Journal of Clinical and Translational Hepatology **2021** vol. 9(5) | 719–730
DOI: 10.14218/JCTH.2021.00173

Review Article

Alcohol and Metabolic-associated Fatty Liver Disease

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Received: 10 May 2021 | **Revised:** 11 June 2021 | **Accepted:** 17 June 2021 | **Published:** 19 July 2021

Abstract

The diagnosis of metabolic-associated fatty liver disease is based on the detection of liver steatosis together with the presence of metabolic dysfunction. According to this new definition, the diagnosis of metabolic-associated fatty liver disease is independent of the amount of alcohol consumed. Actually, alcohol and its metabolites have various effects on metabolic-associated abnormalities during the process of alcohol metabolism. Studies have shown improved metabolic function in light to moderate alcohol drinkers. There are several studies focusing on the role of light to moderate alcohol intake on metabolic dysfunction. However, the results from studies are diverse, and the conclusions are often controversial. This review systematically discusses the effects of alcohol consumption, focusing on light to moderate alcohol consumption, obesity, lipid and glucose metabolism, and blood pressure.

Citation of this article: Sun FR, Wang BY. Alcohol and metabolic-associated fatty liver disease. J Clin Transl Hepatol 2021;9(5):719–730. doi: 10.14218/JCTH.2021.00173.

Introduction

In 2020, the definition of metabolic-associated fatty liver disease (MAFLD) was proposed by Eslam *et al*.[1] Since then, clinical practice guidelines on MAFLD have been published by the Asian Pacific Association for the Study of the Liver.[2] An important significance of this definition is the "positive" criteria for the diagnosis of MAFLD, in contrast to a diagnosis of exclusion. More importantly, it is possible to diagnose MAFLD coexisting with liver injury caused by other reasons. The diagnosis of MAFLD is based on the detection of liver steatosis together with the presence of metabolic dysfunction, such as overweight or obesity, type 2 diabetes mellitus (T2DM), or clinical evidence of metabolic risk abnormalities.[1] The absence of alcohol intake limit is the prominent difference between the diagnostic criteria of MAFLD and the previous diagnostic criteria of non-alcoholic fatty liver disease. As is well known, a lack of ongoing or current consumption of significant amounts of alcohol was an important indicator in the latter.[3] However, the diagnosis of MAFLD is independent of the amount of alcohol consumed. Thus, it is possible to diagnose MAFLD coexisting with alcoholic-related liver disease (ALD).

Alcohol consumption is common in the general population. There are several common drinking patterns, including chronic heavy drinking,[4] light alcohol consumption, moderate alcohol consumption (MAC),[4,5] and binge drinking (Table 1). It has been well accepted that chronic heavy drinking is related with high risk of ALD and should be avoided. Compared with the chronic heavy drinking population, the non-heavy drinking population is much larger. Binge drinking, which is often related with serious social problems and deteriorative health problems, is another popular drinking pattern nowadays, especially among young people. Binge drinking could happen monthly or weekly, but it is different from chronic regular heavy drinking. The prevalence of binge drinking has significantly increased over the past two decades, with an average annual increase of 0.72% per year.[6] Binge drinking can coexist with MAC or regular heavy drinking, inducing antagonistic or synergistic effects.

Alcohol consumption and metabolic dysfunction are two main causes of chronic liver injury and can interact with each other. Early studies showed that MAC might be associated with improved dyslipidemia and reduced cardiovascular risk, indicating MAC may be related with restored metabolism. Several studies were conducted to investigate the role of light to moderate alcohol consumption (LMAC) in metabolic disorders. It has been demonstrated that alcohol and its metabolites have multiple effects on metabolic-associated factors, such as body weight, glucose and lipid metabolism, and the cardiovascular system. However, there is still no consensus on the effects of alcohol on metabolic-related diseases. At the same time, the above-mentioned metabolic abnormalities are the focus of MAFLD. This review systematically discusses the effects of alcohol consumption on obesity, lipid and glucose metabolism, and blood pressure, focusing on the effects of non-heavy alcohol consumption, to help better understand the relationship between alcohol consumption and MAFLD.

Alcohol consumption and overweight/obesity

Effects of alcohol consumption on body weight

There is a higher risk of overweight/obesity in chronic heavy

Keywords: Alcohol; Metabolic-associated fatty liver disease; Obesity; Insulin resistance; Hypertension.

Abbreviations: ADH, alcohol dehydrogenase; ALD, alcoholic-related liver disease; ALDH, aldehyde dehydrogenase; AMPK, 5′-AMP-activated protein kinase; BMI, body mass index; CI, confidence interval; CYP, cytochrome P450; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, hazard ratio; IL, interleukin; IR, insulin resistance; LMAC, light to moderate alcohol consumption; MAC, moderate alcohol consumption; MAFLD, metabolic-associated fatty liver disease; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; OR, odds ratio; SBP, systolic blood pressure; SREBP, sterol regulatory element-binding proteins; T2DM, type 2 diabetes mellitus; TG, triglyceride; TNF-alpha, tumor necrosis factor-α; WC, waist circumference.

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Table 1. Drinking patterns in this review

Drinking pattern		Definition
Chronic heavy drinking		Chronic alcohol consumption (generally more than 5 years) more than 60 g on one occasion[4]
Binge drinking		Alcohol consumption >40 g for women and >50 g for men within about 2 h[1]
Non-heavy drinking	MAC	Regular alcohol drinking <30-42 g/day for men and <20-28 g/day for women[4,5]
	Light alcohol consumption	Regular alcohol drinking <10-20 g/day for most studies

MAC, moderate alcohol consumption.

drinkers, mainly showing as higher body mass index (BMI) and increased waist circumference (WC).[7,8] A previous study showed a 17% higher risk for WC gain in men consuming 1,000 mL/day beer compared with those drinking less than 250 mL/day beer.[9] There seems to be a stronger connection between heavy drinking and increased body weight in men at different ages than in women.[8,10] In elderly men, greater BMI (+4.8%) and WC (+5%) were shown to be related to alcohol intake ≥50 g/day.[8] Energy from alcohol metabolism (7.1 kcal generated by 1 g ethanol) accounts for the increased total energy intake in heavy drinkers, partly contributing to increased body weight and BMI. Studies showed that alcohol intake of more than 3–5 drinks/day can dramatically increase the energy intake from alcohol.[7,8] More importantly, chronic heavy drinking has been proven to induce pancreatic β-cell dysfunction in human and animal models,[11,12] with decreased insulin-secretory ability and disrupted glucose homeostasis. Both increased energy intake and pancreatic β-cell dysfunction contribute to the pathogenesis of obesity in heavy drinkers. Heavy drinking-associated pancreatic β-cell dysfunction may play a more crucial role than increased energy intake in the development of MAFLD.

