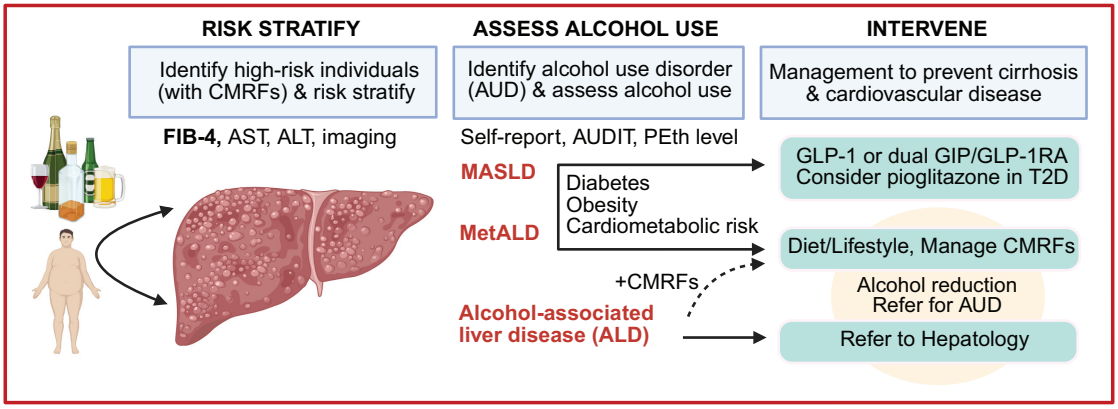
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Integrating Alcohol Use Into MASLD Care: A Practical Guide for Diabetes and Obesity Care Teams

Anastasia-Stefania Alexopoulos and Kenneth Cusi

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- The detrimental and synergistic effect of alcohol and CMRFs on liver and overall health is recognized in the new MASLD nomenclature, with the new diagnostic entity: MetALD
- MetALD is defined according to the presence of ≥1 CRMF and "moderate" alcohol use, i.e., >20-30 g alcohol daily
- Diabetes and obesity care teams have the tools available to risk stratify liver disease, identify alcohol use disorders, and implement behavioral and pharmacological interventions to prevent cirrhosis and cardiovascular disease in MASLD/MetALD

AUDIT, Alcohol Use Disorders Identification Test; CMRFs, cardiometabolic risk factors; FIB-4, Fibrosis-4 index; GLP-1, glucagon-like peptide 1; MASLD, metabolic dysfunction–associated steatotic liver disease; MetALD, metabolic dysfunction– and alcohol-associated liver disease; PEth, phosphatidylethanol; RA, receptor agonist; T2D, type 2 diabetes.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Alcohol acts synergistically with metabolic disease to worsen liver and cardiometabolic health; recent changes in nomenclature now require clinicians to explicitly address alcohol as a cofactor in disease progression.
- **What is the specific question(s) we wanted to answer?**
  How does alcohol affect metabolic dysfunction–associated steatotic liver disease (MASLD), and how should the matter of alcohol use be integrated into liver and cardiometabolic care?
- **What did we find?**
  Even light-to-moderate alcohol use may accelerate MASLD progression. Alcohol evaluation should be integrated into routine metabolic care.
- **What are the implications of our findings?**
  There is a need for diabetes and obesity care teams to routinely assess and address alcohol as part of MASLD management, with integration into existing care pathways and recognition of alcohol use as a potentially modifiable target to improve outcomes.

Integrating Alcohol Use Into MASLD Care: A Practical Guide for Diabetes and Obesity Care Teams

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Metabolic dysfunction–associated steatotic liver disease (MASLD) affects the majority of individuals with diabetes and severe obesity, and is one of the most common indications for liver transplantation in the U.S. Emerging evidence underscores the synergistic and detrimental impact of alcohol and metabolic disease on liver and overall health. In 2023, the nomenclature for steatotic liver disease was revised to include a new subcategory known as MetALD (metabolic dysfunction– and alcohol-associated liver disease), which acknowledges alcohol use as a cofactor in liver injury alongside metabolic risk factors. This review offers key insights into the role of alcohol use as both a direct hepatotoxin and an indirect contributor to insulin resistance, dyslipidemia, and obesity. Notably, even light-to-moderate alcohol intake may hasten MASLD progression to cirrhosis and hepatocellular carcinoma, especially in individuals with existing metabolic disease, and can worsen cardiovascular disease risk. MetALD is associated with increased all-cause, cancer-related, and liver-related mortality in comparison with MASLD, reinforcing the importance of accurate alcohol assessment in managing diabetes and obesity. Diagnosis now requires stratifying alcohol use and integrating tools such as the Alcohol Use Disorders Identification Test (AUDIT) questionnaire and phosphatidylethanol testing. The caveats and use of these tools in clinical practice are discussed. Management strategies for MASLD focus on lifestyle changes, weight loss, and medications such as glucagon-like peptide 1 receptor agonists, with emerging evidence suggesting that these agents may also reduce alcohol consumption. However, treatment data on MetALD are limited. This review offers practical guidance for health care professionals on how to integrate alcohol use into existing, recommended MASLD care pathways.

Metabolic dysfunction–associated steatotic liver disease (MASLD) affects up to 70% of people with type 2 diabetes and up to 90% of people with severe obesity and is one of the leading indications for liver transplantation in the U.S. (1). While insulin resistance and obesity play an important role in the pathophysiology of MASLD, there has been increasing appreciation of the overlap between metabolic drivers of liver disease and other common daily risk factors, especially alcohol consumption. Up until recently, U.S.-based recommendations advised that women limit their alcohol intake to no more than one drink per day and men to no more than two drinks per day. Notably, these alcohol limits had been similar since the 1980s (2), despite substantial changes in the metabolic health of the U.S. population over the past few decades; i.e., 38%, 11.6%, and 35% of Americans now have prediabetes, diabetes,

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and obesity, respectively (3,4). The U.S. Department of Health and Human Services and the U.S. Department of Agriculture recently issued the 2025–2030 Dietary Guidelines for Americans (5), which no longer specify recommended limits for alcohol consumption. This revision has faced strong opposition from several professional organizations, including the American Association for the Study of Liver Diseases (6). In the face of an obesity and diabetes epidemic—where advanced liver fibrosis is likely to be highly prevalent—improved awareness and understanding of the role of alcohol in MASLD are urgently needed. This includes a reevaluation of what we deem to be "safe" alcohol consumption in diabetes and obesity.

A recent nomenclature change in 2023 (7), from nonalcoholic fatty liver disease (NAFLD) to MASLD, has contributed to an improved understanding of alcohol's role as a co-contributor to MASLD-induced advanced liver disease. Prior to this change, individuals reporting moderate alcohol consumption with cardiometabolic risk factors (e.g., diabetes, obesity) lacked a distinct diagnosis, and despite being a highly prevalent group, were largely overlooked by diabetes and obesity care teams. Based on these new criteria (7), such patients would now be diagnosed with metabolic dysfunction– and alcohol-associated liver disease (MetALD), which reflects the combined influence of metabolic disease and alcohol on liver health. In this review we provide an overview of how alcohol impacts liver health and metabolic disease (i.e., diabetes, obesity), and the clinical implications of considering alcohol use alongside MASLD as we diagnose and treat metabolic liver disease in practice.

ALCOHOL CONSUMPTION AND METABOLIC HEALTH: THE DANGERS OF MODERATE ALCOHOL INTAKE IN PEOPLE WITH OBESITY AND DIABETES

Alcohol and Cardiometabolic Risk Factors

Alcohol can worsen risk factors for metabolic disease and confound diagnosis of MASLD. First, alcohol is a calorically dense source of energy that—when consumed in excess—can lead to obesity. Increasing alcohol consumption is also positively associated with the risk of new-onset hypertension (8) and has been linked to higher plasma triglyceride levels and insulin resistance (9–11). Notably, even low or moderate alcohol intake can worsen glycemic control in patients with diabetes (12,13). For instance, a Mendelian randomization study by Lu et al. (11) found that, among individuals who consume >14 drinks per week, every 1-drink-per-week increase in alcohol use was associated with 1.10-fold higher odds of type 2 diabetes (95% CI 1.06, 1.13) and 1.08-fold higher odds of obesity (95% CI 1.01, 1.10). In a separate Mendelian randomization study (14), a 1-drink-per-day increase was associated with significantly higher odds of hypertension (odds ratio 1.30 [95% CI 1.1, 1.5]) and coronary artery disease (1.70 [95% CI 1.2, 2.4]) in individuals who reported "light" drinking, defined as <8.4 drinks per week. Population-based studies likewise implicate alcohol as a risk factor for metabolic disease. For instance, in a U.S. population-based study (National Health and Nutrition Examination Survey [NHANES] III) (15), individuals who reported moderate or heavy alcohol consumption (vs. light or no alcohol consumption) were more likely to have metabolic syndrome. In a population-based study in Japan, an association was similarly noted between alcohol consumption of >140 g/week (moderate intake) and incidence of MASLD in community-dwelling women (16). Beyond cardiometabolic disease, there appears to be a dose-dependent association between alcohol use and cancer risk; the relative risk of developing a new cancer ranges from approximately 0.9 to 1.3 with light alcohol consumption, rising substantially up to 1.5–5.0 with moderate-to-heavy drinking (17).

