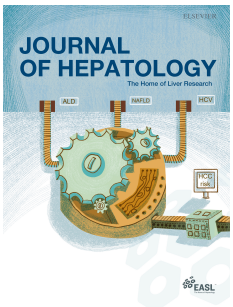

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Alcohol consumption and metabolic syndrome: Clinical and epidemiological impact on liver disease

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Key points:

- Alcohol use and the metabolic syndrome are highly prevalent in the population, frequently co-exist, and both predispose to a wide range of health problems
- Complex relationships exist between alcohol use and many components of the metabolic syndrome
- The metabolic syndrome increases the risk of liver-related outcomes, regardless of the level of alcohol consumption
- Metabolic components seem to modify the dose-response association between alcohol intake and risk of liver disease
- Risk stratification that simultaneously consider alcohol use and metabolic abnormalities can potentially help detect persons at risk for liver-related outcomes at earlier stages

ABSTRACT

Alcohol use and the metabolic syndrome are highly prevalent in the population and frequently co-exist. Both are implicated in a large range of health problems, including chronic liver disease, hepatocellular carcinoma, and liver-related outcomes. Studies have yielded mixed results regarding the effects of mild-moderate alcohol consumption on the risk of metabolic syndrome and fatty liver disease, possibly due to methodological differences. The few available prospective studies indicated that mild-moderate alcohol use had harmful effects on liver-related outcomes. This conclusion was substantiated by systems biology analyses suggesting that alcohol may have a common effect in the systemic and multiorgan metabolic syndrome and fatty liver disease, potentiating an already existing dysregulation of common vital homeostatic pathways. Alcohol and metabolic factors are independently and jointly associated with liver-related outcomes. Indeed, metabolic syndrome increases the risk of liver-related outcomes, regardless of the alcohol intake level. Moreover, the components of metabolic syndrome appear to have additive effects on the risk of liver-related outcomes. A number of population studies have implied that measures of central/abdominal obesity, such as the waist-to-hip ratio, can predict liver-related outcomes more accurately than body mass index, also among individuals who consume harmful quantities of alcohol. Many studies even point to synergistic interactions for liver-related outcomes between harmful alcohol use and many metabolic components. This accumulating evidence showing independent, combined, and modifying effects of alcohol and metabolic factors on the onset and progression of chronic liver disease highlights the multifactorial background of liver disease in the population. The evidence suggests that more holistic approaches could be useful for risk prediction and for diagnostics and treatment planning.

Introduction

Alcohol use and the metabolic syndrome (MetS) are both highly prevalent in the population and they frequently co-exist. Both are implicated in a broad range of health problems, including chronic liver disease, hepatocellular carcinoma (HCC), and liver-related outcomes.[1]

From a population perspective, alcohol harm is not limited to a small minority of individuals with alcohol dependency. However, safe levels of alcohol intake are difficult to define, due to the wide variations among individuals regarding the factors that contribute to susceptibility, including sex, genetics, and multiple effect modifiers.[2] Moreover, definitions of a standard drink or low- and high-risk drinking vary substantially between countries.[3] A standard drink often does not reflect customary serving sizes, and alcohol content varies considerably within and across different beverage types. Nonetheless, the World Health Organization (WHO) advises that neither men nor women should drink more than 20 g/day of pure ethanol (2 standard drinks).[4]

MetS has become a global problem.[5] It is largely attributed to excess caloric intake and physical inactivity. MetS comprises a cluster of factors, including abdominal obesity, hyperglycemia/insulin resistance, dyslipidemia, and arterial hypertension. Moreover, MetS is often present in subjects with non-alcoholic fatty liver disease (NAFLD).

NAFLD and alcohol-related liver disease (ArLD) are the leading causes of chronic liver disease worldwide.[6,7] In the hepatology literature, mild-to-moderate drinking is often distinguished from hazardous/harmful drinking by an arbitrary threshold of regular intake; this threshold is 20 g/day (140 g/week) of pure alcohol for women or 30 g/day (210 g/week) for men.[8,9]

Both dysregulated metabolism and alcohol act as independent and synergistic drivers of liver disease.[1] MetS can prime the liver to alcohol-induced harm, and vice versa; thus, the distinction has blurred between ArLD and NAFLD as separate conditions.

In this review, we summarize the epidemiology of alcohol consumption and MetS and discuss their independent and combined impacts, particularly on liver-related clinical outcomes. Additionally, we suggest potential clinical implications for chronic liver disease.

Global alcohol consumption and associated harm

In 2018, the global average alcohol consumption among individuals aged ≥15 years was 6.2 liters of pure ethanol per person (Figure 1a), 2.6 liters for women and 9.7 liters for men, with substantial variation to these estimates by country.[10] This sex difference is lower in countries with higher overall prevalence of drinking.[11] Although the total alcohol consumption has decreased slightly since the year 2000, the consumption among active drinkers has increased in most parts of the world and is generally 2-3 times higher than the overall consumption levels.[8]

The average worldwide prevalence of heavy episodic drinking (consuming at least 60g of pure ethanol on one occasion at least monthly) is 18.4%, being highest (30–34%) in Europe, high-income Asia Pacific, Central sub-Saharan Africa and Australasia.[12] In 2016, an estimated 1.3% (>100 million people) had alcohol use disorders.[10]

Annually, >2.4 million deaths result from harmful alcohol use (Figure 1b). Alcohol-attributable age-standardized mortality is higher for men (6.8%) than women (2.2%) and among young adults.[11] Cardiovascular diseases were responsible for 34.3% of all alcohol-attributable deaths in 2012, followed by injuries (25.8%) and digestive diseases (16.2%).[13] Again, there is considerable variation by age, sex, and region.

Alcohol use was the seventh leading risk factor for disability-adjusted life years in 2016, and the leading cause of premature mortality and disability among young adults (Figure 1c).[8,11]

Intake of more than two standard drinks per day is associated with an increased risk of all-cause, cardiovascular, and cancer mortality.[14] For cardiovascular subtypes other than myocardial infarction, there is no clear threshold for safe drinking.[15] Among persons >50 years of age, cancers are the predominant source of alcohol-attributable burden in countries with high socio-demographic index.[11]

Whilst alcohol use has decreased in some countries since the beginning of the COVID-19 pandemic, heavy episodic drinking and the proportion of people with problematic alcohol use may have increased.[16] In parallel, reports from the US and the UK show that alcohol-related mortality and alcohol-related liver mortality increased by approximately 20% during the COVID-19 pandemic.[17,18] Beyond health outcomes, alcohol use is also associated with wide-ranging social consequences and a large financial burden to society.[19]

Global trends: MetS

Worldwide, MetS-related factors such as high systolic blood pressure, high blood glucose and obesity constitute leading risk factors for death (Figure 1d).

The recognition of MetS over the last three decades started with the description of an insulin-resistance syndrome (or syndrome X) by Reaven, in 1988.[20] Although the focus of syndrome X was insulin resistance, it is now widely recognized that ectopic fat accumulation, manifested as central obesity, is a key component and cause of insulin resistance and MetS (Supplementary Table 1). It has also become clear that patients with MetS often have type 2 diabetes (T2D), NAFLD, an atherogenic lipoprotein phenotype, and hypertension. Among patients with T2D, mortality risk increases with increasing numbers of MetS components.[21]

MetS may develop from an unhealthy lifestyle that includes physical inactivity, a poor-quality energy-dense diet, smoking, and increased alcohol consumption. The first pragmatic diagnostic criteria for MetS, published in 2001, focused on measures of central obesity, dysglycemia, dyslipidemia, and hypertension. Despite limitations related to the dichotomization of continuous variables, for the sake of clinical applicability, MetS was defined by specific thresholds for waist circumference, plasma glucose concentration, high-density lipoprotein cholesterol (HDL-c), fasting triglyceride concentration, and blood pressure. When three or more of these five features exceeded the threshold, MetS was diagnosed. Between 2001–2009 there was considerable debate concerning the number of features required, the threshold for each individual variable, whether central obesity should be obligatory, and whether ethnic-specific thresholds for central obesity are required to define and characterize MetS. These debates resulted in modifications of the diagnostic criteria, and in 2009, the 'harmonized criteria' for MetS were established by consensus among several societies (Supplementary Table 1). Nonetheless, the MetS population is heterogeneous, due to variations in classifications over time and across studies and different combinations of individual features. Thus, prevalence estimates have varied, and it is difficult to draw conclusions about the changes observed in MetS prevalence over the last 20 years.

Not surprisingly, global MetS prevalence estimates have varied between countries. Recently, cross-sectional surveys in West China from 2010–2018 showed that the overall prevalence of MetS ranged between 21.4–27.8%.[22] The MetS prevalence in Sichuan Province (27.8% in 2010, 27.4% in 2018, among individuals aged ≥18 years) was lower than those reported in previous studies from China (33.9% in 2010).[23] However, the 2010 estimate might have been an overestimate, because a lower waist circumference threshold (80 cm) was used for women. The estimated percentages of MetS in other parts of Asia have been similar (e.g., 28–30% in Korean men aged 40–79 years;[24] 30% in Indian adults aged ≥18 years, 2004–2019;[25] and 20–

37% in Bangladesh[26]). Other studies have shown different prevalences across the globe. For example, 36.5% in 2007–2009 in Portugal (individuals aged ≥18 years),[27] 24.3% in Europe,[28] and 44.2% in Mexico.[29] Among US adults, the prevalence of MetS has increased from 36.2% in 1999–2000 to 47.3% in 2017–2018.[30] Over this 20-year period, cardiometabolic health has also significantly worsened, primarily related to worsening levels of adiposity and glucose, as well as increasing blood pressure. In addition, recent evidence shows that worldwide, about 3% of children and 5% of adolescents have MetS.[31]

Alcohol and liver disease: key remarks

Despite an established dose-response relationship between the alcohol quantity consumed and liver disease risk in general, considerable individual variability exists. In most individuals, liver steatosis seems to develop after consuming >60 g/d of alcohol for >2 weeks. However, this condition can be reversed by 4-6 weeks of abstinence.[2] On the other hand, many population-based studies have failed to find clear a correlation between the degree of alcohol intake and the degree of liver steatosis.[32,33] Thus, it seems that consistently high daily alcohol consumption is required for "pure" alcohol-related steatosis to develop.

In contrast, the liver cirrhosis risk appears to begin increasing at lower levels of alcohol consumption. Recently, a meta-analysis that comprised 2,629,272 participants and 5,505 individuals with liver cirrhosis showed that the cirrhosis risk became significant at around 1 drink/day, compared to long-term abstainers, and the risk increased with increasing alcohol intakes.[34] However, the cirrhosis risk has varied widely among studies, and we generally lack studies with data on lifetime alcohol use. In contrast, case-control studies showed no risk increase among individuals that consumed 1–4 drinks/day.[34] Currently, no liver-safe limit of alcohol intake has been firmly established.

Inaccuracy of self-reported alcohol consumption, recall bias, intentional and unintentional underreporting, and large variation in what constitutes a standard drink can confound research

on the relationship between alcohol consumption and alcohol-related harm. This was recently highlighted by a study detecting repeated moderate to excessive alcohol consumption in 29% of patients with presumed NAFLD when assessed by alcohol biomarkers.[35]

Despite the relationship between alcohol dose and liver disease risk, only 10 to 20% of individuals with chronic heavy alcohol use develop liver cirrhosis or alcoholic hepatitis. This observation highlights the key role of effect modifiers.[36] For example, women are more susceptible to ArLD than men at any given alcohol intake level.[2] Genetic factors are involved in the individual susceptibility to both alcohol use disorder and ArLD. Other key effect modifiers of ArLD risk include the drinking pattern (binge drinking, drinking outside meals), the beverage type (lower risk for wine), the diet (coffee seems protective), smoking, the gut microbiome, iron overload, viral hepatitis, comorbidity, and metabolic factors.[2]

Metabolic drivers of liver disease

MetS has emerged as an independent driver of liver fibrosis[37,38] and liver-related outcomes.[39,40] A recent meta-analysis of 19 studies with 1,561,457 participants concluded that MetS was associated with a 112% increase in the risk of liver-related clinical outcomes, among non-Asians, and a 73% increase among Asians.[39] MetS is also associated with HCC.[40–42] In a recent US study, MetS was the greatest contributor to population-level HCC (attributable fraction: 32%).[43] Moreover, the presence of MetS could predict liver-related mortality in various chronic liver diseases.[44] Among the individual components of MetS, diabetes and obesity have been highly linked to liver-related outcomes in numerous studies.[40,41,44–52] However, the strong interrelationship among the MetS components make it difficult to disentangle their independent risk effects. Large studies are often limited to registry-based coding, which often lacks direct measurements of metabolic factors.

A recent large US study of 271,906 patients with NAFLD and a mean 9-year follow-up reported that each additional metabolic trait (diabetes, obesity, hypertension, dyslipidemia)

was associated with a stepwise increase in the risk of liver-related outcomes (cirrhosis or HCC). All four metabolic traits contributed independently to the risk, but diabetes had the strongest association with incident HCC (hazard ratio [HR]: 2.8).[48] However, that study did not assess abdominal obesity.

In a population-based study of 578,700 individuals, obesity and hyperglycemia were independently associated with incident HCC (relative risk: 1.5), even after adjusting for alcohol use. In contrast, total cholesterol was inversely related to incident HCC, and blood pressure and triglycerides were not significantly associated with incident HCC.[41] Other studies have confirmed that MetS components had an additive impact on HCC risk.[40,53]

Obesity is typically expressed in terms of body mass index (BMI, kg/m^2). Nonetheless, when assessing metabolic health, abdominal waist circumference seems to be the "vital sign".[1,51,51] Several population-based studies have agreed that measures of central/abdominal obesity are better predictors of liver disease than BMI,[47,1,54,55,53,56,38,57,53] and BMI may not provide added prognostic value.[54,47,1,55] Furthermore, longitudinal studies have suggested that the waist-to-hip ratio (WHR) provided advantages over other anthropometric measures.[1,54] The WHR reflects the distribution of metabolically-harmful visceral fat (waist circumference), beneficial lower-body subcutaneous fat (hip circumference), and gluteofemoral muscle mass (hip circumference).[58] Moreover, the hip circumference could predict liver disease independently of waist circumference, and the hip circumference substantially modified the association between waist circumference and liver disease.[59]

Altered lipid metabolism is a hallmark of NAFLD, and low serum HDL-c and high triglyceride levels are often present with insulin resistance.[60] However, at a population level, no specific lipid signature consistently predicts liver disease. This lack of consistency is probably due to the complex way that circulating lipid levels are affected by dysmetabolism,

ageing, sex, ethnicity, menopause, alcohol, genetics, and liver synthesis dysfunction.[47,61,62,48,63,64]

Arterial hypertension has been highlighted as an independent risk factor for liver disease.[45,44,38,37,55,65,52,66] However, the findings are mixed, and the confounding effects of alcohol and diet on blood pressure may have been incompletely addressed.

