United States and US$35 billion in central Europe.[5] ALD is the most common cause of liver-related death in Western populations and a leading indication for liver transplantation in both Europe and the United States.[1]

NAFLD and ALD share many features in common, including genetic risk factors, many pathophysiological pathways, and histological features.[6,7] Both NAFLD and ALD typically progress from steatosis to steatohepatitis, fibrosis, cirrhosis, and HCC. However, although most obese persons have NAFLD, less than 5% of NAFLD patients will ever develop complicated liver disease.[8] Similarly, although there is a strong dose–response relationship between per capita alcohol consumption and liver cirrhosis mortality in the population,[9] only 10 to 15% of heavy drinkers develop cirrhosis during their lifetime.[10,11] Determinants of cirrhosis development remain incompletely understood.

Globally, overweight and obesity rates have nearly tripled since the 1970s.[1] The current average prevalence of obesity in OECD (Organisation for Economic Co-operation and Development) countries is 23%, with the United States having the highest rate (38%).[12]

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Alcohol consumption in the population varies in different regions, but around 60% of adults in Europe and the United States drink alcohol. Among the active drinkers (abstainers excluded), the average per capita annual consumption is 15 to 17 L of pure alcohol.[13] Consequently, many persons with obesity and/or metabolic disorders also drink alcohol.

Recent studies emphasize the interaction between alcohol and obesity in the development of liver disease.[14–16] Metabolic risk might sensitize the liver to alcohol damage and vice versa. Alcohol and obesity seems to have synergistic harm on the liver in certain situations (►**Fig. 1**).[14–17] We discuss recent evidence on interactions between alcohol and obesity, and their contribution to liver morbidity in the population.

Effects of Alcohol on Obesity

Pure ethanol contains 7 kcal/g and can significantly contribute to dietary calorific excess. Light-to-moderate alcohol intake does not seem to be associated with weight gain, whereas heavy drinking is.[18,19] Light wine consumption might even protect against weight gain,[19] but residual confounding from other associated lifestyle factors and dietary patterns cannot be excluded. Beer intake > 500 mL/day has been associated with abdominal obesity ("beer belly").[20]

In contrast, persons with chronic alcohol abuse or cirrhosis tend to show increased energy expenditure with preferential use of lipids as fuel. This shift toward lipid oxidation to meet energy requirements is likely to contribute to the reduced overall fat mass in such persons.[21]

Alcohol has numerous complex effects on, for instance, food intake regulation, psychosocial well-being, sleeping, and depression symptoms, all of which may influence body weight. Such effects have substantial interindividual variation, and this may in part explain the somewhat conflicting results seen in studies[18,19] on the associations between alcohol and obesity.

Obesity and Liver Disease

Obesity is associated with NAFLD and is a cofactor in many other liver diseases.[22–26] This cofactor effect of obesity may be mediated by the additive effect from coexistent NAFLD. Alternatively, obesity-associated metabolic abnormalities might exacerbate liver injury from other causes such as alcohol or viruses.[27]

Body mass index (BMI) has traditionally been the anthropometric measure of choice to diagnose overweight and obesity. However, alternative measures that reflect abdominal (also called visceral or central) adiposity, such as waist circumference and waist–hip ratio (WHR), seem superior to BMI in predicting incident liver disease.[14,28–31]

A recent population study that analyzed a large number of anthropometric measures in predicting incident severe liver disease found WHR to be the strongest predictor (men: hazard ratio [HR] for 1 standard deviation [SD] of 1.46 and c-statistics of 0.70; women: HR per 1 SD of 1.30 and c-statistics of 0.63).[30] This effect of WHR was independent of BMI, and BMI showed no predictive value independent of WHR. In this study, BMI was, in fact, the poorest predictor of all tested anthropometric measures (men: HR per 1 SD of 1.26, c-statistics of 0.68; women: HR per 1 SD of 1.12 and c-statistics of 0.60). Recently, these findings have been confirmed by others.[31,32] However, BMI seems to have a **U**-shaped association with liver disease,[22] and treating BMI as a linear predictor in many studies may have led to an attenuation of the risk effect of BMI.