Figure 1 shows how alcohol leads to progressive liver disease both indirectly via effects on lifestyle and metabolic disease and through its direct effects on the liver. In considering the effects of alcohol on metabolic risk in clinical practice, it is important to note that changes due to alcohol may persist beyond abstinence (9), and the duration of abstinence required to reverse alcohol-related effects—particularly in the context of metabolic disease—is largely unknown. Thus, a thorough alcohol history remains relevant, even if patients report no current alcohol use.

Liver Metabolic Effects of Alcohol in Diabetes and Obesity

Data suggest that even light-to-moderate alcohol consumption is associated with increased risk of MASLD, advanced fibrosis, and hepatocellular carcinoma (HCC) (18–22). Most studies have been cross-sectional in design (23) and, thus, very limited in terms of the ability to comment on the pattern of alcohol drinking, cumulative exposure, and temporal relationship between alcohol and MASLD. Additionally, investigators of multiple studies have reported on the risk of MASLD but do not comment on the risk of advanced liver fibrosis (24,25), which is a more clinically relevant endpoint, as fibrosis (vs. steatosis alone) predicts liver-related and all-cause mortality (26,27). In longitudinal population-based cohorts that examine the impact of alcohol on liver events (i.e., fibrosis progression, nonfatal/fatal liver events, HCC), even light alcohol consumption has been associated with worse liver outcomes in the presence of MASLD (28). In a Finnish cohort, a dose-dependent increase in mortality was observed for alcohol use, beginning with as little as one alcoholic beverage per week (29).

Quantity of alcohol intake and how this relates to development of liver disease can vary considerably among individuals, and liver-related outcomes are strongly influenced by the presence and number of cardiometabolic risk factors (30). In most people, consuming >60 g/day alcohol for >2 weeks can lead to steatosis, yet this can be reversed by days to weeks of abstinence in otherwise healthy individuals (31,32); the duration of abstinence needed to reverse alcohol-associated steatosis in diabetes and obesity is largely unknown. It is generally understood that high daily alcohol consumption is required for "pure" alcohol-related liver disease (ALD) to develop (30); however, more often than not, an interplay between metabolic and alcohol-related liver injury exists and leads to the development and accelerated progression of liver disease (Fig. 1).

Overall, alcohol use has a synergistic effect with diabetes and obesity to worsen insulin resistance and chronic liver injury (33,34). As shown in Fig. 1, alcohol worsens MASLD by increasing hepatic fat accumulation, promoting oxidative and cellular stress, triggering inflammation and fibrosis through macrophage and stellate cell activation, and compounding diabetes-, obesity-, and gut dysbiosis–related lipotoxic and inflammatory pathways.

There is no established intake of alcohol that is "safe" in the presence of MASLD—which is present in most people with

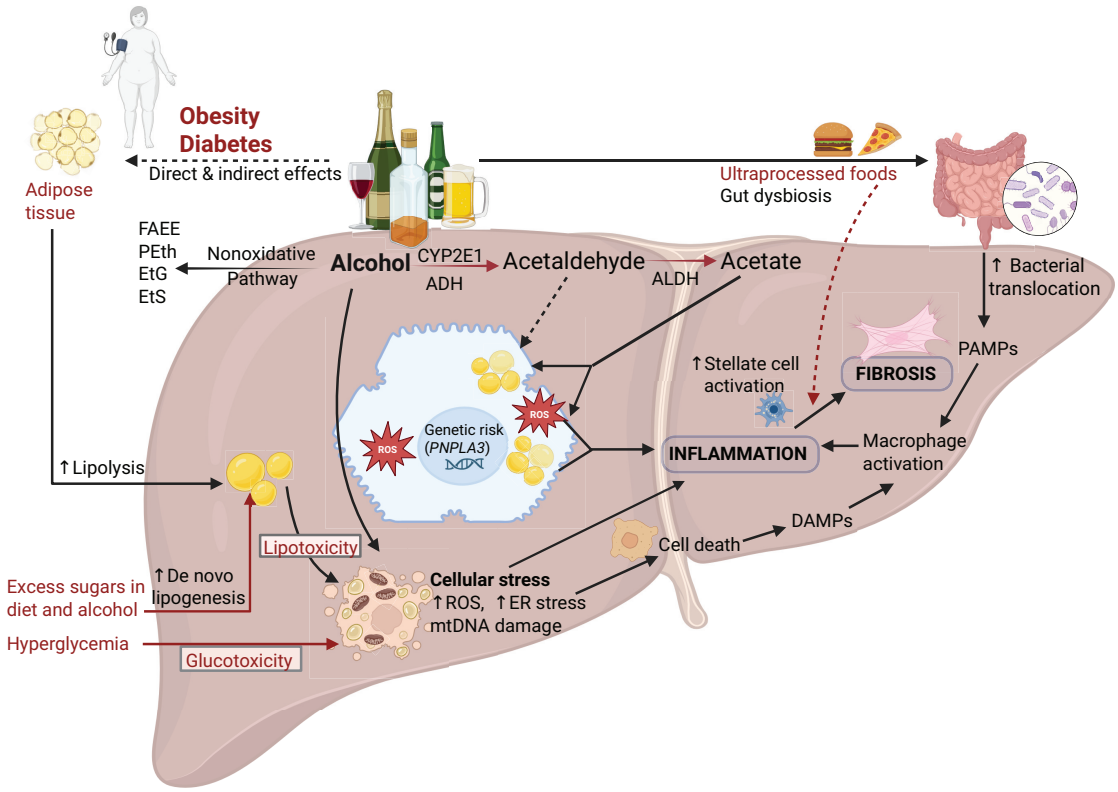


Figure 1—The overlapping mechanisms of alcohol and metabolic disease in promoting steatohepatitis and liver fibrosis. Chronic alcohol use indirectly contributes to steatotic liver disease by promoting unhealthy lifestyle behaviors (i.e., ultraprocessed foods, sedentary lifestyle) and directly by contributing to excess dietary sugars, adiposity, and hepatocyte injury. Alcohol is primarily metabolized by ADH and CYP2E1 to produce acetaldehyde, which in turn is metabolized to acetate, providing substrate for lipogenesis (105–107). Accumulation of hepatic triglycerides is further driven by *1*) alcohol- and acetaldehyde-mediated reduction of fatty acid β-oxidation (not shown here) and *2*) upregulation of lipogenic pathways by acetaldehyde (108). Alcohol and its metabolites also induce cellular stress directly via mitochondrial DNA damage, endoplasmic reticulum stress, and oxidative stress; this can lead to hepatocyte death and the release of damage-associated molecular patterns (DAMPs) (e.g., mitochondrial DNA, uric acid). DAMPs signal tissue injury and activate resident macrophages that cause hepatic inflammation. This inflammation stimulates stellate cells to proliferate and produce extracellular matrix leading to fibrosis. Obesity- and diabetes-induced lipotoxicity and glucotoxicity contribute to inflammation by inducing oxidative stress and mitochondrial dysfunction. Further, alcohol-mediated alterations in the gut microbiome cause an increase in gut permeability and translocation of pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (or endotoxin) into the portal circulation—this likewise activates macrophages and production of proinflammatory cytokines that drive further liver fibrosis (106). In diabetes and obesity, excess adiposity and sugars in the diet contribute to hepatic triglyceride accumulation via increase in lipolysis (and thus delivery of fatty acids to the liver) and de novo lipogenesis, respectively. Notably, obesity and ultraprocessed foods are linked to gut dysbiosis and worse gut permeability (109), compounding the effects of alcohol on this pathway. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP2E1, cytochrome P450 2E1; ER, endoplasmic reticulum; EtG, ethyl glucuronide; EtS, ethyl sulfate; FAEE, fatty acid ethyl ester; ROS, reactive oxygen species.

diabetes and obesity—and there is likely a dose-dependent relationship between alcohol and MASLD progression that begins with even light alcohol consumption. A thorough alcohol history and counseling regarding its risks are important in managing patients with preexisting diabetes and obesity. Current clinical practice guidelines and consensus reports recommend limiting alcohol intake in MASLD, and abstaining in the presence of clinically significant fibrosis (1,35–38).

