

Review

Open Access



From NAFLD to MAFLD and MASLD: a tale of alcohol, stigma and metabolic dysfunction

Stefano Ciardullo^{1,2} , Gianluca Perseghin^{1,2}

¹Department of Medicine and Rehabilitation, Policlinico di Monza, Monza 20900, Italy.

²School of Medicine and Surgery, University of Milano Bicocca, Milan 20900, Italy.

Correspondence to: Dr. Stefano Ciardullo, Department of Medicine and Rehabilitation, Policlinico di Monza, Via Modigliani 10, Monza 20900, Italy. E-mail: stefano.ciardullo@unimib.it

How to cite this article: Ciardullo S, Perseghin G. From NAFLD to MAFLD and MASLD: a tale of alcohol, stigma and metabolic dysfunction. *Metab Target Organ Damage* 2024;4:30. <https://dx.doi.org/10.20517/mtod.2024.39>

Received: 7 May 2024 **First Decision:** 1 Jul 2024 **Revised:** 9 Aug 2024 **Accepted:** 21 Aug 2024 **Published:** 28 Aug 2024

Academic Editor: Amedeo Lonardo **Copy Editor:** Yu-Fei Wang **Production Editor:** Yu-Fei Wang

Abstract

Liver steatosis is a frequent finding in clinical practice and it is estimated to affect 30% of the general adult population worldwide. It became one of the leading causes of end-stage liver disease and hepatocellular carcinoma. From its first description, a diagnosis of nonalcoholic fatty liver disease (NAFLD) required the exclusion of excessive alcohol consumption and concomitant chronic liver diseases of different origins, making it a diagnosis of exclusion. In recent years, the need to stress the strict association between liver steatosis and metabolic dysfunction (i.e., insulin resistance, overweight/obesity, type 2 diabetes, and metabolic syndrome), as well as the desire to define a condition in a positive rather than negative way, led to new definitions and new diagnostic criteria. Metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed by Eslam *et al.* in 2020. More recently, a Delphi consensus endorsed by several international hepatologic societies proposed a new terminology [metabolic dysfunction-associated steatotic liver disease (MASLD)] and a new set of diagnostic criteria. The MAFLD and MASLD definitions have a good degree of concordance. They mainly differ in the number of metabolic derangements needed to define “metabolic dysfunction” in normal-weight individuals and in alcohol consumption. Indeed, while MAFLD does not exclude patients with significant alcohol consumption, the recent Delphi consensus included the metabolic dysfunction and alcohol-related liver disease (MetALD) disease entity, a condition in which steatosis, metabolic dysfunction, and moderate alcohol intake coexist. In the present narrative review, we underline the strengths and possible limitations of each definition and summarize available evidence from epidemiologic studies evaluating the clinical usefulness of each set of diagnostic criteria.



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



Keywords: Nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-related liver disease (MetALD), insulin resistance, nomenclature

HISTORICAL AND EPIDEMIOLOGIC ASPECTS

Descriptions of liver steatosis by pathologists date back to the first half of the nineteenth century^[1,2]. Several Authors identified associations between liver fat and alcohol consumption, visceral adiposity and conditions such as tuberculosis^[3,4]. Decades later, in the mid-twentieth century, sporadic observations started to suggest a possible link between liver fat and the development of more advanced forms of liver disease, including cirrhosis^[5]. Nonetheless, this association remained controversial for many years, with many authors skeptical of this theory^[6,7].

The first description of liver steatosis with inflammation and a thorough description of the associated histologic changes were made in 1980 by Ludwig *et al.*^[8]. The Authors studied a sample of middle-aged patients with overweight obesity and a high prevalence of type 2 diabetes who consumed little or no alcohol. They showed that the histologic changes within their livers were undistinguishable from those typically associated with elevated alcohol consumption (including lobular inflammation, Mallory bodies, and various degrees of liver fibrosis). Therefore, they named this condition “nonalcoholic steatohepatitis (NASH)”. In the following years, the term nonalcoholic fatty liver disease (NAFLD) was introduced as an umbrella term including patients with liver steatosis not related to alcohol and all stages of histologic changes in terms of inflammation and fibrosis^[9]. It became clear that this was not always a benign condition and that it could lead to liver cirrhosis and related complications^[10].

In the last few decades, the interest in this condition increased dramatically and several pieces of the puzzle were put into place. On the one hand, many studies showed that insulin resistance was a major contributor to the development and progression of NAFLD^[11], which was strictly associated with features of the metabolic syndrome including diabetes^[12], visceral adiposity^[13], hypertension^[14], and dyslipidemia^[15]. Indeed, paralleling the increasing rates of obesity and type 2 diabetes, NAFLD became by far the most common chronic liver condition worldwide, affecting 30% of adults^[16-19] and 10%-15% of children/adolescents^[20,21], with significant differences across continents. On the other, specific histologic scoring systems were introduced to evaluate the grade and stage of the disease and assist in the standardization of histology-based studies^[22]. It became evident that the degree of liver fibrosis was the major predictor of the future development of liver-related events and hepatocellular carcinoma, as it occurs in several chronic liver conditions^[23-25]. Nonetheless, it should be mentioned that approximately 30% of cases of hepatocellular carcinoma diagnosed in patients with NAFLD/metabolic dysfunction-associated steatotic liver disease (MASLD) develop on a non-cirrhotic liver, making it extremely challenging to detect in the early stages^[26,27].

Today, NAFLD is viewed as a heterogeneous condition with a complex pathophysiology [Figure 1]. Noxious stimuli are from different origins. Apart from lifestyle factors related to excessive caloric intake, reduced energy expenditure and the relative increase in visceral and ectopic fat deposition^[28], ethnicity and genetic factors can influence its development and progression^[29]. The most robust associations have been made with variants in the *PNPLA3*^[30], *TM6SF2*^[31], and *MBOAT7* genes^[32,33]. It is believed that genetic factors, alongside differences in lifestyle, diet, metabolic comorbidity profile and socioeconomic status, account for a large proportion of the differences in prevalence across different ethnic groups^[34]. Indeed, several studies have shown a higher prevalence of NAFLD/MASLD among Hispanic individuals and a lower prevalence among African individuals, compared with non-Hispanic whites^[35]. Moreover, environmental factors such as pollutants and endocrine disruptors are believed to play a significant role as well^[36-38].

