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

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## Summary

Alcohol use and 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 (*i.e.* decompensation or liver transplantation). 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 have indicated that mild-moderate alcohol use is associated with an increase in liver-related outcomes. This conclusion was substantiated by systems biology analyses suggesting that alcohol and metabolic syndrome may play a similar role in 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 alcohol intake. Moreover, the components of metabolic syndrome appear to have additive effects when it comes to 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 BMI, including in individuals who consume harmful quantities of alcohol. Many studies even point to synergistic interactions 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 available evidence suggests that more holistic approaches could be useful for risk prediction, diagnostics and treatment planning.

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## Introduction

Alcohol use and 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 (*i.e.* decompensation or liver transplantation).<sup>1</sup>

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 because of wide variations in the factors that contribute to susceptibility, including sex, genetics, and multiple effect modifiers.<sup>2</sup> Moreover, definitions of a standard drink or low- and high-risk drinking vary substantially between countries.<sup>3</sup> 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).<sup>4</sup>

MetS has become a global problem.<sup>5</sup> It is largely attributed to excess caloric intake and physical inactivity. MetS

comprises a cluster of factors, including abdominal obesity, hyperglycaemia/insulin resistance, dyslipidaemia, and arterial hypertension. Moreover, MetS is often present in participants with non-alcoholic fatty liver disease (NAFLD).

NAFLD and alcohol-related liver disease (ALD) are the leading causes of chronic liver disease worldwide.<sup>6,7</sup> 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.<sup>8,9</sup>

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

In this review, we summarise the epidemiology of alcohol consumption and MetS and discuss their independent and combined impacts, particularly on liver-related clinical

Keywords: alcohol use; liver disease; NAFLD; metabolic syndrome; cardiovascular disease; hepatocellular carcinoma.

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## Keypoints

- Alcohol use and 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 components of metabolic syndrome.
- 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 considers alcohol use and metabolic abnormalities can potentially help detect persons at risk of liver-related outcomes at earlier stages.

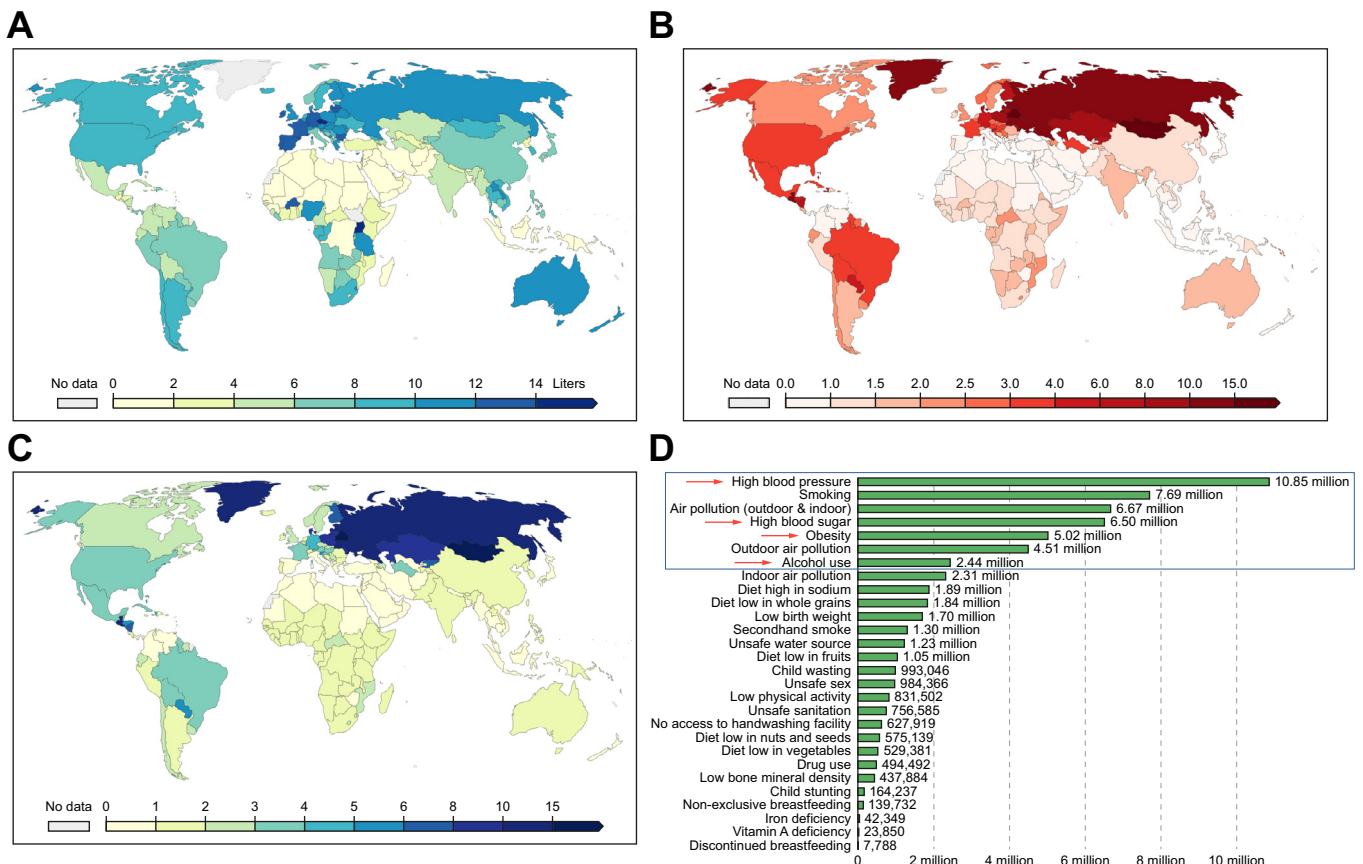
outcomes. Additionally, we look at the potential clinical implications of alcohol consumption and MetS on chronic liver disease.