In the presence of harmful alcohol consumption, advanced liver disease and related outcomes can be strongly predicted by the presence of MetS, particularly diabetes/insulin resistance and obesity (especially WHR).[67,44,68,57,64,69] Obesity is also associated with elevated mortality risk in individuals with alcoholic hepatitis.[70] However, when liver dysfunction worsens, obesity, dyslipidemia, and arterial hypertension can be masked by sarcopenia, dysfunctional synthesis, and vasodilatation, respectively.

Alcohol consumption and MetS prevalence

It is well known that excessive amounts of alcohol are toxic to all body tissues and systems. However, in diverse epidemiological studies, mild-to-moderate drinking has been associated with reduced risks of MetS-related phenotypes, including T2D,[71] arterial hypertension,[72] obesity,[73,74] cardiovascular disease,[75,76] systemic inflammation,[77] and all-cause mortality.[78,79] More importantly, abundant evidence has suggested that mild-to-moderate alcohol consumption is associated with a lower MetS prevalence. Indeed, mild-to-moderate alcohol consumption seems to have a favorable influence on the intermediate phenotypes of arterial hypertension, T2D, lipids, central obesity, and cardiovascular disease.

Table 1 summarizes the evidence collected from several studies worldwide. These studies included 265,223 individuals and focused on the prevalence of MetS and moderate alcohol consumption. The descriptions of individual studies include whether the analyses examined covariates. Unfortunately, results are not consistent among studies. A potential explanation

for the discrepancies is the heterogeneous nature of confounders, which were not uniformly or adequately assessed across studies (Table 1). In addition, definitions of alcohol consumption patterns varied extensively among studies. Interestingly, most studies concluded that prospective studies were needed and that the epidemiological evidence was inconclusive.

A recent meta-analysis found that in people who drank more than two drinks per day, a reduction in alcohol intake led to reductions in blood pressure levels.[80] and a recent South Korean study performed sequential assessments of alcohol use. Their results suggested that a change in alcohol use over time was correlated with the MetS risk.[81] However, it should also be borne in mind that ethnic differences in alcohol metabolism or consumption patterns may exist that influence the relationship between alcohol consumption and features of the MetS.

Interactions between harmful alcohol use and MetS: effects on liver-related outcomes

Alcohol use and metabolic factors are independently and jointly associated with chronic liver disease.[67] MetS increases the risk of liver-related outcomes, regardless of the alcohol intake level (Figure 2).[82] The importance of joint effects was highlighted in a population-based Finnish study on 10,993 subjects with NAFLD. They found that 42% of future liver-related outcomes were actually alcohol-related, and the alcohol-related events were relatively more common among young NAFLD patients.[83] Similarly, a recent French study on 52,066 patients hospitalized with diabetes found that most liver-related complications were attributable to alcohol use disorders, whereas <10% were attributed to obesity or MetS.[84]

Synergism, or a supra-additive interaction effect, describes an interaction between two exposures (e.g., harmful alcohol use and MetS), where the effect on the outcome (e.g., liver disease) is greater than the sum of the individual effects. Several epidemiological studies (reviewed in [1,85]) have shown supra-additive effects of harmful drinking and metabolic factors on liver disease. Nonetheless, the study methodologies were heterogeneous, and few studies investigated clinical outcomes.[1,85]

A Finnish population-based study found that MetS and weekly binge drinking (≥60 g ethanol/occasion) had substantial supra-additive effects on liver-related outcomes.[86] Similarly, a US study involving individuals with ultrasound-verified liver steatosis reported a supra-additive effect of MetS and excessive drinking (≥3 daily drinks for men and ≥1.5 for women) on all-cause mortality.[87] In both studies,[86,87] hazardous drinking was associated with the outcome only in the presence of MetS. Other studies have reported profound supra-additive effects of hazardous drinking and diabetes on HCC and other liver-related outcomes. The proportion of the effect attributable to such interaction was estimated at 60-74%.[85]

Findings are more mixed regarding supra-additive interactions between hazardous alcohol use and high BMI.[85,88–90] With competing-risk methodology and a cohort from the general population, we recently found that liver-related outcomes were affected by an interaction between harmful alcohol consumption and a high WHR, but not between alcohol and BMI.[91] That finding supported the notion that WHR is a key obesity measure in this context. One study estimated that, in the general population, for abdominally-obese men with a WHR in the highest tertile, consuming one unit/day of alcohol was associated with a liver-related outcome risk similar to that associated with consuming 4 units/day in men with lower WHRs (Figure 3).[61] However, it remains unclear to what extent this epidemiologic synergism is behavioral. For example, it might be explained by unmeasured confounding from other unhealthy lifestyle habits that are common in individuals with concurrent high-risk alcohol consumption and MetS/obesity.

The intricate relationship between alcohol consumption and NAFLD: Does moderate alcohol consumption affect the natural history of nonalcoholic fatty liver disease?

Study results disagree on whether social or mild-to-moderate alcohol consumption is detrimental or beneficial in the natural history of NAFLD.[92] Quantitative evidence from cross-sectional studies (sample size =43172 subjects) assessed in a meta-analysis suggested

that moderate alcohol consumption had a protective effect (~31%) on the risk of developing NAFLD (Figure 4).[93] This beneficial effect appeared to be independent of covariates, like BMI, but it was influenced by sex.[93] More importantly, quantitative evidence suggested that moderate alcohol consumption was associated with an average protective effect of about 50% on the risk of developing NASH.[93] A more recent meta-analysis also suggested that moderate alcohol consumption was associated with reduced odds of developing NASH and advanced fibrosis.[94] However, most of these studies employed observational cross-sectional designs. Moreover, in each study, potential confounding was not properly assessed, the cumulative effect of moderate alcohol consumption was not adequately quantified, and causality could not be ascertained.

What makes the relationship between moderate alcohol consumption and NAFLD so complex? Many aspects are not measured very precisely in observational studies; thus, the presumed beneficial effects of moderate alcohol consumption are inconsistent across studies. In the absence of robust clinical trials, the evidence has been recently reassessed and even questioned. A Mendelian randomization study used a genetic variant (rs1229984 A>G) in the alcohol dehydrogenase (*ADH1B*) gene as a proxy for long-term alcohol exposure. Those results suggested that moderate alcohol consumption had no beneficial effect on NAFLD disease severity.[95] In contrast, a recent large population-based study showed that moderate alcohol consumption reduced NASH severity, in a dose-dependent manner, among carriers of both *ADH1B-rs1229984* alleles, although carriers of the *ADH1B*2* allele (A allele) showed more significant benefit.[96] Nevertheless, this "protective" effect disappeared when the BMI was >37 kg/m^2.[96] Additionally, a longitudinal NAFLD study that involved ~14 years of follow-up showed that moderate alcohol consumption was associated with fibrosis progression.[97]

Other studies have shown that critical aspects of co-existing comorbidities can significantly impact the burden of liver-related disease and mortality (Figure 4). Blomdahl et al. found that, among patients with NAFLD and T2D, those with moderate alcohol consumption had significantly higher advanced fibrosis rates than those with low-level alcohol consumption. Those results suggested that insulin resistance and alcohol had a synergistic effect on NAFLD progression.[98]

Åberg et al. also found that insulin resistance was a significant risk factor for severe liver-related outcomes.[47]

A multicenter, retrospective cohort study from Japan that included patients with ultrasound-verified NAFLD showed a 0.05% annual HCC incidence rate in subjects that consumed <20 g/day of alcohol. Increasing levels of alcohol consumption were associated with increases in the annual HCC incidence rates, as follows: 0.06% with 20-39 g/day (HR, 1.54), 0.16% with 40-69 g/day (HR, 3.49), and 0.22% with ≥70 g/day ethanol consumption (HR, 10.58).[99] A recent meta-analysis assessed two cohort studies to determine the effects of modest alcohol intake on NAFLD histological severity, histological progression, and the risk of HCC development. They found that moderate alcohol intake was associated with a pooled HR of 3.77 for developing HCC (Figure 4).[94] Kimura et al. also showed that moderate drinking appeared to be a risk factor for HCC in patients with NAFLD, particularly those with advanced fibrosis.[100]

A prospective study in a general population cohort based in the US showed that modest alcohol consumption was associated with a significant reduction in all-cause mortality. However, drinking more than an average of 1.5 drinks/day (≥21 g/day alcohol) was associated with an increase in mortality among patients with NAFLD.[101] Åberg et al. found that, among individuals with NAFLD, alcohol consumption dose-dependently increased the risk of incident advanced liver disease and malignancies.[102] Moreover, consuming 10-19 g/day of

alcohol, in general, or 0-9 g/day of non-wine beverages, doubled the risk of advanced liver disease, compared to lifetime abstainers. In contrast, low-to-moderate alcohol use was associated with reduced mortality and cardiovascular disease risk, but only among individuals that had never smoked tobacco.[102] Finally, Jarvis et al. reviewed the current literature and performed a narrative synthesis of the data. They concluded that any level of alcohol consumption was associated with worse liver outcomes in NAFLD, even when drinking within the recommended limits.[103]

Potential mechanisms of interaction

The frequent co-occurrence of high-risk alcohol intake and MetS in the population indicates that the multiple pathogenetic mechanisms of ArLD and NAFLD often act in parallel to drive disease. ArLD and NAFLD have similar histologic features, many common pathogenetic mechanisms,[104,105] and a shared genetic background (e.g., *PNPLA3*, *TM6SF2*, *MBOAT7*, *HSD17B13*, *APOE*, *GPAM*).[104,106] The precise mechanisms underlying the synergism between alcohol and metabolic dysfunction remain elusive. However, they might involve combined effects on mitochondrial dysfunction, oxidative stress,[107–109] CYP2E1 activity,[110] innate immune response activation,[111] hepatic stellate cell activation,[112] gut microbiota and increased gut permeability,[113,114] bile acid metabolism (e.g., farnesoid X receptor and fibroblast growth factor 21),[115,116] lipid metabolism,[117] and adipocyte dysfunction with subsequent increases in lipolysis and proinflammatory factor release.[118]

Mouse studies have demonstrated that moderate obesity and alcohol use can synergistically induce steatohepatitis and liver fibrosis.[111] Furthermore, obesity-induced steatosis seems to sensitize the liver to alcoholic toxicity[119] In addition, a high-fat diet sensitizes adipose tissue to alcohol-induced lipolysis.[118] Similarly, a recent human experimental study showed that alcohol intoxication induced rapid changes in circulating lipids, and that the alcohol-induced effects on lipid metabolism and lipotoxicity were amplified in the presence of NAFLD.[120]

Moreover, alcohol is an energy-dense molecule and can therefore induce metabolic dysfunction and contribute to obesity through caloric excess.[117] One gram of ethanol is nearly as energy dense as one gram of dietary fat.

Endogenous ethanol production by gut microbiota has been proposed to contribute to liver disease progression in NAFLD.[121,121–123] This hypothesis was recently substantiated by a large population-based study.[124] Moreover, in a Finnish population-based cohort (n=7115), a specific gut microbial signature could predict both overall incident liver disease and alcohol-related liver disease, and the same signature could distinguish patients with NAFLD from healthy controls in an independent US cohort.[125] Additionally, several other pathways and molecules, including micro-RNAs, DNA methylation, and extracellular vesicles, have been postulated to play roles in both ArLD and NAFLD.[126,127] Figure 5 illustrates some of the effects of MetS, alcohol consumption, and intestinal factors on fatty liver disease, highlighting how liver-specific pathways are affected by a variety of MetS-associated factors.

Systems biology analyses elucidate the interrelationship between alcohol and MetS

The number of genes and proteins associated with the effects of alcohol consumption and the individual components of MetS is overwhelming, particularly evidence from experimental studies and or high-throughput experiments. Moreover, the interaction between alcohol consumption and systemic metabolic deregulation is characterized by multicausality and multidimensionality (i.e., a single factor is influenced by factors in several dimensions, including host factors, the exposome, and the microbiota). This complexity makes it difficult to study the interrelationship between alcohol consumption and systemic metabolic dysregulation. In addition, the diseases clustered in MetS show strong co-occurrence and associations with other conditions, including cancer.

We employed a systems biology strategy to integrate existing evidence and to visualize relevant gene/protein networks. This approach allows, at least in part, the integration of

systems-level and multidimensional information. Likewise, systems biology differs from standard analyses as it makes use of diverse strategies, such as gene enrichment analysis, protein-protein interaction networks, and gene prioritization, based on multi-level data extracted by computational data mining.[128] Moreover, it takes into account the complexity of biological system dynamics. We used gene ontology (GO) terms, derived from published records and restricted to human studies, to construct Reactome pathways with an enrichment analysis. Among the list of disease-associated genes (N=569, 716, 725, 465, and 872, for diabetes, dyslipidemia, hypertension, obesity, and fatty liver, respectively), 380 genes that were highly associated with fatty liver were also associated with the other four MetS components (Figure 6a). Significantly enriched genes were involved in the following biological processes, based on GO terms: metabolism, energy pathways, cell communication, signal transduction, immune response, and anti-apoptosis.[129] Although related to ethanol metabolism, xenobiotic metabolism was not significantly enriched (Figure 6b). The only significantly enriched transcription factor was hepatic nuclear factor 1 homeobox A (HNF1A), which is a member of a hepatic transcription factor family highly associated with diabetes.[129]

To obtain and visualize networks that corresponded to each cluster (i.e., disease-associated genes), we analyzed all the clusters simultaneously with the ClueGO Cytoscape application V2.5.8.[130] Regardless of the underlying disease, the associated genes belonged to common Reactome pathways (Figure 6c). Interestingly, although some genes (a minority) were associated with a particular clinical entity, the pathways enriched in these genes were common in all MetS components. Figure 6c shows that all the disease-related genes contributed equivalently to each pathway, except for pathways that involved toll-like receptor (TLR) cascades and PI3K/AKT signaling (Figure 6a). Those pathways were slightly more enriched in fatty liver-associated genes than in MetS-related genes. TLRs play a significant

role in hepatic inflammation and injury. They also play roles in the cross-talk between NAFLD severity and insulin resistance, obesity, and systemic inflammation.[131] Moreover, TLRs mediate the effect of gut-derived endotoxins on liver cells, caused by the effects of alcohol-related impairments in gut permeability [132] and changes in the gut microbiota.[133] A recent human study explored the intrahepatic localization of Gram-negative-derived lipopolysaccharides in patients with NASH. They showed that endotoxins derived from gut bacteria were frequently observed in the portal tracts of patients with severe fibrosis.[134]

Although we cannot disregard the potential biases encountered in text mining, the evidence indicates that alcohol and MetS may have common systemic and multiorgan effects, including fatty liver. Both alcohol and MetS appear to potentiate an existing dysregulation of vital homeostatic pathways.