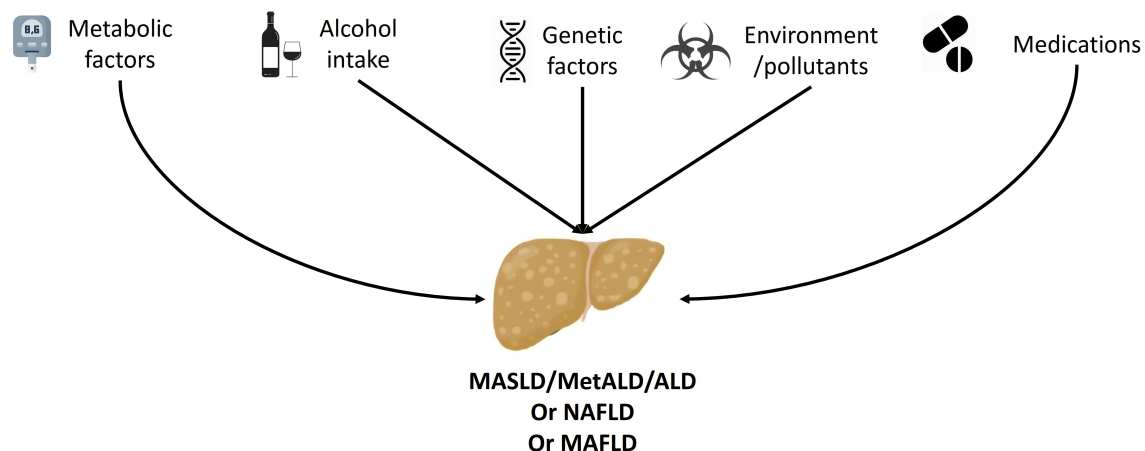


Figure 1. Factors contributing to the development of liver steatosis. MASLD: Metabolic dysfunction-associated steatotic liver disease; NAFLD: nonalcoholic fatty liver disease; MAFLD: metabolic dysfunction-associated fatty liver disease; MetALD: metabolic dysfunction and alcohol-related liver disease; ALD: alcoholic liver disease.

Nonetheless, several areas of uncertainty remain in our understanding of this condition. These span from a more comprehensive understanding of its pathophysiology, to unlocking the key drivers of inflammation and fibrosis, identifying accurate and available diagnostic tests, the cost-effectiveness of screening strategies, the molecular mechanisms linking NAFLD/MASLD to extrahepatic complications, and whether treatment can reduce liver-related events^[39].

Finally, in terms of natural history, cohort studies have shown that patients with NAFLD are at increased risk of developing diabetes^[40], chronic kidney disease^[41,42], extrahepatic cancers^[43] and cardiovascular disease (CVD)^[44], and heart failure [Figure 2]^[45]. Indeed, CVD (together with cancer) represents the most common cause of death in these patients, while liver-related mortality becomes a significant concern once inflammation and fibrosis are present^[46,47].

ALCOHOL CONSUMPTION AND PERCEIVED STIGMA

Following the advent of highly effective treatments for hepatitis C and widespread hepatitis B vaccination, alcohol-related liver disease (ALD) and NAFLD became the most common disease entities leading to cirrhosis and liver transplantation in developed countries^[48]. Indeed, alcohol use and obesity have been identified as the major forces driving liver disease in the general population^[49].

While in some instances, it is clear that one factor (metabolic dysfunction or alcohol) is the predominant noxious stimulus leading to liver disease progression, these two conditions frequently overlap^[50]. Furthermore, their negative impact on liver health is synergistic rather than additive and if combined with genetic polymorphisms (i.e., variants in the *PNPLA3* gene), they can increase the risk of liver cirrhosis, hepatocellular carcinoma, and death by more than eightfold^[51]. Alcohol consumption is highly prevalent worldwide. According to the World Health Organization's global status report on alcohol and health, 43% of people worldwide consumed alcohol in 2018, with the average consumption per capita per year reaching 6.4 liters in 2016^[52]. Spirits were the most commonly consumed alcoholic beverages, followed by beer and wine. Moreover, 5.1% of the general population met the definition of alcohol use disorder according to the Diagnostic and Statistical Manual of Mental Disorders. When interpreting these results, it is important to note that the data are only as reliable as the original source data. For instance, consumer surveys assessing

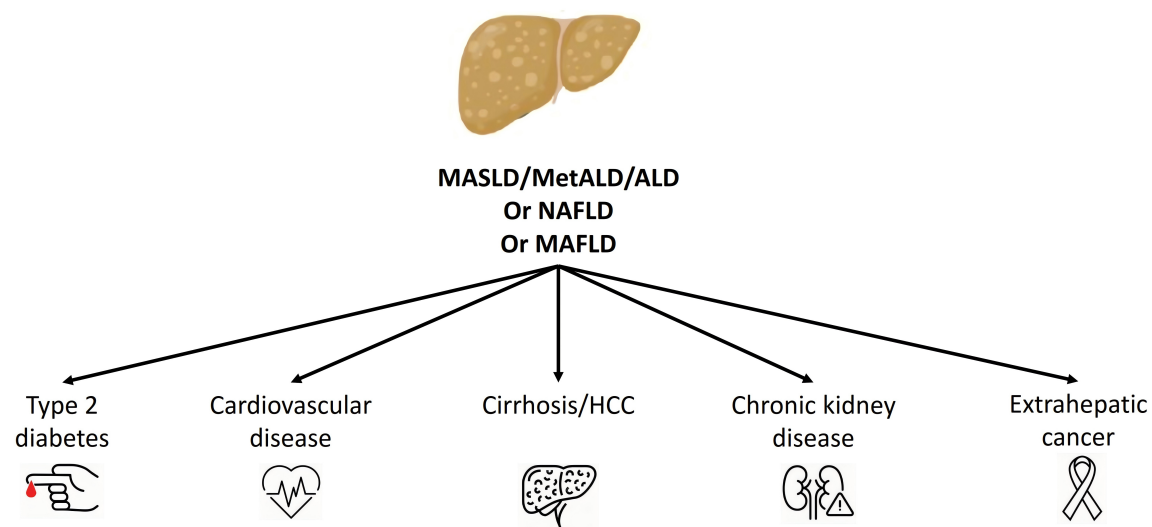


Figure 2. Intra- and extrahepatic complications of liver steatosis. MASLD: Metabolic dysfunction-associated steatotic liver disease; NAFLD: nonalcoholic fatty liver disease; MAFLD: metabolic dysfunction-associated fatty liver disease; MetALD: metabolic dysfunction and alcohol-related liver disease; ALD: alcoholic liver disease; HCC: hepatocellular carcinoma.

people's self-reported alcohol consumption usually show overall consumption figures, which are much lower, quite often around 40%-60% compared with supply-based estimates (i.e., data on the production and trade of alcohol). Moreover, the quality of the data might differ from country to country.

A relevant question in terms of distinguishing between NAFLD and ALD is whether there is a safe threshold for alcohol consumption in the setting of liver steatosis. On this aspect, recent studies seem to identify a linear relationship between alcohol use and health outcomes, with no specific threshold, especially in young individuals^[53,54]. Nonetheless, defining a safe threshold of alcohol is complex because it is influenced by multiple factors, including age, sex, diet, drinking behavior, and other disease conditions. This has been one of the criticisms of the NAFLD definition, as it allows quantities of alcohol intake that are not considered safe anymore.