### Global alcohol consumption and associated harm

In 2018, the global average alcohol consumption among individuals aged  $\geq 15$  years was 6.2 L of pure ethanol per person (Fig. 1A), 2.6 L for women and 9.7 L for men, with substantial variations by country.<sup>10</sup> This sex difference is lower in countries

with a higher overall prevalence of drinking.<sup>11</sup> 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-fold higher than the overall consumption levels.<sup>8</sup>

The average worldwide prevalence of heavy episodic drinking (consuming at least 60 g 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



**Fig. 1. Global trends: alcohol-related epidemiology and mortality/disability statistics.** (A) Annual average alcohol consumption per person (aged  $\geq 15$  years, 2018). To account for different alcohol contents among alcoholic drinks (e.g., beer, wine, spirits), quantities are expressed in litres of pure alcohol per year (<https://ourworldindata.org/alcohol-consumption>). (B) Death rates from alcohol use disorders (2019). Globally, 2.4 million alcohol-related premature deaths/year (<https://ourworldindata.org/alcohol-consumption>). (C) The disease burden from alcohol use disorders (2019). Alcohol use is a leading risk factor for death and disability. DALYs are a time-based measure combining years of life lost due to premature mortality and years of life 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 (2019); in most high-income countries, risk factors are metabolic syndrome components and alcohol use (<https://ourworldindata.org/causes-of-death>). DALYs, disability-adjusted life years.

and Australasia.<sup>12</sup> In 2016, an estimated 1.3% (~100 million people) of the global population had alcohol use disorders.<sup>10</sup>

Annually, >2.4 million deaths result from harmful alcohol use (Fig. 1B). Alcohol-attributable age-standardised mortality is higher for men (6.8%) than women (2.2%) and among young adults.<sup>11</sup> Cardiovascular diseases were responsible for 34.3% of all alcohol-attributable deaths in 2012, followed by injuries (25.8%) and digestive diseases (16.2%).<sup>13</sup> 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 (Fig. 1C).<sup>8,11</sup>

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

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.<sup>16</sup> 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.<sup>17,18</sup> Beyond health outcomes, alcohol use is also associated with wide-ranging social consequences and a large financial burden to society.<sup>19</sup>

## Global trends: MetS

Worldwide, MetS-related factors such as high systolic blood pressure, high blood glucose and obesity constitute leading risk factors for death (Fig. 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.<sup>20</sup> Although the focus of syndrome X was insulin resistance, it is now widely recognised that ectopic fat accumulation such as visceral obesity is a key component and cause of insulin resistance and MetS (Table S1). 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.<sup>21</sup>

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, dysglycaemia, dyslipidaemia, and hypertension. Despite limitations related to the dichotomisation of continuous variables, for the sake of clinical applicability, MetS was defined by specific thresholds for waist circumference, plasma glucose concentration, HDL-cholesterol, 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 characterise

MetS. These debates resulted in modifications to the diagnostic criteria, and in 2009, the ‘harmonised criteria’ for MetS were established by consensus among several societies (Table S1). 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.

Unsurprisingly, 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%.<sup>22</sup> The MetS prevalence in Sichuan Province (27.8% in 2010, 27.4% in 2018, among individuals aged ≥18 years) was lower than that reported in previous studies from China (33.9% in 2010).<sup>23</sup> 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;<sup>24</sup> 30% in Indian adults aged ≥18 years, 2004–2019;<sup>25</sup> and 20–37% in Bangladesh<sup>26</sup>). Other studies have shown different prevalences across the globe. For example, 36.5% in 2007–2009 in Portugal (individuals aged ≥18 years),<sup>27</sup> 24.3% in Europe,<sup>28</sup> and 44.2% in Mexico.<sup>29</sup> Among US adults, the prevalence of MetS has increased from 36.2% in 1999–2000 to 47.3% in 2017–2018.<sup>30</sup> 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.<sup>31</sup>

## Alcohol and liver disease: Key remarks

Despite an established dose-response relationship between the quantity of alcohol consumed and liver disease risk in general, considerable individual variability exists. In most individuals, liver steatosis seems to develop after consuming >60 g/day of alcohol for >2 weeks. However, this condition can be reversed by 4–6 weeks of abstinence.<sup>2</sup> 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.<sup>32,33</sup> Thus, it seems that consistently high daily alcohol consumption is required for “pure” alcohol-related steatosis to develop.

In contrast, the risk of cirrhosis 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 cirrhosis showed that the cirrhosis risk became significant at around one drink/day, compared to long-term abstainers, and the risk increased with increasing alcohol intake.<sup>34</sup> 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 who consumed 1–4 drinks/day.<sup>34</sup> Currently, no liver-safe limit of alcohol consumption 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 individuals with presumed NAFLD when assessed by alcohol biomarkers.<sup>35</sup>

Despite the relationship between alcohol dose and liver disease risk, only 10 to 20% of individuals with chronic heavy alcohol use develop cirrhosis or alcoholic hepatitis. This observation highlights the key role of effect modifiers.<sup>36</sup> For example, women are more susceptible to ALD than men at any given level of alcohol consumption.<sup>2</sup> Genetic factors are involved in the individual susceptibility to both alcohol use disorder and ALD. Other key effect modifiers of ALD 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.<sup>2</sup>

### Metabolic drivers of liver disease

MetS has emerged as an independent driver of liver fibrosis<sup>37,38</sup> and liver-related outcomes.<sup>39,40</sup> 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.<sup>39</sup> MetS is also associated with HCC.<sup>40–42</sup> In a recent US study, MetS was the greatest contributor to population-level HCC (attributable fraction: 32%).<sup>43</sup> Moreover, the presence of MetS could predict liver-related mortality in various chronic liver diseases.<sup>44</sup> Among the individual components of MetS, diabetes and obesity have been closely linked to liver-related outcomes in numerous studies.<sup>40,41,44–52</sup> 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 individuals with NAFLD and a mean 9-year follow-up reported that each additional metabolic trait (diabetes, obesity, hypertension, dyslipidaemia) 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).<sup>48</sup> However, this study did not assess abdominal obesity.

