DR. FREDRIK ABERG (Orcid ID : 0000-0002-3833-0705)

Article type : Critical Review

Interaction between alcohol use and metabolic risk factors for liver disease: a critical review of epidemiological studies

Fredrik Åberg, MD, PhD (1, 2)
Martti Färkkilä, professor (3)
Ville Männistö, MD, PhD (4,5)

(1) Transplantation and Liver Surgery Clinic, Helsinki University Hospital, Helsinki University, Helsinki, Finland
(2) The Transplant Institute, Sahlgrenska University Hospital, Gothenburg, Sweden
(3) Clinic of Gastroenterology, Helsinki University and Helsinki University Hospital, Helsinki, Finland
(4) Department of Medicine, University of Eastern Finland and Kuopio University Hospital, Finland
(5) Department of Experimental Vascular Medicine, Amsterdam UMC, Location AMC at University of Amsterdam, Amsterdam, The Netherlands

Correspondence: Fredrik Åberg, MD, PhD. HUCH Meilahti Hospital, PB 372, 00029 HUS, Finland. Email: fredrik.aberg@helsinki.fi, telephone +35894711

Conflict of interest: The authors declare no conflict of interest for this work.

Abbreviations

ALT, alanine aminotransferase

AST, aspartate aminotransferase

BMI, body mass index

GGT, gamma-glutamyltransferase

HCC, hepatocellular carcinoma

MetS, metabolic syndrome

NAFLD, non-alcoholic fatty liver disease

ABSTRACT

Co-existence of alcohol use and metabolic risk – the two commonest population risk factors for non-viral chronic liver disease – is a growing concern. Clinical and mechanistic evidence point to considerable supra-additive interaction effects for the development and progression of chronic liver disease between hazardous alcohol use and metabolic abnormalities including obesity, diabetes, and the metabolic syndrome. Intermittent binge drinking once monthly or more often seems to be associated with progression of liver disease even when average alcohol intake is within the currently allowed limits for a diagnosis of non-alcoholic fatty liver disease (NAFLD), and supra-additive interaction between binge drinking and the metabolic syndrome has been reported. There are contradictory findings regarding the association between low alcohol use and liver steatosis, but, clearly, the mechanisms of alcoholic hepatotoxicity extend beyond simple fat accumulation. The presence of liver steatosis seems to amplify alcoholic hepatotoxicity. Recent longitudinal studies of NAFLD subjects report low alcohol use associated with both increased fibrosis progression and an elevated risk for liver cancer and severe liver disease. There is no clear safe limit of alcohol intake in the presence of NAFLD or metabolic risk. The interaction effects between alcohol and metabolic dysfunction merit increased attention in public health policy, individual counseling, and risk stratification. Based on current evidence, a strict dichotomization of liver disease into either pure alcoholic or non-alcoholic may be inappropriate.

Introduction

Chronic liver disease and its complications is a growing global public health burden. Worldwide, liver cirrhosis is the 11th leading cause of death, and hepatocellular carcinoma is the 4th leading cause of cancer death (Asrani et al., 2019).

Alcohol use and obesity and associated metabolic abnormalities are key independent population risk factors for non-viral liver cirrhosis, hepatocellular carcinoma (HCC), and for prognosis in established liver disease (Stepanova et al., 2010).

At the population level, there is an exponential dose-response relationship between alcohol consumption and the risk for liver cirrhosis (Rehm et al., 2010; Thun et al., 1997; Askgaard et al., 2015; Bellentani et al., 2000; Hagstrom et al., 2018). Both in general contexts (WHO, 2018) and in liver-specific contexts (European Association for the Study of the Liver, 2016; Chalasani et al., 2018), hazardous alcohol use is currently considered as a regular intake of more than 20 grams of pure alcohol per day for women (140g/wk) or 30 grams for men (210g/wk), and these same cutoffs have been used to separate alcoholic liver disease from non-alcoholic fatty liver disease (NAFLD). However, the risk for liver cirrhosis begins to increase at alcohol consumption around 12-24 grams of alcohol per day or even lower, and no liver-safe limit of alcohol intake has been firmly established (Roerecke et al., 2019; Rehm et al., 2010). Individual susceptibility to liver toxicity from alcohol is wide and seems to depend on drinking pattern (binge drinking, drinking outside meals), beverage type (lower risk for wine), gender, genetic and environmental factors, diet, gut microbiome and co-morbidity.

Obesity, especially abdominal obesity, is associated with metabolic abnormalities and NAFLD (Liu et al., 2010; Harris et al., 2017; Hagstrom et al., 2018; Caballeria et al., 2018) and is also a co-factor in other types of liver diseases including alcoholic liver disease (Åberg et al., 2019; Diehl and Day, 2017). NAFLD affects an estimated 25% of individuals in the general population, and over 90% of those severely obese (Younossi et al., 2016), but less than 5% of NAFLD patients eventually develop end-stage liver disease.

There is considerable overlap in the molecular pathways between alcoholic and non-alcoholic liver disease, and the diseases share genetic risk factors and histologic features in common. Animal

studies have suggested synergism between the hepatotoxic effects of alcohol and high-fat diet-induced obesity (Minato et al., 2014; Xu et al., 2011; Duly et al., 2015).

Currently around 23% of adults are obese, rising to 38% in the USA (OECD, 2017). Similarly, an estimated quarter of the world's population suffers from the metabolic syndrome (MetS) (O'Neill and O'Driscoll, 2015). Alcohol consumption in the population varies by region, but around 60% of adults in Europe and the USA drink alcohol. When abstainers are excluded, average annual consumption per capita among the actively drinking population is 15-17 litres of pure alcohol per year (WHO, 2018). Therefore, many persons with obesity and/or metabolic disorders also consume significant amounts of alcohol, and the synergistic interaction between them can potentially have enormous impact on the population incidence of liver disease. In support of this, we recently showed that 40% of cases of advanced non-viral liver disease in the general population occurs in individuals with co-existent metabolic risk and regular alcohol intake, but with a risk profile that does not fit either pure NAFLD or pure alcoholic liver disease (Åberg et al., 2019b).

On the other hand, light alcohol consumption has been associated with improved insulin sensitivity and lipid profile, inhibition of platelet activation, reduction of fibrinogen level, and anti-inflammatory effects (Davies et al., 2002; Sierksma et al., 2004) possibly mediated through phenol and polyphenol content in wine and beer (Gresele et al., 2011). This is substantiated by some studies suggesting an association between low alcohol use and reduced prevalence of hepatic steatosis (Gunji et al., 2009; Yamada et al., 2010; Moriya et al., 2011; Hiramine et al., 2011; Hamaguchi et al., 2012; Dunn et al., 2012; Mitchell et al., 2018; Sookoian et al., 2014; Moriya et al., 2015; Kwon et al., 2014; Hagstrom et al., 2017), but the evidence is conflicting and suffers from methodological weaknesses. The recent Global Burden of Disease study concluded that the level of alcohol consumption that minimizes health loss is zero (GBD 2016 Alcohol Collaborators, 2018).

The purpose of this critical review is to discuss the following aspects based on recently published epidemiological and clinical evidence:

1) Does the combined effects of hazardous alcohol use and metabolic disorders increase the risk for liver disease over and beyond the sum of their individual effects (supra-additive/synergistic interaction) (Figure 1)?
2) Is there a safe, or even beneficial, level of alcohol use in persons with NAFLD or metabolic dysfunction (Figure 1)?

Methods

For the purpose of this review, we conducted a search of the PubMed database and applied citation chaining. For the first part, we included studies reporting interactions between hazardous alcohol use (>200g/wk) and obesity or other metabolic factors for liver outcomes. As hazardous alcohol intake usually represented the highest drinking category in these studies, we used the highest drinking category when evaluating interaction effects. Regarding obesity, we concentrated on body-mass index (BMI) ≥30kg/m2 if this was reported. If alternative anthropometric measures were reported, we also included these. From the relative risk estimates reported in the article, we calculated attributable proportion due to interaction (Figure 1) according to Rothman (Rothman, 2002). For the second part (low alcohol use), we focused on studies analyzing clinically meaningful liver outcomes (fibrosis, steatohepatitis, or clinical endpoints) in the presence of baseline hepatic steatosis or metabolic risk. We relied on the definition of NAFLD used in the various studies, which usually involved consumption below 20 grams of pure alcohol per day for women and below 30 grams per day for men.