It is, therefore, of great importance to obtain a reliable estimate of patients' alcohol consumption. This is frequently difficult to achieve in clinical practice, as we currently lack objective and reliable biomarkers for widespread use^[55,56]. Generally, the use of the AUDIT questionnaire is recommended as a rapid screening tool^[57], even though it was developed to detect harmful use of alcohol rather than moderate alcohol use. Nonetheless, relying only on patient reports can result in unrealistic estimates due to perceived stigma and recall bias. This aspect was recently shown in an elegant study performed in Austria^[58]. The Authors included a total of 184 patients. They performed an AUDIT questionnaire on all patients and measured ethyl glucuronide (a metabolite of ethanol) in hair (hEtG) and urine (uEtG). They found that 28.6% of patients previously classified as having NAFLD were at moderate to high risk of alcohol-related liver damage^[59]. These results challenge clinical practice and dichotomous definitions, highlighting the need to develop reliable markers of alcohol consumption that can be routinely used in the context of liver steatosis.

One of the major factors leading to under-reporting alcohol consumption is social stigma, a problem that affects many chronic metabolic and psychiatric disorders^[60,61]. This aspect has been identified as one of the reasons to move from the NAFLD definition (which has the term "alcoholic", even though with a negative

particle before it) to a positive definition related to metabolic dysfunction in both the metabolic dysfunction-associated fatty liver disease (MAFLD) and MASLD definitions. While stigma on alcohol consumption is frequently perceived, fewer data are available on whether the word “non-alcoholic” contained in NAFLD/NASH may also carry this unpleasant burden.

The potential stigma related to the term NAFLD has been recently investigated in a global survey completed by both patients and healthcare providers^[62]. The survey showed that the degree of perceived stigma was highly heterogeneous across countries (it was generally higher in the United States) and differed significantly between patients and physicians. Overall, patients reported more commonly stigmatization related to overweight-obesity (26%) than related to NAFLD (8%). They generally felt similarly comfortable with the terms NAFLD and MAFLD. Among practitioners, the word “nonalcoholic” was considered stigmatizing by 34% of respondents, while the word “fatty” by 38%. These discrepancies and geographical differences led some Authors to propose continuing the use of both the NAFLD and MAFLD/MASLD terminology within the scientific community^[63].

COMPARING THE DEFINITIONS OF NAFLD, MAFLD AND MASLD

Diagnostic criteria for the three considered definitions are shown in [Figure 3](#). As described before, international guidelines recommended diagnosing NAFLD by demonstrating excessive fat content in the liver (steatosis in $\geq 5\%$ of hepatocytes as evaluated through liver biopsy or histology). Moreover, they recommended excluding other causes of steatosis (such as specific medications and genetic disorders), co-existence of other forms of chronic liver disease (such as chronic viral hepatitis, autoimmune disease, hemochromatosis, and Wilson’s disease, among others) and the concomitant use of significant amounts of alcohol^[64-68]. Agreement on the exact threshold for defining excessive alcohol consumption is not universal; it has been defined as ≥ 30 g/day in men and ≥ 20 g/day in women, or 2 standard drinks per day for men and 1 standard drink per day for women.

In contrast, to diagnose MAFLD, evidence of liver steatosis may come from histology, imaging techniques, or even serum-based biomarkers [such as the fatty liver index (FLI)]. Furthermore, metabolic dysfunction needs to be present^[69]. It is defined as the presence of overweight or obesity (with BMI thresholds differing according to ethnicity), type 2 diabetes (T2D) or, in normal-weight individuals, as the presence of at least two of the following features: increased waist circumference, elevated blood pressure, elevated plasma triglycerides, low plasma High-density lipoprotein (HDL-cholesterol), pre-diabetes, an elevated homeostatic model assessment of insulin resistance (HOMA-IR), an elevated high-sensitivity C-reactive protein. Importantly, exclusion of other forms of chronic liver disease and significant alcohol consumption is not needed to perform the diagnosis, leading to the possibility of diagnosing patients with more than one chronic liver condition.

The recent Delphi consensus, in an effort to provide a more transparent, universal, and systematic process, redefined the whole landscape of liver steatosis. When steatosis is present (mainly detected through imaging or histology), a diagnosis of steatotic liver disease (SLD) can be made^[70]. Within SLD, MASLD is characterized by the absence of significant alcohol consumption (using 30/20 g/day in men and women, respectively, as a threshold), other specific etiologies (e.g., drug-induced liver injury or monogenic forms), and evidence of at least one of the following cardio-metabolic criteria: elevated BMI or waist circumference, pre-diabetes or T2D, elevated blood pressure, elevated triglycerides, and low HDL-cholesterol. In the case of steatosis, metabolic dysfunction, and a higher alcohol intake (20-50 and 30-60 g/day in women and men, respectively), a diagnosis of “MASLD and increased alcohol intake (MetALD)” can be made. For even higher alcohol consumption, a diagnosis of ALD is recommended. Finally, in the case of SLD without

Features	NAFLD	MAFLD	MASLD
Exclusion of excessive alcohol consumption	✓	✗	✓
Exclusion of other chronic liver diseases	✓	✗	✗
Exclusion of other causes of steatosis	✓	✗	✓
Metabolic dysfunction	✗	✓	✓
Overweight/Obesity	✗	✓	✓
Type 2 diabetes	✗	✓	✓
Number of criteria needed if normal weight	-	2	1

Figure 3. Comparison between the NAFLD, MAFLD and MASLD definitions. NAFLD: Nonalcoholic fatty liver disease; MAFLD: metabolic dysfunction-associated fatty liver disease; MASLD: Metabolic dysfunction-associated steatotic liver disease.

metabolic dysfunction or a specific etiology, cryptogenic SLD is diagnosed.

Several studies have made comparisons between these disease entities. Based on the definitions themselves, it is possible to estimate the features of patients in the non-overlapping groups. Patients with MAFLD but without NAFLD are characterized by the presence of coexisting forms of liver disease or significant alcohol consumption (features that prevent a diagnosis of NAFLD). It is, therefore, conceivable that these patients are at higher risk of liver-related events due to multiple etiologies simultaneously leading to hepatocyte injury. On the opposite side, those who meet the NAFLD, but not the MAFLD definition, are normal-weight individuals with zero or just one criterion for metabolic dysfunction, without other forms of liver disease and without significant alcohol consumption. Therefore, it is conceivable that these individuals may be characterized by a lower risk of both liver-related events and cardiovascular disease. Indeed, available studies found that patients with MAFLD are usually characterized by a higher prevalence of significant liver fibrosis and by a higher cardiovascular risk compared with patients with NAFLD^[71]. On the other hand, the degree of concordance between the two definitions is related to the prevalence of other forms of liver disease (such as viral hepatitis) and significant alcohol consumption within the considered population^[72]. For instance, in a study we performed based on data obtained in the general US population, where liver steatosis and fibrosis were evaluated through vibration-controlled transient elastography (VCTE), the degree of overlap was high (Cohen's κ 0.92)^[73]. This was related to the low proportion of normal-weight individuals without metabolic alterations in people with steatosis (NAFLD-only), as well as to the low prevalence of viral hepatitis and (self-reported) significant alcohol consumption (MAFLD-only) in this setting. Moreover, we showed that none of the patients falling in the NAFLD-only group had evidence of advanced liver fibrosis either by VCTE or according to noninvasive serum biomarkers such as FIB-4 or NAFLD Fibrosis Score (NFS). Conversely, in a study performed in Japan, the degree of overlap between the two definitions was much lower. This was related to a much higher proportion of normal-weight individuals among patients with steatosis and a higher prevalence of significant alcohol consumption compared to the US^[71]. Similar to our results, the Authors reported lower values of liver stiffness and noninvasive biomarkers of fibrosis in patients in the NAFLD-only group compared with the MAFLD-only group.