In a population-based study of 578,700 individuals, obesity and hyperglycaemia 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.<sup>41</sup> Other studies have confirmed that MetS components had an additive impact on HCC risk.<sup>40,53</sup>

Obesity is typically expressed in terms of BMI (kg/m<sup>2</sup>). Nonetheless, when assessing metabolic health, abdominal waist circumference seems to be the “vital sign”.<sup>1,51,51</sup> Several population-based studies have agreed that measures of central/abdominal obesity are better predictors of liver disease than BMI,<sup>1,38,47,53,53–57</sup> and BMI may not provide added prognostic value.<sup>1,47,54,55</sup> Furthermore, longitudinal studies have

suggested that the waist-to-hip ratio (WHR) provides advantages over other anthropometric measures.<sup>1,54</sup> 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).<sup>58</sup> 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.<sup>59</sup>

Altered lipid metabolism is a hallmark of NAFLD, and low serum HDL-c and high triglyceride levels are often present alongside insulin resistance.<sup>60</sup> 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 synthetic dysfunction.<sup>47,48,61–64</sup>

Arterial hypertension has been highlighted as an independent risk factor for liver disease.<sup>37,38,44,45,52,55,65,66</sup> 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).<sup>44,57,64,67–69</sup> Obesity is also associated with elevated mortality risk in individuals with alcoholic hepatitis.<sup>70</sup> However, when liver dysfunction worsens, obesity, dyslipidaemia, 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,<sup>71</sup> arterial hypertension,<sup>72</sup> obesity,<sup>73,74</sup> cardiovascular disease,<sup>75,76</sup> systemic inflammation,<sup>77</sup> and all-cause mortality.<sup>78,79</sup> 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 favourable influence on the intermediate phenotypes of arterial hypertension, T2D, lipids, central obesity, and cardiovascular disease.

Table 1 summarises 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



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

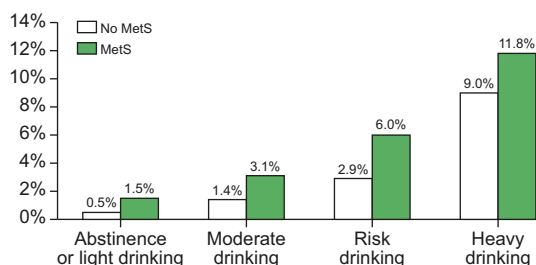
Reference/Country	Population sample (n)	Alcohol consumption definition	Covariate adjustments	Main results	Conclusion and key message
Freiberg <i>et al.</i> 2004 <sup>146</sup> /US.	8,125 individuals from the Third National Health and Nutrition Examination Survey (NHANES III) (1988–1994)	Alcohol consumption defined as $\geq 1$ alcoholic drink per month.	Age, sex, race/ethnicity, education, income, tobacco use, physical activity, and diet	Individuals that consumed 1–19 or $\geq 20$ drinks/month of alcohol had ORs for MetS of 0.65 and 0.34, respectively, compared to current non-drinkers. 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 favourable influence on lipids, waist circumference, and fasting insulin.
Fan <i>et al.</i> 2008 <sup>147</sup> /US.	1,529 individuals from the National Health and Nutrition Examination Survey 1999–2002	Categories: $<1$ drink/week, 1–2 drinks/week, $\geq 3$ drinks/week	Demographics, family history of CVD and diabetes, and lifestyle factors	More than 2 drinks/day increased the risk of developing 4 of the 5 MetS components, including HBP, high triglycerides, increased abdominal girth, and elevated blood glucose.	Public health messages should emphasise the potential cardiometabolic risk associated with drinking.
Fan <i>et al.</i> 2008 <sup>148</sup> /China	3,953 participants from the general population of Shanghai	Current alcohol consumption was defined as more than 1 alcoholic drink/month	Age and sex	Prevalence of abdominal obesity, low serum HDL-c, and diabetes mellitus were lower in individuals that consumed 2 or more alcoholic 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 favourably influences HDL-c, waist circumference, and diabetes mellitus.
Hirakawa <i>et al.</i> 2015 <sup>149</sup> /Japan	22,349 men from Japan	Drinking categories: none, light ( $<20$ g ethanol/day), heavy ( $\geq 20$ and $<60$ g ethanol/day) and very heavy ( $\geq 60$ g ethanol/day)	Not specified	The prevalence of MetS was significantly lower among light drinkers and higher in very heavy drinkers, compared to non-drinkers.	A significant association was observed between very heavy alcohol intake ( $\geq 60$ g/day) and the prevalence of MetS.
Wakabayashi <i>et al.</i> 2010 <sup>150</sup> /Japan	30,585 individuals from Yamagata Prefecture, Japan	Drinking categories: None; light: $<22$ g/day; heavy: $\geq 22$ and $<44$ g/day; very heavy: $\geq 44$ g/day	Age, BMI, smoking history, history of hypertension therapy, dyslipidaemia, or diabetes mellitus	Prevalence of MetS was lowest in light drinkers (both men and women) and higher in very heavy drinkers.	Light drinking is associated with a lower risk of MetS in Japanese men and women
Oh <i>et al.</i> 2018 <sup>151</sup> /Republic of Korea	39,055 individuals 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 <i>et al.</i> 2017 <sup>152</sup> /Ansan and Ansong City, Republic of Korea	10,037 individuals 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 <i>et al.</i> 2018 <sup>153</sup> /Republic of Korea	3,833 individuals 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 fibre; 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 <i>et al.</i> 2014 <sup>154</sup> /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 consumers of beer or spirits/mixed drinks.	Light alcohol consumption may moderate the negative association between smoking and MetS.