The effects of occasional binge drinking on body weight may be not obvious in the short term. However, frequent binge drinking could significantly increase the risk of becoming overweight and obese[13] and the risk of abdominal obesity in men.[14] On the one hand, frequent binge drinking has a similar effect as chronic heavy drinking as it involves increased energy intake. On the other hand, binge drinking could induce systemic insulin resistance (IR) by impairing hypothalamic insulin action, manifesting as suppressed hepatic glucose production and white adipose tissue lipolysis.[15] Besides, binge drinking is often accompanied by increased high-fat food intake and even binge eating,[16] indicating a much higher energy intake, thereby increasing the body weight. As a result, the increased energy intake and the glucose and lipid metabolism abnormalities induced by impaired insulin signaling eventually lead to increased body weight.

Clinical studies have shown that moderate drinking may help maintain normal weight and is associated with a lower prevalence of obesity than in non-drinkers,[17,18] showing as lower BMI values (by 1.34 kg/m^2),[19] a lower total abdominal fat volume, and less subcutaneous adipose tissue.[20] Among normal-weight middle-aged and older women, LMAC is associated with smaller weight gain and a lower risk of becoming overweight and/or obese compared to non-drinkers.[21] Similarly, LMAC does not increase the risk of increase in the BMI and WC in elderly men.[8] Moderate wine consumption (150 mL/day), as part of a Mediterranean diet, in persons with controlled diabetes does not promote weight gain or abdominal adiposity.[22] These results indicate a potentially beneficial effect of moderate drinking on maintaining a normal body weight in different populations, a different effect from that of heavy or binge drinking.

LMAC could regulate body weight through several mechanisms. Alcohol tends to increase appetite and food intake, probably through short-time reward effects of food and through the regulation of the expression of various neurotransmitters,[23,24] leading to increased total energy intake. However, the energy obtained from alcohol becomes part of the total daily energy intake in the long term; accordingly, the energy intake, excluding the calories from alcohol, decreases.[21] The reward effects of food gradually weaken and are even offset due to the reduction in total food intake or carbohydrate/fat intake.[23] Therefore, body weight probably does not increase significantly in chronic regular drinkers. Besides, MAC could decrease the body weight by improving IR, an opposite effect compared with heavy or binge drinking, showing as decreased body weight, decreased liver weight and triglyceride (TG) levels, and reduced glycemia and insulinemia in animal models.[25] Hence, LMAC drinkers tend to avoid significant body weight gain, in contrast to heavy drinkers.[26] Changes in body weight could be the result of an imbalance between (i) the regulation of the central nervous system and peripheral insulin function and (ii) energy use. However, the exact underlying mechanisms remain unclear, and more studies are required.

Combined effects of overweight/obesity and alcohol on liver

Heavy and binge drinking are often associated with high risk of fatty liver disease. Overweight/obesity can further promote the development of fatty liver disease.[27,28] Long-term obesity (longer than 10 years), especially abdominal obesity, is an important risk factor for alcoholic-related liver cirrhosis and alcoholic hepatitis[29,30] and is associated with an increased risk of 3-month mortality in alcoholic hepatitis (hazard ratio [HR]: 2.22, 95% confidence interval [CI]: 1.1–4.3).[31] A binge-like drinking pattern is independently associated with significant liver fibrosis progression in overweight/obese patients with MAFLD.[28] These results demonstrate that there are synergistic effects of high alcohol intake and of being overweight/obese on liver injury and an increased risk of fatty liver disease.

LMAC seems to play different roles in fatty liver disease. Studies showed that LMAC reduces the risk of fatty liver disease by 22.6% in general population,[32,33] and it reduces the risk of fatty liver disease by 31.3% in overweight and obese people.[33] Mild liver inflammation and fibrosis with a low risk of advanced liver fibrosis (stage F3/F4) were found in obese patients with MAC, compared with non-drinkers.[34–37] Our previous studies also showed that chronic MAC is related with alleviated liver fibrosis in a high-fat and high-cholesterol diet-induced liver fibrosis model, probably via reduced activation of Kupffer cells and hepatic stellate cells.[38] However, an increased risk of advanced liver cirrhosis in LMAC has been reported. A recent Asian population study showed that MAC reduced the risk of hepatic steatosis in overweight/obese individuals, while MAC increased the risk of advanced liver fibrosis (HR: 1.49, 95% CI: 1.33–1.66), as estimated by the fibrosis-4 index in overweight or obese individuals af-

ter a 15.7-year follow-up.[39] In another cross-sectional study among obese patients with T2DM, LMAC was found to be associated with an increased probability of advanced fibrosis in biopsy-proven MAFLD (odds ratio [OR]: 5.5–9.7, 95% CI: 1.05–69.6).[40] So far, the long-term impacts of LMAC on liver cirrhosis among obese people are still uncertain. More histological evidence is urgently needed to verify the role of LMAC in liver cirrhosis among obese people.