The association between obesity and liver disease seems to be driven largely by metabolic risk, including insulin resistance, type 2 diabetes, dyslipidemia, and hypertension.[33,34] A high waist circumference or WHR reflects the "apple-shaped" central distribution of body fat, which is strongly associated with metabolic abnormalities.

In parallel, an increasing number of components of the metabolic syndrome (MetS), visceral obesity, type 2 diabetes, and insulin resistance are strongly associated with progression of NAFLD,[35] whereas a high BMI per se is not directly associated with more advanced NAFLD stages.[36,37] In fact, metabolically healthy ("pear-shaped") obesity was associated with less adipose tissue inflammation and less liver fibrosis than metabolically unhealthy ("apple-shaped") obesity.[33]

In a longitudinal population study, the metabolic features that best predicted incident advanced liver disease in nonrisk alcohol drinkers were abdominal obesity (HR: 1.03 per cm

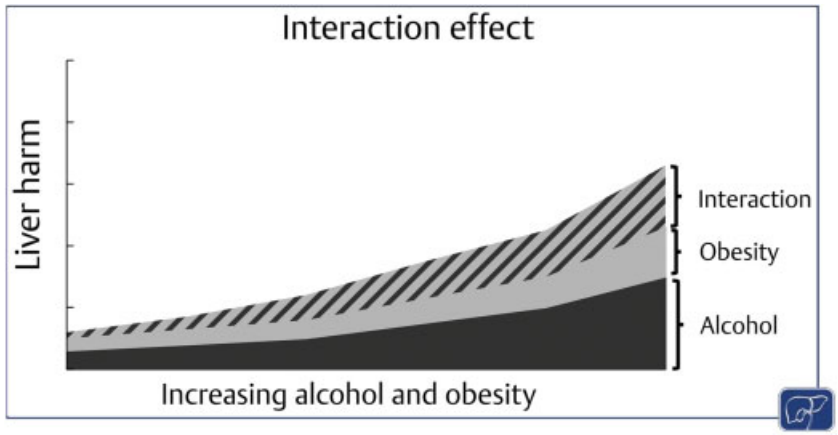

Fig. 1 The concept of synergistic interaction. Synergistic or supra-additive interaction refers to a situation in which the combined effect (liver toxicity) of two exposures (alcohol and obesity) is greater than the sum of their individual effects.

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increase in waist circumference), insulin resistance (HR: 1.04 per unit increase in homeostasis model of assessment of insulin resistance), and a low LDL (low-density lipoprotein) cholesterol level (HR: 0.54 per mmol/L increase in LDL cholesterol).[14] Therefore, measures of body fat distribution seems to have a predictive value for liver disease independent of other metabolic risk factors.

Features of the MetS also predict HCC and survival in CLD regardless of the primary etiology of the liver disease.[38,39]

Alcoholic Liver Disease and Obesity

The arbitrary threshold of alcohol intake currently used to discriminate ALD from NAFLD—30 g/day for men and 20 g/day for women—is based on the assumption that alcohol intake below these levels is insufficient to induce hepatic steatosis[40–42] and has a low risk of (alcoholic) cirrhosis.[9] However, this threshold does not take into consideration the pattern of alcohol use, binge-drinking, beverage preference, or other demographic factors than gender.

Although in most cohort studies of "pure" alcoholic liver cirrhosis,[43–45] patients have a history of consuming 6 to 12 drinks per day for an average of 30 to 40 years, these cohorts are preselected as typical ALD. Alcohol use at much lower levels may be a contributing factor in other types of liver disease labeled as nonalcoholic and thereby excluded from cohort studies of ALD. Alcohol toxicity seems to depend on the drinking pattern including frequency and quantity, beverage type (lower risk for wine), drinking outside meals, and binge-drinking.[10,46–49] However, the drinking pattern alone is insufficient to explain liver disease development since it does not significantly differ from the pattern of individuals with longstanding alcohol-use disorder without liver disease.[44,45] Alcoholic liver toxicity is also modified by genetics, gender, environmental factors, diet, gut microbiota, and comorbidity including obesity and metabolic risk. Changes in gut microbiota (dysbiosis) have been described in both ALD and NAFLD.[50]