Genes Interact With Alcohol and Metabolic Factors to Increase MASLD and Fibrosis

In addition to modifiable risk factors (i.e., alcohol, insulin resistance, diabetes, obesity), an individual's risk of progressive liver disease is influenced by genetic (i.e., nonmodifiable) factors and the gene-environment interaction. Figure 2 is a schematic representation to help the clinician be aware that across the spectrum of alcohol intake there are multiple drivers of steatotic liver disease, ranging from the individual genetic risk for liver disease to an obesogenic environment that promotes the development of type 2 diabetes and other cardiometabolic risk factors. The best studied genotype in the context of MASLD is *PNPLA3*, which has been found to interact with insulin resistance and obesity to multiplicatively increase risk of MASLD (39–41). For instance, the risk of major adverse liver outcomes is more than twofold greater for individuals with type 2 diabetes who have the *PNPLA3* risk allele versus those with diabetes who do not have the allele (40). Interestingly, individuals with *PNPLA3* risk alleles also experience greater reduction in hepatic steatosis from a Mediterranean-stye diet compared with those without the alleles (42), in addition to having a markedly higher risk of liver-related mortality with exposure to even low levels of alcohol use (43). Other relevant genetic variants and gene-environment interactions exist, yet data are more limited. For example, the *GCKR* genotype interacts with insulin resistance and triglycerides to multiplicatively increase risk of hepatic steatosis

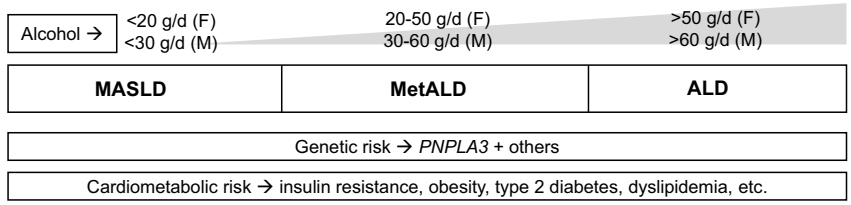


Figure 2—Drivers of steatotic liver disease. Schematic representation of the spectrum of alcohol use and of key drivers of steatotic liver disease, ranging from the individual genetic risk for liver disease to environmental factors that promote the development of type 2 diabetes, obesity, and other cardiometabolic risk factors. d, day; F, female; M, male.

(44). In alcohol-related liver disease, the *HSD17B13* genotype has been shown to protect against development of cirrhosis and HCC (45,46).

METALD: A NEW DIAGNOSTIC FRAMEWORK ACCOUNTING FOR THE HARMS OF MODERATE ALCOHOL USE

Alongside the nomenclature change from NAFLD to MASLD came a fundamental shift in the diagnostic framework of MASLD, which now more clearly establishes a subcategory of liver disease (MetALD) where moderate alcohol use is recognized as an important cofactor in disease progression to cirrhosis (7). The positive contributions of the name change and areas in need of more research have recently been reviewed (1). Liver disease predominantly from MASLD is diagnosed in the presence of one or more cardiometabolic risk factors (such as prediabetes or diabetes, obesity, hypertension, and atherogenic dyslipidemia) in the absence of moderate or heavy alcohol consumption (Table 1). Individuals with steatosis and one or more cardiometabolic risk factors who report moderate alcohol use are now categorized as having MetALD—these patients did not previously fit into any diagnostic criteria, and data suggest that MetALD is in fact more prevalent than ALD (47–49). Finally, those who report heavy alcohol consumption and have steatotic liver disease, regardless of the presence of cardiometabolic risk factors, continue to be diagnosed with ALD. Although ALD is a distinct form of liver disease in which alcohol is the predominant driver of disease progression, it should be noted that patients with ALD have a burden of cardiometabolic risk factors similar to that of MASLD/MetALD (50) and are thus commonly seen in diabetes and obesity clinics where they require management of these risk factors.

Table 1 includes a summary of how self-reported alcohol use (and phosphatidylethanol [PEth] levels) is used to classify forms of steatotic liver disease, including how alcohol intake by grams equates to drinks per day or week. Figure 3 is adapted from the National Institute on Alcohol Abuse and Alcoholism (51) and offers a reminder of what constitutes a standard drink size, i.e., 14 g alcohol. Thresholds for moderate and heavy alcohol use are lower in women, since, on average, the same amount of alcohol exposure leads to higher blood alcohol concentrations in women as compared with men (51). This is for multiple reasons: *1*) women tend to weigh less than men; *2*) alcohol is highly soluble in water, with women having lower total body water content than men; and *3*) women may have less first-pass metabolism of alcohol than men, leading to slower metabolism (51,52).

It is worth noting that daily "light" alcohol consumption in MASLD may reach as high as 2–3 standard drinks per day; in such cases, alcohol is likely to be an important contributor to progressive liver disease. Further, "moderate" alcohol intake that defines MetALD (i.e., >20/30 g daily in women/men) can overlap with the National Institute on Alcohol Abuse and Alcoholism thresholds for heavy drinking based on weekly intake (i.e., may exceed 8 drinks per week in women or 15 drinks per week in men) (51). Thus, the MetALD subcategory is likely to include patients in whom alcohol is a predominant contributor to progressive liver disease, yet whose alcohol intake is below thresholds that are used to define ALD. This is supported by data showing a twofold increase in the 5-year risk of liver decompensation when alcohol consumption rises from <20/30 g per day (MASLD) to >20/30 g per day (MetALD) (34).

While the risks of MASLD and ALD have previously been well characterized and understood by clinicians, MetALD represents a new entity with unique long-term risks that are not completely understood. A recent artificial intelligence–based analysis of liver biopsy specimens identified distinct collagen distribution patterns across MASLD, MetALD, and ALD, supporting the presence of distinct fibrotic progression pathways that may underlie differences in disease trajectory and clinical outcomes (53). Compared to MASLD, MetALD has an

Table 1—Definition of light, moderate, and heavy alcohol consumption in MASLD, MetALD, and ALD in the presence of cardiometabolic risk factors

	Light alcohol use (MASLD)	Moderate alcohol use (MetALD)	Heavy alcohol use (ALD)*
Female	<20 g/d (<1.5 drinks/d), <140 g/w (<10 drinks/w)	20–50 g/d (1.5–3.5 drinks/d), 140–350 g/w (10–25 drinks/w)	>50 g/d (>3.5 drinks/d), >350 g/w (>25 drinks/w)
Male	<30 g/d (<2 drinks/d), <210 g/w (<15 drinks/w)	30–60 g/d (2–4 drinks/d), 210–420 g/w (15–30 drinks/w)	>60 g/d (>4 drinks/d), >420 g/w (>30 drinks/w)
PEth levels**	<20 ng/mL	20–200 ng/mL	>200 ng/mL

Note: The above drink estimates are approximated based on the standard drink size of 14 g, which equates to 12 ounces (355 mL) of beer with 5% alcohol, 8 ounces (237 mL) of malt liquor with 7% alcohol, 5 ounces (148 mL) of wine with 12% alcohol, or one shot (1.5 ounces or 44 mL) of liquor or distilled spirits (80-proof liquor). d, day; w, week. *Regardless of how many metabolic risk factors are present, this level of alcohol consumption is categorized as ALD. **Note: PEth levels approximate alcohol use and should not be interpreted as a direct quantitative equivalence to alcohol intake (in grams) listed.



Figure 3—The amounts of common alcoholic beverages that constitute 14 g alcohol, or one standard drink. An individual who consumes more than 1.5 standard drinks (women) or 2.0 standard drinks (men) daily would meet the criteria for MetALD rather than MASLD. *For fortified wine, 3–4 fl oz (or 88–118 mL) constitutes 14 g alcohol, or one standard drink. Adapted from the National Institute on Alcohol Abuse and Alcoholism (49). Figure created with BioRender.com.

overall worse prognosis, including higher rates of HCC (54), and liver- and all-cause mortality (34,53,55–58), independent of age, sex, and liver stiffness measures (50). In a retrospective cohort study by Ochoa-Allemant et al. (59), posttransplant patients with MetALD were more likely to experience worse outcomes than those with ALD, including higher risks of waitlist removal and graft failure. A recent study by Ibrahim et al. (60) likewise noted that liver recompensation rates were lower in MetALD versus ALD in individuals with decompensated liver diseases referred for liver transplant evaluation. Notably, excess mortality in MetALD appears to be predominantly driven by cardiovascular disease and extrahepatic malignancies rather than liver-related death (61). Collectively, these data highlight MetALD as a distinct subclass of steatotic liver disease with unique risks, and it is incumbent upon clinicians to assess alcohol use so that MetALD can be distinguished from MASLD in clinical practice.

Assessing Alcohol Use

As outlined in Table 1, the new diagnostic framework for steatotic liver disease categorizes alcohol use as light, moderate, and heavy, which in the presence of hepatic steatosis and cardiometabolic risk factors correlates to a diagnosis of MASLD, MetALD, and ALD, respectively.