More recently, several studies compared NAFLD with MASLD. By definitions, in this case, the NAFLD-only group is characterized by normal-weight individuals without signs of metabolic dysfunction; on the other hand, few patients may be diagnosed with MASLD only if they have concomitant viral hepatitis (which is not considered as an exclusion criterion in the MASLD definition). Importantly, the degree of overlap between NAFLD and MASLD is even higher than between NAFLD and MAFLD, due to the exclusion of significant alcohol intake in both definitions. For instance, in a recent study from Sweden on a large cohort of patients diagnosed with NAFLD (most of whom have available data on liver histology), only 4 out of 1,333 (0.3%) did not meet the MASLD criteria^[74]. The Authors, therefore, conclude that no further studies are necessary to evaluate the natural history of MASLD as it is superimposable to that of NAFLD; similarly, given the high degree of concordance of the two definitions, there is no need to re-evaluate the performance of noninvasive biomarkers of liver fibrosis compared with liver biopsy in patients with MASLD^[75]. It should be noted, however, that these conclusions may not apply to different countries and regions, especially those with a high proportion of lean NAFLD patients.

In a recent study performed using data from the 2017-2020 NHANES database (representative of the overall US population), we showed that among participants with SLD, MASLD comprised the largest part (89.4%), followed by MetALD/ALD (7.7%), with a very low proportion of participants falling in the cryptogenic SLD category^[76]. In a subsequent study performed in South Korea, MASLD accounted for approximately 75% of SLD cases, MetALD accounted for 20%, while 3.3% fell in the cryptogenic SLD category. Moreover, 95.80% of the NAFLD cases fulfilled the new criteria for MASLD^[77,78]. In general, studies performed in Asian countries are more likely to identify participants with SLD that do not meet any metabolic dysfunction criteria and, therefore, fall in the cryptogenic SLD category (i.e., that can be diagnosed with NAFLD but not with MASLD). An interesting aspect of the new Delphi consensus is the introduction of a new disease entity called MetALD, which represents patients with coexisting metabolic dysfunction, steatosis, and significant alcohol intake. The introduction of this condition may represent a way to further study the impact of alcohol on different outcomes in the setting of SLD^[79,80]. In our study, these patients were characterized by a higher FIB-4 score compared with patients with MASLD (as expected due to alcohol increasing the AST/ALT ratio), while no significant difference was present in the proportion of patients with elevated LSM^[73]. More recently, a few cohort studies evaluated the association between MASLD, MetALD, and hard clinical outcomes such as all-cause mortality, cardiovascular events, and cancer-related mortality^[81-84]. Most studies were performed in general population settings and used either imaging or noninvasive scores to identify steatosis. We summarized evidence from these studies in a systematic review and meta-analysis^[85]. Briefly, compared with patients without SLD, both MASLD and MetALD were independently associated with a higher risk of cardiovascular disease and all-cause mortality. Importantly, MetALD was also associated with a higher risk of cancer-related mortality, while MASLD was not. Furthermore, Israelsen *et al.* showed that the risk of liver-related events increased progressively from MASLD to MetALD to ALD, stressing the importance of alcohol consumption on clinical outcomes throughout the spectrum of SLD^[79].

Given that MASLD was recently introduced, studies comparing it to MAFLD are limited in number. There are two main differences between these definitions. First, while MAFLD includes patients with significant alcohol consumption, MASLD does not (as MetALD and ALD perform this task). Second, while both include patients with overweight/obesity or type 2 diabetes, the main difference applies to normal-weight individuals. While MASLD only needs one criterion for metabolic dysfunction, MAFLD needs two. Therefore, when comparing the features of patients in non-overlapping groups, those with MASLD-only are characterized by normal weight and a single metabolic abnormality^[86]. It is conceivable that these patients (similarly to the NAFLD-only group) are at low risk for both liver-related events and cardiovascular mortality. As the two definitions differ mostly in the number of metabolic abnormalities that need to be

present in normal-weight individuals, a recent Indian study evaluated which definition performed better in this patient population^[87]. The Authors included 170 patients with lean NAFLD. Among them, 142 (83.5%) fulfilled the MASLD definition, while only 84 (49.4%) patients satisfied the MAFLD criteria (even though data on HOMA-IR and hs-CRP were not available for most patients). According to the MAFLD definition, half of all lean NAFLD patients could not receive a specific diagnosis, while according to the recent Delphi consensus, 16.5% would be diagnosed with cryptogenic SLD. Unfortunately, genetic data were not available in this study. While the Authors carefully excluded patients with drug-induced liver injury, chronic viral hepatitis, malnutrition, celiac disease, and Wilson's disease, potential other etiologies were not evaluated. Nonetheless, it is unlikely that rare genetic metabolic disorders could account for all the remaining cases and the underlying pathophysiology of SLD in this small subgroup remains elusive.

On the opposite side, patients in the MAFLD-only group have a higher alcohol intake in the presence of metabolic dysfunction; this group should be characterized by a higher risk of liver-related events and probably cardiovascular outcomes, as suggested by a recent population-based study^[88]. It should be noted, however, that by looking at the definitions, one can expect a high degree of overlap between this MAFLD-only group and patients with MetALD.

THE HURDLES OF DEFINING METABOLIC DYSFUNCTION

As recently reviewed^[89], the history of the debate about metabolic health and metabolic dysfunction dates back at least to the 1988 Banting Lecture by Gerald Reaven, discussing the insulin resistance syndrome^[90]. Several definitions of the metabolic syndrome have been proposed. While they all focus on the same cluster of variables (i.e., waist circumference, triglycerides, HDL-cholesterol, blood pressure and blood glucose levels), the number of alterations needed to make a diagnosis and the specific threshold to be applied for each component varied. The most frequently cited are the recommendations from the National Cholesterol Education Program (NCEP)-ATP III^[91] published in 2001, later harmonized by Alberti *et al.*^[92]. According to these definitions, metabolic syndrome can be diagnosed when the patient meets at least three of the five considered components. While the effort to achieve a global consensus on the definition of this prevalent condition is commended, relevant criticisms of the definition have been put forward by eminent Authors. First, this definition does not include any measure of insulin resistance, which is believed to be the pathophysiological defect underlying this cluster of manifestations^[93]. Indeed, accurate measurement of insulin resistance would require performing the gold standard euglycemic, hyperinsulinemic clamp^[94], which is time-consuming and elaborate and not well suited for large-scale application. Nonetheless, several easier-to-perform biomarkers based on fasting insulin and fasting glucose levels, such as HOMA-IR, QUICKI, and their variations, have been proposed^[95-98]. They exhibit moderate performance compared to the glucose clamp technique^[99], but still need measurement of insulin levels, which are somewhat assay-dependent^[100]; consequently, measurement of insulin resistance is not recommended by most international guidelines in any specific condition. Second, while metabolic syndrome needs three metabolic alterations to be present and define a yes/no condition, evidence shows that the risk for cardiovascular disease and mortality increases progressively with the increasing number of metabolic alterations present, without a specific cut-off^[101]. Another interesting aspect is related to the impact of different metabolic risk factors on liver-related outcomes. In a recent large cohort study conducted in patients with T2D, the comorbidity with the largest association with incident major adverse liver outcomes (MALOs) was hypertension (aHR 2.06, 95%CI: 1.57–2.71), while dyslipidemia, obesity, and albuminuria contributed to a lesser extent^[102]. The study confirmed that the higher the number of traits of metabolic syndrome present, the higher the risk of MALOs.