The relevance of metabolic risk factors for liver disease progression may have been underestimated in cohort studies of ALD cases because many metabolic conditions such as obesity, dyslipidemia, and hypertension tend to disappear as end-stage liver disease develops. Indeed, among alcohol risk drinkers in the general population without manifest liver disease, abdominal obesity (HR: 1.6 per 1 SD increase in WHR), diabetes (HR: 3.4), hypertension (HR: 2.5), lipid abnormalities (HR: 2.1 for HDL cholesterol; HR: 1.2 for triglycerides), and inactive lifestyle (HR: 1.6 for exercise less than once monthly) predicted the development of advanced liver disease during follow-up independently of alcohol.[51]

NAFLD is known to recur in most patients after liver transplantation as transplantation does not treat the cause of steatosis. Interestingly, the rate of posttransplant steatosis in the ALD group was likewise particularly high (37 vs 26%), despite alcohol abstinence, further indicating that many ALD patients also have underlying risk factors for NAFLD (metabolic risk, gut dysbiosis) contributing to their liver disease all along.[52,53]

ALD and NAFLD: Common Pathophysiological Pathways

There are considerable overlap and similarities in both the molecular pathways[54] and liver histology between ALD and NAFLD. Both ALD and NAFLD are heterogenic diseases where multiple pathogenic mechanisms contribute to disease progression in any single patient.[55,56] Common to both ALD and NAFLD is that transition from steatosis to steatohepatitis is related to mitochondrial dysfunction and oxidative stress.[57] In addition, intestinal dysbiosis, barrier disruption, and endotoxemia are implicated in both ALD and NAFLD,[55,58,59] and the diseases share a common genetic background.[7] A single variant in the patatin-like phospholipase-containing domain 3 (*PNPLA3*) gene, the rs738409[G], has been associated with more rapid progression of fatty liver disease to fibrosis and cirrhosis, with an approximately two- to threefold risk for decompensated cirrhosis and HCC among carriers of the risk variant both in NAFLD and ALD.[7,60–63] Other genetic risk variants, such as rs72613567:TA in HSD17B13, also overlap between NAFLD and ALD.[7,64]

There are several mechanistic links between ALD and NAFLD. First, many animal models on alcoholic liver injury such as the basic Lieber-DeCarli model[65] include a high-fat diet component, making them basically models of ALD–NAFLD interaction to begin with. Second, there seems to be a common activation of innate immune responses, with synergism between alcohol and obesity.[66] Third, ethanol degradation through the cytochrome P450 2E1 (CYP2E1) pathway catalyzes hepatotoxic reactive oxygen species.[59] Diabetes and obesity can induce *CYP2E1*, thereby causing relatively increased ethanol degradation through the *CYP2E1* pathway, which might amplify alcohol hepatotoxicity.[59] Fourth, according to the endogenous alcohol hypothesis, especially in obesity, the intestinal microbiome can produce ethanol to hepatotoxic levels.[67] These findings have been substantiated by observations of upregulation of genes involved in alcohol metabolism pathways in NAFLD despite complete alcohol abstinence.[67–69] Finally, alcohol can disrupt extrahepatic fat tissue function and cause adipocyte death with subsequent proinflammatory responses and increased lipolysis, thereby contributing to liver damage by indirect mechanisms.[21] As an example of mechanistic synergism between alcohol and obesity, it has been shown that a high-fat diet sensitizes adipose tissue to alcohol-induced lipolysis.[21]

In mice, moderate obesity (a 28–35% weight increase) and alcohol synergistically induce steatohepatitis and liver fibrosis over and beyond their individual effects.[66] Possible mechanisms include increased plasma adiponectin activation, defective hepatic AMP (adenosine monophosphate)-activated protein kinase signaling, heightened endoplasmic reticulum stress, and suppression of genes involved in mitochondrial functions.[66] Minato et al further showed that alcohol administered once a week in a binge-drinking fashion to mice with hepatic steatosis aggravated hepatic oxidative stress and promoted steatohepatitis from obesity-induced steatosis; no such effects of binge alcohol were seen in nonsteatotic mice.[70] Duly et al similarly showed that on a background of high-fat

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diet-induced hepatic steatosis, intermittent binge-drinking synergistically increased steatosis, inflammation, and fibrosis in mice livers compared with binge-drinking or a high-fat diet alone.[71] These findings suggest that binge-drinking particularly may serve as a "second hit" in the development of steatohepatitis in NAFLD.