(continued on next page)

Table 1. (continued)

Reference/Country	Population sample (n)	Alcohol consumption definition	Covariate adjustments	Main results	Conclusion and key message
Baghdan <i>et al.</i> 2021 <sup>155</sup> /African-origin cohorts	2,506 participants in 5 African-origin cohorts from Ghana, Jamaica, South Africa, Seychelles, and the US.	Drinking categories: None; light (1–3 drinks/day for men and 1–2 drinks/day for women); heavy ( $\geq 4$ drinks/day for men and $\geq 3$ 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 non-drinkers (ORs of 1.05 and 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 5 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 <i>et al.</i> 2016 <sup>156</sup> /Brazil	15,105 participants from the Brazilian Longitudinal Study of Adult Health	Categories: $\leq 4$ 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 ( $\leq 4$ 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; $\geq 14$ 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 <i>et al.</i> 2015 <sup>157</sup> /Venezuela	2,230 individuals from Maracaibo City, Venezuela	Habitual drinkers were defined as individuals that consumed $\geq 1$ g/day of alcohol	Age, ethnic groups, socioeconomic status, educational status, occupational status, family history of hypertension and diabetes, tobacco use, 4 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 <i>et al.</i> 2015 <sup>158</sup> /China	20,502 participants from rural China	Drinking categories: None, light ( $\leq 5.7$ g/day for women; $\leq 16.4$ g/day for men), moderate ( $\leq 17.7$ g/day for women; $\leq 45.2$ g/day for men), and severe ( $> 17.7$ g/day for women; $> 45.2$ g/day for men)	Age at interview, BMI, education, marriage status, personal income, occupation, exercise, smoking status, tea consumption, and intake of meat, fish, soy products, fruit, and vegetables	Alcohol consumption was associated with a lower prevalence of MetS in women; any alcoholic beverage might reduce the risk 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.	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 for MetS prevention in Chinese women.
Choi <i>et al.</i> 2019 <sup>81</sup> /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: $\geq 40.0$ g/day; female: $\geq 20.0$ 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
<b>Total number of individuals: 265,223</b>					

CVD, cardiovascular disease; HBP, high blood pressure; HDL-c, HDL-cholesterol; LDL-c, LDL-cholesterol; MetS, metabolic syndrome; OR, odds ratio.



**Fig. 2. Combined effects of alcohol and metabolic syndrome on liver-related outcomes.** Cumulative 20-year incidence of severe liver-related outcomes (hospitalisation, cancer, or death), according to the baseline level of alcohol consumption and the absence/presence of MetS (data based on results reported in ref.<sup>82</sup>). MetS, metabolic syndrome.

reductions in blood pressure levels.<sup>80</sup> 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 risk of MetS.<sup>81</sup> However, ethnic differences in alcohol metabolism or consumption patterns may exist that influence the relationship between alcohol consumption and features of 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.<sup>67</sup> MetS increases the risk of liver-related outcomes, regardless of alcohol intake (Fig. 2).<sup>82</sup> The importance of joint effects was highlighted in a population-based Finnish study on 10,993 individuals 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 people with NAFLD.<sup>83</sup> Similarly, a recent French study on 52,066 individuals hospitalised with diabetes found that most liver-related complications were attributable to alcohol use disorders, whereas <10% were attributed to obesity or MetS.<sup>84</sup>

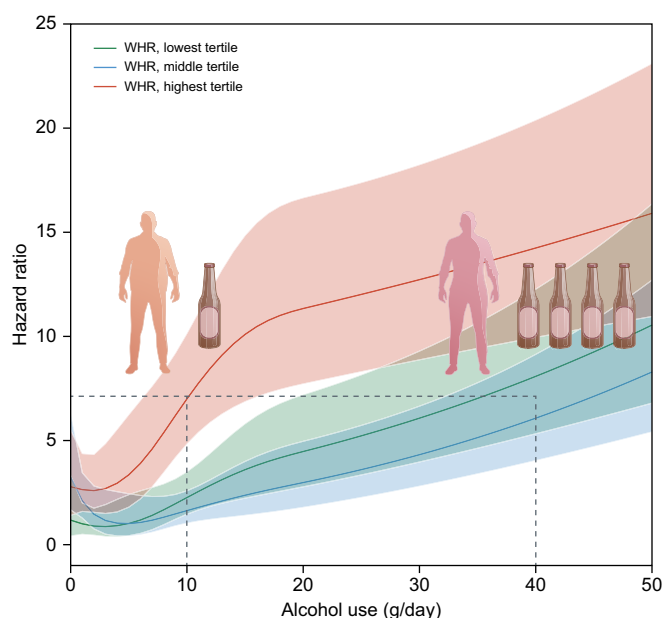
Synergism, or a supra-additive interaction effect, describes an interaction between two exposures (e.g., harmful alcohol use and MetS), where the effect on the outcome (e.g., liver disease) is greater than the sum of the individual effects. Several epidemiological studies (reviewed in<sup>1,85</sup>) 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.<sup>1,85</sup>

A Finnish population-based study found that MetS and weekly binge drinking ( $\geq 60$  g ethanol/occasion) had substantial supra-additive effects on liver-related outcomes.<sup>86</sup> Similarly, a US study involving individuals with ultrasound-verified liver steatosis reported a supra-additive effect of MetS and excessive drinking ( $\geq 3$  daily drinks for men and  $\geq 1.5$  for women) on all-cause mortality.<sup>87</sup> In both studies,<sup>86,87</sup> 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 an interaction was estimated at 60–74%.<sup>85</sup>

Findings are more mixed regarding supra-additive interactions between hazardous alcohol use and high BMI.<sup>85,88–90</sup> 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.<sup>91</sup> This 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 1 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 (Fig. 3).<sup>61</sup> However, it remains unclear to what extent this epidemiologic synergism is behavioural. 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.