In addition to quantifying current alcohol consumption by type of beverage, frequency, and quantity, it is also essential to obtain a history of prior alcohol use and patterns of drinking. For example, binge drinking (versus not) is a pattern associated with higher odds of steatotic liver disease (62), with potentially greater risk among individuals with underlying cardiometabolic risk factors (32). The Alcohol Use Disorders Identification Test (AUDIT) is a validated 10-item screening tool that provides valuable insight into drinking behaviors and alcohol-related problems; a score of >15 indicates a high likelihood of alcohol dependence. AUDIT-Consumption (AUDIT-C) is an abbreviated, three-item version of this tool that is commonly used in clinical practice (https://www.mdcalc.com/calc/2021/audit-c-alcohol-use); it has high sensitivity for detecting unhealthy alcohol use in women who score ≥3 (73%–97%; 95% CI 62–69) and men who score ≥4 (82%–100%; 95% CI 75–100) (63). However, clinicians should be aware that specificity of the AUDIT-C is low for both sexes (as low as 28% in some studies) (63), as someone may screen positive on the basis of frequency of use alone (i.e., drinking two to three times per week = 3 points), without any regard for the quantity. For this reason, AUDIT-C should be used as an initial screen, and assessment of severity is a critical next step. While many patients who screen positive will have unhealthy alcohol use and can be counseled on reducing alcohol intake by their endocrinology and/or primary care teams, a minority will have alcohol use disorder (AUD) and require referral for more intensive behavioral and medication approaches (63).

Assessment of alcohol use in clinical practice is usually by self-report (including AUDIT-C), and thus subjective. Unfortunately, alcohol use is often underreported by patients due to a combination of recall bias and fear of judgement (64). This can make it challenging to accurately discern among MASLD, MetALD, and ALD. Biomarkers of alcohol use offer the potential for objective alcohol assessment; however, such tools are generally underused in clinical practice.

PEth is one commercially available biomarker that can be used to assess alcohol use in the preceding 2–3 weeks and has emerged as a valuable test in clinical practice. PEth is an abnormal phospholipid that is only formed in the presence of alcohol, via the action of enzyme phospholipase D; once incorporated into red blood cell membranes, it accumulates with ongoing alcohol exposure and is cleared gradually, with a biphasic half-life of ∼3–10 days (65). Notable advantages of PEth over other biomarkers include *1*) its high specificity for detecting both recent and longer-term alcohol exposure (vs. ethyl glucuronide and ethyl sulfate that measure short-term use only) (65,66), *2*) its clearance is independent of hepatic metabolism and should not be affected by underlying liver disease (65), and *3*) current PEth assays are effective at detecting even low alcohol consumption, which is not the case for other biomarkers of chronic alcohol use, such as carbohydrate-deficient transferrin (CDT) (67).

PEth levels of <20 ng/mL suggest abstinence or low alcohol consumption, whereas levels >80 ng/mL are usually seen in individuals with heavier alcohol consumption. Based on expert opinion, PEth levels in the range of 21–200 ng/mL denote MetALD as a likely etiology of liver disease, whereas levels >200 ng/mL are more in keeping with ALD (68) (Table 1). Recent data suggest that between 16% and 39% of individuals categorized as having MASLD (by self-report) would be reclassified as having MetALD or ALD based on PEth level (48,49, 69,70). Given the dynamic nature of alcohol consumption, it is not uncommon for steatotic liver disease to be reclassified over time. A recent study demonstrated that 38% of individuals with an initial diagnosis of MASLD were reclassified at 2 years, with reclassification rates as high as 62% and 69% for MetALD and ALD, respectively (69). Regardless of how individuals are classified, higher PEth levels are associated with major adverse liver outcomes (e.g., cirrhosis, decompensation, HCC, liver transplant, liver death), both in the presence

and absence of steatotic liver disease (49). These data highlight PEth as a valuable, objective biomarker for alcohol use that can help clinicians classify steatotic liver disease, as well as identify when alcohol is a major co-contributor to liver disease progression alongside metabolic risk factors. PEth and other new biomarkers of alcohol consumption are currently the focus of extensive research. In certain clinical scenarios, combining biomarkers (e.g., PEth with urinary ethyl glucuronide) may offer complementary insights into patterns of alcohol use. However, evidence supporting this combined approach remains limited outside the hepatology setting (71).

While PEth is a valuable biomarker of alcohol exposure, there are some caveats with its use in practice. PEth may be falsely low in conditions that shorten the red cell life span (e.g., hemolytic anemia) (72,73) and falsely elevated in blood transfusion (i.e., via PEth introduced from donor cells) (74). Access to PEth testing, which is done by liquid chromatography–tandem mass spectrometry, may be limited in certain practice settings. The value of ordering PEth should also be balanced against its cost in clinical practice, which can range from approximately $120 up to $300 per test in the U.S. Additionally, it is important for clinicians to be aware that discrepancies between reported and objective alcohol intake by PEth are common, and these conversations should be approached sensitively to preserve trust within the patient-clinician relationship (73). Taken together, more work is needed to develop more robust guidance on PEth use by diabetes and obesity care teams.

Overall, integrating self-reported alcohol intake (including drinking patterns and history of heavy use), AUDIT-C screening, and PEth testing allows for a thorough assessment of alcohol use in patients with diabetes, obesity, and steatotic liver disease (73). The American Diabetes Association recommends alcohol assessment at the initial patient visit and annually thereafter (75), although this recommendation has traditionally referred to self-reported rather than objective measures of alcohol use. It remains uncertain in which clinical contexts, and at what intervals, PEth testing should be performed in patients with diabetes, obesity, and steatotic liver disease. From a practical perspective, time constraints and competing clinical priorities may limit any integration of alcohol assessment into routine diabetes and obesity care. Limited access to AUD specialists and hepatology may likewise hinder real-world implementation of MetALD assessment and care across many practice settings. Strategies to streamline alcohol evaluation—such as leveraging electronic health record tools or adopting new models of care—should be explored to facilitate evidence-based assessment (at minimum by self-report and AUDIT-C) within existing resource constraints.

TREATMENT APPROACHES IN MASLD AND METALD

Management of MASLD in Diabetes and Obesity

Lifestyle changes in overweight or obesity leading to weight loss are a mainstay of obesity, T2D, and MASLD management (1). In MASLD, >5% weight loss can reverse steatosis and ≥10% can reverse steatohepatitis and fibrosis, however, there is large interindividual variability depending on dietary nutrient composition, concomitant physical activity, genetic background, and other poorly understood factors (35,75). In patients with MASLD who have obesity and diabetes, diet/lifestyle counseling and structured programs to promote healthy behaviors (i.e., exercise and low-calorie, low-sugar, minimally processed diet) are critical, and glucagon-like peptide 1 (GLP-1) receptor agonists should be considered as the pharmacologic treatment of choice to support weight loss, (76) especially in the setting of steatohepatitis (1,35,75). (See Table 2.) The best studied is semaglutide; in a phase 2 randomized controlled trial (RCT) (77) and a more recent phase 3 RCT (78), significant benefit was shown with semaglutide in individuals with metabolic dysfunction–associated steatohepatitis (MASH). Specifically, a dose of 2.4 mg semaglutide weekly led to resolution of steatohepatitis without worsening of fibrosis in 62.9% of the 534 participants in the semaglutide group and 34.3% of the 266 participants in the placebo group (estimated difference 28.7% [95% CI 21.1, 36.2]; $P < 0.001$) (78). Importantly, a reduction in liver fibrosis was observed in 32.7% of participants in the semaglutide group vs. 16.1% in the placebo group (estimated difference 16.5% [95% CI 10.2, 22.8]; $P < 0.001$) (76), and these results led to the U.S. Food and Drug Administration approval of semaglutide for MASH in August 2025.

As summarized in Table 2, dual gastrointestinal peptide (GIP) and GLP-1 agonists such as tirzepatide may induce more weight loss than GLP-1 receptor agonists (i.e., semaglutide) (76,79), with significant improvements noted in both steatohepatitis and fibrosis in a phase 2 RCT (80). Benefits for steatohepatitis and fibrosis have also been reported with survodutide (81), a dual GLP-1 and glucagon receptor agonist that is now in phase 3 trials. Finally, tests are underway for a number of single, dual, and triple agents for obesity, T2D, and MASLD (82,83). Patients should be cautioned about the potential for rapid weight loss with both GLP-1 and dual GIP/GLP-1 receptor agonists, and no more than 1–2 lbs of weight loss should be targeted per week, particularly for individuals with cirrhosis in whom sarcopenia is a common clinical challenge (84). It is advised that such patients also meet with a nutritionist to ensure adequate dietary protein intake, with a concomitant strength training plan to preserve, and ideally improve, functional muscle mass while losing weight.