Interactions between hazardous alcohol use and obesity in clinical studies

We found 15 studies analyzing interactions between obesity and alcohol use for liver outcomes; 8 were cross-sectional (1 case-control) and 7 longitudinal (Table 1). The longitudinal studies all used cohort methods and were mostly based on various population surveys, thus considered fairly representative of the general population.

All studies analyzed obesity by BMI (Table 1). Only one study considered waist circumference in addition to BMI (Åberg et al., 2018). BMI <25 kg/m2 was used as the reference group in interaction analyses in 8 of 15 studies; 3 studies used BMI <30 kg/m2 as reference, one study used BMI 25-27.4 kg/m2 (Yi et al., 2016), and 2 studies did not provide sufficient data for relative risks

compared to a reference group. Four studies explicitly stated to exclude underweight subjects from the reference group. In interaction analyses, obesity was most often defined by a BMI ≥30 kg/m2.

There was wide variation among studies in categorization of alcohol intake, both with regard to the reference group and the highest consumption category (Table 1). Only 2 studies analyzed sex-specific limits for alcohol intake (Åberg et al., 2018; Lau et al., 2015), and only 1 study explicitly also analyzed binge drinking (Lau et al., 2015).

The outcome considered was abnormal liver enzymes in 5 studies, ultrasound-diagnosed steatosis in 3, HCC in 3, liver mortality in 1, and a composite endpoint of liver-related hospital admission, mortality (and HCC) in 3.

Supra-additive interaction between obesity and alcohol use was seen in 4 of 5 studies analyzing liver enzymes (especially for gamma-glutamyltransferase (GGT)), and in 1 of 3 studies analyzing steatosis. It should be noted that an elevated GGT may also reflect hazardous alcohol use without liver injury (Niemelä and Alatalo, 2010). Of the 7 studies analyzing clinical liver outcomes, 5 found considerable supra-additive harmful effects between alcohol use and BMI, and additionally 1 study found such effects for waist circumference but not for BMI (Åberg et al., 2018). These studies showing interaction were from England, Scotland, Finland and Taiwan. In contrast, Yi et al (Yi et al., 2016) reported the highest risk of death from non-neoplastic liver disease in underweight hazardous drinkers, and found no supra-additive interaction between obesity and alcohol use compared to subjects with a BMI 25-27.4 kg/m2 and alcohol use <9 g/wk. This South-Korean study was restricted to men, relied on self-reported weights, defined obesity as a BMI ≥27.5 kg/m2, and excluded liver cancer mortality from the outcome (Yi et al., 2016). The lower limit of alcohol intake in the highest drinking category was also relatively low (126 g/wk, based on the study's definition of a standard drink).

In studies reporting supra-additive interaction, the fraction of risk attributable to interaction between drinking and obesity varied between 26-88% for elevated liver enzymes, and between 25-67% for clinical liver outcomes (Table 1). Lau et al (Lau et al., 2015) also reported supra-additive interaction between obesity and binge drinking (at least 5 drinks per day at least 1 time during the last month) for liver steatosis in men, but not in women.

Interaction between hazardous alcohol use and other metabolic factors

The association between obesity and liver disease is considered to be driven largely by associated metabolic abnormalities, primarily insulin resistance (Gutierrez-Grobe et al., 2017; Ampuero et al., 2018).

We found 5 studies (1 cross-sectional, 2 case-control and 2 longitudinal) that analyzed interactions for liver-disease risk between alcohol and other metabolic factors than obesity; 3 analyzed diabetes and 2 analyzed metabolic syndrome (Table 2). There was a profound interaction effect between hazardous drinking and diabetes for the liver risk in all 3 studies, with estimates of proportion attributable to interaction around 60-74% (Table 2). Park et al (Park et al., 2013) reported supra-additive interaction between hazardous drinking and the metabolic syndrome for GGT and aspartate aminotransferase (AST) elevation, and non-significantly so for alanine aminotransferase (ALT). In our longitudinal population study (Åberg et al., 2017), we found a supra-additive interaction effect between weekly binge drinking and presence of the MetS for clinical liver outcomes (hospital admission, liver cancer or liver death) when adjusted for age and average alcohol use (Figure 2).

In addition to these studies, Younossi et al (Younossi et al., 2019) reported supra-additive interaction between hazardous alcohol use and the MetS for all-cause death in subjects with baseline liver steatosis, based on the NHANES III survey. However, they found that the interaction term between binge drinking and MetS was non-significant for all-cause death in these subjects.

Low alcohol intake in the presence of NAFLD and/or metabolic risk

There are no randomized trials evaluating the effects of low alcohol intake in patients with NAFLD. Several observational studies link light-moderate alcohol use, as compared to abstinence, with a reduced risk for liver steatosis (Dunn et al., 2012; Mitchell et al., 2018; Sookoian et al., 2014; Kwon et al., 2014; Hagstrom et al., 2017; Dixon et al., 2001). However, recent reviews (Ajmera et al., 2017; Boyle et al., 2018) have raised several important methodological concerns with these studies, including incomplete adjustment for confounders such as physical activity, dietary factors, smoking, socioeconomic status and co-morbidity. The studies are mostly cross-

sectional and use surrogate endpoints such as steatosis or liver enzymes (Gunji et al., 2009; Yamada et al., 2010; Moriya et al., 2011; Hiramine et al., 2011; Hamaguchi et al., 2012; Sookoian et al., 2014; Moriya et al., 2015). The majority of these studies come from Japan, and ethnicity may influence alcohol metabolism and thereby modify alcoholic liver toxicity (Kourkoumpetis and Sood, 2019). In fact, the findings in the Japanese studies are in sharp contrast with those in some similar Western studies (Lau et al., 2015; Ruhl and Everhart, 2005; Suomela et al., 2015; Alatalo et al., 2008), and in contrast with longitudinal general population-based studies reporting increased risk for severe liver disease at alcohol intake even lower than 2 drinks/day (Rehm et al., 2010; Askgaard et al., 2015; Hagstrom et al., 2018; Åberg et al., 2018; Simpson et al., 2019; Sahlman et al., 2019). Simple liver steatosis or elevated liver enzymes may be poor outcome measures in population studies due to unclear prognostic relevance. We focus this part of our review on studies analyzing defined endpoints with acknowledged clinical relevance (steatohepatitis, fibrosis, or symptomatic liver disease), specifically in populations with NAFLD or metabolic risk. We found 17 such studies (10 cross-sectional, 7 longitudinal), summarized in Table 3.

Of 10 cross-sectional studies, 9 were based on selected patient populations from hospital clinics with biopsy-confirmed NAFLD or obese subjects undergoing bariatric surgery (Table 3). The population-based studies instead defined steatosis using ultrasound or specific indices (fatty liver index, hepatic steatosis index). The upper limit for low alcohol intake in these studies was typically set at ~20-30 g/day depending on the study.

Six studies stated explicitly how they treated former drinkers (current abstainers with previous drinking) (Dunn et al., 2012; Kwon et al., 2014; Dixon et al., 2001; Åberg et al., 2019a; Ascha et al., 2010; Ajmera et al., 2018), 6 stated how they treated binge drinkers (Dunn et al., 2012; Mitchell et al., 2018; Younossi et al., 2019; Åberg et al., 2019a; Ajmera et al., 2018; Ekstedt et al., 2009) and 5 evaluated lifetime drinking in their analyses (Dunn et al., 2012; Mitchell et al., 2018; Kwon et al., 2014; Hagstrom et al., 2017; Ajmera et al., 2018). Two studies had repeated measurements of alcohol use over time (Ajmera et al., 2018; Ekstedt et al., 2009), although these findings were not explicitly reported. There was a wide variation in the factors adjusted for in multivariate analyses (Table 3).

In cross-sectional clinical studies with liver histology, 2 (Dixon et al., 2001; Cotrim et al., 2009) reported no independent effect of low alcohol intake on liver-disease severity, whereas 5 (Dunn et al., 2012; Mitchell et al., 2018; Sookoian et al., 2014; Kwon et al., 2014; Hagstrom et al., 2017) reported less severe liver disease with low alcohol intake compared to abstinence. Dietary factors were poorly adjusted for in these studies.

Dunn et al (Dunn et al., 2012) reported lower odds of steatohepatitis (OR 0.56) and fibrosis (OR 0.56) among modest drinkers compared to lifetime abstainers. This study was based on patients referred to specialized clinics participating in the NASH Clinical Research Network. Mitchell et al (Mitchell et al., 2018) found less liver fibrosis in exclusive light wine drinkers, but not in exclusive beer drinkers, compared to lifetime abstinent subjects. The association with reduced liver fibrosis was not seen in subjects reporting binge drinking.