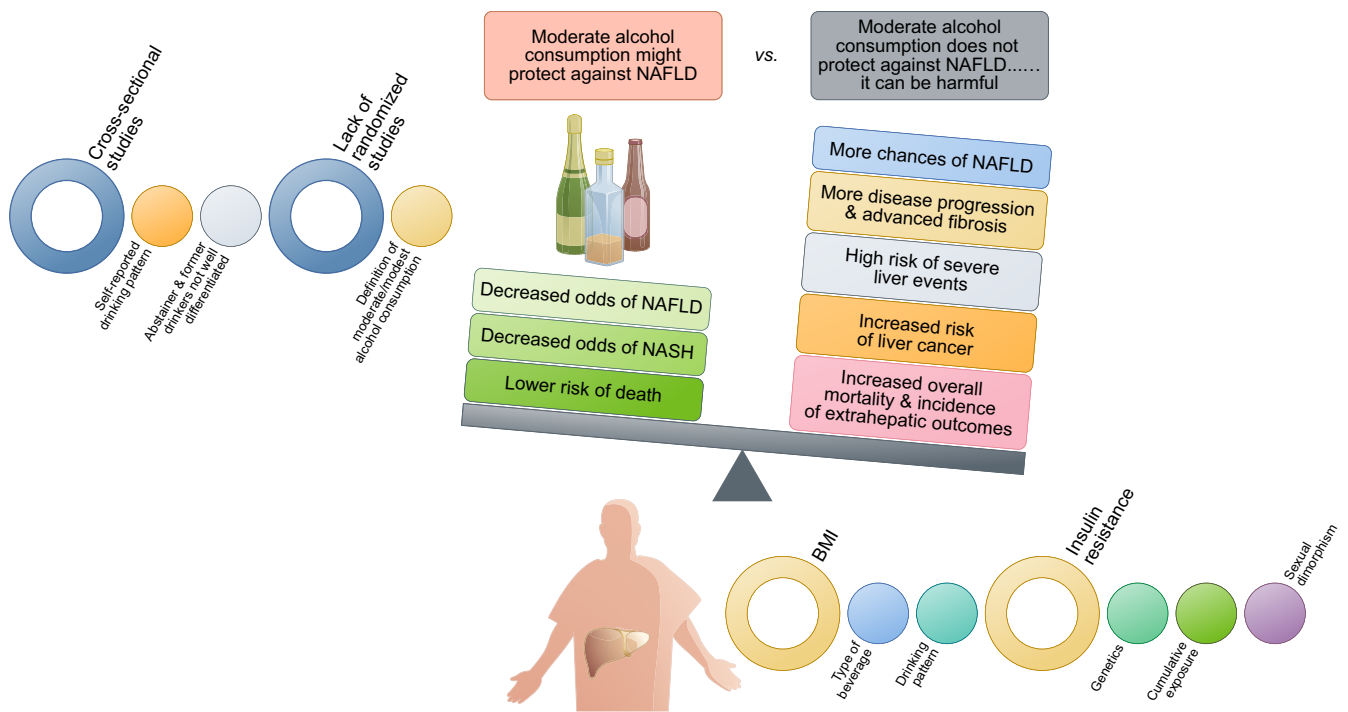
### The intricate relationship between alcohol consumption and NAFLD: Does moderate alcohol consumption affect the natural history of NAFLD?

Study results disagree on whether social or mild-to-moderate alcohol consumption has a detrimental or beneficial impact on the natural history of NAFLD.<sup>92</sup> Quantitative evidence from cross-sectional studies (sample size = 43,172 individuals) assessed in a meta-analysis suggested that moderate alcohol consumption had a protective effect ( $\sim 31\%$ ) on the risk of developing NAFLD (Fig. 4).<sup>93</sup> This beneficial effect appeared to be independent of covariates, like BMI, but was influenced by sex.<sup>93</sup> More importantly, quantitative evidence suggested that moderate alcohol consumption was associated with an



**Fig. 3. Abdominal obesity increases alcohol-related liver toxicity by fourfold.** The figure shows the hazard ratios for the risk of incident severe liver disease according to alcohol consumption in a man with different WHRs. In the highest tertile of WHR (red) in the population, for a man that consumes 1 alcoholic drink daily (10 g ethanol) risk is similar to that of a man with a low WHR (green) who consumes 4 alcoholic drinks daily (40 g ethanol). Results are based on Cox regression analysis adjusted for age, diabetes, smoking, and body mass index.<sup>61</sup> WHR, waist-to-hip ratio.





**Fig. 4. The intricate relationship between alcohol consumption and NAFLD and the synergistic effects of covariates.** Summary of the evidence supporting the favourable (left) and unfavourable (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. *ADH1B*, alcohol dehydrogenase 1B; *ADH1B\*1*, ancestral allele G of the rs1229984 variant; *ADH1B\*2*, allele A of the rs1229984 variant; CKD, chronic kidney disease; CVD, cardiovascular disease; FU, follow-up; HCC, hepatocellular carcinoma; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio.

average reduction in the risk of developing NASH of about 50%.<sup>93</sup> A more recent meta-analysis also suggested that moderate alcohol consumption was associated with reduced odds of developing NASH and advanced fibrosis.<sup>94</sup> 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.