ALD and NAFLD: Epidemiological Interactions

Several cross-sectional studies have shown combined effects of alcohol and obesity on transaminase levels[72–74] and steatosis.[17,75] In contrast, other studies have suggested protective effects of light alcohol intake in the form of a reduced prevalence of NAFLD and liver fibrosis,[76–80] possibly driven by an association between light alcohol intake and improved lipid profiles, anti-inflammatory effects, and improved insulin sensitivity.[81,82] As recently reviewed,[83] however, there are major methodological concerns with these studies, including a cross-sectional design, use of surrogate end points, and incomplete adjustment for confounders such as physical activity, smoking, dietary factors (for instance, coffee), socioeconomic status, comorbidity, and ethnicity. Many studies failed to consider the pattern and type of alcohol use and the lifetime alcohol intake in addition to average alcohol intake, and did not separate between lifetime abstainers and current abstainers, the latter of which may be enriched in former heavy drinkers. In addition, underreporting of alcohol use is a major concern particularly when assessing patients who know they have a liver disease. In fact, recent studies analyzing specific alcohol-use markers such as ethyl glucuronide or phosphatidylethanol showed high rates (up to 57%) of undetected moderate to high alcohol use in patients with presumed NAFLD.[79,84] Prospective population cohort studies have an advantage over clinic-based studies in this regard since healthy participants are more likely to respond honestly.

A growing number of longitudinal population studies that excluded subjects with baseline liver disease report synergistic effects between alcohol use and obesity in the risk of future clinical liver disease, cirrhosis, and/or HCC.[14,15,22,46,85] This interaction effect is most profound when obesity is measured by the WHR[16] compared with BMI or waist circumference.[14] Among men in the highest tertile of WHR, one daily alcohol drink yielded a similar relative risk for incident advanced liver disease as four daily drinks in nonobese men (►**Fig. 2**).[16] This means that in the presence of marked central obesity, hepatic toxicity of alcohol increases by several folds.

Few studies have analyzed interactions for liver disease risk between alcohol and other metabolic factors besides obesity. In our general population study, we observed a marked interaction effect between alcohol risk use and diabetes in the development of incident liver disease (►**Fig. 3**).[14]

In a recent U.S. population study of individuals with ultrasound-based hepatic steatosis, excessive alcohol use (> three drinks/day for men or > 1.5 drinks/day for women) was associated with increased overall mortality (HR: 2.5) among persons with concomitant MetS but not among persons without MetS (HR: 1.1).[86]

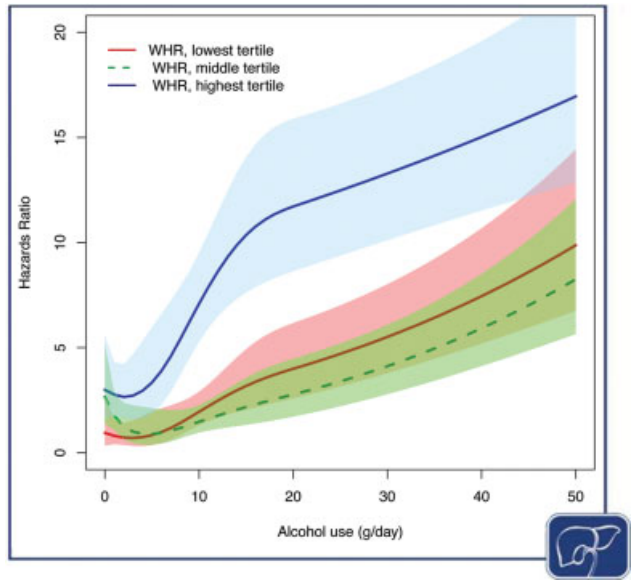

Fig. 2 Interaction between average alcohol intake (grams of ethanol per week) and WHR in the development of incident clinical liver disease among men in the Finnish general population. WHR, waist-hip ratio. (Reproduced with permission of Sahlman et al.[16])

Binge-Drinking

Intermittent heavy drinking or binge-drinking typically refers to drinking 60 g ethanol or more on one occasion at least once during the last month.[13] Up to 26% of adults in Europe and 21% in the United States report such binge-drinking at least once monthly.[13] Unfortunately, epidemiological studies assessing alcohol use by a standard quantity–frequency approach tend to neglect the issue of binge-drinking.[87]