Clinical implications for liver disease

Accumulating evidence shows that alcohol and metabolic factors have independent, combined, and modifying effects on the onset and progression of chronic liver disease. This is analogous to cardiovascular medicine, where it is well established that multiple factors drive cardiovascular risk, and the risk can be quantified with risk-factor prediction scores. Similarly, it is now increasingly appreciated that liver disease has a multifactorial background, where the contribution of several common risk factors in combination may produce a higher overall risk than any significantly elevated single factor.[67,38,37,47,82,44,48,43,84,41,57,1,85,68,64,87,103,52,135] Therefore, in the context of chronic liver disease, risk prediction models that incorporate multiple factors could be useful for risk stratification, diagnostics, and therapeutic purposes.

To that end, the **C**hronic **Liv**er **D**isease (CLivD) risk score was recently developed and validated (Figure 7).[135] The CLivD score is based on age, sex, alcohol use, diabetes, WHR, smoking, and the level of serum gamma-glutamyltransferase – all are readily accessible and

inexpensive to analyze. The CLivD score predicts the 15-year risk of future severe liver disease in the general population. Its performance (C-index 0.77-0.78) is comparable to that of many cardiovascular risk scores (C-index 0.71-0.78).[135,136] Moreover, the competing risk of death was accounted for in the construction of the CLivD score. This score can enable the early identification of individuals in the community that are at high-risk, before the development of advanced liver fibrosis, as part of other healthcare contacts. The CLivD score is conceptually different from non-invasive fibrosis tests. Ongoing studies will evaluate the ability of the CLivD score to provide holistic referral pathways, individualized follow-up, and evaluations of the response to liver-oriented interventions. Future studies will seek to incorporate genetic data, gut microbiota, and novel biomarkers into risk predictions.[125,137]

It is crucial to assess drinking habits, including binge drinking, with standardized approaches (e.g., AUDIT-C or CAGE) for all patients with liver disease.[138] Moreover, continued alcohol consumption might impair the response to NAFLD drug therapies. Alcohol-use biomarkers, such as phosphatidylethanol, can assist in revealing undetected high-risk drinking.[98]

Currently, the potential health benefits of low alcohol use remain controversial and unclear at the individual level; therefore, counseling should not advocate alcohol use for beneficial purposes.[19] In liver steatosis, alcohol use of around 2-3 drinks/day seems to double the risk of liver-related outcomes.[102,139,140] However, in simple steatosis (i.e., in the absence of steatohepatitis or advanced fibrosis), the absolute risk of liver-related outcomes is generally low, and increases in risk due to low alcohol use are thus small. In contrast, in steatohepatitis or advanced fibrosis, any alcohol use should be discouraged, due to the high absolute risks.[103,138] This distinction requires more active evaluations of liver fibrosis stage in the community. In cirrhosis, regardless of the main etiology, complete alcohol abstinence is important.

Although limited, the available evidence supports the active management of metabolic factors in caring for patients with liver disease, including those who actively consume alcohol. Adequate metabolic control measures, with metformin, statins, aspirin, and angiotensin-converting enzyme inhibitors, have been associated with beneficial outcomes in chronic liver disease.[141–145]

Conclusions and prospects for future research

- The combined effects of alcohol use and metabolic factors on clinical liver-related outcomes should be assessed further in longitudinal studies with repeated exposure assessments.
- Alcohol intake should be quantified with accurate biomarkers.
- The combination of harmful alcohol use and metabolic factors is linked to generally unhealthy lifestyles; therefore, multivariable analyses should seek to clarify potential unmeasured or residual confounding that might contribute to the synergism between harmful alcohol use and metabolic factors; moreover, mechanistic studies are needed to clarify biologic synergism.
- Studies should assess factors that modify individual susceptibility to alcohol-induced harm or potential alcohol-related benefits.
- Studies are needed to clarify the most effective interventions for reducing harm from alcohol intake and metabolic factors, both on population and individual levels. Feasible ways of implementing these measures should be explored.
- The efficacy of combined interventions to reduce drinking and improve lifestyle should be studied prospectively, particularly among patients at risk of liver disease and advanced fibrosis.
- Studies are needed to clarify the optimal treatment for metabolic risk factors among individuals that actively consume alcohol. It remains to be determined whether active

alcohol use modifies the proposed benefits from treatments, such as metformin, statins, and aspirin, on liver-related outcomes.

Abbreviations: ADH1B, alcohol dehydrogenase; ArLD, alcohol-related liver disease; BMI, body mass index; CLivD, Chronic Liver Disease score; GO, gene ontology; HCC, hepatocellular carcinoma; HR, hazards ratio; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2D, type 2 diabetes; TLR, toll-like receptor; WHO, World Health Organization; WHR, waist-to-hip ratio

References

[1] Åberg F, Färkkilä M. Drinking and Obesity: Alcoholic Liver Disease/Nonalcoholic Fatty Liver Disease Interactions. Semin Liver Dis 2020;40:154–62. https://doi.org/10.1055/s-0040-1701443.

[2] Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and Treatment of Alcohol-Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases. Hepatology 2020;71:306–33. https://doi.org/10.1002/hep.30866.

[3] Kalinowski A, Humphreys K. Governmental standard drink definitions and low-risk alcohol consumption guidelines in 37 countries. Addiction 2016;111:1293–8. https://doi.org/10.1111/add.13341.

[4] Babor TF, Higgins-Biddle JC. Brief Intervention for Hazardous and Harmful Drinking: A Manual for Use in Primary Care n.d. https://www.who.int/publications-detail-redirect/brief-intervention-for-hazardous-and-harmful-drinking-(audit) (accessed May 23, 2022).

[5] Saklayen MG. The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep 2018;20:12. https://doi.org/10.1007/s11906-018-0812-z.

[6] Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L, et al. Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies. J Hepatol 2018;69:718–35. https://doi.org/10.1016/j.jhep.2018.05.011.

[7] GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020;5:245–66. https://doi.org/10.1016/S2468-1253(19)30349-8.

[8] Poznyak V, Rekve D. Global status report on alcohol and health 2018 n.d. https://www.who.int/publications-detail-redirect/9789241565639 (accessed May 27, 2022).

[9] European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–402. https://doi.org/10.1016/j.jhep.2015.11.004.

[10] How common is alcohol and drug dependency across the world? Our World in Data n.d. https://ourworldindata.org/alcohol-and-drug-dependency (accessed May 27, 2022).

[11] GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018;392:1015–35. https://doi.org/10.1016/S0140-6736(18)31310-2.

[12] Peacock A, Leung J, Larney S, Colledge S, Hickman M, Rehm J, et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction 2018;113:1905–26. https://doi.org/10.1111/add.14234.

[13] Monteiro MG, Rehm J, Shield KD, Stockwell T. Alcohol Consumption: An Overview of International Trends. In: Quah SR, editor. International Encyclopedia of Public Health (Second Edition), Oxford: Academic Press; 2017, p. 45–57. https://doi.org/10.1016/B978-0-12-803678-5.00012-6.

[14] Di Castelnuovo A, Costanzo S, Bonaccio M, McElduff P, Linneberg A,

Salomaa V, et al. Alcohol intake and total mortality in 142 960 individuals from the MORGAM Project: a population-based study. Addiction 2022;117:312–25. https://doi.org/10.1111/add.15593.

[15] Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet 2018;391:1513–23. https://doi.org/10.1016/S0140-6736(18)30134-X.

[16] Sohi I, Chrystoja BR, Rehm J, Wells S, Monteiro M, Ali S, et al. Changes in alcohol use during the COVID-19 pandemic and previous pandemics: A systematic review. Alcohol Clin Exp Res 2022;46:498–513. https://doi.org/10.1111/acer.14792.

[17] White AM, Castle I-JP, Powell PA, Hingson RW, Koob GF. Alcohol-Related Deaths During the COVID-19 Pandemic. JAMA 2022;327:1704–6. https://doi.org/10.1001/jama.2022.4308.

[18] Alcohol-specific deaths in the UK - Office for National Statistics n.d. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/alcoholrelateddeathsintheunitedkingdom/registeredin2020 (accessed July 30, 2022).

[19] Gilmore W, Chikritzhs T, Stockwell T, Jernigan D, Naimi T, Gilmore I. Alcohol: taking a population perspective. Nat Rev Gastroenterol Hepatol 2016;13:426–34. https://doi.org/10.1038/nrgastro.2016.70.

[20] Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595–607. https://doi.org/10.2337/diab.37.12.1595.

[21] Guzder RN, Gatling W, Mullee MA, Byrne CD. Impact of metabolic syndrome criteria on cardiovascular disease risk in people with newly diagnosed type 2 diabetes. Diabetologia 2006;49:49–55. https://doi.org/10.1007/s00125-005-0063-9.

[22] Xu X, Zeng J, Yang W, Dong T, Zhang X, Cheng S, et al. Prevalence of metabolic syndrome among the adult population in western China and the association with socioeconomic and individual factors: four cross-sectional studies. BMJ Open 2022;12:e052457. https://doi.org/10.1136/bmjopen-2021-052457.

[23] Lu J, Wang L, Li M, Xu Y, Jiang Y, Wang W, et al. Metabolic Syndrome Among Adults in China: The 2010 China Noncommunicable Disease Surveillance. J Clin Endocrinol Metab 2017;102:507–15. https://doi.org/10.1210/jc.2016-2477.

[24] Lee BJ, Kim JY. Identification of metabolic syndrome using phenotypes consisting of triglyceride levels with anthropometric indices in Korean adults. BMC Endocr Disord 2020;20:29. https://doi.org/10.1186/s12902-020-0510-0.

[25] Krishnamoorthy Y, Rajaa S, Murali S, Rehman T, Sahoo J, Kar SS. Prevalence of metabolic syndrome among adult population in India: A systematic review and meta-analysis. PLoS One 2020;15:e0240971. https://doi.org/10.1371/journal.pone.0240971.

[26] Chowdhury MZI, Anik AM, Farhana Z, Bristi PD, Abu Al Mamun BM, Uddin MJ, et al. Prevalence of metabolic syndrome in Bangladesh: a systematic review and meta-analysis of the studies. BMC Public Health 2018;18:308. https://doi.org/10.1186/s12889-018-5209-z.

[27] Raposo L, Severo M, Barros H, Santos AC. The prevalence of the metabolic syndrome in Portugal: the PORMETS study. BMC Public Health 2017;17:555. https://doi.org/10.1186/s12889-017-4471-9.

[28] Scuteri A, Laurent S, Cucca F, Cockcroft J, Cunha PG, Mañas LR, et al. Metabolic syndrome across Europe: different clusters of risk factors. Eur J Prev Cardiol 2015;22:486–91. https://doi.org/10.1177/2047487314525529.

[29] Ortiz-Rodríguez MA, Bautista-Ortiz LF, Villa AR, Antúnez-Bautista PK, Aldaz-Rodríguez MV, Estrada-Luna D, et al. Prevalence of Metabolic Syndrome Among Mexican Adults. Metab Syndr Relat Disord 2022. https://doi.org/10.1089/met.2021.0115.

[30] O'Hearn M, Lauren BN, Wong JB, Kim DD, Mozaffarian D. Trends and Disparities in Cardiometabolic Health Among U.S. Adults, 1999-2018. J Am Coll Cardiol 2022;80:138–51. https://doi.org/10.1016/j.jacc.2022.04.046.

[31] Noubiap JJ, Nansseu JR, Lontchi-Yimagou E, Nkeck JR, Nyaga UF, Ngouo AT, et al. Global, regional, and country estimates of metabolic syndrome burden in children and adolescents in 2020: a systematic review and modelling analysis. Lancet Child Adolesc Health 2022;6:158–70. https://doi.org/10.1016/S2352-4642(21)00374-6.

[32] Wilman HR, Kelly M, Garratt S, Matthews PM, Milanesi M, Herlihy A, et al. Characterisation of liver fat in the UK Biobank cohort. PLoS One 2017;12:e0172921. https://doi.org/10.1371/journal.pone.0172921.

[33] Abeysekera KWM, Fernandes GS, Hammerton G, Portal AJ, Gordon FH, Heron J, et al. Prevalence of steatosis and fibrosis in young adults in the UK: a population-based study. Lancet Gastroenterol Hepatol 2020;5:295–305. https://doi.org/10.1016/S2468-1253(19)30419-4.

[34] Roerecke M, Vafaei A, Hasan OSM, Chrystoja BR, Cruz M, Lee R, et al. Alcohol Consumption and Risk of Liver Cirrhosis: A Systematic Review and Meta-Analysis. Am J Gastroenterol 2019;114:1574–86. https://doi.org/10.14309/ajg.0000000000000340.

[35] Staufer K, Huber-Schönauer U, Strebinger G, Pimingstorfer P, Suesse S, Scherzer T-M, et al. Ethyl glucuronide in hair detects a high rate of harmful alcohol consumption in presumed non-alcoholic fatty liver disease. J Hepatol 2022:S0168-8278(22)00316-6. https://doi.org/10.1016/j.jhep.2022.04.040.

[36] Singal AK, Mathurin P. Diagnosis and Treatment of Alcohol-Associated Liver Disease: A Review. JAMA 2021;326:165–76. https://doi.org/10.1001/jama.2021.7683.

[37] Long MT, Zhang X, Xu H, Liu C-T, Corey KE, Chung RT, et al. Hepatic Fibrosis Associates With Multiple Cardiometabolic Disease Risk Factors: The Framingham Heart Study. Hepatology 2021;73:548–59. https://doi.org/10.1002/hep.31608.

[38] Bazerbachi F, Haffar S, Wang Z, Cabezas J, Arias-Loste MT, Crespo J, et al. Range of Normal Liver Stiffness and Factors Associated With Increased Stiffness Measurements in Apparently Healthy Individuals. Clin Gastroenterol Hepatol 2019;17:54-64.e1. https://doi.org/10.1016/j.cgh.2018.08.069.