Finally, some perceive metabolic syndrome as a way to medicalize people who do not fit the criteria for well-defined conditions such as hypertension or diabetes mellitus.

Given these premises, it does not come as a surprise that the definition of metabolic dysfunction differs between MASLD and MAFLD. The MAFLD criteria were clearly based on the metabolic syndrome criteria, but they introduced insulin resistance (HOMA-IR) and low-grade inflammation (hs-CRP) as novel contributors^[103]. Indeed, these two aspects play pivotal roles in the development and progression of chronic metabolic conditions including liver steatosis and their inclusion aims at reminding clinicians of this aspect. Nonetheless, the main criticism of this approach is related to the fact that these biomarkers are seldom (if not never) measured in routine clinical practice.

The other aspect that has been subject to debate is whether BMI-based definitions of overweight and obesity (which are considered by both MAFLD and MASLD) are enough to define disease. Indeed, a recent report from Korea using magnetic resonance showed that a quarter of patients with MAFLD were “metabolically healthy” (≤ 1 risk factor and no diabetes), and more than half did not have metabolic syndrome^[104]. The concept of metabolically healthy obesity was fueled by several studies showing similar mortality rates in patients with overweight/obesity without metabolic syndrome, compared to normal-weight individuals^[105-107]. Moreover, a frequently cited meta-analysis published in 2013 did not show any increased risk of all-cause mortality in patients with grade I obesity (0.95, 95%CI: 0.88-1.01) and even a reduced risk of death in people with overweight (HR 0.94, 95%CI: 0.91-0.96)^[108]. These results provided evidence for the so-called “obesity paradox”, i.e., the observation that among patients with a specific health condition, those with higher BMIs might have a prognostic benefit^[109,110]. Nonetheless, these results have been questioned more recently. For instance, a subsequent large meta-analysis including more than 10 million individuals from > 200 studies performed across the globe showed that all-cause mortality was minimal in the 20-25 kg/m² group, while both people in the overweight (1.07, 1.07–1.08 for BMI 25.0-27.5 kg/m²; 1.20, 1.18–1.22 for BMI 27.5–30.0 kg/m²) and those in the class I obesity (1.45, 95%CI: 1.41–1.48) groups had higher mortality rates^[111]. Subsequent studies showed that, while the prognosis of metabolically healthy obese (MHO) individuals might be better compared with metabolically unhealthy (MUO) patients, their overall risk of dying is higher than that of metabolically healthy normal-weight individuals^[112]. Furthermore, it is highly likely that the MHO phenotype, although not rare in the general population (especially among young women), is a transient state, with many patients (especially if they do not lose significant amounts of weight) switching to a MUO phenotype with increasing age^[113]. For this reason, even recognizing the limitations associated with BMI as a measure of overall adiposity, we agree with the inclusion of overweight/obesity as a diagnostic criterion.

CONCLUSION

In conclusion, we believe that the recent debate on the best terminology and diagnostic criteria in the field of liver steatosis fueled an interesting debate and led to increased awareness of this condition among clinicians^[114]. The major advantage of the new definitions is their acknowledgment of the strict association between liver steatosis and metabolic factors, leading some Authors in the past to consider SLD as the hepatic manifestation of the metabolic syndrome^[115]. While clinicians might be confused by subtle changes in the acronyms and related disease definitions, evidence shows that several aspects should be kept in mind, regardless of terminology. First, the higher the number of concomitant metabolic abnormalities, the higher the risk of both liver-related and cardiovascular-related mortality. Second, whether or not it interferes with diagnostic criteria, careful evaluation for potential coexisting chronic liver conditions is of great prognostic importance. Third, notwithstanding the limitations related to its estimation, evaluation of alcohol intake should be performed in all patients with SLD and alcohol intake should be limited to a minimum (if not

completely eliminated) in this patient population. On this point, future studies evaluating the natural history of MetALD compared with MASLD might shed more light on whether thresholds for alcohol consumption have a strong evidence base.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Ciardullo S, Perseghin G

Performed data acquisition and provided administrative, technical, and material support: Ciardullo S, Perseghin G

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Stefano Ciardullo is a Junior Editorial Board member of the journal *Metabolism and Target Organ Damage*. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2024.

REFERENCES

1. Addison T. Observations on fatty degeneration of the liver. *Guy's Hosp Rep* 1836;1:485.
2. Ayonrinde OT. Historical narrative from fatty liver in the nineteenth century to contemporary NAFLD - reconciling the present with the past. *JHEP Rep* 2021;3:100261. DOI PubMed PMC
3. von Rokitsansky K F. A manual of pathological anatomy. Sydenham society;1854. Available from: https://books.google.com/books?hl=zh-CN&lr=&id=06AEAAAAQAAJ&oi=fnd&pg=PR7&dq=A+manual+of+pathological+anatomy&ots=XIBROfcSFg&sig=I2CoVm53BEMvZgjinm_kZCPfWPBs#v=onepage&q=A%20manual%20of%20pathological%20anatomy&f=false.
4. Budd G. On diseases of the liver. Blanchard and Lea;1853. Available from: https://books.google.com/books?hl=zh-CN&lr=&id=-eE2pRbzF3wC&oi=fnd&pg=PA17&dq=On+diseases+of+the+liver&ots=CYMBQc4BLx&sig=1XuS_DvEPs_t_diX-gPP6-xYI_0#v=onepage&q=On%20diseases%20of%20the%20liver&f=false.
5. Connor CL. Fatty infiltration of the liver and the development of cirrhosis in diabetes and chronic alcoholism. *Am J Pathol* 1938;14:347. PubMed PMC
6. Himsworth HP. Discussion: liver damage of metabolic origin. *Proceedings of the Royal Society of Medicine* 1949;42:201-6. DOI
7. Dible JH. Degeneration, necrosis and fibrosis in the liver. *Br Med J* 1951;1:833-41. DOI PubMed PMC
8. Ludwig J, Viggiano TR, McGill DB, Ott BJ. Nonalcoholic steatohepatitis: mayo clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980;55:434-8. PubMed
9. Schaffner F, Thaler H. Nonalcoholic fatty liver disease. *Prog Liver Dis* 1986;8:283-98. PubMed
10. Lee RG. Nonalcoholic steatohepatitis: a study of 49 patients. *Hum Pathol* 1989;20:594-8. DOI PubMed
11. Marchesini G, Brizi M, Morselli-Labate AM, et al. Association of nonalcoholic fatty liver disease with insulin resistance. *Am J Med* 1999;107:450-5. DOI PubMed
12. Ciardullo S, Monti T, Perseghin G. High prevalence of advanced liver fibrosis assessed by transient elastography among U.S. adults with type 2 diabetes. *Diabetes Care* 2021;44:519-25. DOI PubMed