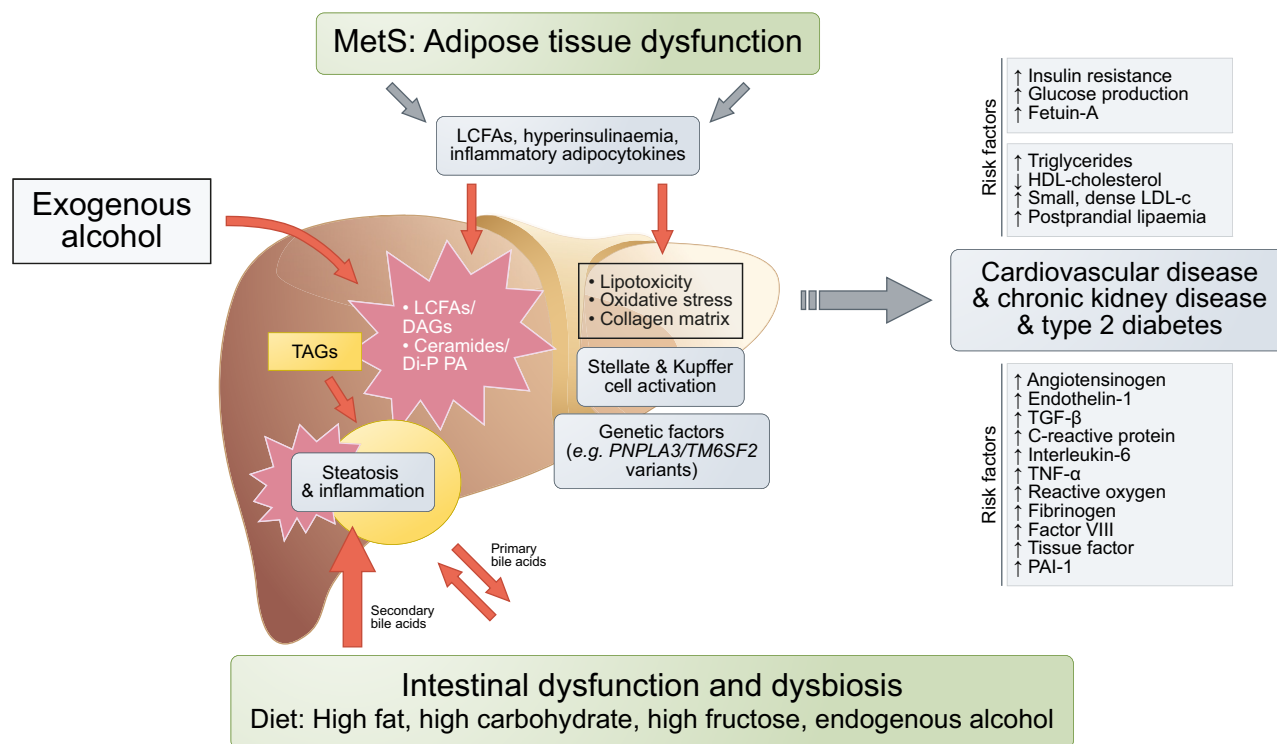
What makes the relationship between moderate alcohol consumption and NAFLD so complex? Many aspects are not measured very precisely in observational studies; thus, the presumed beneficial effects of moderate alcohol consumption are inconsistent across studies. In the absence of robust clinical trials,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

involved ~14 years of follow-up showed that moderate alcohol consumption was associated with fibrosis progression.<sup>97</sup>

Other studies have shown that critical aspects of co-existing comorbidities can significantly impact the burden of liver-related disease and mortality (Fig. 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. Their results suggested that insulin resistance and alcohol had a synergistic effect on NAFLD progression.<sup>98</sup>

Åberg *et al.* also found that insulin resistance was a significant risk factor for severe liver-related outcomes.<sup>47</sup>

A multicentre, retrospective cohort study from Japan that included patients with ultrasound-verified NAFLD reported an annual HCC incidence rate of 0.05% in individuals who consumed <20 g/day of alcohol. Increasing levels of alcohol consumption were associated with increases in annual HCC incidence rates: 0.06% for 20-39 g/day (HR 1.54), 0.16% for 40-69 g/day (HR 3.49), and 0.22% for ≥70 g/day (HR 10.58).<sup>99</sup> A recent meta-analysis assessed two cohort studies to determine the effects of modest alcohol intake on the histological severity of NAFLD, 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 (Fig. 4).<sup>94</sup> 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.<sup>100</sup>



**Fig. 5. Effects of MetS, 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. DAGs, diacylglycerols; di-P PA, di-palmitoyl phosphatidic acid; 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, triacylglycerols; *TM6SF2*, transmembrane 6 superfamily member 2; TGF-β, transforming growth factor-β; TNF-α, tumour necrosis factor-α.