[39] Ren H, Wang J, Gao Y, Yang F, Huang W. Metabolic syndrome and liver-related events: a systematic review and meta-analysis. BMC Endocr Disord 2019;19:40. https://doi.org/10.1186/s12902-019-0366-3.

[40] Turati F, Talamini R, Pelucchi C, Polesel J, Franceschi S, Crispo A, et al. Metabolic syndrome and hepatocellular carcinoma risk. Br J Cancer 2013;108:222–8. https://doi.org/10.1038/bjc.2012.492.

[41] Borena W, Strohmaier S, Lukanova A, Bjørge T, Lindkvist B, Hallmans G, et al. Metabolic risk factors and primary liver cancer in a prospective study of 578,700 adults. Int J Cancer 2012;131:193–200. https://doi.org/10.1002/ijc.26338.

[42] Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. Hepatology 2011;54:463–71. https://doi.org/10.1002/hep.24397.

[43] Makarova-Rusher OV, Altekruse SF, McNeel TS, Ulahannan S, Duffy AG, Graubard BI, et al. Population attributable fractions of risk factors for hepatocellular carcinoma in the United States. Cancer 2016;122:1757–65. https://doi.org/10.1002/cncr.29971.

[44] Stepanova M, Rafiq N, Younossi ZM. Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: a population-based study. Gut 2010;59:1410–5. https://doi.org/10.1136/gut.2010.213553.

[45] Jarvis H, Craig D, Barker R, Spiers G, Stow D, Anstee QM, et al. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies. PLoS Med 2020;17:e1003100. https://doi.org/10.1371/journal.pmed.1003100.

[46] Alexander M, Loomis AK, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, Ansell D, et al. Risks and clinical predictors of cirrhosis and hepatocellular carcinoma diagnoses in adults with diagnosed NAFLD: real-world study of 18 million patients in four European cohorts. BMC Med 2019;17:95. https://doi.org/10.1186/s12916-019-1321-x.

[47] Åberg F, Helenius-Hietala J, Puukka P, Färkkilä M, Jula A. Interaction between alcohol consumption and metabolic syndrome in predicting severe liver disease in the general population. Hepatology 2018;67:2141–9. https://doi.org/10.1002/hep.29631.

[48] Kanwal F, Kramer JR, Li L, Dai J, Natarajan Y, Yu X, et al. Effect of Metabolic Traits on the Risk of Cirrhosis and Hepatocellular Cancer in Nonalcoholic Fatty Liver Disease. Hepatology 2020;71:808–19. https://doi.org/10.1002/hep.31014.

[49] Chen Y, Wang X, Wang J, Yan Z, Luo J. Excess body weight and the risk of primary liver cancer: an updated meta-analysis of prospective studies. Eur J Cancer 2012;48:2137–45. https://doi.org/10.1016/j.ejca.2012.02.063.

[50] Wang C, Wang X, Gong G, Ben Q, Qiu W, Chen Y, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. Int J Cancer 2012;130:1639–48. https://doi.org/10.1002/ijc.26165.

[51] De Vincentis A, Tavaglione F, Jamialahmadi O, Picardi A, Antonelli Incalzi R, Valenti L, et al. A Polygenic Risk Score to Refine Risk Stratification and Prediction for Severe Liver Disease by Clinical Fibrosis Scores. Clin Gastroenterol Hepatol 2022;20:658–73. https://doi.org/10.1016/j.cgh.2021.05.056.

[52] Björkström K, Franzén S, Eliasson B, Miftaraj M, Gudbjörnsdottir S, Trolle-Lagerros Y, et al. Risk Factors for Severe Liver Disease in Patients With Type 2 Diabetes. Clin Gastroenterol Hepatol 2019;17:2769-2775.e4. https://doi.org/10.1016/j.cgh.2019.04.038.

[53] Pang Y, Kartsonaki C, Guo Y, Chen Y, Yang L, Bian Z, et al. Central adiposity in relation to risk of liver cancer in Chinese adults: A prospective study of 0.5 million people. Int J Cancer 2019;145:1245–53. https://doi.org/10.1002/ijc.32148.

[54] Andreasson A, Carlsson AC, Önnerhag K, Hagström H. Waist/Hip Ratio Better Predicts Development of Severe Liver Disease Within 20 Years Than Body Mass Index: A Population-based Cohort Study. Clin Gastroenterol Hepatol 2017;15:1294-1301.e2. https://doi.org/10.1016/j.cgh.2017.02.040.

[55] De Vincentis A, Tavaglione F, Spagnuolo R, Pujia R, Tuccinardi D, Mascianà G, et al. Metabolic and genetic determinants for progression to severe liver disease in subjects with obesity from the UK Biobank. Int J Obes (Lond) 2022;46:486–93. https://doi.org/10.1038/s41366-021-01015-w.

[56] Ioannou GN, Weiss NS, Boyko EJ, Kowdley KV, Kahn SE, Carithers RL, et al. Is central obesity associated with cirrhosis-related death or hospitalization? A population-based, cohort study. Clin Gastroenterol Hepatol 2005;3:67–74. https://doi.org/10.1016/s1542-3565(04)00442-2.

[57] Whitfield JB, Masson S, Liangpunsakul S, Mueller S, Aithal GP, Eyer F, et al. Obesity, Diabetes, Coffee, Tea, and Cannabis Use Alter Risk for Alcohol-Related Cirrhosis in 2 Large Cohorts of High-Risk Drinkers. Am J Gastroenterol 2021;116:106–15. https://doi.org/10.14309/ajg.0000000000000833.

[58] Stefan N. Causes, consequences, and treatment of metabolically unhealthy fat distribution. Lancet Diabetes Endocrinol 2020;8:616–27. https://doi.org/10.1016/S2213-8587(20)30110-8.

[59] Danielsson O, Nissinen MJ, Jula A, Salomaa V, Männistö S, Lundqvist A, et al. Waist and hip circumference are independently associated with the risk of liver disease in population-based studies. Liver Int 2021;41:2903–13. https://doi.org/10.1111/liv.15053.

[60] Nemes K, Åberg F. Interpreting lipoproteins in nonalcoholic fatty liver disease. Curr Opin Lipidol 2017;28:355–60. https://doi.org/10.1097/MOL.0000000000000427.

[61] Sahlman P, Nissinen M, Puukka P, Jula A, Salomaa V, Männistö S, et al. Genetic and lifestyle risk factors for advanced liver disease among men and women. J Gastroenterol Hepatol 2020;35:291–8. https://doi.org/10.1111/jgh.14770.

[62] Jiang ZG, Mukamal K, Tapper E, Robson SC, Tsugawa Y. Low LDL-C and high HDL-C levels are associated with elevated serum transaminases amongst adults in the United States: a cross-sectional study. PLoS One 2014;9:e85366. https://doi.org/10.1371/journal.pone.0085366.

[63] Trieb M, Rainer F, Stadlbauer V, Douschan P, Horvath A, Binder L, et al. HDL-related biomarkers are robust predictors of survival in patients with chronic liver failure. J Hepatol 2020;73:113–20. https://doi.org/10.1016/j.jhep.2020.01.026.

[64] Israelsen M, Juel HB, Detlefsen S, Madsen BS, Rasmussen DN, Larsen TR, et al. Metabolic and Genetic Risk Factors Are the Strongest Predictors of Severity of Alcohol-Related Liver Fibrosis. Clin Gastroenterol Hepatol 2020:S1542-3565(20)31628-1. https://doi.org/10.1016/j.cgh.2020.11.038.

[65] Oikonomou D, Georgiopoulos G, Katsi V, Kourek C, Tsioufis C, Alexopoulou A, et al. Non-alcoholic fatty liver disease and hypertension: coprevalent or correlated? Eur J Gastroenterol Hepatol 2018;30:979–85. https://doi.org/10.1097/MEG.0000000000001191.

[66] Zhang Y, Zhang T, Zhang C, Tang F, Zhong N, Li H, et al. Identification of reciprocal causality between non-alcoholic fatty liver disease and metabolic syndrome by a simplified Bayesian network in a Chinese population. BMJ Open 2015;5:e008204. https://doi.org/10.1136/bmjopen-2015-008204.

[67] Pose E, Pera G, Torán P, Gratacós-Ginès J, Avitabile E, Expósito C, et al. Interaction between metabolic syndrome and alcohol consumption, risk factors of liver fibrosis: A population-based study. Liver Int 2021;41:1556–64. https://doi.org/10.1111/liv.14830.

[68] Decraecker M, Dutartre D, Hiriart J-B, Irles-Depé M, Marraud des Grottes H, Chermak F, et al. Long-term prognosis of patients with alcohol-related liver disease or non-alcoholic fatty liver disease according to metabolic syndrome or alcohol use. Liver Int 2022;42:350–62. https://doi.org/10.1111/liv.15081.

[69] Åberg F, Puukka P, Sahlman P, Nissinen M, Salomaa V, Männistö S, et al. Metabolic risk factors for advanced liver disease among alcohol risk users in the general population. J Hepatol 2019;70:E273.

[70] Parker R, Kim SJ, Im GY, Nahas J, Dhesi B, Vergis N, et al. Obesity in acute alcoholic hepatitis increases morbidity and mortality. EBioMedicine 2019;45:511–8. https://doi.org/10.1016/j.ebiom.2019.03.046.

[71] Knott C, Bell S, Britton A. Alcohol Consumption and the Risk of Type 2 Diabetes: A Systematic Review and Dose-Response Meta-analysis of More Than 1.9 Million Individuals From 38 Observational Studies. Diabetes Care 2015;38:1804–12. https://doi.org/10.2337/dc15-0710.

[72] Briasoulis A, Agarwal V, Messerli FH. Alcohol consumption and the risk of hypertension in men and women: a systematic review and meta-analysis. J Clin Hypertens (Greenwich) 2012;14:792–8. https://doi.org/10.1111/jch.12008.

[73] Sayon-Orea C, Martinez-Gonzalez MA, Bes-Rastrollo M. Alcohol consumption and body weight: a systematic review. Nutr Rev 2011;69:419–31. https://doi.org/10.1111/j.1753-4887.2011.00403.x.

[74] Arif AA, Rohrer JE. Patterns of alcohol drinking and its association with obesity: data from the Third National Health and Nutrition Examination Survey, 1988-1994. BMC Public Health 2005;5:126. https://doi.org/10.1186/1471-2458-5-126.

[75] Cho Y, Shin S-Y, Won S, Relton CL, Davey Smith G, Shin M-J. Alcohol intake and cardiovascular risk factors: A Mendelian randomisation study. Sci Rep 2015;5:18422. https://doi.org/10.1038/srep18422.

[76] Holmes MV, Dale CE, Zuccolo L, Silverwood RJ, Guo Y, Ye Z, et al. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. BMJ 2014;349:g4164. https://doi.org/10.1136/bmj.g4164.

[77] Albert MA, Glynn RJ, Ridker PM. Alcohol consumption and plasma concentration of C-reactive protein. Circulation 2003;107:443–7. https://doi.org/10.1161/01.cir.0000045669.16499.ec.

[78] Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med 2006;166:2437–45. https://doi.org/10.1001/archinte.166.22.2437.

[79] Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Cardiovascular and overall mortality risk in relation to alcohol consumption in patients with cardiovascular disease. Circulation 2010;121:1951–9. https://doi.org/10.1161/CIRCULATIONAHA.109.865840.

[80] Roerecke M, Kaczorowski J, Tobe SW, Gmel G, Hasan OSM, Rehm J. The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. Lancet Public Health 2017;2:e108–20. https://doi.org/10.1016/S2468-2667(17)30003-8.

[81] Choi S, Kim K, Lee JK, Choi JY, Shin A, Park SK, et al. Association between Change in Alcohol Consumption and Metabolic Syndrome: Analysis from the Health Examinees Study. Diabetes Metab J 2019;43:615–26. https://doi.org/10.4093/dmj.2018.0128.

[82] Åberg F, Puukka P, Salomaa V, Männistö S, Lundqvist A, Valsta L, et al. Combined Effects of Alcohol and Metabolic Disorders in Patients With Chronic Liver Disease. Clin Gastroenterol Hepatol 2020;18:995-997.e2. https://doi.org/10.1016/j.cgh.2019.06.036.

[83] Männistö VT, Salomaa V, Färkkilä M, Jula A, Männistö S, Erlund I, et al. Incidence of liver-related morbidity and mortality in a population cohort of non-alcoholic fatty liver disease. Liver Int 2021. https://doi.org/10.1111/liv.15004.

[84] Mallet V, Parlati L, Martinino A, Scarano Pereira JP, Jimenez CN, Sakka M, et al. Burden of liver disease progression in hospitalized patients with type 2 diabetes mellitus. J Hepatol 2022;76:265–74. https://doi.org/10.1016/j.jhep.2021.09.030.

[85] Åberg F, Färkkilä M, Männistö V. Interaction Between Alcohol Use and Metabolic Risk Factors for Liver Disease: A Critical Review of Epidemiological Studies. Alcohol Clin Exp Res 2020;44:384–403. https://doi.org/10.1111/acer.14271.

[86] Åberg F, Helenius-Hietala J, Puukka P, Jula A. Binge drinking and the risk of liver events: A population-based cohort study. Liver Int 2017;37:1373–81. https://doi.org/10.1111/liv.13408.

[87] Younossi ZM, Stepanova M, Ong J, Yilmaz Y, Duseja A, Eguchi Y, et al. Effects of Alcohol Consumption and Metabolic Syndrome on Mortality in Patients With Nonalcoholic and Alcohol-Related Fatty Liver Disease. Clin Gastroenterol Hepatol 2019;17:1625-1633.e1. https://doi.org/10.1016/j.cgh.2018.11.033.

[88] Innes H, Crooks CJ, Aspinall E, Card TR, Hamill V, Dillon J, et al. Characterising the risk interplay between alcohol intake and body mass index on cirrhosis morbidity. Hepatology 2021. https://doi.org/10.1002/hep.32123.

[89] Hart CL, Morrison DS, Batty GD, Mitchell RJ, Davey Smith G. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. BMJ 2010;340:c1240. https://doi.org/10.1136/bmj.c1240.

[90] Glyn-Owen K, Böhning D, Parkes J, Roderick P, Buchanan R. The combined effect of alcohol and body mass index on risk of chronic liver disease: A systematic review and meta-analysis of cohort studies. Liver Int 2021;41:1216–26. https://doi.org/10.1111/liv.14754.

[91] Åberg F, Salomaa V, Färkkilä M, Jula A, Männistö S, Perola M, et al. Abdominal obesity is key when evaluating interactions between alcohol use and obesity for liver disease. Journal of Hepatology 2022;77(S1):S80-81 (abstract OS109) https://doi.org/10.1016/S0168-8278(22)00422-6.