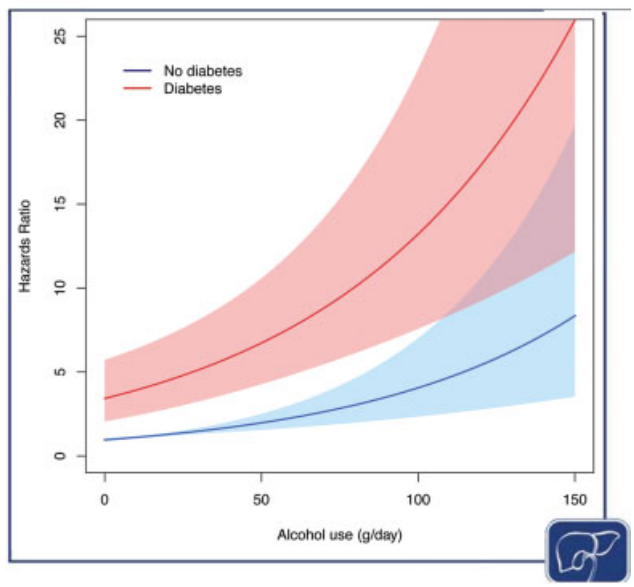

Fig. 3 Interaction between average alcohol intake (grams of ethanol per week) and diabetes in the development of incident clinical liver disease in the Finnish general population. (Reproduced with permission of Åberg et al.[14])

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Alcoholic liver cirrhosis has typically been considered the consequence of daily drinking rather than intermittent binge-drinking,[47] which has been explained by the liver's capacity to recover after each episode of drinking during the break from alcohol intake. However, in the context of obesity and NAFLD, the already injured steatotic liver may lack this capacity to recover. This hypothesis is supported by recent animal[70,71] and human[17] studies. Binge-drinking has several potentially harmful effects on the liver[88] and was, for example, shown to induce insulin resistance that lasted even after blood alcohol levels had become undetectable.[89]

In a Finnish population study, we found that binge-drinking was associated with around threefold (HR: 2.8–3.5 for weekly binge-drinking depending on the level of adjustment) increased risk for advanced liver disease regardless of the level of average alcohol use.[46] Moreover, we found an interaction effect between weekly binge-drinking and MetS. In fact, binge-drinking was a significant risk factor for liver disease only among those with the MetS but not among those without it (►**Fig. 4**).[46]

Another study of 71 patients with biopsy-proven NAFLD (alcohol intake < 140 g/week) found that binge-drinking (60 g ethanol per occasion for men, 48 g for women) as infrequently as once a month was associated with a more rapid progression of liver fibrosis.[90]

Furthermore, in recent population studies of NAFLD, binge-drinking emerged as an independent risk factor for progression to advanced clinical liver disease (HR: 1.5–2.7 among monthly to weekly binge drinkers)[91] and all-cause death (HR: 1.5 among monthly binge drinkers).[86] The corollary of these recent studies is that binge-drinking seems to be an important risk factor for advanced liver disease and mortality among persons with the MetS and/or hepatic steatosis.

Are There Safe Limits of Alcohol Use in NAFLD?

There are no randomized trials assessing light-to-moderate alcohol use in NAFLD. The existing literature comprises somewhat conflicting findings, as discussed earlier. A possible protective effect of alcohol from liver fibrosis has not been confirmed in longitudinal studies.[82,90,92]

One recent longitudinal study of 285 patients with biopsy-confirmed NAFLD found that alcohol intake of $\leq$ two drinks/day was associated with lower odds (odds ratio: 0.32) of histological steatohepatitis resolution compared with total abstinence.[93] This finding is in sharp contrast to that in a previous cross-sectional study, in part, based on the same patients, which showed beneficial liver effects of low alcohol use.[78] A recent Mendelian randomization study categorized patients with NAFLD based on a genotype in the aldehyde dehydrogenase gene that is associated with a lower level of alcohol consumption.[94] The NAFLD patients genetically prone to drink less alcohol had less hepatic steatosis and less features of steatohepatitis on histology compared with the NAFLD patients lacking this genetic constraint to alcohol use.[94] This points to the harmful effects of alcohol use in NAFLD.