Furthermore, Hagström et al (Hagstrom et al., 2017) also found less liver fibrosis among those reporting low alcohol consumption, but, somewhat paradoxically, they found an association between elevated alcohol markers (phosphatidylethanol) and more liver fibrosis.

Wong et al (Wong et al., 2012) evaluated a population-based cohort of 922 subjects from Hong Kong for liver steatosis and fibrosis by magnetic resonance spectroscopy and transient elastography, respectively, and reported a weak direct correlation between alcohol use and prevalent steatosis (non-significant in multivariate analysis), but no association with liver fibrosis.

In a recent longitudinal study with paired liver biopsies of NAFLD patients, Ajmera et al (Ajmera et al., 2018) found low alcohol use (≤2 drinks/day) associated with lower odds of NASH resolution compared with abstinence (OR 0.32) on adjusted analysis, and the drinkers exhibited less reduction over time in steatosis grade and AST level. The study excluded former drinkers from the abstinent group. These data provide strong evidence for liver harm from low alcohol use, strongly challenging the cross-sectional studies above, although partly based on the same patients (Dunn et al., 2012).

Ekstedt et al (Ekstedt et al., 2009) found binge drinking at least once monthly associated with faster fibrosis progression in NAFLD.

A recent Mendelian randomization study categorized patients with NAFLD based on their aldehyde dehydrogenase genotype to those prone to consume more or less alcohol (Sookoian et al., 2016). The NAFLD patients genetically prone to drink less alcohol had less hepatic steatosis and less features of steatohepatitis on histology compared to those prone to drink more alcohol, which again suggests harmful effects of alcohol use in NAFLD.

In a large longitudinal Korean population cohort of 58 927 individuals with ultrasound-based steatosis, Chang et al (Chang et al., 2019) found light to moderate alcohol intake associated with a worsening of liver fibrosis over time based on non-invasive fibrosis markers. However, although suitable for ruling out advanced fibrosis, these non-invasive fibrosis markers have a low positive predictive value for fibrosis, and have not been validated for assessing change in fibrosis over time. Age is a component in the scores used, and a rising score is thus, in part, a consequence of aging itself. It therefore remains unclear whether the worsening in the fibrosis scores over time truly reflect fibrosis progression.

Another longitudinal Japanese study of NAFLD patients from a specialized hepatology center found increased HCC risk with increasing alcohol use, becoming significant at ≥40 g/day (Kawamura et al., 2016).

We recently reported the findings from a large cohort study of 8345 individuals with hepatic steatosis (fatty liver index >60) from the Finnish general population with linkage to nationwide reliable registries for hard clinical endpoints (hospital admission, cancer, or death related to advanced liver disease), and with adjustment for multiple acknowledged confounders and with exclusion of former drinkers (Åberg et al., 2019a). In this study, the presence of steatosis at baseline amplified the dose-dependent risk relationship between alcohol and incident liver disease. Among subjects with baseline steatosis, we found no benefits from low alcohol intake with regards to the risk for incident advanced clinical liver disease (Åberg et al., 2019a). Consuming more than 10 g/day of alcohol increased the risk for liver disease in a dose-dependent fashion regardless of the level of adjustment for confounders. One drink per day of non-wine beverages, or 2 drinks per day as wine, doubled the risk for advanced liver disease compared to lifetime abstinence or minimal alcohol intake.

Extending these findings, among obese men in the general population with a waist-hip ratio in the highest tertile, 1 daily alcohol drink yielded a similar relative risk for incident liver disease as 4 daily drinks in non-obese men (Figure 3) (Sahlman et al., 2019). This means that, in the presence of marked abdominal obesity, hepatic toxicity of alcohol increases by a number of four.

Vilar-Gomez et al (Vilar-Gomez et al., 2018) found that, in patients with NAFLD-cirrhosis, low alcohol use (<30 g/day for men and <20g/d for women) was associated with an increased risk of death or liver transplantation (hazards ratio 2.3), hepatic decompensation (hazards ratio 1.7), and HCC (hazards ratio 3.2) compared to abstinence, a finding that reinforces the need for absolute alcohol abstinence in patients with cirrhosis. Two additional studies found an increased risk for HCC among NAFLD patients with advanced fibrosis or cirrhosis reporting any alcohol use (Ascha et al., 2010; Kimura et al., 2018).

Extra-hepatic outcomes in NAFLD

A J-shaped cardiovascular- and mortality benefit from low alcohol use in the general population is widely reported (Di Castelnuovo et al., 2006), but has recently been questioned by the findings from a robust meta-analysis (Wood et al., 2018).

A recent study in NAFLD patients with prospectively assessed alcohol consumption over time found no association between low alcohol use and the presence of cardiovascular risk factors or subclinical cardiovascular disease (VanWagner et al., 2017).

There are conflicting data regarding a J-shaped relationship between low alcohol use and all-cause death in NAFLD cohorts in recent population-based studies (Younossi et al., 2019; Åberg et al., 2019a; Hajifathalian et al., 2019). In our longitudinal population study, such a J-shaped association between low alcohol use and all-cause death was only seen among never smokers, not among current or former smokers (Åberg et al., 2019a). Alcohol intake more than 30 g/day was associated with increased mortality in all NAFLD subjects.

Even low alcohol intake is associated with an increased risk for several types of cancer both in the general population (Cao et al., 2015; Bagnardi et al., 2013) and in individuals with NAFLD (Åberg et al., 2019a).

Discussion

Interaction between hazardous alcohol use and metabolic risk

The majority of studies report significant supra-additive interaction between hazardous alcohol use and obesity for various liver outcomes including clinical ones (hospital admission due to liver disease, liver cancer and liver-related death). Based on longitudinal studies with clinical liver endpoints, approximately 50% of the excess risk for liver disease from the combination of hazardous alcohol use and obesity is due to their interaction effects, whereas the remaining 50% is due to the independent effects of alcohol and obesity. However, there was considerable variation by study to the interaction estimate (range 0-67%), largely explained by methodological differences. Alcohol, metabolic factors and their interactions may also affect the various liver outcomes differently.

The synergistic interactions observed in these epidemiological studies are well in line with mechanistic studies showing hepatotoxic effects from the combined exposure to alcohol and high-fat diet above and beyond the sum of their individual effects (Minato et al., 2014; Xu et al., 2011; Duly et al., 2015).

A number of caveats merit consideration when interpreting the epidemiologic findings. Many studies failed to exclude former heavy drinkers from the reference group. Former drinkers may be enriched with more co-morbidity and other factors affecting the choice to abstain from alcohol but simultaneously raising the risk for liver disease (sick quitter bias). This may attenuate the observed harm from alcohol in epidemiological studies.

Similarly, there seems to be a U-shaped association between BMI and incident liver outcomes (Liu et al., 2010), where underweight might reflect liver disease or other form of illness. In addition, in case-control studies where BMI is measured when the patient is already ill may not

reflect the person's usual weight. Prospective population cohort studies have an advantage in this regard as BMI will generally reflect a healthy weight.

None of the longitudinal studies with clinical endpoints seems to have excluded both underweight subjects and previous heavy drinkers from the reference group. If one were to apply these exclusion criteria, the synergistic interaction would expectedly be even more pronounced.

BMI is an imperfect index for obesity when assessing risk for liver disease. Measures that better 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 (Åberg et al., 2018; Pang et al., 2015; Andreasson et al., 2017; Ioannou et al., 2005). The supra-additive interaction effect also seems to become stronger when obesity is measured by the WHR (Sahlman et al., 2019) or waist circumference (Åberg et al., 2018).

Binge drinking

Binge drinking, or heavy episodic drinking, is generally defined as drinking 60 gram alcohol or more on one occasion at least once during the last month (WHO, 2018). Binge drinking has a number of potentially harmful effects on the liver (Llerena et al., 2015), and has, for example, been shown to induce insulin resistance that lasts even after blood alcohol levels become undetectable (Lindtner et al., 2013). This contrasts to the improved insulin sensitivity associated with low alcohol use.

Binge drinking habits may be neglected in studies assessing alcohol use through a quantity-frequency approach, in which the respondent reports the frequency of drinking during a specific time-period and, separately, the typical amount of alcohol consumed on the days that they drank. This approach may fail to capture variations in drinking around a reported typical quantity, such as with irregular binge drinking. For example, a person who drinks two drinks daily and a person who drinks the same amount plus ten additional drinks on Saturday might report the same typical quantity of two drinks per occasion. Thus, there is a need to explicitly address the issue of binge drinking.