Pioglitazone (a peroxisome proliferator–activated receptor γ agonist) is another recommended pharmacologic approach in individuals with confirmed or high suspicion of MASH. Pioglitazone improves insulin sensitivity, and importantly, it can reverse steatohepatitis (1,35,37) and was reported in a meta-analysis to prevent liver fibrosis progression and improve advanced fibrosis stage (85). Sodium–glucose cotransporter 2 (SGLT2) inhibitors are another class of glucose-lowering medication with significant cardiorenal benefits (1), and data suggest that SGLT2 inhibitors reduce steatosis, although its role in liver necroinflammation and fibrosis in patients with diabetes and MASLD remains to be fully established. Some studies have reported hepatic and metabolic benefits in individuals with cirrhosis (84), but again, more work is needed (86). Additional studies are underway to examine the effect of SGLT2 inhibitors in MASLD, alone and in combination with other medications (13,86).

Special Considerations in Managing Metabolic Disease in MetALD

Patients with MetALD previously were excluded from MASLD trials, so robust data on the efficacy and safety of MASLD treatment approaches in MetALD are lacking and no specific recommendations exist for this group. Until further data emerge,

Table 2—Treatment options for MASLD and MetALD in diabetes and obesity

Treatment approach	MASLD	MetALD	ALD with active AUD
Diabetes, obesity, and MASLD treatments			
Behavioral and lifestyle interventions	Recommended	Recommended	Recommended
GLP-1 or dual GIP/GLP-1 receptor agonist (e.g., liraglutide, tirzepatide)	Recommended	Potential benefit, may reduce alcohol cravings (93)	Safety concerns (nutritional, sarcopenia risk) (85)
Bariatric surgery	Recommended	Insufficient data, concern for increased alcohol misuse postsurgery (88)	Increased AUD risk (101). Avoid in cirrhosis
Diabetes treatments			
Pioglitazone	Recommended if MASH present	Insufficient data	Insufficient data
SGLT2 inhibitor	Potential benefit (1), reduces steatosis	Insufficient data	Possible increase in ketoacidosis risk
Obesity treatments			
Bupropion/naltrexone	May be of benefit via weight loss (35)	No data	Safety concern as lowers seizure threshold
Topiramate	May be of benefit via weight loss (35)	No data	AUD treatment option
Phentermine	May be of benefit via weight loss (35)	Increased CV side effects (e.g., tachycardia) (102). No data in MetALD	Increased CV side effects (e.g., tachycardia) (102). Avoid in ALD
Orlistat	May be of benefit via weight loss (35)	Nutritional concerns; may increase absorption of alcohol if consumed with fatty meal (103). No data in MetALD	Nutritional concerns; may increase absorption of alcohol if consumed with fatty meal (103). Avoid in ALD
MASLD-specific treatments			
Resmetirom	Recommended for F2–F3 fibrosis (1,104)	Insufficient data	Not recommended
Semaglutide	Recommended for F2–F3 fibrosis (1,76)	Potential benefit but insufficient data	Insufficient data

CV, cardiovascular.

MetALD can be approached similarly to MASLD, with a few exceptions, summarized in Table 2. For instance, a number of weight loss medications should be approached with caution in individuals with moderate or heavy alcohol consumption, including naltrexone/bupropion (seizures), phentermine (cardiovascular effects), and orlistat (nutritional/absorption concerns), for which overall modest benefit has been reported in MASLD (35). Additionally, the safety and efficacy of bariatric surgery have not been established in MetALD, and there are concerns that individuals may be at higher risk of alcohol-induced liver injury after bariatric surgery due to altered alcohol metabolism resulting in increased shunting of alcohol to the liver (9). These altered pharmacokinetics, in addition to alterations in the rewarding properties of alcohol, may also be contributing to the small, yet significant, risk of new-onset AUD after patients have undergone bariatric surgery (87).

The Emerging Role of GLP-1 Receptor Agonists in Addressing Harmful Alcohol Use

A therapeutic approach that has demonstrated promise in MetALD is use of GLP-1 and dual GLP-1/GIP receptor agonists. Early clinical studies suggest that these agents may reduce alcohol cravings and overall intake (9,88,89)—Fig. 4 includes an overview of how GLP-1 receptor agonists may modulate reward processing and alcohol cravings. In a retrospective cohort study of >80,000 patients with obesity, investigators found that semaglutide (vs. other obesity medications) was associated with a 50%–56% lower risk of AUD (both incidence and recurrence) over a 1-year follow-up period (90).

To date, only two RCTs examining GLP-1 receptor agonist use in AUD have been published. The first RCT was conducted in 2022, and no significant effect of exenatide on alcohol consumption was found; however, a secondary analysis found that exenatide reduced heavy drinking days and total alcohol intake in the subgroup with comorbid obesity (i.e., BMI >30 kg/m^2) (91). In this RCT, investigators also noted an attenuation of cue reactivity in the ventral striatum and septal area on functional MRI imaging of participants taking exenatide; these are key areas of the brain linked to drug reward and addiction (91). A recently published RCT included evaluation of the effects of once-weekly semaglutide on alcohol consumption and cravings in AUD, with findings that semaglutide reduced the number of drinks consumed per drinking day (−0.41 self-reported drinks per day [95% CI −0.73, −0.09]; $P = 0.04$) in addition to weekly alcohol cravings (92). While further evidence is needed to demonstrate efficacy of these medications in MetALD, collectively, these and other data (93–96) suggest efficacy in lowering alcohol use and underscore the potential for GLP-1 and dual GLP-1/GIP receptor agonists to promote alcohol reduction, and support AUD treatment, in patients with comorbid metabolic disease.

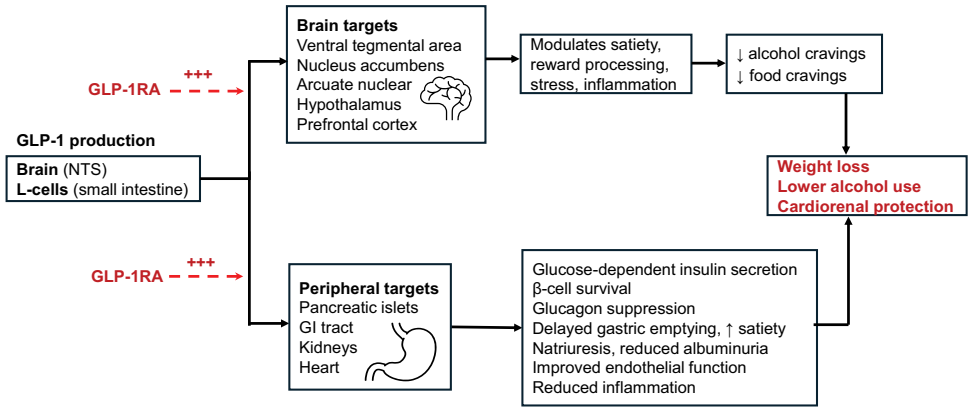


Figure 4—A schematic of how GLP-1 receptor agonists (GLP-1RA) improve metabolic health and reduce alcohol use. NTS, nucleus tractus solitarius; GI, gastrointestinal.

Alcohol Cessation and Reduction

Abstinence from alcohol is a central goal of MetALD treatment, as it eliminates the direct effects of alcohol on liver parenchyma, while also removing excess calories consumed via alcoholic beverages. If AUD is identified, patients should be referred to professionals with experience managing AUD. Medications for AUD include acamprosate, disulfiram, naltrexone, and topiramate. As above, early data suggest possible benefit of GLP-1 and dual GLP-1/GIP receptor agonists for reducing alcohol cravings, but these are not approved therapies for AUD.

Studies suggest that alcohol reduction is linked to lower blood pressures (97) and reduced risk of developing metabolic syndrome (98) and cardiovascular events (99). Further research is warranted to better characterize changes in cardiometabolic risk associated with alcohol cessation or reduction in the setting of steatotic liver disease. For clinicians managing patients with diabetes and obesity who are attempting to reduce alcohol use, it is important to be aware of the possibility that patients may use unhealthy foods as an alternate reward stimulus in place of alcohol. Such maladaptive behaviors should be identified and addressed to avoid worsening of MASLD while patients are working on reducing alcohol intake. Such complexities highlight the importance of a collaborative, interprofessional approach to effectively managing patients with MetALD, and MASLD (Fig. 5).