13. Ciardullo S, Oltolini A, Cannistraci R, Muraca E, Perseghin G. Sex-related association of nonalcoholic fatty liver disease and liver fibrosis with body fat distribution in the general US population. *Am J Clin Nutr* 2022;115:1528-34. DOI PubMed
14. Ciardullo S, Monti T, Grassi G, Mancía G, Perseghin G. Blood pressure, glycemic status and advanced liver fibrosis assessed by transient elastography in the general United States population. *J Hypertens* 2021;39:1621-7. DOI PubMed PMC
15. Ciardullo S, Perseghin G. Statin use is associated with lower prevalence of advanced liver fibrosis in patients with type 2 diabetes. *Metabolism* 2021;121:154752. DOI PubMed
16. Younossi ZM, Stepanova M, Younossi Y, et al. Epidemiology of chronic liver diseases in the USA in the past three decades. *Gut* 2020;69:564-8. DOI PubMed
17. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:73-84. DOI PubMed
18. Younossi ZM, Golabi P, Price JK, et al. The global epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among patients with type 2 diabetes. *Clin Gastroenterol Hepatol* 2024;21:S1542-3565(24)00287. DOI PubMed
19. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol* 2019;71:793-801. DOI PubMed
20. Ciardullo S, Monti T, Perseghin G. Prevalence of liver steatosis and fibrosis detected by transient elastography in adolescents in the 2017-2018 national health and nutrition examination survey. *Clin Gastroenterol Hepatol* 2021;19:384-390.e1. DOI PubMed
21. Ciardullo S, Carbone M, Invernizzi P, Perseghin G. Impact of the new definition of metabolic dysfunction-associated fatty liver disease on detection of significant liver fibrosis in US adolescents. *Hepatol Commun* 2022;6:2070-8. DOI PubMed PMC
22. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol* 1999;94:2467-74. DOI PubMed
23. Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015;61:1547-54. DOI PubMed
24. 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;65:1557-65. DOI PubMed PMC
25. Taylor RS, Taylor RJ, Bayliss S, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterology* 2020;158:1611-1625.e12. DOI PubMed
26. Bucci L, Garuti F, Lenzi B, et al; Italian Liver Cancer Group. The evolutionary scenario of hepatocellular carcinoma in Italy: an update. *Liver Int* 2017;37:259-70. DOI PubMed
27. Piscaglia F, Svegliati-Baroni G, Barchetti A, et al; HCC-NAFLD Italian Study Group. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. *Hepatology* 2016;63:827-38. DOI PubMed
28. Perseghin G, Bonfanti R, Magni S, et al. Insulin resistance and whole body energy homeostasis in obese adolescents with fatty liver disease. *Am J Physiol Endocrinol Metab* 2006;291:E697-703. DOI PubMed
29. Valenti LVC, Moretti V. Implications of the evolving knowledge of the genetic architecture of MASLD. *Nat Rev Gastroenterol Hepatol* 2024;21:5-6. DOI PubMed
30. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 2008;40:1461-5. DOI PubMed PMC
31. Palmer ND, Musani SK, Yerges-Armstrong LM, et al. Characterization of European ancestry nonalcoholic fatty liver disease-associated variants in individuals of African and Hispanic descent. *Hepatology* 2013;58:966-75. DOI PubMed PMC
32. Krawczyk M, Rau M, Schattenberg JM, et al; NAFLD Clinical Study Group. Combined effects of the PNPLA3 rs738409, TM6SF2 rs58542926, and MBOAT7 rs641738 variants on NAFLD severity: a multicenter biopsy-based study. *J Lipid Res* 2017;58:247-55. DOI PubMed PMC
33. Liu YL, Reeves HL, Burt AD, et al. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. *Nat Commun* 2014;5:4309. DOI PubMed PMC
34. Riaz K, Swain MG, Congly SE, Kaplan GG, Shaheen AA. Race and ethnicity in non-alcoholic fatty liver disease (NAFLD): a narrative review. *Nutrients* 2022;14:4556. DOI PubMed PMC
35. Rich NE, Oji S, Mufti AR, et al. Racial and ethnic disparities in nonalcoholic fatty liver disease prevalence, severity, and outcomes in the united states: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2018;16:198-210.e2. DOI PubMed PMC
36. Tovoli F, Stefanini B, Mandrioli D, et al. Exploring occupational toxicant exposures in patients with metabolic dysfunction-associated steatotic liver disease: a prospective pilot study. *Dig Liver Dis* 2024;56:571-8. DOI PubMed
37. Polyzos SA, Kountouras J, Deretzi G, Zavos C, Mantzoros CS. The emerging role of endocrine disruptors in pathogenesis of insulin resistance: a concept implicating nonalcoholic fatty liver disease. *Curr Mol Med* 2012;12:68-82. DOI PubMed
38. Cheng WC, Wong PY, Wu CD, Cheng PN, Lee PC, Li CY. Non-linear association between long-term air pollution exposure and risk of metabolic dysfunction-associated steatotic liver disease. *Environ Health Prev Med* 2024;29:7. DOI PubMed PMC
39. Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol* 2015;62:S47-64. DOI PubMed
40. Mantovani A, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. *Gut* 2021;70:962-9. DOI PubMed
41. Mantovani A, Zaza G, Byrne CD, et al. Nonalcoholic fatty liver disease increases risk of incident chronic kidney disease: a systematic review and meta-analysis. *Metabolism* 2018;79:64-76. DOI PubMed
42. Ciardullo S, Ballabeni C, Trevisan R, Perseghin G. Liver fibrosis assessed by transient elastography is independently associated with