Binge drinking has been associated with NAFLD progression in both clinical and mechanistic studies (Llerena et al., 2015; Ventura-Cots et al., 2017). Binge drinking seems to counteract any potential benefit from low alcohol use in NAFLD (Mitchell et al., 2018), and the risk associated with binge drinking seems to arise at binge drinking episodes as infrequently as once monthly (Åberg et al., 2017; Younossi et al., 2019). Binge drinking emerged as a significant risk factor for liver disease only among those with the MetS, but not among those without it (Åberg et al., 2017). It could be speculated that a liver affected by steatosis may lack the capacity of a normal liver to recover after each episode of drinking during the break from alcohol intake. In support of this, animal studies show that intermittent alcohol administration serves as a "second hit" by aggravating hepatic oxidative stress and promoting steatohepatitis and fibrosis in mice with obesity-induced steatosis (Minato et al., 2014; Duly et al., 2015).

Low alcohol use in the presence of NAFLD or metabolic risk

Although cross-sectional studies report less liver fibrosis among NAFLD subjects with low alcohol use compared to complete abstinence, the findings are conflicting among studies, the potential benefit seems to be restricted to wine and non-binge drinking, and, most importantly, these findings have not been replicated in longitudinal studies. On the contrary, all longitudinal studies that analyzed specific histological or clinical liver outcomes report a tendency towards harm to the liver from low alcohol use, without any clear threshold effect.

A weakness of cross-sectional studies over longitudinal ones is that the predictor and outcome is measured at the same time, thereby limiting the ability to establish temporal relationship or causality. On the other hand, many longitudinal studies are unable to determine changes over time in the level of alcohol intake, or whether subjects develop additional risk factors over time.

A good example of the difference between cross-sectional and longitudinal analyzes are the studies by Dunn et al (Dunn et al., 2012) and Ajmera et al (Ajmera et al., 2018), which were in part based on the same patient population. Although both studies evaluated lifetime drinking and made careful efforts to exclude previous drinkers and binge drinkers and adjusted for multiple confounders, the cross-sectional study by Dunn et al (Dunn et al., 2012) found protective effects of low alcohol use, whereas the longitudinal study by Ajmera et al (Ajmera et al., 2018) reported harmful effects. Similarly, although low alcohol use has been found protective from steatosis in

numerous cross-sectional Japanese studies, the only longitudinal ones reported increased HCC risk (Kawamura et al., 2016; Kimura et al., 2018).

Clinic-based studies with liver biopsies often had limited statistical power for multivariate analyses, whereas many large population studies had limited availability of confounding variables, thereby risking incomplete adjustment for relevant confounding, especially diet. It is well known that individuals with low alcohol use tend to exhibit healthier dietary habits, healthier lifestyle, higher socioeconomic status, and increased physical activity compared to complete abstainers (Mukamal et al., 2006; Fillmore et al., 1998). These factors are difficult to fully adjust for in observational studies. Such incomplete adjustment may exaggerate the protective effect of low alcohol use in NAFLD.

Many studies adjusted the effect of alcohol for BMI. Alcohol use may cause obesity through excess calories, and obesity is a risk factor for chronic liver disease. Therefore, some of the effects of alcohol may be mediated through excess calories and obesity. Adjustment for BMI when analyzing associations between alcohol and liver disease may hence lead to an over-adjustment bias, i.e. subjects who consume more alcohol are more likely to gain weight, which in turn increases their risk of liver disease. This tends to attenuate the observed risks from alcohol.

Failure to separate lifetime abstainers from current abstainers (previous alcohol use, currently quit drinking) in many studies also leaves the potential for a sick quitter bias. Current abstainers may be enriched with former heavy drinkers who present a more severe liver disease that actually reflect irreversible alcoholic liver disease. Those with more severe liver disease may also be the ones that choose to quit drinking as a consequence of disease, thereby entering the “non-exposed” group.

There is concern for selection bias especially in clinic-based studies (Delgado-Rodriguez and Llorca, 2004). Considering that the level of alcohol intake is itself involved in the definition of NAFLD, filtering from clinical decision-making has already taken place when liver disease in a patient with active alcohol use is categorized as NAFLD; this may result in a distorted spectrum of baseline disease. Referral criteria of patients to liver clinics, recruitment to clinical studies, and the number and characteristics of similar patients refusing study participation were often not clearly

specified. Survey-based general population studies have an advantage in this regard, as they do not suffer the same selection bias inherent to clinic-based studies.

Alcohol intake was usually ascertained through the use of questionnaires, or in the clinical setting, often by physician interviews. Such physician interviews have been shown to be less accurate in discovering underlying alcohol risk use than cognitive lifetime drinking histories (Hayashi et al., 2004).

Both intentional and unintentional underreporting of alcohol use is of major concern. Awareness of a liver condition may lead to intentional underreporting of alcohol use by the patient in clinical studies due to a fear that alcohol use will have a negative impact on the care provided. Indeed, several studies suggest undetected significant alcohol use in many patients with hepatic steatosis labeled as NAFLD (Hagstrom et al., 2017; Hayashi et al., 2004; Staufer et al., 2019). Again, prospective population-based studies have an advantage over clinic-based studies, since healthy participants are more likely to respond honestly, and study subjects are often unaware of having steatosis when it is defined by specific laboratory indices such as the fatty liver index.

Unintentional underreporting of alcohol use is also a concern. It is difficult for anyone to accurately quantify a unit of alcohol, especially as serving size and alcohol content within and across beverage type may vary considerably. Quantification of alcohol intake typically relies on recall of past drinking, for instance during the last year, with a significant risk for recall bias (Stockwell et al., 2004). Underreporting alcohol use tends to increase as risk drinking behaviors increases, but this is complex and inconsistent (Isted et al., 2015). A general underreporting of alcohol intake might overestimate the level of alcohol intake needed to induce liver harm, but underreporting may also be skewed rather than general, whereby the net effect becomes less predictable.

Suggestions for future research

A key limitation with current longitudinal studies is that alcohol intake is usually assessed only at one point in time. There is a need for large longitudinal population-based studies that measure alcohol intake at several time points to assess the impact of changes over time in alcohol use patterns.

Given that underreporting of alcohol use generally increases together with increasing alcohol use, and that hazardous alcohol use can contribute to weight gain, potentially there may be more underreporting of alcohol use in the obese group than in non-obese groups. Therefore, some of the interaction effect between obesity and hazardous alcohol use could actually represent the effect of unmeasured alcohol intake. To overcome this uncertainty related to questionnaire-based ascertainment of alcohol use, there is a need for studies quantifying alcohol intake by sensitive and specific biomarkers such as phosphatidylethanol (Viel et al., 2012).

More study is also needed on how to best incorporate the interaction effects between alcohol and metabolic risk in clinically useful risk stratification strategies. More data is needed on which specific obesity-related metabolic components drive these harmful interaction effects for liver disease. Factors influencing individual susceptibility to alcohol toxicity, including genetics, also deserve further study.

It seems that binge drinking is associated with progression of liver disease even when average alcohol consumption is within the currently allowed limits to receive a NAFLD diagnosis. Binge drinking probably warrants explicit consideration when designing drug trials in NAFLD, and should be incorporated in the diagnostic criteria of NAFLD.

Conclusions

Although not entirely consistent, current epidemiologic and clinical evidence point to considerable supra-additive interaction for the risk of liver disease between hazardous alcohol use and metabolic abnormalities including obesity, diabetes and the MetS. This merits increased attention in disease prevention, risk stratification, and individual counseling.

There is no clear safe limit of alcohol intake in the presence of NAFLD or metabolic risk. The presence of steatosis seems to amplify alcoholic liver toxicity. Recent studies based on unselected population cohorts of subjects unaware of having steatosis with longitudinal follow-up for clinical liver outcomes, and with comprehensive adjustment for confounders, report low alcohol use being associated with an elevated risk for incident liver disease. However, in individuals with NAFLD

without advanced liver fibrosis, the absolute risk increase from maximum 1 daily standard glass of wine (10g of ethanol) seems small.

Although low alcohol use might ameliorate insulin resistance and thereby possibly reduce hepatic steatosis, alcohol's numerous detrimental effects extend well beyond simple fat accumulation, and the net effect seems to be harmful already at low doses. There is no clinical evidence to support that low alcohol would protect from symptomatic liver disease. In NAFLD with advanced liver disease or particular risk for progressive liver disease, complete alcohol abstinence is advised.