Adipose tissue can serve as another important source of proinflammatory factors that contribute to liver injury. Proteome analysis of serum inflammatory factors showed higher expression of chemokines (C-X-C motif and C-C motif ligands), interleukins (ILs), and tumor necrosis factor-alpha (TNF-α) in obese individuals than in non-obese controls; for example, CXCL 11 was markedly upregulated (by 40%) in obese patients and in adipose tissue in a murine model.[31] In adipose tissue, adipocytes can recruit immune cells (such as macrophages, neutrophils, and lymphocytes) and polarize them to their proinflammatory phenotypes to increase the production of proinflammatory cytokines, such as IL-1β, IL-6, IL-12, and TNF-α, and chemokines, promoting tissue inflammation. Macrophages of the proinflammatory M1 phenotype can induce adipocyte death, increasing the release of inflammatory mediators from adipocytes into the extracellular environment, which could recruit and polarize more macrophages.[41] In obese people, especially those with abdominal obesity, large amounts of subcutaneous adipose tissue and visceral fat could be important sources of inflammatory factors, which may enhance the effects of heavy drinking on the liver, leading to aggravated liver inflammation.

Cytochrome P450 (CYP) 2E1 is an important enzyme involved in many metabolic processes (including alcohol metabolism). CYP2E1 expression could be induced by alcohol, a high-fat or fructose diet, obesity, and drugs. Excessive CYP2E1 expression is associated with liver inflammation via intrahepatic and extrahepatic mechanisms. Elevated hepatic CYP2E1 mediates endoplasmic reticulum stress and oxidative stress in mitochondria, which contributes to the pathogenesis of ALD and MAFLD.[42] In the gut, CYP2E1-mediated oxidative and nitrative stress is related with gut leakiness and endotoxemia, contributing to liver lipid accumulation, increased proinflammatory cytokine production, and infiltration of macrophages in the liver.[43] In addition, CYP2E1-induced apoptosis under the coexistence of obesity and binge drinking is involved in liver injury.[44,45] Occasional or short-time binge drinking-induced liver injury could probably be restored by compensatory liver function. However, chronic frequent binge drinking or heavy drinking is not favorable for the recovery of the liver. Moreover, repeated inflammatory stimulation of the liver promotes the progression of liver fibrosis.[46] Meanwhile, binge eating and high fat intake during binge drinking lead to an increased fat accumulation in the adipose tissue, contributing to the secretion of proinflammatory factors.

Taken together, obesity- and alcohol-induced liver inflammation and fibrosis progression are probably related with interactions among the adipose tissue, the gut, and the liver. Heavy and binge drinking can result in the secretion of more inflammatory factors, contributing to the development of fatty liver disease. The relatively weak proinflammatory effects of LMAC, together with the potential role of LMAC in relieving IR, reduce the risk of fatty liver disease. However, in patients with long-term obesity or T2DM, the protective effects of LMAC may be overshadowed by the increased risk of liver fibrosis or cirrhosis.

Alcohol and lipid metabolism

Elevated plasma TG and decreased high-density lipoprotein (HDL)-cholesterol levels are two important indicators for the diagnosis of MAFLD. The liver is the main organ for both lipid and alcohol metabolism. Increased serum and hepatic TG concentrations are common in alcohol-drinking individuals and animals, including LMAC.[47–51] TG levels are significantly elevated in heavy drinkers compared with other drinkers and non-drinkers.[48] Similarly, binge drinking is associated with a significantly increased risk of elevated TG levels.[52] Binge drinking with a high-fat diet or chronic alcohol consumption can synergistically increase peripheral TG levels.[53,54] Mechanistic target of rapamycin (mTOR) signaling is considered to play fundamental roles in regulating lipid biosynthesis and metabolism in response to nutrition, showing as mTOR complex 1 (mTORC1) induced lipogenesis through its effect on sterol regulatory element-binding proteins (SREBP), inhibited breakdown of intracellular TG, and reduced fatty acid β-oxidation.[55] Recently, studies have demonstrated that mTORC1 is necessary for alcohol to activate hepatic lipogenesis through its effect on SREBP and to inhibit fatty acid β-oxidation, showing as enhanced mTORC1 activity in experimental animals and patients of ALD, characterized by an increase in mTOR-mediated phosphorylation and activity of S6K1, the downstream kinase of mTORC1. Importantly, the concomitant reduction of sirtuin 1 and DEPTOR, an inhibitor of mTOR kinase, signaling was linked to elevated lipogenesis and decreased fatty acid β-oxidation in human liver specimens with ALD. Inhibition of mTORC1 with rapamycin or DEPTOR overexpression ameliorated alcoholic steatosis and liver injury in animals,[56] indicating that inhibition of mTORC1 could be a therapeutic target in ALD in the future.

Elevated TG levels are related with alcohol and with enhanced expression levels of enzymes involved in lipid metabolism. During alcohol metabolism, ethanol is first metabolized to acetaldehyde by alcohol dehydrogenase (ADH) and then oxidized to acetic acid by aldehyde dehydrogenase (ALDH). In this process, the consumption of NAD^+ is increased and the generation of NADH is increased, resulting in a significant increase in the ratio of NADH:NAD^+. The increased ratio further promotes the synthesis of free fatty acids, inhibits fatty acid β-oxidation, and eventually leads to the accumulation of TG in hepatocytes.[57,58] Alcohol also upregulates the expression of fatty acid synthase[59] and SREBP-1c and downregulates acetyl-CoA carboxylase, the rate-limiting enzyme in fatty acid synthesis, and 5′-AMP-activated protein kinase (AMPK), the central regulator of fatty acid β-oxidation.[60,61] A net effect is enhanced fatty acid synthesis, further promoting the synthesis of TG. Long-term heavy alcohol consumption is also related to impaired adiponectin-sirtuin 1-AMPK signaling, a central signaling system controlling the lipid metabolism pathways,[62] thereby promoting hepatic steatosis. Therefore, higher amounts of alcohol intake seem more likely to show hepatic steatosis-promoting effects compared with lower amounts of alcohol intake. Besides, insulin is an important hormone involved in lipid metabolism. In the normal state, insulin helps maintain a dynamic balance of lipid metabolism by promoting the export of lipoproteins from the liver and inhibiting lipolysis in adipocytes to facilitate fat storage in adipose tissue.[63] Impaired insulin signaling and IR result in decreased serum insulin levels and dysfunction.[15,63] Consequently, the effects of insulin in the regulation of free fatty acids are attenuated, contributing to enhanced lipolysis in adipocytes and increased peripheral lipid levels.

