

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 Bangladesh²⁶). 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/m²). 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/m².⁹⁶ 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 toxicity¹¹⁹ 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 permeability¹³² 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 **Chronic Liver Disease (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

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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/m² 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: \geq 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, 1-4 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 Ansong 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.