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FIGURE LEGENDS

Figure 1. The concept of interaction between alcohol and obesity for the risk of liver disease. Obesity and metabolic risk may modify the effects on the liver of low alcohol use (<1-3 drinks/day), with some studies reporting harm and other studies reporting benefits from low alcohol use compared to abstinence. Regarding hazardous alcohol use, studies suggest supra-additive interaction effects between exposure to alcohol (R_{alco}) and obesity (R_{obe}), so that the combined risk effect of having both exposures (R_{combi}) is higher than the sum of their individual risk effects ($R_{alco} + R_{obe}$).

Figure 2. Hazards ratios for the contribution of weekly binge drinking, the metabolic syndrome (MetS), and their combination (interaction) to the risk for incident clinical liver disease in comparison to subjects without the MetS who reported no binge drinking or binge drinking less often than once monthly (baseline risk) in the Finnish Health 2000 study. The attributable proportion due to interaction in this example is 29% ((4.61 – 2.26 – 2.03 + 1) / 4.61 = 0.29). (Reprinted with permission from Åberg F et al. Binge drinking and the risk for liver events: A population-based cohort study. Liver International 2017;37:1373 (Åberg et al., 2017).

Figure 3. Interaction between average alcohol intake (grams of ethanol per week) and waist-hip ratio for the risk of incident clinical liver disease among men in the Finnish general population. (Reprinted with permission from Sahlman P et al. Genetic and lifestyle risk factors for advanced liver disease among men and women. Journal of Gastroenterology and Hepatology 2019 (Sahlman et al., 2019).

Table 1. Studies analyzing interaction between hazardous alcohol use and obesity for various liver outcomes.

Author, year	Country	Study design	Study subjects	Outcome measure	Categories	Findings	Adjustments	Supra-additive interaction	Attributable proportion
Liver-function tests									
Ruhl, 2005	USA	Cross-sectional	13 580 men and women recruited in 1988-1994 (NHANES III)	Elevated ALT or AST	Reference: BMI <25 kg/m^2 + nondrinker Drinker: ≥2 drinks/d Obese: BMI ≥30 kg/m^2	Obese OR 2.1 Drinker OR 1.6 Obese drinker OR 5.4	Age, sex, ethnicity, smoking, caffeine consumption, HbA1c	Yes	50%
Alatalo, 2008	Finland	Cross-sectional	2 164 apparently health men and women recruited in a survey to establish enzyme reference intervals in the Nordic countries	Elevated ALT, AST or GGT	Reference: BMI 19-24.9 kg/m^2 + abstainer Drinker: 0-280 g/wk Obese: BMI ≥30 kg/m^2	Relative differences (%) in mean levels compared to reference group			
						ALT: obese +52% Drinker +5% Obese drinker +105%	-	Yes	
						AST: obese +18% Drinker +5% Obese drinker +41%	-	Yes	
						GGT: obese +36% Drinker +18% Obese drinker +123%	-	Yes	
Adams, 2008	Australia	Cross-sectional	2 610 men and women, 20-80yrs, residing in Busselton recruited in 1994 for a health	Elevated ALT or GGT	-	Numbers not given for calculation	Age	No	

			survey						
Loomba, 2009	USA	Cross-sectional	2 364 men and women, mean age 70 yrs, recruited in 1984-1987 (Rancho Bernardo Study)	Elevated ALT	Reference: BMI 18.5-24.9 kg/m^2 + nondrinker Drinker: >210 g/wk Obese: BMI ≥30 kg/m^2	Obese OR 1.4 Drinker OR 2.1 Obese drinker OR 8.9	Age, sex, total cholesterol, serum triglycerides, fasting plasma glucose, systolic blood pressure, diabetes	Yes	72%
				Elevated AST	Reference: BMI 18.5-24.9 kg/m^2 + nondrinker Drinker: >210 g/wk Obese: BMI ≥30 kg/m^2	Obese OR 1.3 Drinker OR 2.3 Obese drinker OR 21	Age, sex, total cholesterol, serum triglycerides, fasting plasma glucose, systolic blood pressure, diabetes	Yes	88%
Shen, 2010	China	Longitudinal	500 men and women with normal liver tests and without liver disease recruited in 1999 for an epidemiological survey in Zheijian Province,	Elevated ALT or GGT	Reference: BMI <25 kg/m^2 + alcohol use <280 g/wk Drinker: ≥280 g/wk Overweight/obese: BMI ≥25 kg/m^2	Overweight/obese RR 1.40 (0.84-2.33) Drinker RR 2.20 (1.38-3.50) Overweight/obese drinker RR 3.49 (2.24-5.43)	-	Yes	26%

			follow-up 7 yrs						
Steatosis									
Bellentani, 2000	Italy	Cross-sectional	257 men and women recruited in 1997 (Dionysos study)	Steatosis on US	Reference: BMI <25 kg/m^2 + alcohol use <210 g/wk and lifetime alcohol use <100kg Drinker: ≥420 g/wk or lifetime use ≥100kg Obese: BMI >30 kg/m^2	Obese RR 4.6 (2.5-11.0) Drinker RR 2.8 (1.4-7.1) Obese drinker RR 5.8 (3.2-12.3)	-	No	
Lau, 2015	Germany	Cross-sectional	4 009 men and women (The Study of Health in Pomerania)	Steatosis on US	MEN Reference: BMI <25 kg/m^2 + current abstainers Drinker: ≥420 g/wk Obese: BMI ≥30 kg/m^2 WOMEN Reference: BMI <25 kg/m^2 + current abstainers Drinker: >140 g/wk Obese: BMI ≥30 kg/m^2	MEN Obese ? (data not given) Drinker OR 21.5 Obese drinker OR 101.6 WOMEN Obese ? (data not given) Drinker OR 0.15 Obese drinker HR 3.30	Age, HbA1c	Yes	?
					BINGE Reference: BMI <25 kg/m^2 + nonbinge drinking Binge drinker: ≥5 drinks/d ≥1 time during the last month Obese: BMI ≥30 kg/m^2	MEN Obese OR 8.96 Binge drinker OR 2.73 Obese binge drinker OR 14.10 WOMEN Obese OR 7.31 Binge drinker OR 1.69 Obese binge drinker OR 7.71	Age, HbA1c, average daily alcohol use	MEN: Yes, WOMEN: No	MEN 24%
Takahashi,	Japan	Cross-	8 029 men and	Steatosis		Highest prevalence of	-	No	

2015		sectional	women, mean age 50 yrs, undergoing general health examination at 3 health centers recruited in 2009-2010	on US		steatosis in obese (BMI >30 kg/m^2) low-drinking (<140 g/wk) men and obese (BMI >30 kg/m^2) heavy-drinking (>350 g/wk) women			
Clinical outcomes									
Marrero, 2005	USA	Case-control	70 with HCC and 70 with liver cirrhosis without HCC recruited in 2002-2003 from hospital clinics	HCC	Reference: BMI <30 kg/m^2 + alcohol use <100 drinks per lifetime Drinker: ≥100 drinks per lifetime Obese: BMI ≥30 kg/m^2	Obese OR 1.2 (1.4-17.3) Drinker OR 2.6 (1.8-7.6) Obese drinker OR 5.5 (1.8-20)	-	Yes	49%
Loomba, 2010	Taiwan	Longitudinal	2 260 Taiwanese hepatitis B-positive men recruited in the REVEAL-HBV study, follow-up 14 yrs	HCC	Reference: BMI <30 kg/m^2 + nondrinker Drinker: alcohol use ≥4 d/wk for ≥1yr Obese: BMI ≥30 kg/m^2	Obese HR 0.64 (0.16-2.63) Drinker HR 1.64 (1.12-2.40) Obese drinker HR 3.40 (1.24-9.34)	Age, ALT, HBV-DNA, baseline cirrhosis	Yes	62%
Loomba, 2013	Taiwan	Longitudinal	23 712 Taiwanese residents	HCC	Reference: BMI <30 kg/m^2 + nondrinker Drinker: alcohol use ≥4 d/wk for	Obese HR 1.17 (0.65-2.11) Drinker HR 1.46 (1.07-1.98)	Age, sex, smoking, ALT, HBsAg, anti-HCV	Yes	67% (unadjusted as reported