[92] Sookoian S, Pirola CJ. How Safe Is Moderate Alcohol Consumption in Overweight and Obese Individuals? Gastroenterology 2016;150:1698-1703.e2. https://doi.org/10.1053/j.gastro.2016.01.002.

[93] Sookoian S, Castaño GO, Pirola CJ. Modest alcohol consumption decreases the risk of non-alcoholic fatty liver disease: a meta-analysis of 43 175 individuals. Gut 2014;63:530–2. https://doi.org/10.1136/gutjnl-2013-305718.

[94] Wongtrakul W, Niltwat S, Charatcharoenwitthaya P. The Effects of Modest Alcohol Consumption on Non-alcoholic Fatty Liver Disease: A Systematic Review and Meta-

Analysis. Front Med (Lausanne) 2021;8:744713. https://doi.org/10.3389/fmed.2021.744713.

[95] Sookoian S, Flichman D, Castaño GO, Pirola CJ. Mendelian randomisation suggests no beneficial effect of moderate alcohol consumption on the severity of nonalcoholic fatty liver disease. Aliment Pharmacol Ther 2016;44:1224–34. https://doi.org/10.1111/apt.13828.

[96] Vilar-Gomez E, Sookoian S, Pirola CJ, Liang T, Gawrieh S, Cummings O, et al. ADH1B∗2 Is Associated With Reduced Severity of Nonalcoholic Fatty Liver Disease in Adults, Independent of Alcohol Consumption. Gastroenterology 2020;159:929–43. https://doi.org/10.1053/j.gastro.2020.05.054.

[97] Ekstedt M, Franzén LE, Holmqvist M, Bendtsen P, Mathiesen UL, Bodemar G, et al. Alcohol consumption is associated with progression of hepatic fibrosis in non-alcoholic fatty liver disease. Scand J Gastroenterol 2009;44:366–74. https://doi.org/10.1080/00365520802555991.

[98] Blomdahl J, Nasr P, Ekstedt M, Kechagias S. Moderate alcohol consumption is associated with advanced fibrosis in non-alcoholic fatty liver disease and shows a synergistic effect with type 2 diabetes mellitus. Metabolism 2021;115:154439. https://doi.org/10.1016/j.metabol.2020.154439.

[99] Kawamura Y, Arase Y, Ikeda K, Akuta N, Kobayashi M, Saitoh S, et al. Effects of Alcohol Consumption on Hepatocarcinogenesis in Japanese Patients With Fatty Liver Disease. Clin Gastroenterol Hepatol 2016;14:597–605. https://doi.org/10.1016/j.cgh.2015.11.019.

[100] Kimura T, Tanaka N, Fujimori N, Sugiura A, Yamazaki T, Joshita S, et al. Mild drinking habit is a risk factor for hepatocarcinogenesis in non-alcoholic fatty liver disease with advanced fibrosis. World J Gastroenterol 2018;24:1440–50. https://doi.org/10.3748/wjg.v24.i13.1440.

[101] Hajifathalian K, Torabi Sagvand B, McCullough AJ. Effect of Alcohol Consumption on Survival in Nonalcoholic Fatty Liver Disease: A National Prospective Cohort Study. Hepatology 2019;70:511–21. https://doi.org/10.1002/hep.30226.

[102] Åberg F, Puukka P, Salomaa V, Männistö S, Lundqvist A, Valsta L, et al. Risks of Light and Moderate Alcohol Use in Fatty Liver Disease: Follow-Up of Population Cohorts. Hepatology 2020;71:835–48. https://doi.org/10.1002/hep.30864.

[103] Jarvis H, O'Keefe H, Craig D, Stow D, Hanratty B, Anstee QM. Does moderate alcohol consumption accelerate the progression of liver disease in NAFLD? A systematic review and narrative synthesis. BMJ Open 2022;12:e049767. https://doi.org/10.1136/bmjopen-2021-049767.

[104] Romeo S, Sanyal A, Valenti L. Leveraging Human Genetics to Identify Potential New Treatments for Fatty Liver Disease. Cell Metab 2020;31:35–45. https://doi.org/10.1016/j.cmet.2019.12.002.

[105] Boyle M, Masson S, Anstee QM. The bidirectional impacts of alcohol consumption and the metabolic syndrome: Cofactors for progressive fatty liver disease. J Hepatol 2018;68:251–67. https://doi.org/10.1016/j.jhep.2017.11.006.

[106] Jamialahmadi O, Mancina RM, Ciociola E, Tavaglione F, Luukkonen PK, Baselli G, et al. Exome-Wide Association Study on Alanine Aminotransferase Identifies Sequence Variants in the GPAM and APOE Associated With Fatty Liver Disease. Gastroenterology 2021;160:1634-1646.e7. https://doi.org/10.1053/j.gastro.2020.12.023.

[107] Sakaguchi S, Takahashi S, Sasaki T, Kumagai T, Nagata K. Progression of alcoholic and non-alcoholic steatohepatitis: common metabolic aspects of innate immune system and oxidative stress. Drug Metab Pharmacokinet 2011;26:30–46. https://doi.org/10.2133/dmpk.dmpk-10-rv-087.

[108] Arrese M, Cabrera D, Kalergis AM, Feldstein AE. Innate Immunity and Inflammation in NAFLD/NASH. Dig Dis Sci 2016;61:1294–303. https://doi.org/10.1007/s10620-016-4049-x.

[109] Li S, Tan H-Y, Wang N, Feng Y, Wang X, Feng Y. Recent Insights Into the Role of Immune Cells in Alcoholic Liver Disease. Front Immunol 2019;10:1328. https://doi.org/10.3389/fimmu.2019.01328.

[110] Harjumäki R, Pridgeon CS, Ingelman-Sundberg M. CYP2E1 in Alcoholic and Non-Alcoholic Liver Injury. Roles of ROS, Reactive Intermediates and Lipid Overload. Int J Mol Sci 2021;22:8221. https://doi.org/10.3390/ijms22158221.

[111] Xu J, Lai KKY, Verlinsky A, Lugea A, French SW, Cooper MP, et al. Synergistic steatohepatitis by moderate obesity and alcohol in mice despite increased adiponectin and p-AMPK. J Hepatol 2011;55:673–82. https://doi.org/10.1016/j.jhep.2010.12.034.

[112] Ramos-Tovar E, Muriel P. Molecular Mechanisms That Link Oxidative Stress, Inflammation, and Fibrosis in the Liver. Antioxidants (Basel) 2020;9:E1279. https://doi.org/10.3390/antiox9121279.

[113] Lang S, Schnabl B. Microbiota and Fatty Liver Disease-the Known, the Unknown, and the Future. Cell Host Microbe 2020;28:233–44. https://doi.org/10.1016/j.chom.2020.07.007.

[114] Lemmer P, Manka P, Best J, Kahraman A, Kälsch J, Vilchez-Vargas R, et al. Effects of Moderate Alcohol Consumption in Non-Alcoholic Fatty Liver Disease. J Clin Med 2022;11:890. https://doi.org/10.3390/jcm11030890.

[115] Idalsoaga F, Kulkarni AV, Mousa OY, Arrese M, Arab JP. Non-alcoholic Fatty Liver Disease and Alcohol-Related Liver Disease: Two Intertwined Entities. Front Med (Lausanne) 2020;7:448. https://doi.org/10.3389/fmed.2020.00448.

[116] Luo Y, Decato BE, Charles ED, Shevell DE, McNaney C, Shipkova P, et al. Pegbelfermin selectively reduces secondary bile acid concentrations in patients with non-alcoholic steatohepatitis. JHEP Rep 2022;4:100392. https://doi.org/10.1016/j.jhepr.2021.100392.

[117] Sun F-R, Wang B-Y. Alcohol and Metabolic-associated Fatty Liver Disease. J Clin Transl Hepatol 2021;9:719–30. https://doi.org/10.14218/JCTH.2021.00173.

[118] Parker R, Kim S-J, Gao B. Alcohol, adipose tissue and liver disease: mechanistic links and clinical considerations. Nat Rev Gastroenterol Hepatol 2018;15:50–9. https://doi.org/10.1038/nrgastro.2017.116.

[119] Minato T, Tsutsumi M, Tsuchishima M, Hayashi N, Saito T, Matsue Y, et al. Binge alcohol consumption aggravates oxidative stress and promotes pathogenesis of NASH from obesity-induced simple steatosis. Mol Med 2014;20:490–502. https://doi.org/10.2119/molmed.2014.00048.

[120] Israelsen M, Kim M, Suvitaival T, Madsen BS, Hansen CD, Torp N, et al. Comprehensive lipidomics reveals phenotypic differences in hepatic lipid turnover in ALD and NAFLD during alcohol intoxication. JHEP Rep 2021;3:100325.

https://doi.org/10.1016/j.jhepr.2021.100325.

[121] Chen X, Zhang Z, Li H, Zhao J, Wei X, Lin W, et al. Endogenous ethanol produced by intestinal bacteria induces mitochondrial dysfunction in non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2020;35:2009–19. https://doi.org/10.1111/jgh.15027.

[122] Cope K, Risby T, Diehl AM. Increased gastrointestinal ethanol production in obese mice: implications for fatty liver disease pathogenesis. Gastroenterology 2000;119:1340–7. https://doi.org/10.1053/gast.2000.19267.

[123] de Medeiros IC, de Lima JG. Is nonalcoholic fatty liver disease an endogenous alcoholic fatty liver disease? - A mechanistic hypothesis. Med Hypotheses 2015;85:148–52. https://doi.org/10.1016/j.mehy.2015.04.021.

[124] Ruuskanen MO, Åberg F, Männistö V, Havulinna AS, Méric G, Liu Y, et al. Links between gut microbiome composition and fatty liver disease in a large population sample. Gut Microbes 2021;13:1–22. https://doi.org/10.1080/19490976.2021.1888673.

[125] Liu Y, Méric G, Havulinna AS, Teo SM, Åberg F, Ruuskanen M, et al. Early prediction of incident liver disease using conventional risk factors and gut-microbiome-augmented gradient boosting. Cell Metab 2022;34:719-730.e4. https://doi.org/10.1016/j.cmet.2022.03.002.

[126] Meroni M, Longo M, Rametta R, Dongiovanni P. Genetic and Epigenetic Modifiers of Alcoholic Liver Disease. Int J Mol Sci 2018;19:E3857. https://doi.org/10.3390/ijms19123857.

[127] Eslam M, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: Clinical impact. J Hepatol 2018;68:268–79. https://doi.org/10.1016/j.jhep.2017.09.003.

[128] Sookoian S, Pirola CJ. Systems biology elucidates common pathogenic mechanisms between nonalcoholic and alcoholic-fatty liver disease. PLoS One 2013;8:e58895. https://doi.org/10.1371/journal.pone.0058895.

[129] Sookoian S, Pirola CJ. Review article: shared disease mechanisms between non-alcoholic fatty liver disease and metabolic syndrome - translating knowledge from systems biology to the bedside. Aliment Pharmacol Ther 2019;49:516–27. https://doi.org/10.1111/apt.15163.

[130] Bindea G, Mlecnik B, Hackl H, Charoentong P, Tosolini M, Kirilovsky A, et al. ClueGO: a Cytoscape plug-in to decipher functionally grouped gene ontology and pathway annotation networks. Bioinformatics 2009;25:1091–3. https://doi.org/10.1093/bioinformatics/btp101.

[131] Guo J, Friedman SL. Toll-like receptor 4 signaling in liver injury and hepatic fibrogenesis. Fibrogenesis Tissue Repair 2010;3:21. https://doi.org/10.1186/1755-1536-3-21.

[132] Mandrekar P, Szabo G. Signalling pathways in alcohol-induced liver inflammation. J Hepatol 2009;50:1258–66. https://doi.org/10.1016/j.jhep.2009.03.007.

[133] Fairfield B, Schnabl B. Gut dysbiosis as a driver in alcohol-induced liver injury. JHEP Rep 2021;3:100220. https://doi.org/10.1016/j.jhepr.2020.100220.

[134] Sookoian S, Salatino A, Castaño GO, Landa MS, Fijalkowky C, Garaycoechea M, et al. Intrahepatic bacterial metataxonomic signature in non-alcoholic fatty liver disease. Gut 2020;69:1483–91. https://doi.org/10.1136/gutjnl-2019-318811.

[135] Åberg F, Luukkonen PK, But A, Salomaa V, Britton A, Petersen KM, et al. Development and validation of a model to predict incident chronic liver disease in the general

population: The CLivD score. J Hepatol 2022;77:302–11. https://doi.org/10.1016/j.jhep.2022.02.021.

[136] Lenselink C, Ties D, Pleijhuis R, van der Harst P. Validation and comparison of 28 risk prediction models for coronary artery disease. Eur J Prev Cardiol 2022;29:666–74. https://doi.org/10.1093/eurjpc/zwab095.

[137] Emdin CA, Haas M, Ajmera V, Simon TG, Homburger J, Neben C, et al. Association of Genetic Variation With Cirrhosis: A Multi-Trait Genome-Wide Association and Gene-Environment Interaction Study. Gastroenterology 2021;160:1620-1633.e13. https://doi.org/10.1053/j.gastro.2020.12.011.

[138] Leggio L, Mellinger JL. Alcohol use disorder in community management of chronic liver diseases. Hepatology 2022. https://doi.org/10.1002/hep.32531.

[139] Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology 2018;155:443-457.e17. https://doi.org/10.1053/j.gastro.2018.04.034.

[140] Sinn DH, Kang D, Guallar E, Hong YS, Cho J, Gwak G-Y. Modest alcohol intake and mortality in individuals with elevated alanine aminotransferase levels: a nationwide cohort study. BMC Med 2022;20:18. https://doi.org/10.1186/s12916-021-02215-x.

[141] Simon TG, Duberg A-S, Aleman S, Chung RT, Chan AT, Ludvigsson JF. Association of Aspirin with Hepatocellular Carcinoma and Liver-Related Mortality. N Engl J Med 2020;382:1018–28. https://doi.org/10.1056/NEJMoa1912035.

[142] Kramer JR, Natarajan Y, Dai J, Yu X, Li L, El-Serag HB, et al. Effect of diabetes medications and glycemic control on risk of hepatocellular cancer in patients with nonalcoholic fatty liver disease. Hepatology 2021. https://doi.org/10.1002/hep.32244.

[143] Bosch J, Gracia-Sancho J, Abraldes JG. Cirrhosis as new indication for statins. Gut 2020;69:953–62. https://doi.org/10.1136/gutjnl-2019-318237.