FUTURE RESEARCH DIRECTIONS IN METALD

MetALD is a newly defined diagnostic entity and several research and clinical gaps remain that, if addressed, could substantially improve its recognition and management. Priorities are to optimize the diagnosis of MetALD and use of PEth testing in routine clinical practice, and to understand *1*) in which clinical scenarios PEth testing is most appropriate, *2*) the optimal approach to PEth testing with respect to other

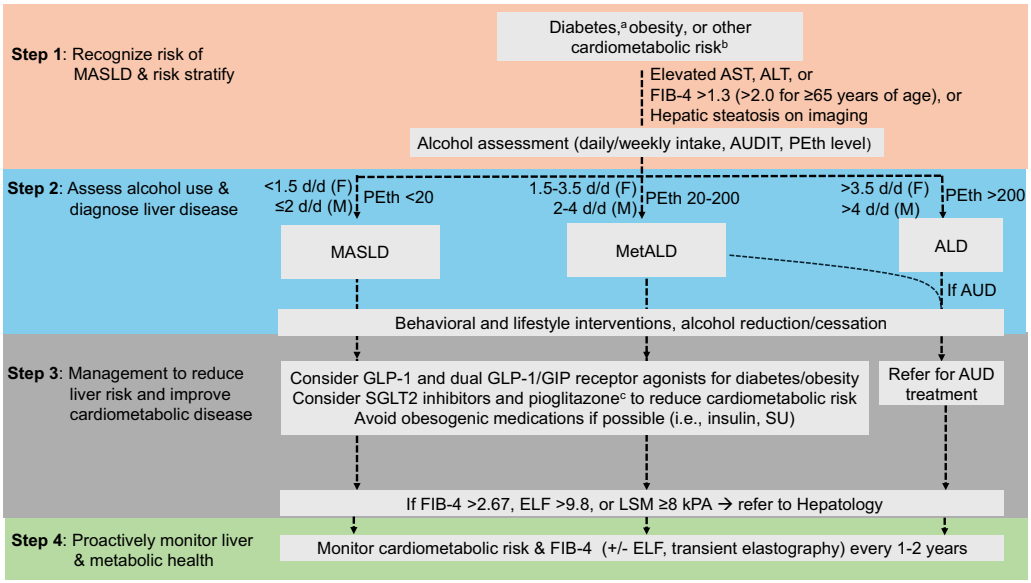


Figure 5—An integrated care pathway for MASLD that includes alcohol assessment in obesity and type 2 diabetes. PEth: nanograms per milliliter. d/d, number of standard drinks (14 g alcohol each) per day; ELF, Enhanced Liver Fibrosis test; FIB-4, Fibrosis-4 index; F, female; GIP, gastrointestinal peptide; LSM, liver stiffness measure (by transient elastography); M, male; SGLT2, sodium–glucose cotransporter 2; SU, sulfonylureas. [a]Patients with type 2 diabetes, or type 1 diabetes with metabolic syndrome. [b]Cardiometabolic risk factors also include prediabetes, blood pressure >130/85 mmHg, triglycerides >150 mg/dL, HDL cholesterol <40 mg/dL in men and <50 mg/dL in women, and BMI >25 kg/m^2. [c]Avoid in congestive heart failure.

evaluation of steatotic liver disease (e.g., viral hepatitis serologies, autoimmune testing), and *3*) the most cost-effective strategies for incorporating PEth into alcohol assessment, beyond its current use by liver specialists. For example, the utility of PEth is limited in cases where patients report heavy alcohol use and the diagnosis of ALD is clear.

Another important area of investigation will be the development of novel biomarkers of alcohol use, as few are commercially available. This will enable accurate diagnosis and monitoring, and the generation of disease-specific data to improve our understanding of MetALD and to support evidence-based care in the future. Researchers should also aim to understand how alcohol interacts with genetics (e.g., *PNPLA3*) as well as established risk factors in MetALD (e.g., nutrition, the microbiome, lipo- and glucotoxicity) and whether optimal treatment halts disease progression. Additional work is needed to clarify the safety and efficacy of pharmacologic therapies for MetALD, including agents such as GLP-1 receptor agonists and resmetirom, which are U.S. Food and Drug Administration approved for MASH. Future clinical trials should aim to delineate potential differences in treatment response between MASLD and MetALD to better inform clinical decision-making.

Efforts should be focused on establishing interprofessional care teams to enhance the diagnosis and management of MASLD and MetALD, thoroughly assess and address cardiometabolic risk factors, offer guidance on alcohol reduction or cessation, and identify patients with suspected significant fibrosis to enable timely referral to hepatology (100). Finally, future research is needed to determine the most effective strategies for increasing awareness among individuals with MASLD about the potential harms of alcohol use - especially in the presence of cardiometabolic risk factors, - and to identify more effective approaches for preventing and treating AUD in this population.

CONCLUSIONS

The last few years have seen an increasing appreciation of how alcohol and metabolic disease interact to worsen liver and cardiometabolic health. Greater awareness about this synergism has led to changes in nomenclature (i.e., NAFLD to MASLD) and a new diagnostic framework that integrates alcohol use to more precisely distinguish among MASLD, MetALD, and ALD. Despite being a relatively new diagnostic entity, MetALD has already established itself as a distinct subclass of metabolic liver disease with potentially worse prognosis than MASLD. We hope this review serves as a call to action for healthcare professionals managing patients with diabetes and obesity to routinely incorporate alcohol assessment into clinical practice. This should be done using a patient-centered approach that combines a detailed medical history, tailored questionnaires, and appropriate use of PEth testing. Clinicians are encouraged to adopt a proactive strategy that enables early detection and timely intervention for MetALD, with the ultimate goals of preventing progression to cirrhosis and reducing cardiovascular risk.

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References

1. Cusi K, Abdelmalek MF, Apovian CM, et al. Metabolic dysfunction-associated steatotic liver disease (MASLD) in people with diabetes: the need for screening and early intervention. A consensus report of the American Diabetes Association. Diabetes Care 2025;48:1057–1082
2. U.S. Department of Agriculture, U.S. Department of Health and Human Services. Nutrition and Your Health, 1980. Accessed 16 February 2026. Available from https://www.dietaryguidelines.gov/sites/default/files/2019-05/1980%20DGA.pdf
3. Centers for Disease Control and Prevention. National Diabetes Statistic Report, 2026. Accessed 16 February 2026. Available from https://www.cdc.gov/diabetes/php/data-research/index.html
4. Centers for Disease Control and Prevention. New CDC Data Show Adult Obesity Prevalence Remains High, 2024. Accessed 16 February 2026. Available from https://www.cdc.gov/media/releases/2024/p0912-adult-obesity.html
5. U.S. Department of Agriculture, U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2026. Accessed 16 February 2026. Available from https://cdn.realfood.gov/DGA.pdf
6. American Association for the Study of Liver Diseases. AASLD raises concern over removal of evidence-based alcohol guidance in 2025–2030 Dietary Guidelines for Americans, 2026. Accessed 16 February 2026. Available from https://www.aasld.org/aasld-raises-concern-over-removal-evidence-based-alcohol-guidance-2025-2030-dietary-guidelines
7. Rinella ME, Lazarus JV, Ratziu V, et al.; NAFLD Nomenclature consensus group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology 2023;78:1966–1986
8. Cecchini M, Filippini T, Whelton PK, et al. Alcohol intake and risk of hypertension: a systematic review and dose-response meta-analysis of nonexperimental cohort studies. Hypertension 2024;81:1701–1715
9. Marek GW, Malhi H. MetALD: does it require a different therapeutic option? Hepatology 2024;80:1424–1440
10. Díaz LA, Arab JP, Louvet A, Bataller R, Arrese M. The intersection between alcohol-related liver disease and nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 2023;20:764–783
11. Lu T, Nakanishi T, Yoshiji S, Butler-Laporte G, Greenwood CMT, Richards JB. Dose-dependent association of alcohol consumption with obesity and type 2 diabetes: Mendelian randomization analyses. J Clin Endocrinol Metab 2023;108:3320–3329
12. Mekary RA, Rimm EB, Giovannucci E, et al. Joint association of glycemic load and alcohol intake with type 2 diabetes incidence in women. Am J Clin Nutr 2011;94:1525–1532
13. Murata C, Suzuki Y, Muramatsu T, et al. Inactive aldehyde dehydrogenase 2 worsens glycemic control in patients with type 2 diabetes mellitus who drink low to moderate amounts of alcohol. Alcohol Clin Exp Res 2000;24:5S–11S
14. Biddinger KJ, Emdin CA, Haas ME, et al. Association of habitual alcohol intake with risk of cardiovascular disease. JAMA Netw Open 2022;5:e223849
15. Younossi ZM, Stepanova M, Ong J, et al.; Global Nash Council. Effects of alcohol consumption and metabolic syndrome on mortality in patients with nonalcoholic and alcohol-related fatty liver disease. Clin Gastroenterol Hepatol 2019;17:1625–1633.e1
16. Sogabe M, Okahisa T, Kagawa M, et al. Influence of alcohol on newly developed metabolic dysfunction-associated fatty liver disease in both sexes: a longitudinal study. Clin Nutr 2023;42:810–816
17. National Cancer Institute. Alcohol and Cancer Risk, 2025. Accessed 16 February 2026. Available from https://www.cancer.gov/about-cancer/causes-prevention/risk/alcohol/alcohol-fact-sheet
18. Seitz HK, Bataller R, Cortez-Pinto H, et al. Alcoholic liver disease. Nat Rev Dis Primers 2018;4:16
19. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA-R, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 2010;51:1972–1978
20. Chang Y, Ryu S, Kim Y, et al. Low levels of alcohol consumption, obesity, and development of fatty liver with and without evidence of advanced fibrosis. Hepatology 2020;71:861–873
21. Marti-Aguado D, Calleja JL, Vilar-Gomez E, et al. Low-to-moderate alcohol consumption is associated with increased fibrosis in individuals with metabolic dysfunction-associated steatotic liver disease. J Hepatol 2024;81:930–940
22. Rehm J, Taylor B, Mohapatra S, et al. Alcohol as a risk factor for liver cirrhosis: a systematic