HDL plays important roles in cholesterol efflux and reverse cholesterol transport. HDL-cholesterol dyslipidemia is considered to be a major independent risk factor for atherosclerotic cardiovascular disease.[64] Alcohol is positively related with HDL metabolism, as plasma HDL-cholesterol concentrations are increased in drinkers compared with non-drinkers.[65–67] Studies have shown elevated HDL-cholesterol

levels in MAC, together with increased apoprotein A-I levels (accounting for 70% of the total HDL protein mass), higher paraoxonase activity, and decreased cardiovascular risk due to its enhanced antioxidative properties.[68–72] The effects of heavy drinking on HDL seem inconsistent. Some studies observed increased HDL-cholesterol levels and enhanced cholesterol efflux potential in heavy drinkers,[66,73] while other studies showed declined HDL levels in patients with alcohol-related fibrosis and cirrhosis.[30,74] It is reasonable to assume that the onset of ALD may influence HDL metabolism. However, chronic heavy drinking with or without ALD was associated with a similar declined capacity of cholesterol efflux and reduced cholesterol uptake from peripheral blood in the hepatocytes,[74,75] suggesting that alcohol per se is responsible for its deleterious effects on cholesterol efflux and reverse cholesterol transport in heavy drinkers.

Serum HDL levels (quantity) reflect its antioxidant effect to some extent. More importantly, the capacity of cholesterol efflux and reverse cholesterol transport (quality) are two key factors in evaluating its antioxidant capacity. Intact hepatocyte structure and function are necessary for HDL metabolism. During the development of alcohol-related fibrosis and cirrhosis, hepatocytes are gradually depleted, and they become incompetent for lipid metabolism. HDL-cholesterol and total cholesterol levels in peripheral blood are probably not decreased or even increased in the early stage of ALD, partly due to a decline in HDL-mediated reverse cholesterol transport. However, lipid metabolism in the liver gradually weakens with the progression of ALD. Eventually, HDL and total cholesterol levels decrease,[76] with declined capacity of cholesterol efflux and reverse cholesterol transport. On the contrary, in LMAC, the liver function is often competent in lipid metabolism; so, higher HDL-cholesterol levels are probably the result of increased synthesis and reverse cholesterol transport, with increased antioxidative properties and capacity of cholesterol efflux, which may prevent lipid deposition in the vessel wall,[77] decreasing the risk of cardiovascular disease. However, more studies are needed to confirm these hypotheses.

Alcohol and T2DM

The quantity and function of insulin are crucial in maintaining the glycemic balance. Alcohol could cause pancreatic β-cell apoptosis[78] and dysfunction, decreasing insulin secretion, resulting in decreased circulating insulin levels.[79,80] With the increase of alcohol amount, the damage of β-cells is gradually aggravated. Heavy alcohol intake could reduce the insulin-secretory ability of pancreatic islets,[12] decrease glucokinase expression, and inhibit insulin receptor expression,[11] promoting the development of T2DM. On the contrary, LMAC seems to be related with lower fasting insulin levels, a similar effect to that observed in healthy people, who are often considered to be associated with higher insulin sensitivity,[81] showing as reduced fasting insulin concentrations by 19.2% and increased insulin sensitivity by 7.2% compared with non-drinkers.[82] The reasons for low insulin levels related with MAC may be different in men and women, demonstrating as higher clearance of insulin in men and lower secretion of basal insulin in women.[83] Presumably, heavy drinking may impair pancreatic β-cell function and disrupt insulin signaling pathways, contributing to the development of diabetes, while lower insulin levels in non-heavy drinkers seem helpful to maintain glycemic homeostasis. Binge drinking has been proven to be an independent risk factor for IR in MAFLD.[84] In terms of mechanism, binge drinking impairs hypothalamic insulin signaling and decreases insulin secretion, playing a central role in increasing the risk of IR and T2DM. In addition, peripheral insulin dysfunction might be involved in IR. More studies are needed to further verify these hypotheses.

Though some studies showed a positive relation between alcohol consumption and the risk of IR and T2DM,[85–87] most studies suggest reduced risks of T2DM in individuals with LMAC. According to a recent umbrella review, high-quality evidence shows that MAC (12–24 g/day) is negatively correlated with the incidence of diabetes.[88] Prospective and cross-sectional studies show a lower presence of IR and impaired glucose tolerance in obese individuals with MAC than in obese non-drinkers.[20,89] Another cross-sectional study showed that LMAC did not decrease the risk of T2DM in obese individuals,[90] indicating that the role of MAC in the regulation of glucose and lipid metabolism in obese people is controversial. Compared with women, men are more likely to benefit from LMAC.[91,92] Men with cardiovascular disease risk factors can benefit from long-term red wine consumption (40 g/day) in several aspects, including decreased plasma insulin levels, improved glucose homeostasis, and increased HDL-cholesterol levels.[69] Hence, LMAC seems to improve IR in individuals with a high risk of T2DM, especially in men. Interestingly, a reduced risk of T2DM in LMAC is often observed among regular drinkers. A study in Japan showed ~4 drinks per drinking day for 4–7 days weekly in men resulted in a lower risk of T2DM compared with non-drinkers.[93] In a large cohort study from Denmark, the lowest risk of T2DM was observed at 14 drinks/week in men and at 9 drinks/week in women. Compared with current alcohol consumers consuming <1 day per week, the consumption of alcohol for 3–4 days per week was associated with a significantly lower risk for diabetes in men.[94]

Alcohol may commonly impair pancreatic β-cell function. However, the risks of IR and T2DM are low in LMAC populations, as shown in several clinical studies, which is probably in part related with lifestyle. In a prospective cohort study with a 10-year follow-up in the Netherlands, individuals with LMAC (5.0–29.9 g/day for men and 5.0–14.9 g/day for women) exhibited a significantly lower risk of T2DM on the basis of one low-risk lifestyle behavior, and an approximately 40% reduced risk of T2DM on the basis of multiple low-risk lifestyle behaviors compared with non-drinkers.[95] Another randomized clinical trial showed that MAC with lifestyle modification reduced the incidence rate of diabetes in individuals at high risk of diabetes (including impaired glucose tolerance, elevated fasting glucose, or BMI ≥24 kg/m^2) after a 3-year follow-up.[80] As is well known, metabolic dysfunction is often related to unhealthy lifestyles, e.g., high-fat diet, lack of exercise, and smoking. In the above studies, a healthy lifestyle often includes an ideal body weight, a healthy diet, moderate exercise, no smoking, and reduced total energy intake, which are helpful in restoring normal metabolism. Additionally, MAC is considered as a healthy behavior. Thus, benefits from LMAC further improve metabolism on the basis of these healthy lifestyles.