[144] Zhang X, Wong GL-H, Yip TC-F, Tse Y-K, Liang LY, Hui VW-K, et al. Angiotensin-converting enzyme inhibitors prevent liver-related events in nonalcoholic fatty liver disease. Hepatology 2021. https://doi.org/10.1002/hep.32294.

[145] Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. Am J Gastroenterol 2013;108:881–91; quiz 892. https://doi.org/10.1038/ajg.2013.5.

[146] Freiberg MS, Cabral HJ, Heeren TC, Vasan RS, Curtis Ellison R, Third National Health and Nutrition Examination Survey. Alcohol consumption and the prevalence of the Metabolic Syndrome in the US.: a cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2954–9. https://doi.org/10.2337/diacare.27.12.2954.

[147] Fan AZ, Russell M, Naimi T, Li Y, Liao Y, Jiles R, et al. Patterns of alcohol consumption and the metabolic syndrome. J Clin Endocrinol Metab 2008;93:3833–8. https://doi.org/10.1210/jc.2007-2788.

[148] Fan J-G, Cai X-B, Li L, Li X-J, Dai F, Zhu J. Alcohol consumption and metabolic syndrome among Shanghai adults: a randomized multistage stratified cluster sampling investigation. World J Gastroenterol 2008;14:2418–24.

https://doi.org/10.3748/wjg.14.2418.

[149] Hirakawa M, Arase Y, Amakawa K, Ohmoto-Sekine Y, Ishihara M, Shiba M, et al. Relationship between Alcohol Intake and Risk Factors for Metabolic Syndrome in Men. Intern Med 2015;54:2139–45. https://doi.org/10.2169/internalmedicine.54.2736.

[150] Wakabayashi I. Cross-sectional relationship between alcohol consumption and prevalence of metabolic syndrome in Japanese men and women. J Atheroscler Thromb 2010;17:695–704. https://doi.org/10.5551/jat.3517.

[151] Oh SS, Kim W, Han K-T, Park E-C, Jang S-I. Alcohol consumption frequency or alcohol intake per drinking session: Which has a larger impact on the metabolic syndrome and its components? Alcohol 2018;71:15–23. https://doi.org/10.1016/j.alcohol.2018.01.005.

[152] Kim SK, Hong S-H, Chung J-H, Cho KB. Association Between Alcohol Consumption and Metabolic Syndrome in a Community-Based Cohort of Korean Adults. Med Sci Monit 2017;23:2104–10. https://doi.org/10.12659/msm.901309.

[153] Baik I, Shin C. Prospective study of alcohol consumption and metabolic syndrome. Am J Clin Nutr 2008;87:1455–63. https://doi.org/10.1093/ajcn/87.5.1455.

[154] Slagter SN, van Vliet-Ostaptchouk JV, Vonk JM, Boezen HM, Boezen HM, Dullaart RPF, et al. Combined effects of smoking and alcohol on metabolic syndrome: the LifeLines cohort study. PLoS One 2014;9:e96406. https://doi.org/10.1371/journal.pone.0096406.

[155] Baghdan D, Dugas LR, Choo-Kang C, Plange-Rhule J, Bovet P, Viswanathan B, et al. The associations between alcohol intake and cardiometabolic risk in African-origin adults spanning the epidemiologic transition. BMC Public Health 2021;21:2210. https://doi.org/10.1186/s12889-021-12128-2.

[156] Vieira BA, Luft VC, Schmidt MI, Chambless LE, Chor D, Barreto SM, et al. Timing and Type of Alcohol Consumption and the Metabolic Syndrome - ELSA-Brasil. PLoS One 2016;11:e0163044. https://doi.org/10.1371/journal.pone.0163044.

[157] Bermúdez V, Martínez MS, Chávez-Castillo M, Olivar LC, Morillo J, Mejías JC, et al. Relationship between Alcohol Consumption and Components of the Metabolic Syndrome in Adult Population from Maracaibo City, Venezuela. Adv Prev Med 2015;2015:352547. https://doi.org/10.1155/2015/352547.

[158] Xiao J, Huang J-P, Xu G-F, Chen D-X, Wu G-Y, Zhang M, et al. Association of alcohol consumption and components of metabolic syndrome among people in rural China. Nutr Metab (Lond) 2015;12:5. https://doi.org/10.1186/s12986-015-0007-4.

Figure legends

Figure 1. Global trends: alcohol-related epidemiology and mortality/disability statistics.

a. Annual average alcohol consumption per person (aged ≥15 years). To account for different alcohol contents among alcoholic drinks (e.g., beer, wine, spirits), quantities are expressed in liters/year of pure alcohol (https://ourworldindata.org/alcohol-consumption).

b. Death rates from alcohol use disorders (2018). Globally, 2.4 million alcohol-related premature deaths/year (https://ourworldindata.org/alcohol-consumption).

c. Alcohol use is a leading risk factor for death and disability. Disability-adjusted life years (DALYs) is a time-based measure combining years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health. (https://ourworldindata.org/alcohol-consumption).

d. Number of deaths per risk factor across all age groups and both sexes; in most high-income countries, risk factors are metabolic syndrome components and alcohol use (https://ourworldindata.org/causes-of-death).

Figure 2. Combined effects of alcohol and metabolic syndrome on liver-related outcomes.

Cumulative 20-year incidence of severe liver-related outcomes (hospitalization, cancer, or death), according to the baseline level of alcohol consumption and the absence/presence of metabolic syndrome (MetS; data based on results reported in ref. [82]).

Figure 3. Abdominal obesity increases alcohol-related liver toxicity by four-fold.

The figure shows the hazards ratios for the risk of incident severe liver disease according to alcohol consumption in a man with difference waist-to-hip ratios (WHRs). In the highest

tertile of WHR (*red*) in the population, for a man that consumes one alcohol drink daily (10 g ethanol) risk is similar to that of a man with a low WHR (*green*) who consumes 4 alcohol drinks daily (40 g ethanol). Results are based on Cox regression analysis adjusted for age, diabetes, smoking, and body-mass index.[61]

Figure 4. The intricate relationship between alcohol consumption and NAFLD and the synergistic effects of covariates.

Summary of the evidence supporting the favorable (*left*) and unfavorable (*right*) effects of modest alcohol consumption on NAFLD and disease severity. (*Top left*) Study limitations. (*Lower right*) Factors that are generally not well measured in observational studies. For instance: the pattern of drinking is often not very well established, and this affects the cumulative exposure to alcohol at baseline; moreover, the type of beverage is typically not correctly estimated; sex differences are generally not included in stratified analyses, and studies typically inadequately address how the sex dimension influences the effects of moderate alcohol consumption on NAFLD and disease progression. These inconsistencies are liable to introduce significant biases in the analyses.

Abbreviations: *ADH1B*, Alcohol dehydrogenase 1B; *ADH1B*1*, ancestral allele G of the rs1229984 variant; *ADH1B*2*, allele A of the rs1229984 variant; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; FU, follow-up; HCC, hepatocellular carcinoma; HR, hazard ratio; OR, odds ratio; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty-liver disease

Figure 5. Effects of metabolic syndrome, alcohol consumption, and intestinal factors on fatty liver disease.

Liver-specific pathways are affected by a variety of MetS-associated factors, such as visceral adipose tissue accumulation, low-grade chronic inflammation, T2D, dysbiosis, and dietary factors, which induce or increase lipotoxicity, insulin resistance, oxidative stress, and chronic inflammation. As the disease progresses, Kupffer cells and stellate cells may become activated, which promotes collagen deposition and fibrosis in the liver. All these intrahepatic processes may also increase the production of other risk factors for cardiovascular disease, chronic kidney disease, and T2D. In addition, intestinal organisms may produce endogenous alcohol, which enters the liver via the portal circulation. Liver alcohol metabolism acts together with MetS to increase liver disease progression and the risks of fibrosis and cirrhosis. Abbreviations: DAGs, di-acylglycerols; di-P PA, di-palmitoyl phosphatidic acid; HDL, high-density lipoprotein; LCFAs, long chain fatty acids; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; PNPLA3, patatin-like phospholipase domain containing 3; PAI-1, plasminogen activator inhibitor-1; TAGs, tri-acyl glycerols; TM6SF2, transmembrane 6 superfamily member 2; TGF-beta, transforming growth factor-beta; TNF-alpha, tumor necrosis factor-alpha.

Figure 6: Systems biology analysis clarifies interrelationships between alcohol and metabolic syndrome

a: **Reactome**. a functionally grouped network with terms as nodes, linked based on their kappa score level (kappa scores ≥ 0.4); only the most significant interactions are shown (pathways with more than five genes); node size represents the term enrichment significance.. Nodes are color-coded according to gene/protein associations, as indicated. Nodes with multiple colors show shared classes, at different percentages. Clusters that contributed more than 70% to the node were considered specific. Edges represent connections between nodes, and each edge length reflects the relatedness of two processes (slightly modified for graphical

convenience). Inset shows the enrichment for toll-like receptors cascades and PI3K/AKT signaling.

b: **Enrichment analysis**. (*Blue bars*) Percentage of genes associated with and shared by all components of the metabolic syndrome. (*Red bars*) *P*-values for FDR over the cutoff reference, 0.05 (*yellow bars*).

c: **Overrepresentation analysis**. The percentage of genes overrepresented in each Reactome shown in (***a***) that participates in the interaction between alcohol, all metabolic syndrome components, and fatty liver disease.

Gene ontology: an ontology is a formal representation of a body of knowledge within a given domain. Reactome is a curated database of pathways and reactions in human biology. Reactions can be considered as pathway 'steps'. Reactome defines a 'reaction' as any event in biology that changes the state of a biological molecule (https://reactome.org).

Complete details can be found in Supplementary appendix.

Figure 7. Chronic Liver Disease (CLivD) risk score simultaneously accounts for alcohol and metabolic dysfunction in predictions of future severe liver disease.

The CLivD score can potentially detect high-risk individuals before they develop advanced liver fibrosis, whereas non-invasive liver fibrosis tests detect advanced subclinical disease. **a.** Analogies to cardiovascular risk predictors. **b**. The absolute risks for two representative 50-year old men with BMI of 30 kg/m^2 and alcohol intake of 28 units/week. The lower individual has a high waist-to-hip ratio, diabetes, and is an active smoker, which leads to substantially higher predicted 15-year risk.

Table 1 Alcohol consumption and the risk of metabolic syndrome: global prevalence trends

Reference/ Country	Population sample (n)	Alcohol consumption definition	Covariate adjustments	Main results	Conclusion and key message
Freiberg et al. 2004[146] / U.S.	8125 individuals from the Third National Health and Nutrition Examination Survey (NHANES III) (1988–1994)	Alcohol consumption defined as ≥1 alcoholic drink per month.	Age, sex, race/ethnicity, education, income, tobacco use, physical activity, and diet	Subjects that consumed 1-19 or ≥20 drinks/month of alcohol had ORs for MetS of 0.65 and 0.34, respectively, compared to current nondrinkers. This association was strongest among whites and among beer and wine drinkers.	Mild-to-moderate alcohol consumption is associated with lower prevalence of MetS, with a favorable influence on lipids, waist circumference, and fasting insulin.
Fan et al. 2008[147] / U.S.	1529 subjects from the National Health and Nutrition Examination Survey 1999–2002	Categories: <1 drink/week, 1–2 drinks/week, ≥3 drinks/week	Demographics, family history of CVD and diabetes, and lifestyle factors	More than two drinks/day increased the risk of developing four of the five MetS components, including HBP, high triglycerides, increased abdominal girth, and elevated blood glucose.	Public health messages should emphasize the potential cardiometabolic risk associated with drinking.
Fan et al. 2008[148] / China	3953 participants from the general population of Shanghai	Current alcohol consumption was defined as more than one alcohol drink/month	Age and sex	Prevalences of abdominal obesity, low serum HDL-c, and diabetes mellitus were lower in subjects that consumed two or more alcohol drinks/month; a trend showed that alcohol intake reduced the prevalence of MetS.	Alcohol consumption is associated with lower MetS prevalence, irrespective of intake quantity, and it favorably influences HDL-c, waist circumference, and diabetes mellitus.
Hirakawa et al. 2015[149] / Japan	22,349 men from Japan	Drinking categories: none, light (<20 g ethanol/day), heavy (≥20 and <60 g ethanol/day) and very heavy (≥60 g ethanol/day)	Not specified	The prevalence of MetS was significantly lower among light drinkers and higher in very heavy drinkers, compared to nondrinkers.	A significant association was observed between very heavy alcohol intake (≥60 g/day) and the prevalence of MetS.
Wakabayashi et al. 2010[150] / Japan	30,585 subjects from Yamagata Prefecture, Japan	Drinking categories: None; light: <22 g/day; heavy: ≥22 and	Age, BMI, smoking history, history of hypertension	Prevalence of MetS was lowest in light drinkers (both men and women) and	Light drinking is associated with a lower risk of MetS in Japanese men and women

