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Letters to the editor

## From NAFLD to MASLD: Promise and pitfalls of a new definition†

To the Editor:

As members of the nomenclature steering committee, we recognize the significant effort involved by all stakeholders in the procedures leading to the proposal of a nomenclature change from non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated steatotic liver disease (MASLD). The new name could potentially remove stigma, which has been highlighted by patient representatives, and bring awareness to the critical role of insulin resistance in the pathophysiology of "metabolic dysfunction" and liver disease. As highlighted below, we are hopeful that this accomplishment will encourage future research and a continued dialogue to address remaining caveats regarding the definition of steatotic liver diseases and its clinical implications.

The MASLD definition change (steatosis plus ≥ 1 cardiometabolic risk factor) was understandably driven, at least in part, by a need for a "positive" diagnosis rather than a "negative" one, *i.e.* by exclusion of excessive alcohol use and any other liver disease (NAFLD). Future work should validate the hypothesis that MASLD supports the intended pathophysiological mechanism that steatosis is driven by insulin resistance and "metabolic dysfunction". This is important because liver-related mortality in NAFLD appears closely related to insulin resistance, as recently reported in 12,878 individuals followed for a median of 22.8 years [1]. Two recent studies show encouraging concordance between NAFLD and MASLD: one study on 3,173 middle-age US adults participating in the National Health and Nutrition Examination Survey 2017–2020 who were screened by transient elastography [2], and another study from Hong Kong in 1,016 randomly selected community participants screened by proton-magnetic resonance spectroscopy [3]. However, one must keep in mind that the prevalence of ≥ 1 cardiometabolic risk factor is very high (>90 %) in the general population aged ≥ 45 and ≥ 1 of these cardiovascular risk factors are already present in 85 % of individuals without steatosis [2]. In contrast, only ~50 % of individuals with MASLD who are overweight have insulin resistance by HOMA-IR [2], suggesting a significant discordance and relative low specificity for these clinical comorbidities as surrogates for insulin resistance. Discordance may be inevitable when a metabolic outcome of insulin resistance (steatosis) is asked to translate into at least one clinical comorbidity (hypertension, atherogenic dyslipidemia, overweight/obese or prediabetes/type 2 diabetes), and when these comorbidities are caused by multiple and incompletely understood mechanisms beyond insulin resistance. Another consideration is that repurposing cardiometabolic risk factors developed for the prediction of cardiovascular disease and type 2 diabetes [4], for the diagnosis of MASLD, potentially transfers to the liver field unresolved issues long debated surrounding the metabolic syndrome [5]. Finally, clinicians must be aware that many people with prediabetes or different forms of diabetes may have steatosis and hyperglycemia but not necessarily insulin resistance or MASLD (*e.g.*, after pancreatectomy, cystic fibrosis, type 1 diabetes and certain diabetes endotypes) [6].

MASLD may assist non-specialists and people with the disease to link insulin resistance and metabolic abnormalities to steatosis, but use of the term may invalidate some prior epidemiological work. While the population identified by the new definitions (*e.g.*, MASLD, MASH) will overlap well in individuals attending tertiary care centers or registries, or participating in NASH/MASH clinical trials, more work is needed to validate MASLD across different populations, as recently performed [2,3]. Instead of assuming that MASLD, despite its new definition, is identical to NAFLD, we need to generate outcomes evidence with carefully designed research. A new, better definition needs to encompass steatosis in all settings, even if having a low risk of advanced fibrosis, as in primary care. More research is urgently needed to validate the proposed definition of MASLD in terms of its sensitivity, specificity, positive predictive value and negative predictive value for insulin resistance compared to steatosis alone (NAFLD). We propose that individuals without ≥ 1 cardiometabolic risk factor criteria would be better classified as having "early" MASLD rather than "cryptogenic steatosis" when all secondary causes have been ruled out. Steatosis without comorbidities may be more common in young adults (age 18-44), where ~40 % are estimated to have insulin resistance but are often not obese [7]. Mislabeling steatosis linked to insulin resistance as "cryptogenic steatosis" may have important clinical consequences as it may favor clinical inertia and downplay an emphasis on lifestyle changes to avoid liver disease progression. Depending on resources, assessment of insulin resistance (*e.g.*, HOMA-IR) and/or oral glucose tolerance test would be helpful in this setting, as prediabetes or diabetes are the most insulin-resistant states and, among metabolic comorbidities, have the greatest negative impact on the development and progression of steatohepatitis.