The beneficial effects of MAC on insulin sensitivity are not fully understood. The expression of some molecules may change during MAC and further influence glucose and lipid metabolism. Adiponectin, an insulin-sensitizing adipokine, has been confirmed to play important roles in maintaining insulin sensitivity and suppressing fatty acid synthesis.[96] Hypoadiponectinemia is closely associated with IR in obesity and diabetes.[97,98] Diet-intervention studies in small groups of young and middle-aged men with or without IR have shown increased adiponectin concentrations after MAC intervention.[99,100] A large population study confirmed that adiponectin levels were higher in men with frequent MAC.[100] Alcohol-induced increases in adiponectin improve insulin sensitivity and glucose metabolism and decrease the risk of IR. Therefore, an improved IR and a decreased risk of T2DM in MAC may be the result of multiple factors, including proper drinking frequencies, low-risk lifestyle, and the

expression of molecules improving glucose metabolism.

Alcohol and blood pressure

Early studies have confirmed that chronic alcohol consumption affects blood pressure,[101] manifesting as increased blood pressure in drinkers.[102–105] The increased risk of elevated blood pressure is associated with the amount of alcohol consumed. However, the "threshold" amount is not quite clear. According to recent studies, the potential "threshold" could not be high, as individuals with alcohol consumption more than 100 g/week show elevated systolic blood pressure (SBP).[66] Chronic LMAC has a greater effect on awake blood pressure, increasing SBP and diastolic blood pressure (DBP) by about 2.5–3.0 mmHg and 2.0 mmHg, respectively, and a weaker effect on blood pressure during sleep, decreasing DBP by 2.0 mmHg.[106,107] Though a study showed a higher risk of hypertension in MAC individuals than in light drinkers,[67] the effect of chronic LMAC on hypertension, which has been investigated in human and animal models, is not that obvious.[66,108,109] A population-based prospective study even showed a significantly lower incidence of hypertension in participants with LMAC after a 20-year follow-up compared with non-drinkers.[110] Age is a well-known risk factor for blood pressure. Elderly people are often at higher risks of hypertension than young people. There is a similar effect of age on drinkers' blood pressure.[111] In young drinkers, elevated HDL-cholesterol levels (≥47 mg/dL) could be a protective factor for MAC, preventing significant increases in blood pressure.[102] In two studies, the incidence of hypertension was higher in individuals who consumed large amounts of alcohol (20–30 g/day or more).[102,103] In middle-aged men, an increased risk of hypertension, even in light drinkers (12 g/day), was observed, irrespective of the levels of HDL-cholesterol.[103] With the increase of age, alcohol consumption ≥140 g/week is associated with significantly increased SBP (5–12 mmHg) and DBP (3–6 mmHg) and an increased risk of hypertension (OR: 1.83, 95% CI: 1.40–2.40) in older men.[108] Therefore, age showed a similar negative relation with blood pressure in drinkers as in other populations. With increasing age, the protective effects of HDL-cholesterol and LMAC on blood pressure are gradually overshadowed by the increased risk of hypertension.

Both chronic heavy drinking and binge drinking (occasional or frequent) are related with an increased risk of hypertension in a dose-dependent manner, especially in men.[52,67,112] Blood pressure is temporarily reduced after binge drinking within approximately 2–3 h, but it could dramatically increase after 24 h.[113,114] An Asian cohort study showed that daily alcohol consumption exceeding 60 g/day significantly increased the risk of hypertension in men.[102] However, a recent population-based study on conventional epidemiology and genetic epidemiology showed that lower amounts of alcohol intake were related with increased blood pressure; SBP was increased by 4.8 mmHg (to a level of about 135 mmHg, 95% CI: 4.5–5.1) and DBP by 4.3 mmHg (95% CI: 3.7–4.9) in men with 280 g/week alcohol intake. In women with similar alcohol intake, SBP and DBP increased by 6.7 mmHg (95% CI: 4.3–9.0) and 3.8 mmHg (95% CI: 2.5–5.1), respectively.[66] Obviously, excessive alcohol intake is related with increased blood pressure, especially in male drinkers. Fortunately, the effects of alcohol consumption are reversible. A reduction in alcohol consumption could help to reduce blood pressure, especially in heavy drinkers. Individuals who drink six or more drinks per day could obtain a reduction in SBP by 5.5 mmHg and in DBP by approximately 4 mmHg if they reduce alcohol consumption by about 50%. Reductions in SBP and DBP are also achievable in other drinkers by reducing alcohol consumption, but to a lower degree.[115] Though effects on blood pressure have been observed for both LMAC and heavy drinking, heavy drinking results in much stronger increases, often reaching blood pressures above 140/90 mmHg, with a significantly higher risk of hypertension compared with other drinkers.