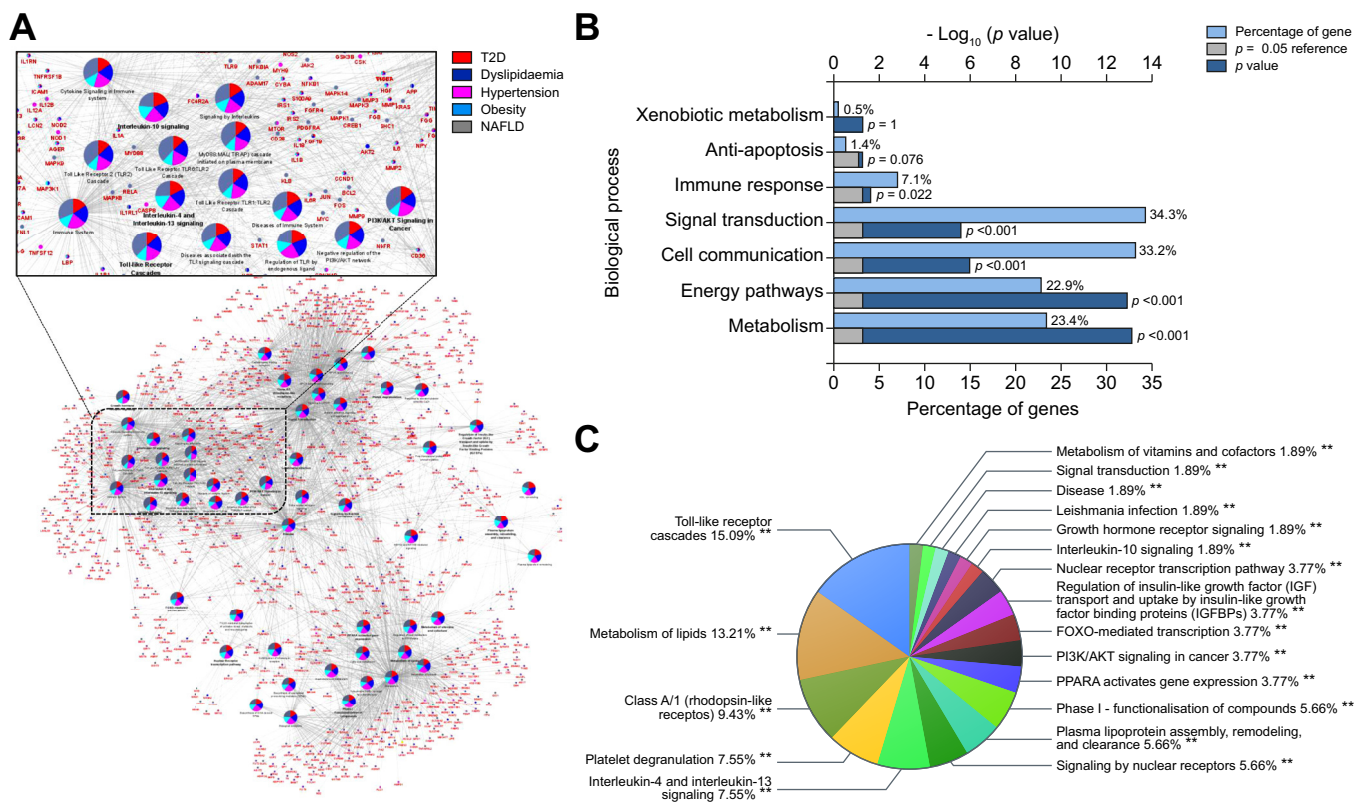
A prospective study in a general population cohort based in the US showed that modest alcohol consumption was associated with a significant reduction in all-cause mortality. However, drinking more than an average of 1.5 drinks/day ( $\geq 21$  g/day alcohol) was associated with an increase in mortality among patients with NAFLD.<sup>101</sup> Åberg *et al.* found that, among individuals with NAFLD, alcohol consumption dose-dependently increased the risk of incident advanced liver disease and malignancies.<sup>102</sup> 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.<sup>102</sup> 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-related outcomes in NAFLD, even when drinking within the recommended limits.<sup>103</sup>

#### 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 ALD and NAFLD often act in parallel to drive disease. ALD and NAFLD have similar histologic features, many

common pathogenetic mechanisms,<sup>104,105</sup> and a shared genetic background (e.g., *PNPLA3*, *TM6SF2*, *MBOAT7*, *HSD17B13*, *APOE*, *GPAM*).<sup>104,106</sup> The precise mechanisms underlying the synergism between alcohol and metabolic dysfunction remain elusive. However, they might involve combined effects on mitochondrial dysfunction, oxidative stress,<sup>107-109</sup> CYP2E1 activity,<sup>110</sup> innate immune response activation,<sup>111</sup> hepatic stellate cell activation,<sup>112</sup> gut microbiota and increased gut permeability,<sup>113,114</sup> bile acid metabolism (e.g., farnesoid X receptor and fibroblast growth factor 21),<sup>115,116</sup> lipid metabolism,<sup>117</sup> and adipocyte dysfunction with subsequent increases in lipolysis and proinflammatory factor release.<sup>118</sup>

Mouse studies have demonstrated that moderate obesity and alcohol use can synergistically induce steatohepatitis and liver fibrosis.<sup>111</sup> Furthermore, obesity-induced steatosis seems to sensitise the liver to alcohol toxicity.<sup>119</sup> In addition, a high-fat diet sensitises adipose tissue to alcohol-induced lipolysis.<sup>118</sup> 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.<sup>120</sup> Moreover, alcohol is an energy-dense molecule and can therefore induce metabolic dysfunction and contribute to obesity through caloric excess.<sup>117</sup> One gram of ethanol is nearly as energy dense as 1 g of dietary fat.



**Fig. 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  $\geq 0.4$ ); only the most significant interactions are shown (pathways with more than 5 genes); node size represents the term enrichment significance. Nodes are color-coded according to gene/protein associations, as indicated. Nodes with multiple colours 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 receptor cascades and PI3K/AKT signalling. (B) Enrichment analysis: (Light blue bars) Percentage of genes associated with and shared by all components of the metabolic syndrome. (Dark blue bars)  $p$  values for FDR over the cut-off reference, 0.05 (Grey 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 the supplementary appendix. FDR, false discovery rate; T2D, type 2 diabetes.