In a recent population cohort study of 8,345 NAFLD patients (defined as a fatty liver index > 60), we found no benefits from low alcohol intake with regard to the risk for incident advanced clinical liver disease.[95] Advanced liver disease was defined as hospitalization, cancer, or death from liver cirrhosis, HCC, or equivalent clinically significant liver events. Consuming more than 10 g/day of alcohol increased the risk of advanced liver disease in a dose–dependent fashion independent of relevant confounders. One drink per day of nonwine beverages or two drinks per day of wine doubled the risk for advanced liver disease.

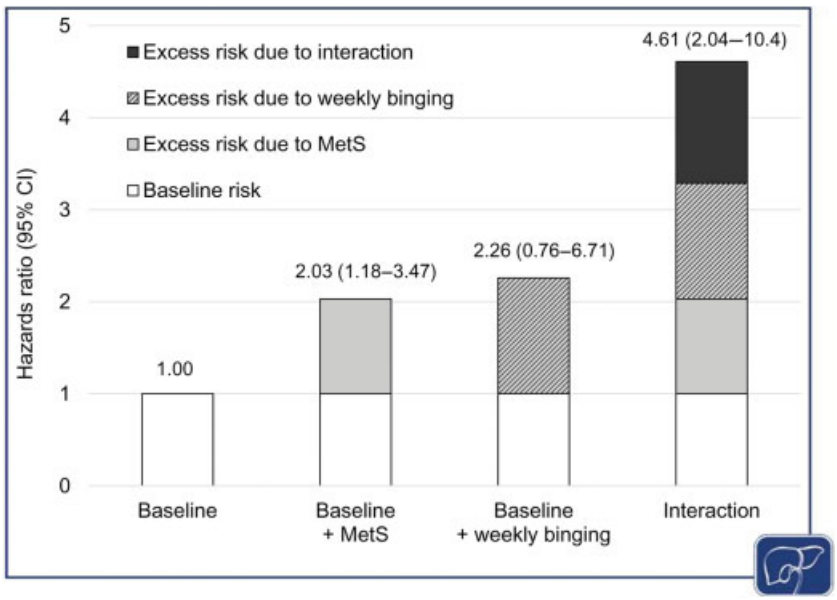

Fig. 4 Hazards ratios for the contribution of weekly binge-drinking and the MetS, and their combination (interaction) in the development of incident clinical liver disease in comparison with participants without MetS who reported no binge-drinking or binge-drinking less often than once monthly (baseline risk). CI, confidence interval; MetS, metabolic syndrome. (Reproduced with permission of Åberg et al.[46])

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Among risk drinkers, we found no influence of beverage type on the risk for liver disease. Similar findings were recently reported in a Korean study analyzing changes over time in noninvasive fibrosis markers.[96]

Extrahepatic Outcomes

In the general population, low alcohol intake has been associated with an increased risk of certain cancers[92] but reduced risks of cardiovascular disease[97]; both of these associations were confirmed in our population NAFLD cohort.[95] However, the association between alcohol and reduced cardiovascular risk may be limited by residual confounding. In fact, a recent study that prospectively assessed alcohol consumption over time found no association between alcohol use and the presence of cardiovascular risk factors or subclinical cardiovascular disease,[98] although this study did not analyze clinical cardiovascular events. A recent analysis of individual participant data of 599,912 current drinkers in 83 prospective studies assessing risk thresholds for alcohol consumption[99] concluded that the threshold for lowest risk of all-cause mortality was $\leq$100 g ethanol per week. For cardiovascular disease subtypes other than myocardial infarction, the alcohol intake level with the lowest risk was zero.