- albuminuria in the general United States population. *Dig Liver Dis* 2021;53:866-72. DOI PubMed
43. Mantovani A, Petracca G, Beatrice G, et al. Non-alcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. *Gut* 2022;71:778-88. DOI PubMed
 44. Shedlock K, Susi A, Gorman GH, Hisle-Gorman E, Erdie-Lalena CR, Nylund CM. Autism spectrum disorders and metabolic complications of obesity. *J Pediatr* 2016;178:183-187.e1. DOI PubMed
 45. Hydes TJ, Kennedy OJ, Glyn-Owen K, et al. Liver fibrosis assessed via noninvasive tests is associated with incident heart failure in a general population cohort. *Clin Gastroenterol Hepatol* 2024;22:1657-67. DOI PubMed
 46. Kasper P, Martin A, Lang S, et al. NAFLD and cardiovascular diseases: a clinical review. *Clin Res Cardiol* 2021;110:921-37. DOI PubMed PMC
 47. Ciardullo S, Morabito G, Rea F, Savaré L, Perseghin G, Corrao G. Time trends in liver-related mortality in people with and without diabetes: results from a population based study. *J Clin Endocrinol Metab* 2024;20:dgae182. DOI PubMed
 48. Younossi ZM, Stepanova M, Ong J, et al. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. *Clin Gastroenterol Hepatol* 2021;19:580-589.e5. DOI PubMed
 49. Karlsen TH, Sheron N, Zelber-Sagi S, et al. The EASL-Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. *Lancet* 2022;399:61-116. DOI PubMed
 50. Israelsen M, Juel HB, Detlefsen S, et al; GALAXY and MicroLiver consortiaks. Metabolic and genetic risk factors are the strongest predictors of severity of alcohol-related liver fibrosis. *Clin Gastroenterol Hepatol* 2022;20:1784-1794.e9. DOI PubMed
 51. Kim HS, Xiao X, Byun J, et al. Synergistic Associations of PNPLA3 I148M Variant, Alcohol intake, and obesity with risk of cirrhosis, hepatocellular carcinoma, and mortality. *JAMA Netw Open* 2022;5:e2234221. DOI PubMed PMC
 52. World Health Organization. Global status report on alcohol and health 2018. Available from: <https://www.who.int/publications/i/item/9789241565639>[DOI:10.4324/9780203029732-13].
 53. Griswold M G, Fullman N, Hawley C, et al. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2018;392:1015-35. DOI PubMed PMC
 54. 2020 Alcohol Collaborators. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the global burden of disease study 2020. *Lancet* 2022;400:185-235. DOI PubMed PMC
 55. Sehrawat TS, Arab JP, Liu M, et al. Circulating extracellular vesicles carrying sphingolipid cargo for the diagnosis and dynamic risk profiling of alcoholic hepatitis. *Hepatology* 2021;73:571-85. DOI PubMed PMC
 56. Nasr P, Wester A, Ekstedt M, et al. Misclassified alcohol-related liver disease is common in presumed metabolic dysfunction-associated steatotic liver disease and highly increases risk for future cirrhosis. *Clin Gastroenterol Hepatol* 2024;22:1048-1057.e2. DOI PubMed
 57. Conigrave KM, Saunders JB, Reznik RB. Predictive capacity of the AUDIT questionnaire for alcohol-related harm. *Addiction* 1995;90:1479-85. DOI PubMed
 58. Staufer K, Huber-Schönauer U, Streibinger G, et al. Ethyl glucuronide in hair detects a high rate of harmful alcohol consumption in presumed non-alcoholic fatty liver disease. *J Hepatol* 2022;77:918-30. DOI
 59. Kintz P. 2014 consensus for the use of alcohol markers in hair for assessment of both abstinence and chronic excessive alcohol consumption. *Forensic Sci Int* 2015;249:A1-2. DOI PubMed
 60. Room R. Stigma, social inequality and alcohol and drug use. *Drug Alcohol Rev* 2005;24:143-55. DOI PubMed
 61. Schomerus G, Lucht M, Holzinger A, Matschinger H, Carta MG, Angermeyer MC. The stigma of alcohol dependence compared with other mental disorders: a review of population studies. *Alcohol Alcohol* 2011;46:105-12. DOI PubMed
 62. Younossi ZM, Alqahtani SA, Alswat K, et al; Global NASH Council. Global survey of stigma among physicians and patients with nonalcoholic fatty liver disease. *J Hepatol* 2024;80:419-30. DOI PubMed
 63. Lonardo A, Bril F, Caldwell SH, et al. Researchers call for more flexible editorial conduct rather than abruptly adopting only the new MASLD nomenclature. *J Hepatol* 2024;80:e192-4. DOI PubMed
 64. Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: a systematic review with comparative analysis. *World J Gastroenterol* 2018;24:3361-73. DOI PubMed PMC
 65. Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016;64:1388-402. DOI PubMed PMC
 66. Glen J, Floros L, Day C, Pryke R; Guideline Development Group. Non-alcoholic fatty liver disease (NAFLD): summary of NICE guidance. *BMJ* 2016;354:i4428. DOI PubMed
 67. Wong VW, Chan WK, Chitturi S, et al. Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017-Part 1: Definition, risk factors and assessment. *J Gastroenterol Hepatol* 2018;33:70-85. DOI PubMed
 68. Association for the Study of the Liver (AISF). AISF position paper on nonalcoholic fatty liver disease (NAFLD): updates and future directions. *Dig Liver Dis* 2017;49:471-83. DOI PubMed
 69. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol* 2020;73:202-9. DOI PubMed
 70. Rinella ME, Lazarus JV, Ratziu V, et al; NAFLD Nomenclature consensus group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Ann Hepatol* 2024;29:101133. DOI PubMed PMC
 71. Yamamura S, Eslam M, Kawaguchi T, et al. MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. *Liver*