Evidence of the effects of alcohol consumption on blood pressure is not as strong in women as in men. According to a recent systematic review and meta-analysis, female drinkers only account for 14% in clinical trials,[115] indicating significant differences in gender distribution. Studies have indicated different effects of alcohol intake on blood pressure in female drinkers compared with male drinkers. Multivariate Cox proportional hazards analysis showed alcohol consumption was not necessarily associated with the risk of hypertension in women.[104] Though MAC could elevate SBP and DBP in premenopausal women, the increase in SBP was not more than 2 mmHg and that in DBP was not more than 1.4 mmHg.[116] Roerecke's systematic review and meta-analysis have shown different incidences of hypertension in men and in women who drank 1–2 drinks/day (relative $risk_{women\ vs.\ men}$=0.79; 95% CI: 0.67–0.93),[117] indicating that women with LMAC were less likely to suffer from hypertension. The increased risk of hypertension was more obvious in women who exceeded two drinks per day.[117] In older women, alcohol amounts below 140 g/week resulted in reductions in SBP of 3–5 mmHg and a reduced risk of hypertension (OR: 0.62, 95% CI: 0.53–0.72) compared with non-drinkers.[108] These results suggest that chronic, regular LMAC in women tends to exert protective effects on blood pressure compared with men. However, data on alcohol consumption in female drinkers are not sufficient, especially in heavy drinkers. More research is needed to explore the relationship between alcohol intake and blood pressure in women.

The main mechanisms underlying the effects of alcohol on blood pressure include a direct effect of alcohol, alcohol metabolic-associated enzymes, and alcohol sensitivity. ADH1B and ALDH2 are two important enzymes in alcohol metabolism. Genetic polymorphisms of ADH1B (rs1229984) and ALDH2 (rs671) are related with the elimination rate of alcohol, alcohol sensitivity, and drinking behavior. The ADH1B*2 allele carrier, with enhanced enzyme activity, is related with more rapid alcohol elimination[118,119] and, possibly, a reduced risk of hypertension and cardiovascular diseases.[119,120] ALDH2 polymorphisms are considered to be associated with alcohol sensitivity and drinking behavior. Enzyme activity is weakened or lost in ALDH2*1/*2 (G/A) and ALDH2*2/*2 (A/A) allele carriers, slowing the process of alcohol metabolism, with higher alcohol sensitivity compared with the wild-type ALDH2*1 (G/G) carriers. In women, LMAC without alcohol sensitivity further decreases SBP by 2 mmHg and is associated with a lower risk of hypertension (OR: 0.62, 95% CI: 0.53–0.72) compared with LMAC with alcohol sensitivity (OR: 0.71, 95% CI: 0.60–0.83). Similarly, in men with alcohol consumption of 140 g/week or more, SBP and DBP were much higher in those with alcohol sensitivity (145 mmHg and 82 mmHg, respectively) than in those without alcohol sensitivity (138 mmHg and 79 mmHg, respectively) and non-drinkers (133 mmHg and 76 mmHg, respectively).[108] The increased risk of hypertension in individuals with ALDH2 polymorphisms may be related with the rate of alcohol metabolism in part because slow elimination of alcohol enhances the effect of alcohol on blood pressure and partly reduces the blood pressure benefits of LMAC.

Limitations and expectations

Many studies show the beneficial effects of LMAC on metabolic functions. However, a recent combined analysis

showed a linear relationship between alcohol consumption and all-cause mortality, with an increase in all-cause mortality among those who consumed more than 100 g/week.[121] This dose is much lower than most guidelines' recommendations and also lower than what is considered a "moderate" amount in most studies. Therefore, drinking in patients should be cautiously guided, especially in those with metabolic dysfunctions. For obese patients with MAFLD and decompensated liver cirrhosis, any amount of alcohol consumption is related with an increased risk of hepatocellular carcinoma.[122,123] Alcohol drinking should be absolutely avoided in these patients.

Alcohol consumption is common in the MAFLD population and is related with metabolic dysfunction (Table 2). Interactions between alcohol and metabolic factors are complicated, and the benefits from non-heavy drinking may be reduced by other factors. A U-shaped or J-shaped relationship between alcohol consumption and the single component of metabolic dysfunction is common in many studies. In fact, there are probably more net-shaped relations among these factors than linear relations in real-world patients. As is well known, liver cirrhosis is an important stage during the development of chronic liver disease, and it is usually irreversible. Unfortunately, most studies on alcohol and MAFLD are focused on early-stage liver disease, and only a few studies focus on MAFLD with liver fibrosis or cirrhosis. Thus, the exact impacts of alcohol consumption (especially non-heavy drinking) on MAFLD and metabolic-associated impairments of target organs, complications, and even tumors are not quite clear. More research studies are needed to explore the long-term effects of alcohol consumption on end-stage MAFLD and metabolic syndrome, to fully understand the effects of alcohol consumption and guide patients who consume alcohol.

Special attention should be paid to several populations. First is ex-drinkers and abstainers. The benefits from LMAC are often shown in current drinkers, usually accounting for the majority of participants in most studies. On the contrary, data on ex-drinkers and abstainers are not enough to analyze the impact of stopping alcohol consumption on metabolic factors well. Studies have shown changes of several metabolic factors after a period of abstinence, e.g., decreased HDL levels and visceral fat area and improved homeostasis, among moderate to heavy drinkers.[124,125] Thus, it is necessary to evaluate the effects of abstinence on metabolism and re-evaluate the effects of LMAC on metabolism after abstinence. Second is female drinkers. There are more male drinkers than female drinkers in the real world and in most clinical trials. Usually, the non-drinkers are mainly female, while the drinkers are mainly male in most studies. With increasing amounts of alcohol consumption, the proportion of males increases dramatically, and the heavy drinkers are almost all men, especially in large, population-based studies.[66,126,127] Thus, there is an almost inevitable sex bias because of the smaller female samples. As shown by some studies, the effects of alcohol are significantly different between male and female drinkers. There seems to be a much closer relationship between alcohol and male sex, including genetic epidemiological characteristics.[128] Therefore, more studies are needed to evaluate the role of alcohol consumption on metabolism in female drinkers. Third is patients with borderline high blood pressure. A criterion of SBP ≥140 mmHg and/or DBP ≥90 mmHg or special drug treatment is considered for the diagnosis of hypertension in many studies. According to the new definition of MAFLD, a blood pressure of ≥135/85 mmHg is considered a metabolic risk abnormality,[1] a more rigorous standard than the former. Therefore, the decreased risk of hypertension upon LMAC could possibly be overestimated in some individuals with other metabolic risk abnormalities. Individuals with blood pressure between 135/85 mmHg and