review and meta-analysis. Drug Alcohol Rev 2010;29:437–445
23. Ajmera VH, Terrault NA, Harrison SA. Is moderate alcohol use in nonalcoholic fatty liver disease good or bad? A critical review. Hepatology 2017;65:2090–2099
24. Hashimoto Y, Hamaguchi M, Kojima T, et al. Modest alcohol consumption reduces the incidence of fatty liver in men: a population-based large-scale cohort study. J Gastroenterol Hepatol 2015;30:546–552
25. Moriya A, Iwasaki Y, Ohguchi S, et al. Roles of alcohol consumption in fatty liver: a longitudinal study. J Hepatol 2015;62:921–927
26. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. Hepatology 2017;65:1557–1565
27. Unalp-Arida A, Ruhl CE. Liver fibrosis scores predict liver disease mortality in the United States population. Hepatology 2017;66:84–95
28. Jarvis H, O'Keefe H, Craig D, Stow D, Hanratty B, Anstee QM. Does moderate alcohol consumption accelerate the progression of liver disease in NAFLD? A systematic review and narrative synthesis. BMJ Open 2022;12:e049767
29. Åberg F, Puukka P, Salomaa V, et al. Risks of light and moderate alcohol use in fatty liver disease: follow-up of population cohorts. Hepatology 2020;71:835–848
30. Åberg F, Byrne CD, Pirola CJ, Männistö V, Sookoian S. Alcohol consumption and metabolic syndrome: clinical and epidemiological impact on liver disease. J Hepatol 2023;78:191–206
31. Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and treatment of alcohol-associated liver diseases: 2019 practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2020;71:306–333
32. Kjærgaard K, Yeoman JM, Eriksen PL, et al. Binge drinking acutely induces hepatic steatosis which is readily reversible: a real-world observational study in healthy adults. JHEP Rep 2026;8:101623
33. Blomdahl J, Nasr P, Ekstedt M, Kechagias S. Moderate alcohol consumption is associated with advanced fibrosis in non-alcoholic fatty liver disease and shows a synergistic effect with type 2 diabetes mellitus. Metabolism 2021;115:154439
34. Israelsen M, Torp N, Johansen S, Thiele M, Krag A. MetALD: new opportunities to understand the role of alcohol in steatotic liver disease. Lancet Gastroenterol Hepatol 2023;8:866–868
35. Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocr Pract 2022;28:528–562
36. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). Obes Facts 2024;17:374–444
37. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023;77:1797–1835
38. Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. Gastroenterology 2021;161:1657–1669
39. Chen VL, Oliveri A, Miller MJ, et al. PNPLA3 genotype and diabetes identify patients with nonalcoholic fatty liver disease at high risk of incident cirrhosis. Gastroenterology 2023;164:966–977.e17
40. Chalasani N, Vilar-Gomez E, Loomba R, et al. PNPLA3 rs738409, age, diabetes, sex, and advanced fibrosis jointly contribute to the risk of major adverse liver outcomes in metabolic dysfunction-associated steatotic liver disease. Hepatology 2024;80:1212–1226
41. Speliotes EK, Schneider CV. PNPLA3 I148M interacts with environmental triggers to cause human disease. Liver Int 2025;45:e16106
42. Chen VL, Du X, Oliveri A, et al. Genetic risk accentuates dietary effects on hepatic steatosis, inflammation and fibrosis in a population-based cohort. J Hepatol 2024;81:379–388
43. Vilar-Gomez E, Gawrieh S, Vuppalanchi R, et al. PNPLA3 rs738409, environmental factors and liver-related mortality in the US population. J Hepatol 2025;82:571–581
44. Barata L, Feitosa MF, Bielak LF, et al. Insulin resistance exacerbates genetic predisposition to nonalcoholic fatty liver disease in individuals without diabetes. Hepatol Commun 2019;3:894–907
45. Schwantes-An T-H, Darlay R, Mathurin P, et al.; GenomALC Consortium. Genome-wide association study and meta-analysis on alcohol-associated liver cirrhosis identifies genetic risk factors. Hepatology 2021;73:1920–1931
46. Stickel F, Lutz P, Buch S, et al. Genetic variation in HSD17B13 reduces the risk of developing cirrhosis and hepatocellular carcinoma in alcohol misusers. Hepatology 2020;72:88–102
47. Lee BP, Dodge JL, Terrault NA. National prevalence estimates for steatotic liver disease and subclassifications using consensus nomenclature. Hepatology 2024;79:666–673
48. Torp N, Bech KT, Schnefeld HL, et al. Phosphatidylethanol and self-reported alcohol intake to subclassify individuals at risk of steatotic liver disease: an analysis of data from a prospective cohort study. Lancet Gastroenterol Hepatol 2025;10:975–985
49. Vaz J, Nasr P, Helander A, et al. Phosphatidylethanol levels distinguish steatotic liver disease subgroups and are associated with risk of major liver outcomes. J Hepatol 2025;83:1011–1022
50. Israelsen M, Torp N, Johansen S, et al.; GALAXY consortium. Validation of the new nomenclature of steatotic liver disease in patients with a history of excessive alcohol intake: an analysis of data from a prospective cohort study. Lancet Gastroenterol Hepatol 2024;9:218–228
51. National Institute on Alcohol Abuse and Alcoholism. Alcohol's Effects on Health, 2025. Accessed 15 February 2026. Available from https://www.niaaa.nih.gov/alcohols-effects-health
52. Baraona E, Abittan CS, Dohmen K, et al. Gender differences in pharmacokinetics of alcohol. Alcohol Clin Exp Res 2001;25:502–507
53. Kim G-A, Jang H, Kim MY, et al. Multicenter prospective cohort study on clinical outcomes and fibrosis patterns in biopsy-proven steatotic liver disease subtypes. Gastroenterology. 29 January 2026 [Epub ahead of print]. DOI: 10.1053/j.gastro.2026.01.007
54. John BV, Bastaich D, Paulus E, Spector S, Dahman B. Hepatocellular carcinoma risk in metabolic dysfunction-associated steatotic liver disease with increased alcohol intake (MetALD). JHEP Rep 2026;8:101639
55. Ochoa-Allemant P, Hubbard RA, Kaplan DE, Serper M. Cause-specific mortality in patients with steatotic liver disease in the United States. J Hepatol 2025;83:860–869
56. Tamaki N, Kimura T, Wakabayashi S-I, et al. Long-term clinical outcomes in steatotic liver disease and incidence of liver-related events, cardiovascular events and all-cause mortality. Aliment Pharmacol Ther 2024;60:61–69
57. Kwak M, Kim H-S, Jiang ZG, et al. MASLD/MetALD and mortality in individuals with any cardio-metabolic risk factor: a population-based study with 26.7 years of follow-up. Hepatology 2025;81:228–237
58. Charatcharoenwitthaya P, Karaketklang K, Aekplakorn W. Impact of metabolic phenotype and alcohol consumption on mortality risk in metabolic dysfunction-associated fatty liver disease: a population-based cohort study. Sci Rep 2024;14:12663
59. Ochoa-Allemant P, Serper M, Wang RX, et al. Waitlisting and liver transplantation for MetALD in the United States: an analysis of the UNOS national registry. Hepatology 2025;81:532–545
60. Ibrahim MA, Ramadan N, Mohamed IB, et al. Clinical outcomes in MetALD compared with ALD in patients referred for liver transplant evaluation. Hepatol Commun 2026;10:e0892
61. Feng Q, Manousou P, Izzi-Engbeaya CN, Loomba R, Thursz M, Woodward M. Unveiling the burden of steatotic liver disease: mortality risks by subtype and fibrosis stage in a nationwide cohort. Liver Int 2026;46:e70485
62. Lau K, Baumeister SE, Lieb W, et al. The combined effects of alcohol consumption and body mass index on hepatic steatosis in a general population sample of European men and women. Aliment Pharmacol Ther 2015;41:467–476
63. Krist AH, Bradley KA. Addressing alcohol use. N Engl J Med 2025;392:1721–1731
64. Krag A, Rinella ME. Steatotic liver disease: a new name to reflect the combined role of alcohol and metabolic dysfunction. Nat Med 2024;30:933–936
65. Rady ED, Cotter TG. Integrating phosphatidylethanol to enhance alcohol quantification in steatotic liver disease and clinical trials. Liver Int 2026;46:e70489
66. Viel G, Boscolo-Berto R, Cecchetto G, Fais P, Nalesso A, Ferrara SD. Phosphatidylethanol in blood as a marker of chronic alcohol use: a systematic review and meta-analysis. Int J Mol Sci 2012;13:14788–14812
67. Walther L, Stenton J, Hansson T, Blomgren A, Andersson A, Isaksson A. PEth cut-off thresholds for hazardous alcohol consumption based on a drinking study. Drug Test Anal 2026;18:108–117
68. Arab JP, Díaz LA, Rehm J, et al. Metabolic dysfunction and alcohol-related liver disease (MetALD): position statement by an expert panel on alcohol-related liver disease. J Hepatol 2025;82:744–756
69. Israelsen M, Thorhauge KH, Andersen P, et al. Steatotic liver disease classification is dynamic, affecting clinical trial eligibility and subclass-specific treatments. Clin Gastroenterol Hepatol 2025;23:2509–2518
70. Tavaglione F, Díaz LA, Ajmera V, et al. Clinical utility of phosphatidylethanol to detect underreported alcohol use and enhance steatotic liver disease subclassification. J Hepatol 2025;83:1023–1034