- Int* 2020;40:3018-30. DOI PubMed
72. Lin S, Huang J, Wang M, et al. Comparison of MAFLD and NAFLD diagnostic criteria in real world. *Liver Int* 2020;40:2082-9. DOI PubMed
73. Ciardullo S, Perseghin G. Prevalence of NAFLD, MAFLD and associated advanced fibrosis in the contemporary United States population. *Liver Int* 2021;41:1290-3. DOI PubMed
74. Hagström H, Vessby J, Ekstedt M, Shang Y. 99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical. *J Hepatol* 2024;80:e76-7. DOI PubMed
75. Ratzliff V, Boursier J; AFEF Group for the Study of Liver Fibrosis. Confirmatory biomarker diagnostic studies are not needed when transitioning from NAFLD to MASLD. *J Hepatol* 2024;80:e51-2. DOI PubMed
76. Perseghin G. Exploring the in vivo mechanisms of action of glucokinase activators in type 2 diabetes. *J Clin Endocrinol Metab* 2010;95:4871-3. DOI PubMed
77. Lee CM, Yoon EL, Kim M, et al. Prevalence, distribution, and hepatic fibrosis burden of the different subtypes of steatotic liver disease in primary care settings. *Hepatology* 2024;79:1393-400. DOI PubMed
78. Lee BP, Dodge JL, Terrault NA. National prevalence estimates for steatotic liver disease and subclassifications using consensus nomenclature. *Hepatology* 24;79:666-73. DOI PubMed PMC
79. 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;9:218-28. DOI PubMed
80. 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;8:866-8. DOI PubMed
81. Choe HJ, Moon JH, Kim W, Koo BK, Cho NH. Steatotic liver disease predicts cardiovascular disease and advanced liver fibrosis: a community-dwelling cohort study with 20-year follow-up. *Metabolism* 2024;153:155800. DOI PubMed
82. Han E, Lee BW, Kang ES, et al. Mortality in metabolic dysfunction-associated steatotic liver disease: a nationwide population-based cohort study. *Metabolism* 2024;152:155789. DOI
83. Kim D, Wijarnpreecha K, Cholanteril G, Ahmed A. Metabolic dysfunction-associated steatotic liver disease and all-cause/cause-specific mortality among adults in the United States. *J Hepatol* 2024;80:e79-81. DOI PubMed
84. Lee HH, Lee HA, Kim EJ, et al. Metabolic dysfunction-associated steatotic liver disease and risk of cardiovascular disease. *Gut* 2024;73:533-40. DOI PubMed
85. Ciardullo S, Mantovani A, Morieri ML, Muraca E, Invernizzi P, Perseghin G. Impact of MASLD and MetALD on clinical outcomes: a meta-analysis of preliminary evidence. *Liver Int* 2024;44:1762-7. DOI PubMed
86. Ramírez-Mejía MM, Jiménez-Gutiérrez C, Eslam M, George J, Méndez-Sánchez N. Breaking new ground: MASLD vs. MAFLD-which holds the key for risk stratification? *Hepatol Int* 2024;18:168-78. DOI PubMed
87. De A, Bhagat N, Mehta M, Taneja S, Duseja A. Metabolic dysfunction-associated steatotic liver disease (MASLD) definition is better than MAFLD criteria for lean patients with NAFLD. *J Hepatol* 2024;80:e61-2. DOI PubMed
88. Pan Z, Shiha G, Esmat G, Méndez-Sánchez N, Eslam M. MAFLD predicts cardiovascular disease risk better than MASLD. *Liver Int* 2024;44:1567-74. DOI PubMed
89. Byrne CD, Targher G. MASLD, MAFLD, or NAFLD criteria: have we re-created the confusion and acrimony surrounding Metabolic syndrome? *Metab Target Organ Damage* 2024;4:10. DOI
90. Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595-607. DOI PubMed
91. National Cholesterol Education Program (US); Expert Panel On Detection, Treatment Of High Blood Cholesterol In Adults. Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III). *The Program*, 2002. Available from: [https://books.google.com/books?hl=zh-CN&lr=&id=VKpLAQAAIAAJ&oi=fnd&pg=PR2&dq=Third+report+of+the+national+cholesterol+education+program+\(NCEP\)+expert+panel+on+detection,+evaluation,+and+treatment+of+high+blood+cholesterol+in+adults&ots=jXkq2nMHhu&sig=07y2oicjyvSXt6TpFIho3hc-ISM#v=onepage&q=Third%20report%20of%20the%20national%20cholesterol%20education%20program%20\(NCEP\)%20expert%20panel%20on%20detection%2C%20evaluation%2C%20and%20treatment%20of%20high%20blood%20cholesterol%20in%20adults&f=false](https://books.google.com/books?hl=zh-CN&lr=&id=VKpLAQAAIAAJ&oi=fnd&pg=PR2&dq=Third+report+of+the+national+cholesterol+education+program+(NCEP)+expert+panel+on+detection,+evaluation,+and+treatment+of+high+blood+cholesterol+in+adults&ots=jXkq2nMHhu&sig=07y2oicjyvSXt6TpFIho3hc-ISM#v=onepage&q=Third%20report%20of%20the%20national%20cholesterol%20education%20program%20(NCEP)%20expert%20panel%20on%20detection%2C%20evaluation%2C%20and%20treatment%20of%20high%20blood%20cholesterol%20in%20adults&f=false).
92. Alberti, KG, Eckel, RH, Grundy SM et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. *Circulation* 2009;120:1640-5. DOI PubMed
93. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991;14:173-94. DOI PubMed
94. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979;237:E214-23. DOI PubMed
95. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412-9. DOI PubMed
96. Perseghin G, Caumo A, Caloni M, Testolin G, Luzi L. Incorporation of the fasting plasma FFA concentration into QUICKI improves its association with insulin sensitivity in nonobese individuals. *J Clin Endocrinol Metab* 2001;86:4776-81. DOI PubMed

97. Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 2000;85:2402-10. DOI PubMed
98. Ciardullo S, Dodesini AR, Lepore G, et al. Development of a new model of insulin sensitivity in patients with type 2 diabetes and association with mortality. *J Clin Endocrinol Metab* 2024;109:1308-17. DOI PubMed
99. Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 2000;23:57-63. DOI PubMed
100. Tohidi M, Arbab P, Ghasemi A. Assay-dependent variability of serum insulin concentrations: a comparison of eight assays. *Scand J Clin Lab Invest* 2017;77:122-9. DOI PubMed
101. Guzder RN, Gatling W, Mullee MA, Byrne CD. Impact of metabolic syndrome criteria on cardiovascular disease risk in people with newly diagnosed type 2 diabetes. *Diabetologia* 2006;49:49-55. DOI PubMed
102. Shang Y, Grip ET, Modica A, et al. Metabolic syndrome traits increase the risk of major adverse liver outcomes in type 2 diabetes. *Diabetes Care* 2024;47:978-85. DOI PubMed PMC
103. Asghar A, Sheikh N. Role of immune cells in obesity induced low grade inflammation and insulin resistance. *Cell Immunol* 2017;315:18-26. DOI PubMed
104. Park H, Yoon EL, Kim M, Cho S, Nah EH, Jun DW. Nomenclature dilemma of metabolic associated fatty liver disease (MAFLD): considerable proportions of mafl are metabolic healthy. *Clin Gastroenterol Hepatol* 2023;21:1041-1049.e3. DOI
105. Stefan N. Metabolically healthy and unhealthy normal weight and obesity. *Endocrinol Metab (Seoul)* 2020;35:487-93. DOI PubMed PMC
106. Hrasko T, Bendlová B, Hainer V, Haluzík M. Metabolically healthy obese individuals - mechanisms and clinical relevance. *Cesk Fysiol* 2016;65:38-46. PubMed
107. Calori G, Lattuada G, Piemonti L, et al. Prevalence, metabolic features, and prognosis of metabolically healthy obese Italian individuals: the cremona study. *Diabetes Care* 2011;34:210-5. DOI PubMed PMC
108. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013;309:71-82. DOI PubMed PMC
109. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol* 2002;39:578-84. DOI PubMed
110. Hainer V, Aldhoon-Hainerová I. Obesity paradox does exist. *Diabetes Care* 2013;36 Suppl 2:S276-81. DOI PubMed PMC
111. Global BMI Mortality Collaboration, Di Angelantonio E, Bhupathiraju ShN, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;388:776-86. DOI PubMed PMC
112. Blüher M. Metabolically healthy obesity. *Endocr Rev* 2020;41:bnaa004. DOI PubMed PMC
113. Mongraw-Chaffin M, Foster MC, Anderson CAM, et al. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. *J Am Coll Cardiol* 2018;71:1857-65. DOI PubMed PMC
114. Singh A, Dhaliwal AS, Singh S, et al. Awareness of nonalcoholic fatty liver disease is increasing but remains very low in a representative us cohort. *Dig Dis Sci* 2020;65:978-86. DOI PubMed
115. Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes* 2001;50:1844-50. DOI PubMed