Table 2. Main clinical studies on alcohol and metabolic dysfunctions included in this review

		Author and year[REF]	Study type	Follow-up	Alcohol beverage	Amount	Population	Main indicators	Ralation type	Main results
Alcohol, obesity, and liver injury	1	Schütze M, 2009[9]	Prospective study	8.5 years	Beer	1,000 mL/day	7,876 men, 12,749 women	WC	U-shaped	Men consuming 1,000 mL/day beer were at 17% higher risk for WC gain compared with very light consumers.
	2	Inan-Eroglu E, 2020[19]	Cross-sectional study	–	Red wine; champagne and white wine; beer and cider; spirits; fortified wine	<14 units/week for women and <21 units/week for men	UK Biobank baseline data, n = 280,183, 48.3% female	BMI	–	Those drinking within the public health guidelines had a lower BMI by 1.34 kg/m^2 (95% CI 1.42–1.26 kg/m^2) compared to never drinkers.
	3	Wang L, 2010[21]	Prospective cohort study	12.9 years	Not mentioned	0 ~ ≥30 g/d	19,220 US women aged 39 years and above with baseline BMI of 18.5–25 kg/m^2	1. Overweight or obese (BMI ≥25 kg/m^2). 2. Obese (BMI ≥30 kg/m^2)	Almost linearly inverse relation	LMAC was associated with smaller weight gain and lower risk of becoming overweight and/or obese.

(continued)

Table 2. *(continued)*

		Author and year[REF]	Study type	Follow-up	Alcohol beverage	Amount	Population	Main indicators	Ralation type	Main results
	4	Golan R, 2017[22]	Randomized controlled study	2 years	Wine	150 mL/day	n = 48, alcohol-abstaining adults with well-controlled T2DM	Bodyweight and abdominal adiposity	–	Moderate wine consumption did not promote weight gain or abdominal adiposity.
	5	Naveau S, 1997[29]	Retrospective study	–	–	≥50 g/day	n = 1,604, patients with ALD. Biopsy-proven liver cirrhosis in most cases.	Liver histology	Synergistic effect	The presence of excess weight for at least 10 years was a risk factor for cirrhosis, acute alcoholic hepatitis, and steatosis.
	6	Kwon HK, 2014[34]	Cross-sectional study	–	–	≤40 g/week	n = 77, obese patients with liver biopsy-proven NAFLD	Liver histology, especially liver cirrhosis	Negative relation	Alcohol consumption of ≥24 gram-years was associated with less severe disease (fibrosis stage 3–4).
	7	Blomdahl J, 2021[40]	Cross-sectional study	–	–	<140 g/week	n = 86, obese patients with biopsy-proven NAFLD	Advanced liver cirrhosis	–	MAC was associated with advanced fibrosis. Patients with T2DM had the highest risk.
Alohol and lipid metabolism	8	Hiramine Y, 2011[48]	Cross-sectional study	–	Not mentioned	0 ~ ≥60 g/day	n = 9,886, men aged 30–69 years	Serum TG	U-shaped	Serum TG was lower in former drinkers than non-drinkers and other drinkers. Serum TG was highest in heavy drinkers than other drinkers.
	9	Sierksma A, 2002[72]	Randomized, controlled, cross-over study	–	Beer	40 g/day for men, 30 g/day for women	10 middle-aged men and 9 postmenopausal women	Apo A-I, HDL-cholesterol, and paraoxonase activity	–	Serum apo A-I, HDL-cholesterol, and paraoxonase activity were significantly increased during 3 weeks of MAC compared with no alcohol consumption.
Alcohol and diabetes	10	Crandall JP, 2009[80]	Randomized controlled study	3.2 years	Beer, wine, and hard liquor	<36 g/day, without heavy or binge drinking	n = 3,175, individuals at high risk of diabetes	Insulin secretion and risk of diabetes	Inverse association	Daily MAC was associated with lower insulin secretion and reduced risk of incident diabetes.

(continued)

Table 2. *(continued)*

		Author and year[REF]	Study type	Follow-up	Alcohol beverage	Amount	Population	Main indicators	Ralation type	Main results
	11	Davies MJ, 2002[82]	Randomized, controlled, cross-over study	8 weeks	Everclear in orange juice	0, 15, or 30 g/day	n = 51, healthy postmenopausal women	Insulin level and sensitivity, TG	Inverse association	Consumption of 30 g/day of alcohol reduced fasting insulin by 19.2% and TG by 10.3%, and increased insulin sensitivity by 7.2% compared with 0 g/day.
	12	Joosten MM, 2010[95]	Prospective study	10.3 years	Beer, wine, and spirits	0 ~ ≥30 g/day	n = 35,625, Dutch adults at low risk of diabetes	Risk of diabetes	Inverse association	On the basis of multiple low-risk lifestyle behaviors, LMAC (5.0–14.9 g/day for women; 5.0–29.9 g/day for men) was associated with ≈40% lower risk compared with abstinence.
Alcohol and hypertension	13	Rodrigues P, 2018[110]	Prospective study	Over 20 years	Beer, wine, and spirits	0 ~ ≥14 drinks/week (1 drink = 14 g of pure ethanol)	n = 2,368, individuals between 18 and 30 years of age	Incidence of hypertension	–	Incidence of hypertension was much lower in LMAC (<14 drink/wk) individuals.
	14	Mori TA, 2015[116]	Randomized controlled, cross-over study	4 weeks for each period	Red wine	146 or 218 g/week	n = 24, women aged 25 to 49 years	24-hour ambulatory blood pressure	Positive relation	High volume alcohol consumption was related with increased SBP (1.6–2 mmHg) and DBP (1.2–1.4 mmHg).
	15	Millwood IY, 2019[66]	Prospective study	About 10 years	Beer, wine, and spirits	0 ~ >420 g/week	n = 512,715 Chinese adults	Risk of hypertension		In individuals with per 280 g/week alcohol intake, SBP and DBP increased by 4.8 mmHg and 4.3 mmHg in men and by 6.7 mmHg and 3.8 mmHg in women, respectively.

BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LMAC, light-to-moderate alcohol consumption; MAC, moderate alcohol consumption; NAFLD, non-alcoholic fatty liver disease; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference.

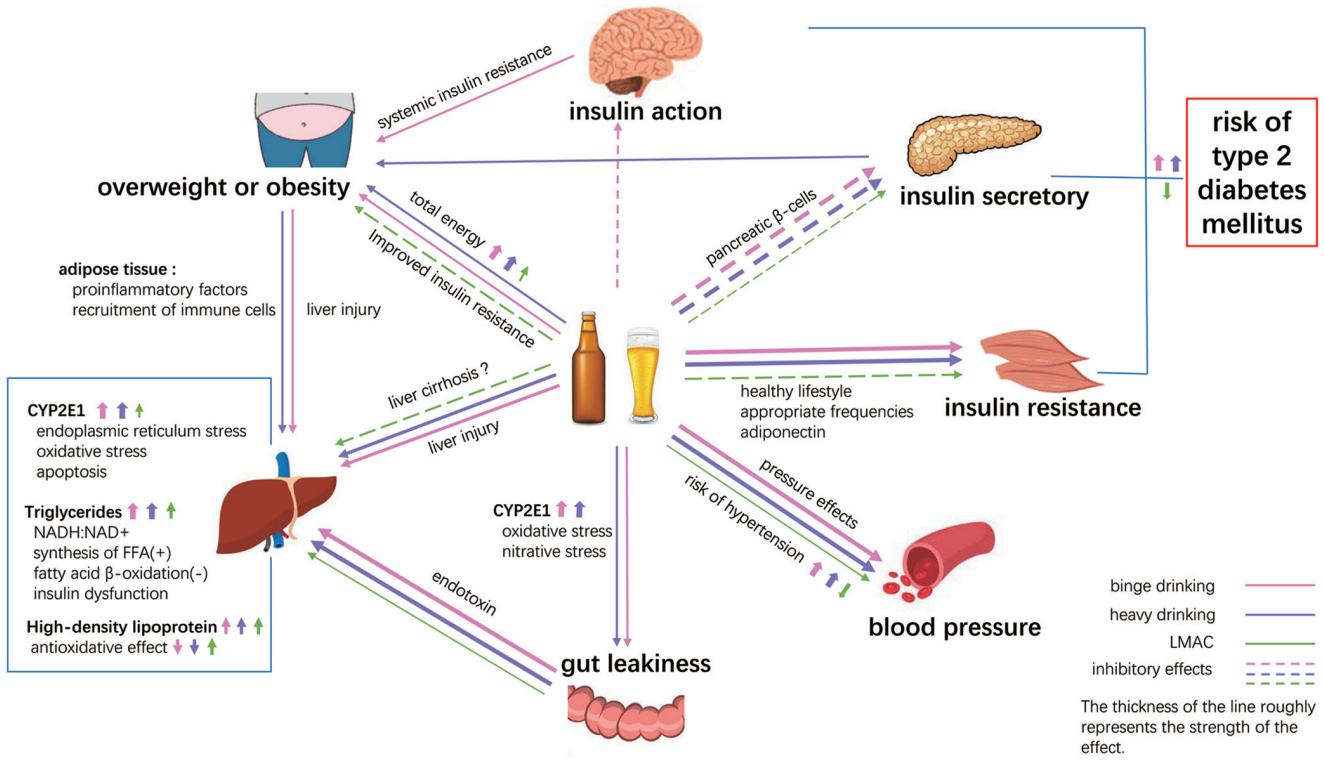

Fig. 1. Relationship between alcohol consumption and metabolic dysfunctions. *Obesity:* heavy drinking and binge drinking are associated with increased body weight and WC due to the obviously increased total energy intake and impaired peripheral or central insulin signaling pathways. LMAC is likely to maintain normal body weight mainly through improved IR. *Liver injury:* heavy or binge drinking in obese individuals exerts synergistic effects on liver injury. Liver-adipose tissue axis and liver-gut axis are two important mechanisms. The long-term effects of LMAC on liver cirrhosis are not quite clear. *Lipid metabolism:* alcohol is related with increased TG and HDL levels. However, the antioxidant effects of HDL are different, showing as enhanced antioxidative properties in LMAC and impaired antioxidative properties in heavy or binge drinkers with poor liver function. *T2DM:* heavy drinking and binge drinking are associated with increased risks of T2DM, mainly through impaired insulin signaling, decreased insulin secretory, and IR. Appropriate frequencies of LMAC, especially in combination with a healthy lifestyle, are related with improved IR and a decreased risk of T2DM, partly through regulating the expression of adiponectin. *Hypertension:* the effects of alcohol consumption on blood pressure are common. Heavy drinking and binge drinking are usually associated with significantly increased blood pressure and the risk of hypertension, while the risk of hypertension is lower in LMAC. ALD, alcoholic-related liver disease; CYP, Cytochrome P450; HDL, high-density lipoprotein; IR, insulin resistance; LMAC, light to moderate alcohol consumption; MAFLD, metabolic-associated fatty liver disease; T2DM, type 2 diabetes mellitus; TG, triglyceride; WC, waist circumference.

140/90 mmHg have shown an increased risk of metabolic dysfunctions.

In conclusion, alcohol drinking is closely related with metabolic dysfunction in several systems, such as the liver-gut axis, the liver-brain axis, the liver-pancreas axis, and the liver-adipose tissue axis (Fig. 1). LMAC combined with a healthy lifestyle may be helpful for maintaining metabolic homeostasis, while heavy drinking and binge drinking are two common dangerous drinking patterns that should be avoided. The new definition of MAFLD is a positive diagnosis of the disease with simple criteria. Though "alcohol" is excluded from the diagnosis, the relationship between MAFLD and alcohol is still close. Much attention should be paid to alcohol consumption during the management of MAFLD.

Funding

None to declare.

Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Writing the manuscript (FRS), and developing the idea for the article and critically revising it (BYW). All authors have read and approved the final version of the manuscript.

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