			recruited in 1991-1992 (cancer screening program), mean follow-up 11.6 yrs		≥1yr Obese: BMI ≥30 kg/m^2	Obese drinker HR 3.82 (1.94-7.52)	antibodies, diabetes		by the authors), 57% (calculated based on adjusted HRs)
Liu, 2010	England and Scotland	Longitudinal	1 230 662 middle-aged women (Million Women Study) recruited in 1996-2001, mean follow-up 6.2 yrs	Liver-related hospital admission or death	Reference: BMI 22.5-25 kg/m^2 + alcohol use <70 g/wk Drinker: ≥150 g/wk Obese: BMI ≥30 kg/m^2	Obese RR 1.35 (1.15-1.59) Drinker RR 3.44 (2.70-4.37) Obese drinker RR 6.53 (4.98-8.55)	Age, recruitment region, alcohol use, smoking, socioeconomic status, physical activity	Yes	42%
Hart, 2010	Scotland	Longitudinal	9 559 men aged 18-92 yrs (Midspan and Collaborative studies) recruited in 1965-1968 and 1970-1973, median follow-up 29 yrs	Liver mortality	Reference: BMI <25 kg/m^2 + alcohol use <120 g/wk Drinker: ≥120 g/wk Overweight/obese: BMI ≥25 kg/m^2	Overweight/obese RR 1.29 (0.60-2.80) Drinker RR 3.66 (1.74-7.71) Overweight/obese drinker RR 9.53 (4.98-18.2)	Age, study, social class, smoking, height, bronchitis, FEV1, angina, ischemia on electrocardiogram, diabetes	Yes	59%
Yi, 2016	South	Longitudinal	101 735 men	Liver	Reference: BMI 25-27.4 kg/m^2 +	Overweight/obese HR 2.8	Age, smoking	No	

	Korea		recruited in a postal survey 2004 (Korean Veterans Health Study), follow-up 6 yrs	mortality (liver cancer excluded)	alcohol use <9 g/wk Drinker: ≥126 g/wk Overweight/obese: BMI ≥27.5 kg/m^2 *	Drinker HR 1.3 Overweight/obese drinker HR 3.6 (highest risk in underweight drinkers, BMI <21, HR 12.7) *	status, physical activity, household income		
Åberg, 2018	Finland	Longitudinal	6 732 men and women, mean age 54 yrs, recruited in 2000-2001 (Health 2000 Study), mean follow-up 11.4 yrs	Liver-related hospital admission, cancer or death	BMI Reference: BMI <25 kg/m^2 + alcohol use <210g/wk for men and <140g/wk Drinker: above these sex-specific limits Obese: BMI >30 kg/m^2	Obese HR 1.48 Drinker HR 5.84 Obese drinker HR 4.06	Age, sex	No	
					WC Reference: WC <102 cm + alcohol use <210g/wk for men and WC <88cm + alcohol use <140g/wk for women Drinker: above these sex-specific limits Obese: WC above these sex-specific limits	Obese HR 1.46 Drinker HR 4.55 Obese drinker HR 6.72	Age, sex	Yes	25%

* Calculated from a subset of 72 152 subjects without baseline liver disease and without viral hepatitis

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase;OR, odds ratio; GGT, gamma-glutamyltransferase; BMI, body mass index; RR, risk ratio; HR, hazards ratio; US, ultrasound; HCC, hepatocellular carcinoma; WC, waist circumference

Table 2. Studies analyzing interaction between hazardous alcohol use and metabolic factors other than obesity for various liver outcomes.

Author, year	Country	Study design	Study subjects	Outcome measure	Categories	Findings	Adjustments	Supra-additive interaction	Attributable proportion
Park, 2013	South Korea	Cross-sectional	5 946 men and women recruited in 2003-2010 (Korean National Cancer Center Cohort)	Elevated ALT, AST or GGT	Reference: No metabolic syndrome + alcohol abstainer Drinker: ≥24 g/day Metabolic syndrome: yes (Adult Treatment Panel III)	GGT ≥30 U/L: Metabolic syndrome OR 1.79 (1.21-2.66) Drinker OR 7.81 (6.07-10.06) Metabolic syndrome + drinker OR 13.43 (8.35-21.60)	Age, gender, education level, smoking status	Yes	36%
						ALT ≥40 U/L: Metabolic syndrome OR ? Drinker OR 1.61 (1.00-2.60) Metabolic syndrome + drinker OR 3.88 (2.00-7.55)	as above	Yes, but non-significant	?
						AST ≥40 U/L: Metabolic syndrome OR ? Drinker OR 3.73 (2.54-5.47) Metabolic syndrome + drinker OR 6.42 (3.64-11.35)	as above	Yes	?
Hassan, 2002	USA	Case-control	115 men and women with hepatocellular carcinoma and 230 matched controls with other malignancies recruited in 1994-	HCC	Reference: No diabetes + alcohol use <439 g/wk Drinker: >439 g/wk Diabetes: yes	Diabetes OR 2.4 (1.3-4.5) Drinker OR 2.6 (1.4-4.9) Diabetes + drinker OR 9.9 (2.5-39.3)	HBsAg, anti-HCV antibodies, smoking status	Yes	60%

			1995 at a single center						
Yuan, 2004	USA	Case-control	295 men and women with hepatocellular carcinoma recruited in 1984-2002 from a population-based cancer registry and 435 matched healthy neighboorhood control subjects	HCC	Reference: No diabetes + alcohol use ≤4 drinks/d Drinker: >4 drinks/d Diabetes: yes	Diabetes OR 2.5 (1.5-4.0) Drinker OR 3.4 (2.2-5.4) Diabetes + drinker OR 17.3 (3.9-77.6)	Age, sex, race, education level, smoking status	Yes	72%
Åberg, 2018	Finland	Longitudinal	6 732 men and women, mean age 54 yrs, recruited in 2000-2001 (Health 2000 Study), mean follow-up 11.4 yrs	Liver-related hospital admission, cancer or death	Reference: No diabetes + alcohol use <210g/wk for men and <140g/wk for women Drinker: above these sex-specific limits Diabetes: yes	Diabetes HR 2.58 Drinker HR 3.56 Diabetes + drinker HR 19.5	Age, sex	Yes	74%
Åberg, 2017	Finland	Longitudinal	6 366 men and women, mean age 54 yrs, recruited in 2000-2001 (Health 2000 Study), mean follow-up 11.4 yrs	Liver-related hospital admission, cancer or death	Reference: No metabolic syndrome + no binge drinking or less than once monthly Binge drinking: ≥60 g/occasion at least weekly Metabolic syndrome: yes (Joint Interim Statement	Metabolic syndrome HR 2.03 (1.18-3.47) Weekly binge drinking HR 2.26 (0.76-6.71) Metabolic syndrome + weekly binge drinking HR 4.61 (2.04-10.4)	Age, average alcohol use	Yes	29%

					criteria)				
Younossi, 2019	USA	Longitudinal	4 264 men and women with fatty liver disease (ultrasound) recruited in 1988-1994 (NHANES III)	All-cause death	Reference: No metabolic syndrome + alcohol use ≤3 drinks/day for men or ≤1.5 drinks/day for women Drinker: above these sex-specific limits Metabolic syndrome: yes (Adult Treatment Panel III)	Metabolic syndrome HR 1.32 (1.04-1.68) Drinker HR ? Metabolic syndrome + drinker 3.35 (2.02-5.55)	?	Yes	?

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; OR, odds ratio; GGT, gamma-glutamyltransferase; HR, hazards ratio; HCC, hepatocellular carcinoma

Table 3. Studies analyzing the effects of light-moderate alcohol consumption on steatohepatitis, liver fibrosis, liver cancer or other symptomatic advanced liver disease in subjects with baseline fatty liver disease or metabolic risk.