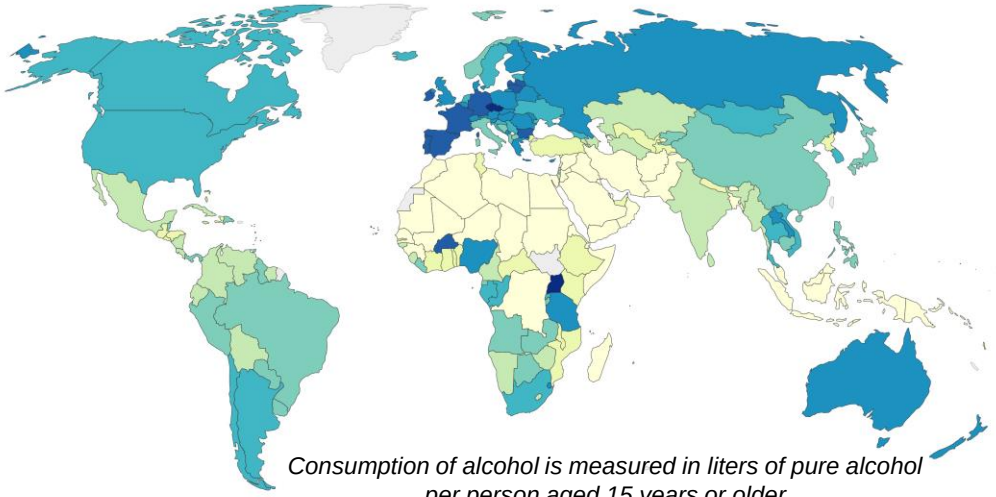
		<44 g/day; very heavy: ≥44 g/day	therapy, dyslipidemia, or diabetes mellitus	higher in very heavy drinkers.	
Oh et al. 2018[151] / Republic of Korea	39,055 subjects from the Korea National Health and Nutritional Examination Survey (KNHANES)	Drinking categories: None, <1 drink/month, 1 drink/month, 2-4 drinks/month, 2-3 drinks/week, and >4 drinks/week	Age, physical activity, region (urban, rural), smoking status, household income, occupation, and educational attainment	Relative to abstaining males, males that consumed alcohol more than 2-3 drinks/week (OR: 1.32) and those that consumed more than 10 drinks/drinking session (OR: 1.71) had greatly increased odds of developing MetS.	Alcohol consumption, even in quantities as small as 3-4 standard drinks per session for females, and 7-9 standard drinks per session for males, is associated with increased risk of MetS.
Kim et al. 2017[152] / Ansan and Ansung City, Republic of Korea	10,037 subjects in a community-based cohort	Drinking categories: None, very light (0.1–5.0 g/day), light (5.1–15.0 g/day), moderate (15.1–30.0 g/day), or heavy (>30 g/day)	Age, sex, hypertension, BMI, and diabetes	Very light alcohol consumption in both men and women was associated with reduced prevalence of MetS (men, OR=0.65; women, OR=0.72)	Alcohol consumption (0.1–5.0 g/day) contributed to reducing the prevalence of MetS and components, including triglyceride and HDL-c.
Baik et al. 2018[153] / Republic of Korea	3833 subjects from the Korean Genome Epidemiology Study	Drinking categories:Very light: 0.1 to 5 g/day; light: 5.1 to 15 g/d; moderate: 15.1 to 30 g/d; heavy: >30 g/d	Age; sex; BMI; income; occupation; marital status; education; smoking status; physical activity; average daily intake of: calories, fat, and dietary fiber; average frequency of consuming red meat, fish, or nuts; and family history of diabetes or hypertension	Multivariate relative risks of MetS were 1.06 for very light drinkers; 1.13 for light drinkers; 1.25 for moderate drinkers, and 1.63 for heavy drinkers	Heavy consumption, particularly liquor consumption, is associated with an increased risk of MetS, due to influences on its components.
Slagter et al. 2014[154] / The Netherlands	64,046 participants from the Life Lines Cohort study	Number of alcoholic drinks/week = the number of drinking days/week multiplied by the average number of units consumed on a drinking day	Age, sex, BMI class, alcohol consumption subgroup, smoking subgroup, and the number of medications used	Consumption of >2 drinks/day increased blood pressure; the strongest associations were among heavy smokers. The overall metabolic profile of wine consumers was better than that of non-consumers or	Light alcohol consumption may moderate the negative association between smoking and MetS.

				consumers of beer or spirits/mixed drinks.	
Baghdan et al. 2021[155] / African-origin cohorts	2506 participants in 5 African-origin cohorts from Ghana, Jamaica, South Africa, Seychelles, and the U.S.	Drinking categories: None; light (1–3 drinks/day for men and 1–2 drinks/day for women); heavy (≥4 drinks/day for men and ≥3 or more drinks/day for women)	Age, sex, smoking status, self-reported physical activity, and site	Light or heavy drinking was not associated with increased odds of high cardiometabolic risk compared to nondrinkers (OR = 1.05 and OR = 1.1, respectively). Light drinking was associated with lower odds of low HDL-c (OR = 0.69) and increased risk of high triglycerides (OR = 1.48).	Associations varied greatly across each of the five sites, suggesting an effect of environmental factors on cardiometabolic risk. These relationships also varied when stratified by sex, which indicated that sex may modify the association between alcohol consumption and cardiometabolic risk.
Vieira et al. 2016[156] / Brazil	15,105 participants from the Brazilian Longitudinal Study of Adult Health	Categories: ≤4 drinks/week, 4 to 7 drinks/week, 7 to 14 drinks/week, >14 drinks/week	Age, sex, educational level, income, socioeconomic status, ethnicity, smoking, BMI, and physical activity	Light alcohol consumption with meals was inversely associated with MetS (≤4 drinks/week: OR= 0.85; 4 to 7 drinks/week: OR= 0.75). Greater alcohol consumption outside meals was associated with MetS (7 to 14 drinks/week: OR= 1.32; ≥14 drinks/week: OR= 1.60)	The alcohol association with MetS differs markedly, depending on whether intake coincided with meals. Beverage preference (wine or beer) appears to underlie at least part of this difference.
Bermúdez et al. 2015[157] / Venezuela	2230 subjects from Maracaibo City, Venezuela	Habitual drinkers were defined as subjects that consumed ≥1 g/day of alcohol	Age, ethnic groups, socioeconomic status, educational status, occupational status, family history of hypertension and diabetes, tobacco use, four domains of physical activity	Alcohol consumption was associated with high triglycerides levels in both sexes. Among men, consuming 28.41–47.33 g/day significantly increased the risks of MetS, hyperglycemia, HBP, high triglyceride levels, and large waist circumference.	The relationship between alcohol consumption, MetS, and its components is complex and not directly proportional.
Xiao et al. 2015[158] / China	20,502 participants from rural China	Drinking categories: None, light (≤5.7 g/day for women; ≤16.4 g/day for men), moderate (≤17.7 g/day for women; ≤45.2 g/day for	Age at interview, BMI, education, marriage status, personal income,	Alcohol consumption was associated with a lower prevalence of MetS in women; any alcoholic beverage might reduce the risk	All alcoholic beverages increased HDL-c levels. Rice wine decreased both the triglyceride level and blood glucose in women only. Rice wine could be a healthy alcoholic beverage

		men), and severe (>17.7 g/day for women; >45.2 g/day for men)	occupation, exercise, smoking status, tea consumption, and intake of meat, fish, soy products, fruit, and vegetables	of low HDL-c in both men and women. Regardless of the type of alcoholic beverage, alcohol consumers had higher HDL-c levels than non-consumers.	for MetS prevention in Chinese women.
Choi et al. 2019[81] / Republic of Korea	41,368 males and females from the Health Examinees-GEM study	Drinking categories: None (0.0 g/day), light (male: 0.1 to 19.9 g/day; female: 0.1 to 9.9 g/day), moderate (male: 20.0 to 39.9 g/day; female: 10.0 to 19.9 g/day), and heavy (male: ≥40.0 g/day; female: ≥20.0 g/day) at initial and each follow-up health examination	Waist circumference, fasting serum glucose, blood pressure, triglycerides, and HDL-c levels	Increasing from persistent light intake to heavy intake led to an elevated risk of MetS. Conversely, reducing from persistent heavy intake to light intake reduced the risk of MetS	Heavy drinkers that reduce their alcohol consumption could benefit from a reduced risk of MetS
Total number of subjects: 265,223					

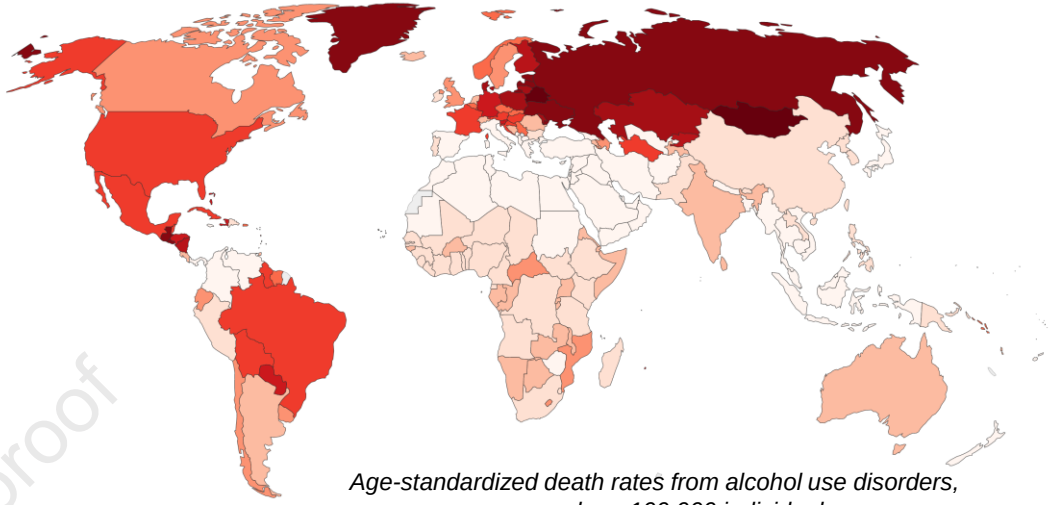
Abbreviations: HBP, high blood pressure; MetS, metabolic syndrome; BMI: body mass index; HDL-c, high-density lipoprotein cholesterol; CVD, cardiovascular disease; OR, odds ratio.

a. Alcohol consumption per person, 2018

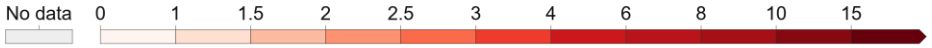


Consumption of alcohol is measured in liters of pure alcohol per person aged 15 years or older

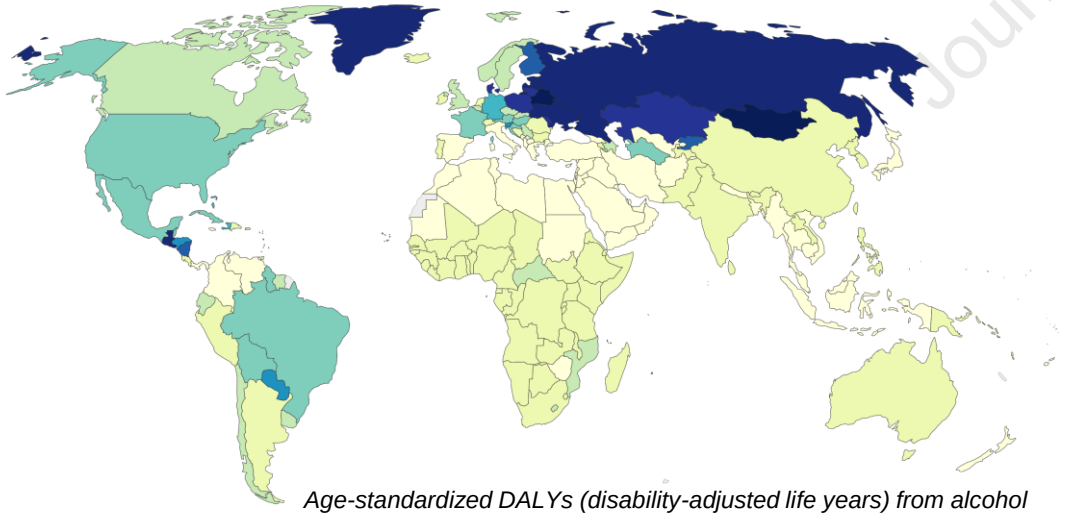
b. Death rates from alcohol use disorders, 2019



Age-standardized death rates from alcohol use disorders, measured per 100,000 individuals

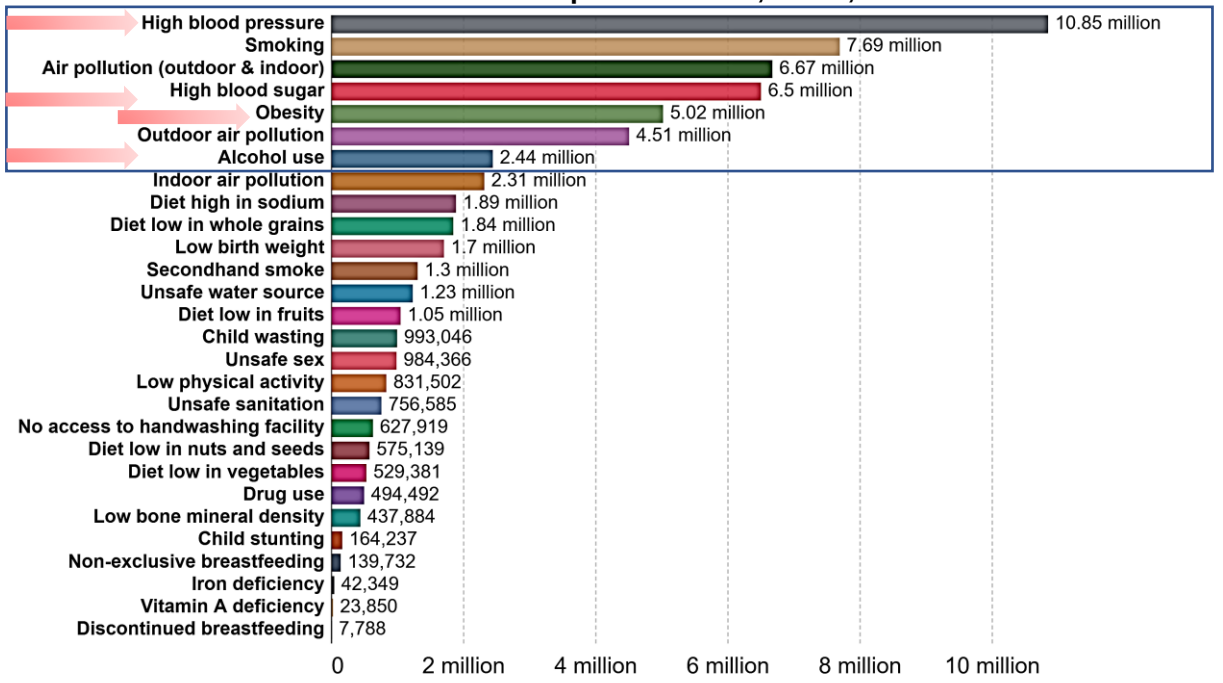


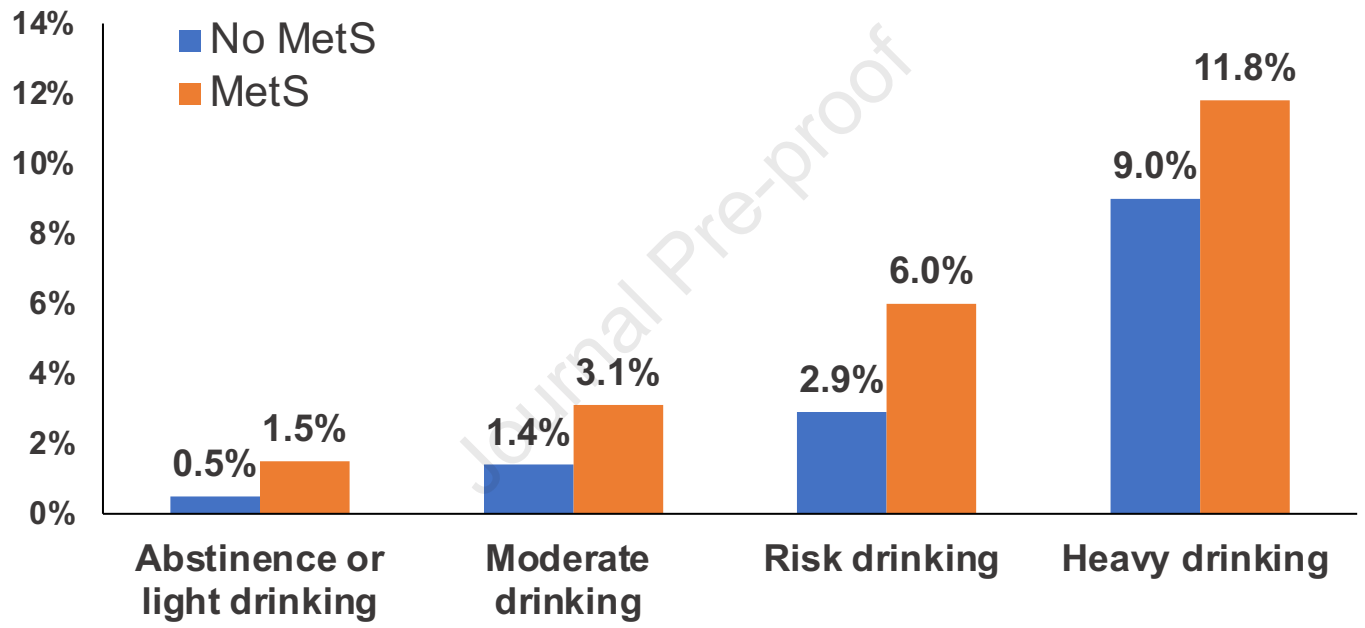
c. The disease burden from alcohol use disorders, 2019