Of note, the decision to change the definition of MASLD was supported by a slim majority (53 % for a change *vs.* 47 % for no change) and would have benefited from a broader debate of the above issues before adoption. Future work and scientific debate may reconsider the "forced" definition that now directly links a biological event (insulin resistance) with the above common clinical cardiometabolic risk factors. The disease is steatosis or steatohepatitis (with its associated risk of fibrosis), without the need to impose upon it a clinical comorbidity to define it, diagnose it, or make it more worthy of our clinical attention. While cardiometabolic risk factors are potentially valuable aids in the diagnosis of insulin resistance and "metabolic dysfunction", they cannot be strictly forced into a relationship with steatosis against their (biological) will.

### Declaration of Competing Interest

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

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## CRediT authorship contribution statement

**Kenneth Cusi:** Writing – original draft, Writing – review & editing. **Zobair Younossi:** Writing – original draft, Writing – review & editing. **Michael Roden:** Writing – original draft, Writing – review & editing.

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## Reply to: "From NAFLD to MASLD: Promise and pitfalls of a new definition'

*To the Editor:*

From the beginning of this process, EASL, AASLD, and ALEH have been united in advancing the field for patients with steatotic liver disease [1]. We recognize that the journey to consensus has been challenging and, as one might expect from a consensus process addressing a topic with numerous divergent opinions, not all individual perspectives and arguments can be accommodated. Guided by a steering committee comprised of 35 international experts, including Cusi, Younossi, and Roden, and supported by a Delphi panel of 234 individuals, the initiative has garnered endorsement from over 70 societies globally. This was a thoughtfully considered exercise lasting over 3 years, reflecting extensive due diligence, and is now actively being implemented across the world.

The core objective of this endeavour was to establish a framework for understanding the spectrum of steatotic liver diseases, encompassing alcohol-related liver disease, in an affirmative and non-stigmatizing manner. Moreover, a key consideration in developing this new nomenclature was to provide a platform that could accommodate new findings and be adapted in the future. In that regard we agree and look forward to new studies that will inform and shape the field in years to come.

In their letter [2], the authors suggest that due to the requirement for a cardiometabolic risk factor (CMRF), the metabolic dysfunction-associated steatotic liver disease (MASLD) diagnosis is subtly different and requires validation in different populations. This comment is surprising as there is almost complete overlap between MASLD and non-alcoholic fatty liver disease (NAFLD), a fact indeed acknowledged by the authors. Data from population-based studies, biomarker consortia, biopsy proven cohorts and incident NAFLD confirm that MASLD, as currently defined, overlaps almost entirely with NAFLD. This consideration was paramount in the discussions about a change in definition to ensure that the prior literature remained valid and relevant. The requirement for at least one CMRF was a topic of much debate with a range of views on whether none, one, two or even more factors be required. A pragmatic view was taken that only one factor should be required to superimpose as much as possible with the previous NAFLD population.

Thus, we find ourselves in disagreement with the reservations the authors express concerning the requirement of a CMRF in the context of hepatic steatosis to make a diagnosis of MASLD. These criteria are not merely meant to act as a surrogate for insulin resistance, rather, they are important comorbidities associated with hepatic steatosis as well as steatohepatitis, fibrosis progression and cardiovascular outcomes. The authors approach the subject positing insulin resistance as the pivotal factor in explaining MASLD. While insulin resistance is undeniably significant both as a cause and consequence of steatotic liver disease, it may not be evident with routine testing. Moreover, Cusi et al. argue that only 50% of individuals who are overweight have insulin resistance, suggesting significant discordance – this was one of the reasons for allowing other established cardiometabolic risk factors that were not all directly restricted to insulin resistance to support the diagnosis.

We acknowledged that there may be individuals with hepatic steatosis who are clinically suspected of having MASLD yet fail to meet any of the cardiometabolic criteria. Hence, there is a caveat in the manuscript noting that these individuals may have possible MASLD as noted in the following excerpt - *'If there is uncertainty and the clinician strongly suspects metabolic dysfunction despite the absence of CMRF, then the term possible MASLD can be considered pending additional testing.'* Moreover, such patients are unlikely to have advanced disease and can be reassessed at a future time. Thus, the proposition of an "early MASLD" group does not seem clinically pertinent, given the minimal liver-related risk in this demographic. It also overlooks the possibility of other, as yet undefined, causes of steatosis.

Maintaining the alcohol thresholds for defining MASLD and providing an affirmative diagnostic framework emphasizing the importance of CRMF are valuable with respect to the current literature and implementation. This consensus-driven approach offers a high-level framework and we agree that fostering research for validation in various contexts is imperative.

Regional liver societies are unified in their support for the nomenclature as it has been presented - the framework is clear, and the path forward entails refinements based on validations and emerging

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EASL, AASLD and ALEH stand united to advance the field of steatotic liver disease