71. Dumortier J, Guillaud O, Boillot O, et al. Phosphatidylethanol and urinary ethylglucuronide to assess alcohol consumption after liver transplantation. Liver Transpl 2026;32:104–106
72. Årving A, Hilberg T, Sovershaev M, Bogstrand ST, Høiseth G. Falsely low phosphatidylethanol may be associated with biomarkers of haemolytic disease. Basic Clin Pharmacol Toxicol 2023;132:223–230
73. Torp N, Israelsen M, Thiele M, Rinella ME, Krag A. Phosphatidylethanol in steatotic liver disease. J Hepatol 2025;83:1189–1203
74. Snozek CLH, Kinard TN, Alegria KN, Jannetto PJ, Langman LJ. Artificial elevation of phosphatidylethanol due to red blood cell transfusion. Clin Biochem 2023;120:110651
75. American Diabetes Association Professional Practice Committee for Diabetes. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of Care in Diabetes—2026. Diabetes Care 2026;49(Suppl. 1):S61–S88
76. American Diabetes Association Professional Practice Committee for Diabetes. 8. Obesity and weight management for the prevention and treatment of diabetes: Standards of Care in Diabetes—2026. Diabetes Care 2026;49(Suppl. 1):S166–S182
77. Newsome PN, Buchholtz K, Cusi K, et al.; NN9931-4296 Investigators. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384:1113–1124
78. Sanyal AJ, Newsome PN, Kliers I, et al.; ESSENCE Study Group. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. N Engl J Med 2025;392:2089–2099
79. Aronne LJ, Horn DB, le Roux CW, et al.; SURMOUNT-5 Trial Investigators. Tirzepatide as compared with semaglutide for the treatment of obesity. N Engl J Med 2025;393:26–36
80. Loomba R, Hartman ML, Lawitz EJ, et al.; SYNERGY-NASH Investigators. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. N Engl J Med 2024;391:299–310
81. Sanyal AJ, Bedossa P, Fraessdorf M, et al.; 1404-0043 Trial Investigators. A phase 2 randomized trial of survodutide in MASH and fibrosis. N Engl J Med 2024;391:311–319
82. Chao AM, Taylor S, Moore M, Amaro A, Wadden TA. Evolving approaches for pharmacological therapy of obesity. Annu Rev Pharmacol Toxicol 2025;65:169–189
83. Zafer M, Tavaglione F, Romero-Gómez M, Loomba R. Review article: GLP-1 receptor agonists and glucagon/GIP/GLP-1 receptor dual or triple agonists-mechanism of action and emerging therapeutic landscape in MASLD. Aliment Pharmacol Ther 2025;61:1872–1888
84. Castera L, Cusi K. Diabetes and cirrhosis: current concepts on diagnosis and management. Hepatology 2023;77:2128–2146
85. Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. JAMA Intern Med 2017;177:633–640
86. Genua I, Cusi K. Pharmacological approaches to nonalcoholic fatty liver disease: current and future therapies. Diabetes Spectr 2024;37:48–58
87. Kenkre JS, Gesell S, Keller A, Milani RM, Scholtz S, Barley EA. Alcohol misuse post metabolic and bariatric surgery: a systematic review of longer-term studies with focus on new onset alcohol use disorder and differences between surgery types. Curr Obes Rep 2024;13:596–616
88. Chuong V, Farokhnia M, Khom S, et al. The glucagon-like peptide-1 (GLP-1) analogue semaglutide reduces alcohol drinking and modulates central GABA neurotransmission. JCI Insight 2023;8:e170671
89. Quddos F, Hubshman Z, Tegge A, et al. Semaglutide and tirzepatide reduce alcohol consumption in individuals with obesity. Sci Rep 2023;13:20998
90. Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Associations of semaglutide with incidence and recurrence of alcohol use disorder in real-world population. Nat Commun 2024;15:4548
91. Klausen MK, Jensen ME, Møller M, et al. Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial. JCI Insight 2022;7:e159863
92. Hendershot CS, Bremmer MP, Paladino MB, et al. Once-weekly semaglutide in adults with alcohol use disorder: a randomized clinical trial. JAMA Psychiatry 2025;82:395–405
93. O'Farrell M, Almohaileb FI, le Roux CW. Glucagon-like peptide-1 analogues reduce alcohol intake. Diabetes Obes Metab 2025;27:1601–1604
94. John BV, Bastaich D, Marchetti D, Perumalswami P, Mustafa MZ, Dahman B; Veterans Analysis of Liver Disease (VALID) Group of Investigators. Association of glucagon-like peptide-1 receptor agonists with liver-related outcomes and all-cause mortality in patients with harmful alcohol use: a target trial emulation study. Am J Gastroenterol 2026;121:697–709
95. Adeniran O, Nieto LM, Amadi C, et al. Alcoholic use disorder outcomes after Roux-en-Y gastric bypass in patients taking GLP-1 RAs: a multicenter analysis. Obesity (Silver Spring) 2025;33:1886–1894
96. Zheng YJ, Soegiharto C, Au HCT, et al. A systematic review on the role of glucagon-like peptide-1 receptor agonists on alcohol-related behaviors: potential therapeutic strategy for alcohol use disorder. Acta Neuropsychiatr 2025;37:e51
97. Suzuki T, Fukui S, Yoneoka D, Aoki J, Fujiwara T. Blood pressure after changes in light-to-moderate alcohol consumption in women and men: longitudinal Japanese annual checkup analysis. J Am Coll Cardiol 2025;86:2031–2044
98. Choi S, Kim K, Lee JK, et al. Association between change in alcohol consumption and metabolic syndrome: analysis from the health examinees study. Diabetes Metab J 2019;43:615–626
99. Kang DO, Lee D-I, Roh S-Y, et al. Reduced alcohol consumption and major adverse cardiovascular events among individuals with previously high alcohol consumption. JAMA Netw Open 2024;7:e244013
100. Sandella R, Rinella ME. Metabolic and alcohol-associated: diagnosis and management. Clin Liver Dis 2026;30:167–183
101. Cooper KM, Colletta A, Hebda N, Devuni D. Alcohol associated liver disease and bariatric surgery: current perspectives and future directions. World J Gastrointest Surg 2024;16:650–657
102. Fourie A, Julyan M, Mostert L, Du Plessis JM. Potential drug-drug interactions with phentermine among long-term phentermine consumers: a retrospective analysis. S Afr Med J 2023;113:63–68
103. Chaikomin R, Russo A, Rayner CK, et al. Effects of lipase inhibition on gastric emptying and alcohol absorption in healthy subjects. Br J Nutr 2006;96:883–887
104. Harrison SA, Bedossa P, Guy CD, et al.; MAESTRO-NASH Investigators. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med 2024;390:497–509
105. Hyun J, Han J, Lee C, Yoon M, Jung Y. Pathophysiological aspects of alcohol metabolism in the liver. Int J Mol Sci 2021;22:5717
106. Mandrekar P, Mandal A. Pathogenesis of alcohol-associated liver disease. Clin Liver Dis 2024;28:647–661
107. Liu S-Y, Tsai I-T, Hsu Y-C. Alcohol-related liver disease: basic mechanisms and clinical perspectives. Int J Mol Sci 2021;22:5170
108. You M, Arteel GE. Effect of ethanol on lipid metabolism. J Hepatol 2019;70:237–248
109. Rondinella D, Raoul PC, Valeriani E, et al. The detrimental impact of ultra-processed foods on the human gut microbiome and gut barrier. Nutrients 2025;17:859