Endogenous ethanol production by gut microbiota has been proposed to contribute to liver disease progression in NAFLD.<sup>121,121–123</sup> This hypothesis was recently substantiated by a large population-based study.<sup>124</sup> Moreover, in a Finnish population-based cohort (N = 7,115), 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.<sup>125</sup> Additionally, several other pathways and molecules, including micro-RNAs, DNA methylation, and extracellular vesicles, have been postulated to play roles in both ALD and NAFLD.<sup>126,127</sup> Fig. 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 both alcohol consumption and the individual components of MetS is overwhelming. Moreover, the interaction between alcohol consumption and systemic metabolic deregulation is

characterised 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 visualise 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 prioritisation, based on multi-level data extracted by computational data mining.<sup>128</sup> 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 and perform enrichment analyses. Among the list of disease-associated genes (n = 569, 716, 725, 465, and 872, for diabetes, dyslipidaemia, hypertension, obesity, and fatty liver, respectively), 380



genes that were highly associated with fatty liver were also associated with the other four MetS components (Fig. 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.<sup>129</sup> Although related to ethanol metabolism, xenobiotic metabolism was not significantly enriched (Fig. 6B). The only significantly enriched transcription factor was HNF1A (hepatic nuclear factor 1 homeobox A), which is a member of a hepatic transcription factor family highly associated with diabetes.<sup>129</sup>

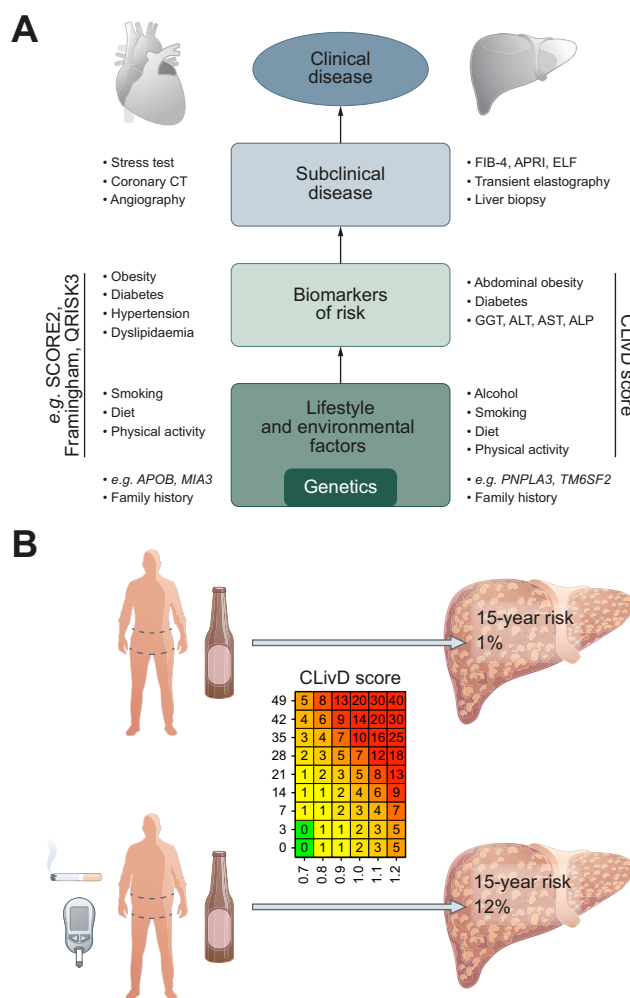
To obtain and visualise networks that corresponded to each cluster (*i.e.*, disease-associated genes), we analysed all the clusters simultaneously with the ClueGO Cytoscape application V2.5.8.<sup>130</sup> Regardless of the underlying disease, the associated genes belonged to common Reactome pathways (Fig. 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. Fig. 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 signalling (Fig. 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.<sup>131</sup> Moreover, alcohol-related impairments in gut permeability<sup>132</sup> and changes in the gut microbiota<sup>133</sup> can lead to the hepatic localisation of gut-derived endotoxins, whose effects on liver cells are mediated by TLRs. A recent human study explored the intrahepatic localisation of 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.<sup>134</sup>

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 that include promoting the development of fatty liver. Indeed, both alcohol and MetS appear to potentiate an existing dysregulation of vital homeostatic pathways.

### Clinical implications for chronic 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.<sup>1,37,38,41,43,44,47,48,52,57,64,67,68,82,84,85,87,103,135</sup> 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 (Fig. 7).<sup>135</sup> 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 analyse. The



**Fig. 7. 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<sup>2</sup> 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. ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; GGT, gamma-glutamyltransferase. CLiVD, chronic liver disease.

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).<sup>135,136</sup> 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, individualised 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.<sup>125,137</sup>

It is crucial to assess drinking habits, including binge drinking, with standardised approaches (e.g., AUDIT-C [alcohol use disorders identification test] or CAGE) for all patients with liver disease.<sup>138</sup> Moreover, continued alcohol consumption might impair the response to drug therapies for NAFLD. Hence, alcohol use biomarkers, such as phosphatidylethanol, could be useful to detect unreported high-risk drinking.<sup>98</sup>

Currently, the potential health benefits of low alcohol use remain controversial and unclear at the individual level; therefore, counselling should not advocate alcohol use for beneficial purposes.<sup>19</sup> In individuals with steatosis, alcohol use of around 2–3 drinks/day seems to double the risk of liver-related outcomes.<sup>102,139,140</sup> However, in those with 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 those with steatohepatitis or advanced fibrosis, any alcohol use should be discouraged, due to the high absolute risks.<sup>103,138</sup> This distinction requires more active evaluations of liver fibrosis stage in the community. In individuals with cirrhosis, regardless of the main aetiology, complete alcohol abstinence is important.

Although limited, the available evidence supports the active management of metabolic factors when 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.<sup>141–145</sup>

## 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 at the population and individual level. 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 of treatments such as metformin, statins, and aspirin, on liver-related outcomes.

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## Abbreviations

ADH1B, alcohol dehydrogenase; ALD, alcohol-related liver disease; CLiVD, Chronic Liver Disease score; GO, gene ontology; HCC, hepatocellular carcinoma; HR, hazard 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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## Conflicts of interest

The authors declare no conflict of interest regarding the content of this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

Review of structure and concept (FÅ and SS); all authors contributed to drafting the manuscript and its critical revision. All authors approved the final version.

## Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2022.08.030>.

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