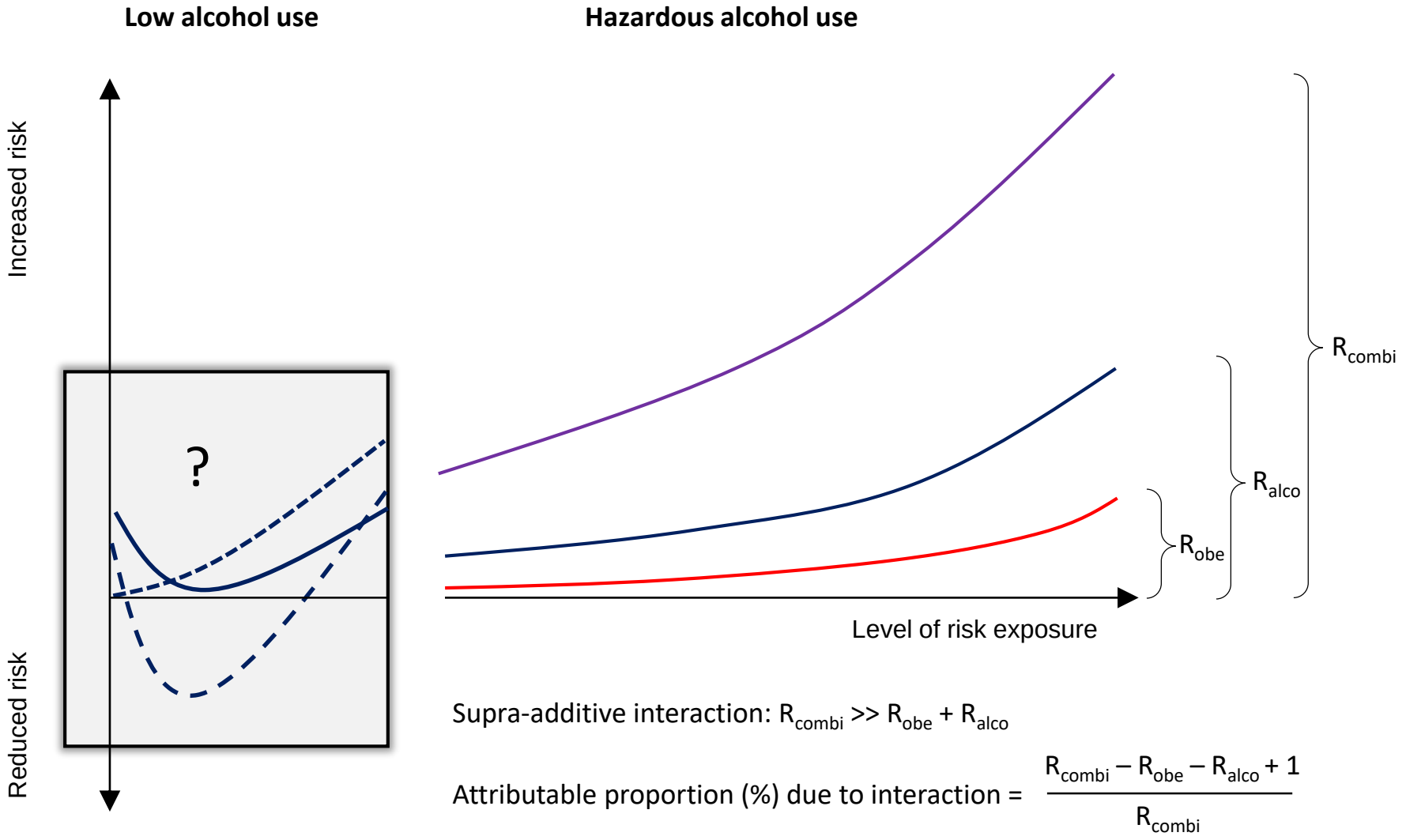
Author, year, design	**Country**	**Study subjects**	**Recruitment**	**Exclusions**	**NAFLD definition**	**Assesment of lifetime drinking**	**Former drinkers**	**Outcome measure**	**Adjustments**	**Effects of light-moderate alcohol use**
Dixon 2001, Cross-sectional	Australia	105 bariatric surgery patients	Hospital clinic	History of alcoholism, alcohol > 200 g/wk, hepatotoxic medication, other liver disease	Histology	No	Excluded	Histology	DM, IR	↓ NASH (non-significant after adjusting for diabetes or IR index)
Cotrim 2009, Cross-sectional	Brazil	132 bariatric surgery patients	Hospital clinic	Alcohol use > 280 g/week, other liver disease	Histology	No	n.r.	Histology	-	↑ insulin sensitivity No impact on histology
Ekstedt 2009, Longitudinal	Sweden	71 NAFLD subjects	Hospital clinic	Absent follow-up biopsy (n=20)	Histology	No	n.r.	Histology	Age, sex, BMI, DM, weight gain, HOMA-IR, fibrosis stage at baseline	Binge drinking → ↑ fibrosis progression
Ascha 2010, Cross-sectional	USA	510 cirrhotic patients (195 with NASH)	Hospital clinic	Other liver disease	Histology or radiology	No	Included	HCC	Age, sex, race, BMI, smoking, DM	Any alcohol use: ↑ HCC risk
Dunn 2012, Cross-sectional	USA	582 NAFLD patients (NASH Clinical Research Network)	Hospital clinic	Alcohol use >20 g/day, monthly binge drinking, former drinkers (current abstainers)	Histology	Yes	Excluded	Histology	Age, sex, race, income, education, BMI, exercise, smoking, total calorie intake	↓ NASH (OR 0.56) ↓ ballooning (OR 0.66) ↓ fibrosis (OR 0.56)
Wong 2012, Cross-sectional	Hong Kong	922 adults (264 with fatty liver)	General population	Alcohol consumption ≥ 140 g/week, other liver disease, decompensated liver disease, contraindication for MRI	MRS + US elastography	No	n.r.	MRS + US elastography	Age, sex, MetS	Weak correlation with liver fat content (r=0.11, non-significant) No association with fibrosis.

Sookoian 2014, Cross-sectional	Argentina	414 NAFLD patients	Hospital clinic	n.r.	Histology	No	n.r.	Histology	n.r.	↓ NAFLD and NASH ↓ liver enzymes and inflammatory markers
Kwon 2014, Cross-sectional	USA	77 NAFLD patients	Hospital clinic	History of long-term alcohol abuse or dependence, or >40 g/week, other liver disease, steatogenic medications	Histology	Yes	Excluded	Histology	Age, sex, BMI, % body fat, HOMA-IR, liver enzymes, selected histological features	Alcohol use ≥24 gram-years: less severe disease (OR 0.26)
Kawamura 2016, Longitudinal	Japan	9 959 NAFLD patients	Hospital clinic	Other liver disease, underlying systemic disease, follow-up <48 weeks	US	No	n.r.	HCC	Age,, albumin, AST, GGT, platelets, DM, triglycerides, HDL cholesterol	Alcohol use ≥40 g/day: ↑ HCC
Hagström 2017, Cross-sectional	Sweden	120 NAFLD patients	Hospital clinic	Alcohol use > 14 units/week	Histology	Yes	n.r.	Histology	Age, DM, hypertension, BMI, smoking	Lifetime alcohol use up to 13 units/week: ↓ fibrosis
Kimura 2018, Cross-sectional	Japan	301 NAFLD patients	Hospital clinic	n.r.	Histology	No	n.r.	HCC	Fibrosis, diabetes, triglycerides	↑ HCC (RR 4.43, P=0.07)
Mitchell 2018, Cross-sectional	USA	187 NAFLD patients	Hospital clinic	Alcohol use ≥210 g/week (male) or ≥140 g/week (female), other liver diseases, steatogenic medications	Histology	Yes	n.r.	Histology	Age, sex, DM, BMI, HOMA-IR	Alcohol use 1-70 g/wk: ↓ advanced fibrosis (OR 0.33), but only in wine- and non-binge drinkers.
Chang 2019, Longitudinal	South Korea	58 927 adults	Hospital clinic	Alcohol use ≥30 g/day for men or ≥20 g/day for women, other liver disease, steatogenic drugs	US	No	n.r.	Non-invasive fibrosis markers (NFS, FIB-4)	Age, sex, center, screening year, smoking, exercise, education, BMI, DM, hypertension, dyslipidemia, HOMA-IR, hs-CRP	Worsening over time in fibrosis markers

Hajifathalian 2018, Longitudinal	USA	4 568 adults with NAFLD (NHANES)	General population	Alcohol use >3 drinks/day (men) or >2 drinks/day (women), viral hepatitis, increased transferrin saturation	Hepatic steatosis index	No	n.r.	All-cause death	Age, sex, smoking , ethnicity, exercise, education, DM, intake of fiber/polyunsaturated fatty acids	0.5-1.5 drinks/day: ↓mortality (HR 0.64) ≥1.5 drinks/day: ↑ mortality (HR 1.45)
Younossi 2019, Longitudinal	USA	4 264 adults with hepatic steatosis (NHANES)	General population	Other liver disease, steatogenic drugs	US	No	n.r.	All-cause death	Age, sex, ethnicity, smoking, MetS,	Alcohol use ≤3 drinks/day (men) or ≤1.5 drinks/day (women): no effect on mortality
Ajmera 2018, Longitudinal	International multicenter	285 NAFLD patients (NASH Clinical Research Network)	Hospital clinic	Alcohol use during 2 years preceding study of >20 g/day (men) or >10 g/day (women), or ≥6 drinks/occasion, other liver disease	Histology	Yes	Excluded	Histology	Age, sex, ethnicity, smoking	Less reduction over time in steatosis grade ↓ NASH resolution (OR 0.32)
Åberg 2019, Longitudinal	Finland	8 345 adults with hepatic steatosis (Health 2000 and FINRISK population surveys)	General population	Alcohol use >50g/day, past drinkers (current abstainers), baseline clinical liver disease, viral hepatitis	Fatty liver index	No	Excluded	- Hospital admission, liver death, liver cancer - All-cause death - Cancer - CVD	Age, sex, BMI, smoking, exercise, DM, marital status, education, employment	↑ liver-related morbidity and mortality, no threshold effect ↑ cancer (↓ CVD) J-shaped association with all-cause death among never smokers