There are conflicting results regarding the association between low alcohol intake and all-cause mortality in subjects with NAFLD.[46,86,95] While we found a **J**-shaped association in our Finnish study,[95] two recent U.S. studies reported contradictory results.[46,86] Hajifathalian et al[100] reported a **J**-shaped association between drinking and all-cause mortality, whereas Younossi et al[86] found no reduced mortality among light drinkers. Although both studies were based on the National Health and Nutrition Examination Survey data, they differed in their definition of hepatic steatosis (ultrasound vs. hepatic steatosis index) and the variables adjusted for in multivariate analyses.[46,86]

In patients with NAFLD cirrhosis, low alcohol use ($<$ 30 g/day for men and $<$ 20 g/day for women) compared with abstinence was associated with an increased risk of death or liver transplantation (HR: 2.3), hepatic decompensation (HR: 1.7), and HCC (HR: 3.2), thereby reinforcing the need for absolute alcohol abstinence in patients with liver cirrhosis.[101]

Implications of ALD/NAFLD Interactions

Alcohol, obesity, and metabolic disorders are continuous variables as such, not dichotomic, with additive harmful interactions. Given the numerous similarities, overlapping features, and interactions both mechanistically and clinically, the current dichotomization of ALD and NAFLD into mutually exclusive diseases seems inappropriate.

In the struggle to tackle a growing burden of liver disease in the population, the dichotomized view of ALD and NAFLD is most likely a suboptimal strategy for the identification and prognostication of at-risk individuals in the general population and in counselling regarding risks. Indeed, in a large number of CLD cases in the population, the liver disease seems to be driven by joint effects of alcohol and metabolic risk.[102]

There seems to be a need for a more holistic approach, where all the risk factors are considered at the same time as a continuum. In addition to measuring liver fibrosis stage, there is a need for indices that quantify a person's individual risk for developing clinical liver disease. Such indices should ideally incorporate key pathophysiological drivers of liver disease, making it also usable in assessing response to therapeutic interventions. Suggestions for future research are summarized in ►**Table 1**.

In clinical practice, alcohol consumption patterns beyond average alcohol intake should be assessed in all patients with liver disease and among those with obesity or the MetS. Longitudinal population studies suggest that there is no general liver-safe limit of alcohol use in the presence of metabolic risk factors or NAFLD. Although low alcohol use may improve insulin sensitivity and thereby possibly reduce hepatic fat content, the numerous detrimental effects of alcohol extend beyond simple steatosis. There is currently no clinical evidence to support that low alcohol would protect from symptomatic liver disease. In addition, in any given individual, the level at which alcohol becomes harmful may vary depending on genetics, intake pattern, beverage type, lifetime consumption, and comorbidity. Because of this individual variation, which is difficult to define, no general safe limit of alcohol can be determined. Even low alcohol intake is associated with cancer risk. In advanced liver fibrosis or particular risk for progressive liver disease, total alcohol abstinence is advisable. On the other hand, among active drinkers with liver disease, attempts are needed to

Table 1 Suggestions for future research on ALD/NAFLD interactions

Large longitudinal studies, with alcohol consumption assessed repeatedly over time
Quantification of alcohol consumption by objective biomarkers such as phosphatidylethanol
Factors influencing individual susceptibility to alcoholic liver toxicity, including genetics
The effects of binge-drinking on metabolic fatty liver disease
Mechanisms of interaction between alcohol and metabolic abnormalities on liver toxicity
Studies on which specific metabolic factors drive the harmful interaction effects with alcohol for liver disease
Interactions between genetic risk, alcohol use, and metabolic abnormalities in the development of liver disease
Studies on how to incorporate the interaction effects between alcohol and metabolic factors in risk stratification
Studies on how to incorporate the interaction effects between alcohol and metabolic factors in the diagnostic criteria of fatty liver disease
Studies on how to incorporate the interaction effects between alcohol and metabolic factors in therapeutic interventions for fatty liver disease

Abbreviations: ALD, alcoholic liver disease; NAFLD, nonalcoholic fatty liver disease.

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also address metabolic and dietary factors, in addition to alcohol withdrawal.[103]

Conclusion

There are strong epidemiological and experimental evidences that alcohol and metabolically unhealthy obesity exerts synergistic effects on the progression toward liver cirrhosis. In fact, a large proportion of the population who develop liver disease have a combination of NAFLD and ALD risk factors. Recent longitudinal studies suggest that even low alcohol use increases the risk of advanced clinical liver disease in NAFLD. On the other hand, several metabolic factors increase the risk of cirrhosis among alcohol risk drinkers. At a population level, the combined effects of alcohol and metabolic factors may be particularly relevant in the large number of persons who are overweight or obese and consume just a little too much alcohol.

Conflict of Interest
None.

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