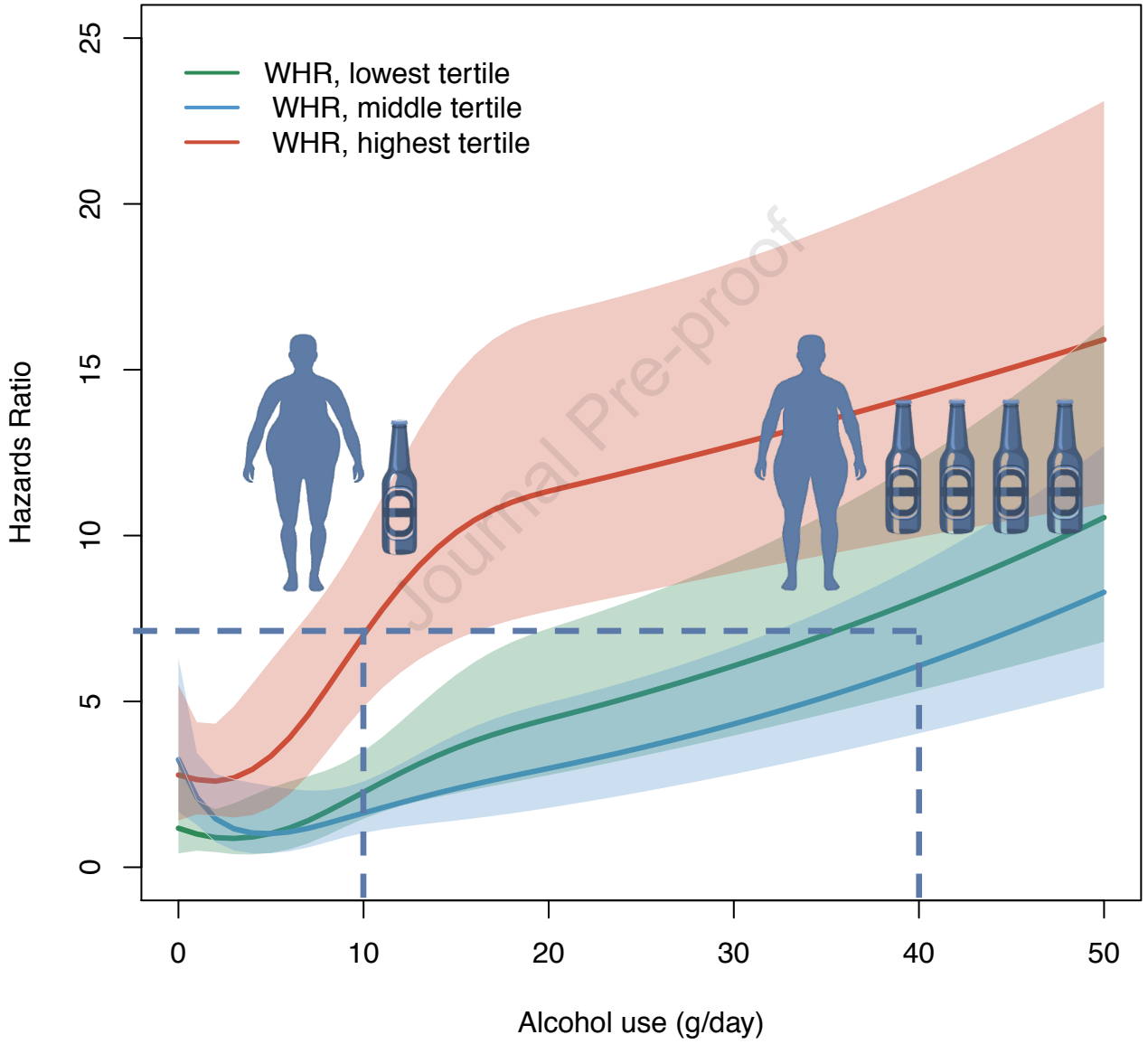


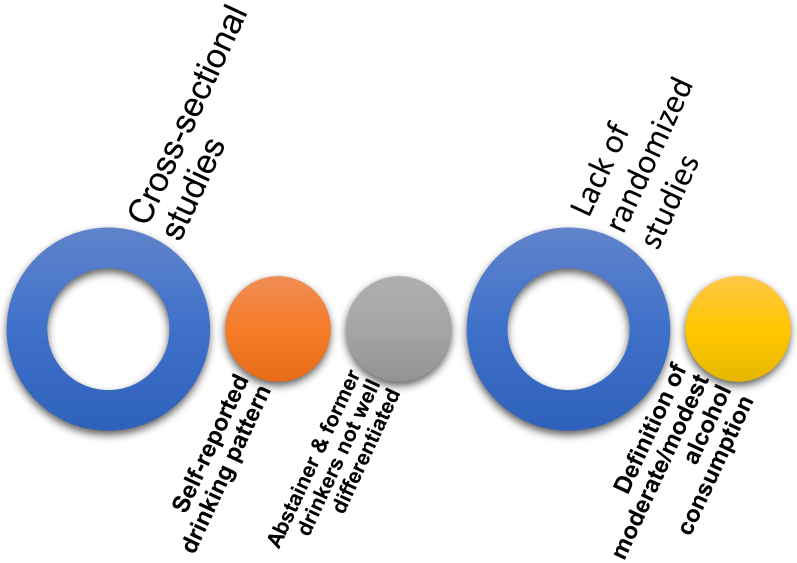
Age-standardized DALYs (disability-adjusted life years) from alcohol use disorders per 100,000 people

d. Number of death per risk factor, world, 2019









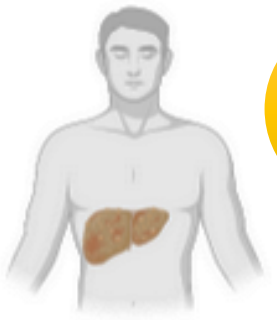
Moderate alcohol consumption might protect against NAFLD

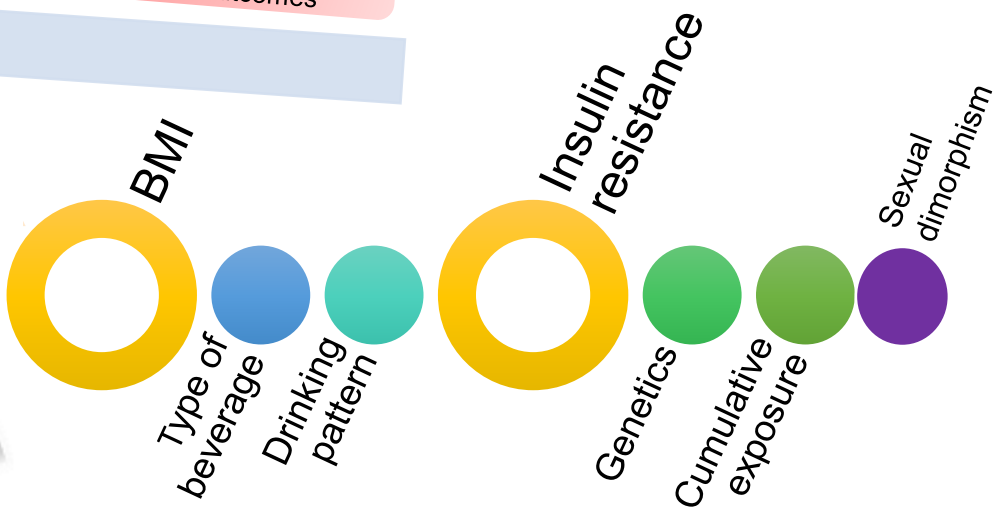
VS

Moderate alcohol consumption is not beneficial to NAFLD…it can be harmful

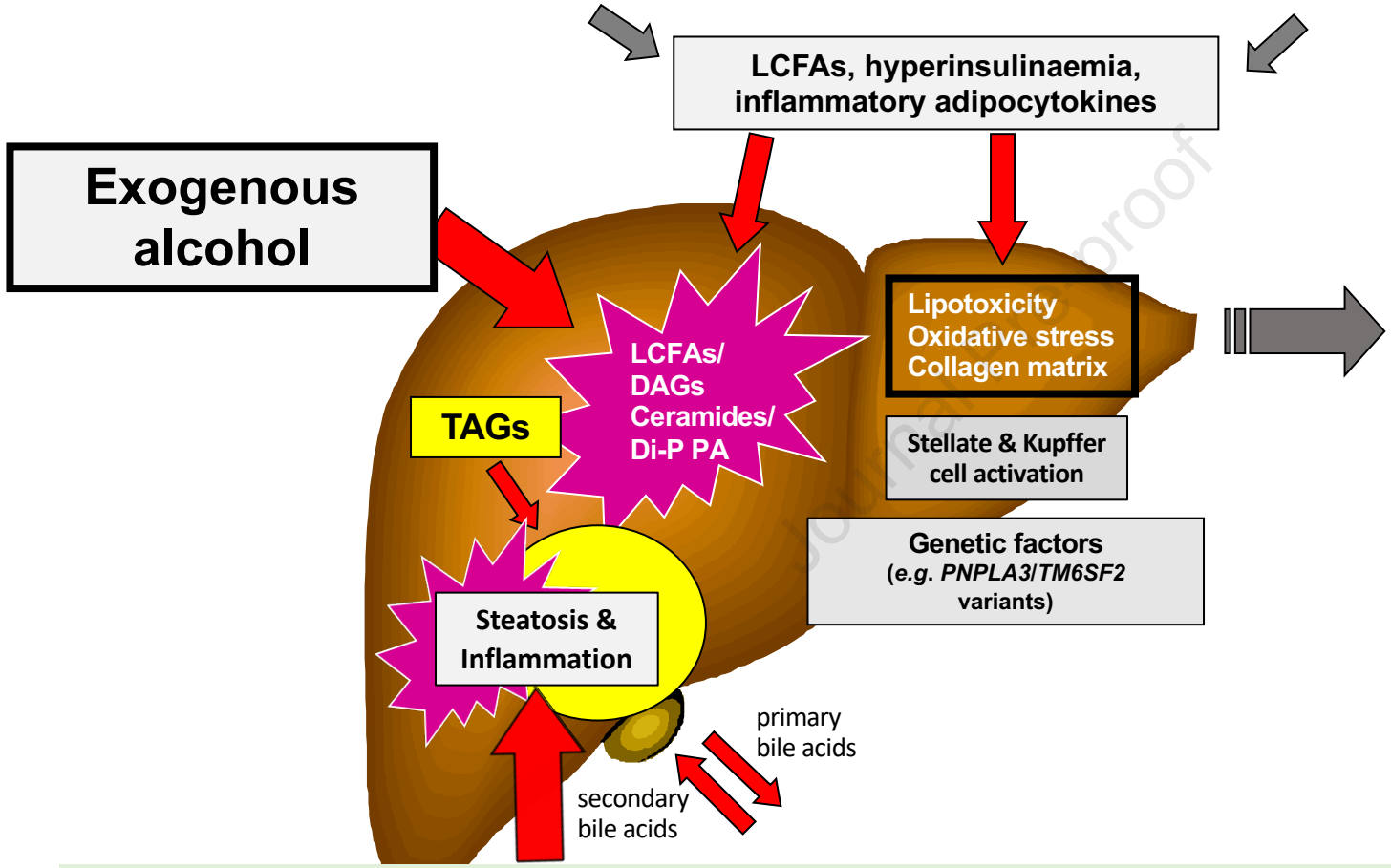
- decreased odds of NAFLD
- decreased odds of NASH
- lower risk of death

- more chances of NAFLD
- more disease progression & advanced fibrosis
- high risk of severe liver events
- Increased risk of liver cancer
- Increased overall mortality & incidence of extra-hepatic outcomes





MetS: adipose tissue dysfunction



RISK FACTORS

- ↑ Insulin resistance
- ↑ Glucose production
- ↑ Fetuin-A

- ↑ Triglycerides
- ↓ HDL-cholesterol
- ↑ Small, dense LDL-C
- ↑ Postprandial lipemia

Cardiovascular disease & Chronic kidney disease & Type 2 diabetes

RISK FACTORS

- ↑ Angiotensinogen
- ↑ Endothelin-1
- ↑ Transforming growth factor-beta

- ↑ C-reactive protein
- ↑ Interleukin-6
- ↑ TNF-alpha
- ↑ Reactive oxigen

- ↑ Fibrinogen
- ↑ Factor VIII
- ↑ Tissue factor
- ↑ PAI-1

Intestinal dysfunction and dysbiosis

Diet: high fat, high carbohydrate, high fructose, endogenous alcohol)