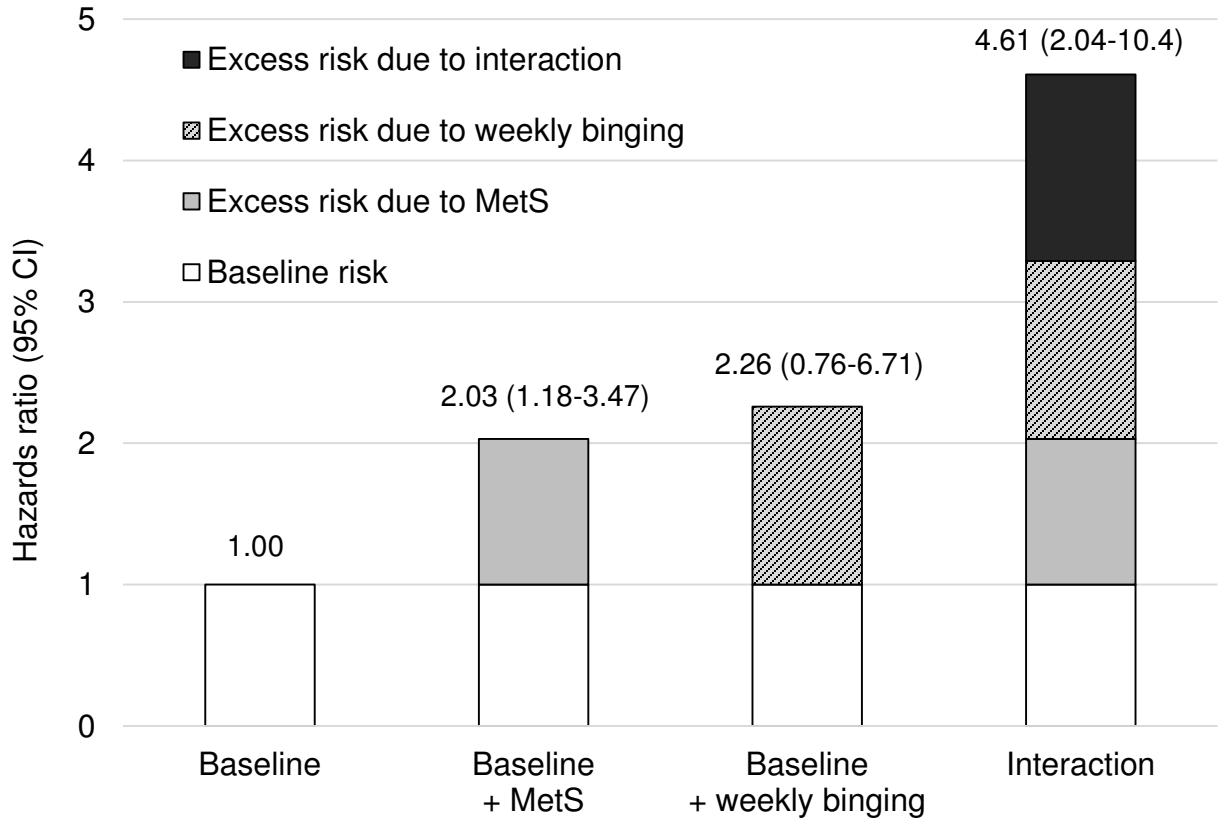
Abbreviations: DM, diabetes mellitus; IR, insulin resistance; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; HCC, hepatocellular carcinoma; MRS, magnetic resonance

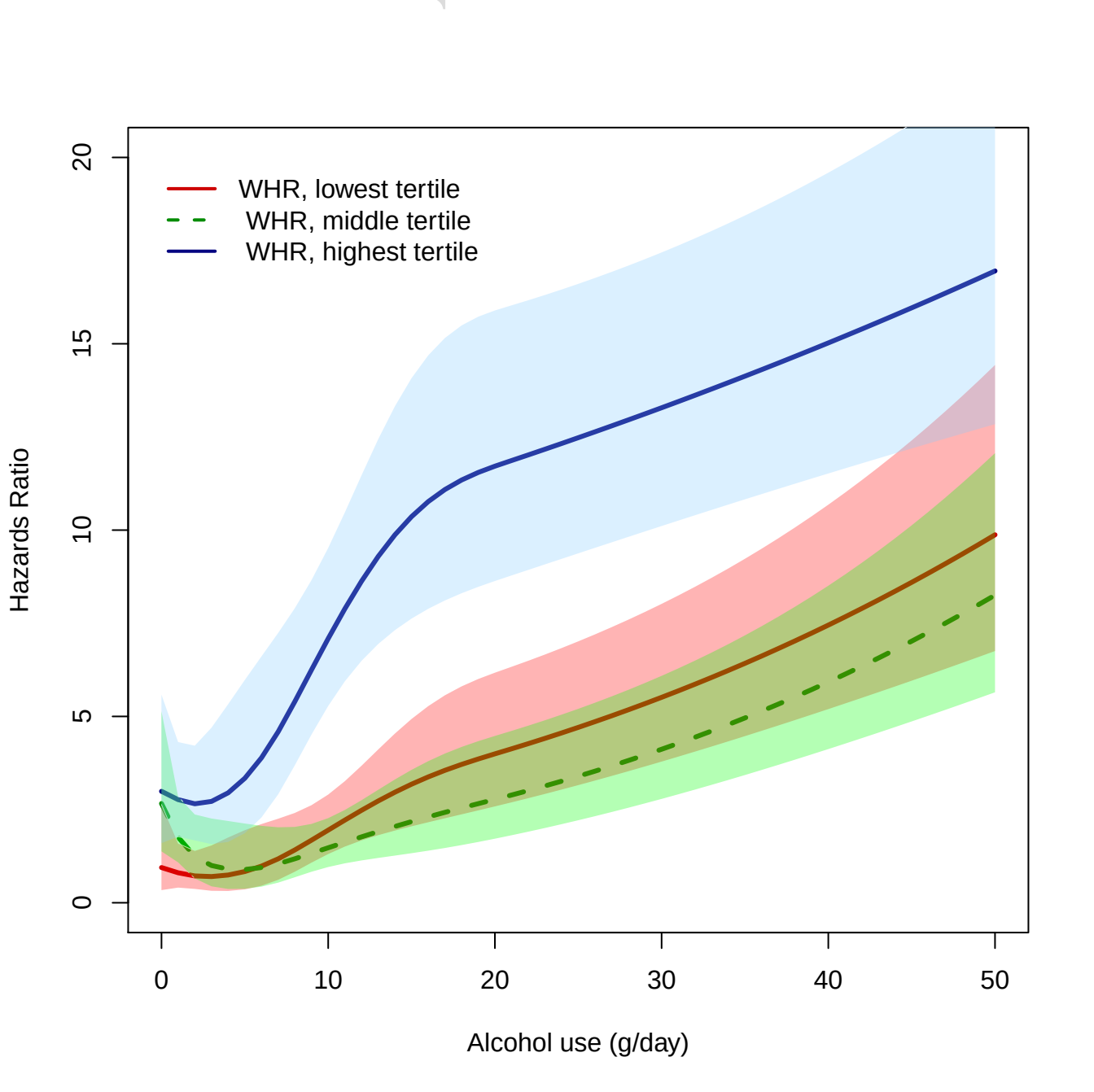
spectroscopy; US, ultrasound; MetS, metabolic syndrome; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; NFS, NAFLD fibrosis score; FIB-4, fibrosis-4 index; CVD, cardiovascular disease



Supra-additive interaction: $R_{combi} >> R_{obe} + R_{alco}$

Attributable proportion (%) due to interaction = $\frac{R_{combi} - R_{obe} - R_{alco} + 1}{R_{combi}}$




WHR, lowest tertile
WHR, middle tertile
WHR, highest tertile
Hazards Ratio
0
5
10
15
20
0
10
20
30
40
50
Alcohol use (g/day)