

# What's in a name? Renaming 'NAFLD' to 'MAFLD'

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## Abstract

In medicine, language matters and the words used to name and describe a disease can have a profound impact on patients and their families. Over the last two decades, many criticisms have been voiced about the nomenclature and definition of non-alcoholic fatty liver disease (NAFLD) in regards not only to the prominent role that alcohol plays in the definition but also on the negative impacts of the nomenclature including trivialization, stigmatization and less consideration of the disease in health policy. Recently, a consensus of international experts proposed that the disease acronym be changed from NAFLD to metabolic (dysfunction) associated fatty liver disease or 'MAFLD'. This change goes far beyond a mere semantic revision and may be the first step that catalyses the process to better conceptualize the disease for health promotion, patient orientation, case identification, ongoing clinical trials and for health services delivery. Here we review the history of, and definitions of MAFLD in the context of advancing our understanding of the pathogenesis of the disease. We also address the reasons, signals, promises, challenges and the way going forward from the name change from various stakeholder perspectives.

## KEYWORDS

MAFLD, metabolic, nomenclature

## 1 | INTRODUCTION

### 1.1 | What's in a name?

It has been nearly four decades since Susan Sontag brought to attention the metaphorical meanings of illness and the consequences of these meanings for the ways that illness is perceived, managed and

most vitally, experienced and lived by patients and their families.<sup>1</sup> It is clear that the consequences of medical nomenclature extend far beyond merely describing a medical condition to substantial social and psychological implications that profoundly influence the way in which subjects, families, society and politicians perceive, and therefore respond to the disease. Unfortunately, there is growing evidence that health professionals do not pay sufficient attention or time to

the branding aspect of medical conditions.<sup>2</sup> A consequence of using inappropriate nomenclature is confusion and mistrust between patients and physicians, stigma, undertreatment of diseases, limited acceptance of treatment options and sub-optimal allocation of funding and resources. In this regard, the WHO recently suggested that the healthcare profession should take more care when naming a disease.<sup>3</sup>

Concerns regarding misnomers for various medical conditions and their negative consequences have been raised over recent years. Examples include those for mental illnesses such as schizophrenia and epilepsy, and primary biliary cirrhosis (cholangitis). Similar calls are currently being considered with regard to reconsidering the nomenclature of 'non-communicable diseases' that cause >70% of global deaths. It has been suggested by many that use of the term 'non' diminishes the importance of the condition and that a simple dichotomization between 'communicable' and 'non-communicable' is a pervasive and false dichotomy.<sup>2,4-6</sup> In this context, serious concerns have been raised regarding the negative consequences of the term non-alcoholic fatty liver disease (NAFLD) and the way it is diagnosed.

Recently, a consensus by an international panel of experts recommended a change in name for NAFLD to metabolic (dysfunction) associated fatty liver disease (MAFLD).<sup>7</sup> Given the dramatic and growing prevalence of MAFLD that affects more than quarter of the global population,<sup>8,9</sup> the serious hepatic and extra-hepatic sequelae,<sup>10-12</sup> and the unavailability of pharmacological therapy, re-naming and re-defining of this disease is welcome.

In this review, we summarize the history of fatty liver disease and discuss the case for a name change from various perspectives (patients, healthcare providers, society and policy makers and scientists). We also discuss the lessons that can be taken from other diseases that have in the past moved through this cycle and end with discussion of the future challenges.

## 2 | HISTORICAL PERSPECTIVE ON FATTY LIVER NOMENCLATURE

The term 'fatty liver' was first described by Thomas Addison from Newcastle upon Tyne, England in 1836.<sup>13</sup> Thereafter, Karl Rokitsky, a pathologist from Vienna, Austria, noticed in autopsy specimens that hepatic fat accumulation may be causative for cirrhosis.<sup>14</sup> In 1884, Pepper first reported fatty liver in a diabetic patient and subsequently in 1885, Bartholow made one of the earliest observations on a potential association between obesity with fatty liver.<sup>15</sup> In 1938 Charles Connor demonstrated a link between fatty liver disease and progression to cirrhosis in diabetics patients.<sup>16</sup> Afterwards, several sporadic reports by pathologists in the 1950s-1970s described similarities between alcoholic liver disease and the hepatic histopathological changes observed in obese and diabetic patients, as summarized in a review by Brunt and colleagues.<sup>17</sup> In 1980, Jurgen Ludwig described a series of 20 patients who denied misuse of alcohol but had chronic liver disease with histological characteristics of alcoholic fatty liver disease. At that time, the disease had no name and Ludwig coined the term NAFLD and non-alcoholic

### Key points

- Metabolic (dysfunction) associated fatty liver disease or 'MAFLD' (formerly known as 'NAFLD') is the primary liver disease in Western countries that affect about quarter of the global population.
- Many criticisms have been voiced about the nomenclature and definition of non-alcoholic fatty liver disease (NAFLD).
- A consensus of international experts convened to undertake in-depth analyses of accuracy of fatty liver disease nomenclature, definition and spectrum of heterogeneity.
- This consortium proposed metabolic (dysfunction) associated fatty liver disease (MAFLD) as more appropriate nomenclature of this disease and they created a simplified and easily applicable comprehensive proposal for redefining of fatty liver disease.
- The proposed redefinition of the disease has the potential to increase patient awareness and understanding and to garner funding more effectively for research efforts to mitigate the impacts of the disease.

steatohepatitis (NASH) to describe the liver pathology. In 1983, Moran et al, described a series of 3 obese children with steatohepatitis.<sup>18</sup> For 40 years since, the disease has stayed with the prefix 'non', implying that it is just an outlier of a main stream condition. At the same time in clinical practice, this condition has grown to become the leading cause of liver disease and liver transplantation.

### 2.1 | Early signals that we need to rename fatty liver disease

Since its original description, clinical and research interest in MAFLD has burgeoned with numerous studies documenting its heritability, natural history and highlighting the pathophysiological link to features of metabolic syndrome, hepatic and extra-hepatic complications.<sup>19-21</sup> This research has led to advancements in our understanding of the causes and pathogenesis of MAFLD, has led to a flurry of clinical trials of drug treatments, and simultaneously emphasized that NAFLD is an incorrect term to describe the liver disease associated with metabolic dysfunction.<sup>22</sup>

The current definition of NAFLD in all guidelines and consensus recommendations requires the exclusion of other causes of liver diseases and of a daily significant amount of alcohol but the exact cut-offs to define 'significant' remains hotly debated. Suggested thresholds of alcohol consumption have varied from  $\leq 1$  drink (14 g) per day to 2-3 drinks (<30 g) in men and <20 g/day for women.<sup>23-26</sup> However, recent data including from a large cohort of 2475 individuals of the Framingham Heart Study with hepatic steatosis determined

by computed tomography suggest that alcohol use is associated with hepatic steatosis even in subjects with presumed NAFLD according to current definitions.<sup>27</sup>

To complicate matters, alcohol intake within the limits of the current definition has been demonstrated in various studies to pose a significant risk for progression of liver disease. For instance, in a study of 58,927 Korean subjects with NAFLD and low baseline fibrosis scores assessed by non-invasive markers (AST to Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4)), light (1.0-9.9 g/d) or moderate (10.0-29.9 g/d (10.0-19.9 g/d for women) alcohol consumption was independently associated with worsening of fibrosis over a median of 4.9 years of follow-up, compared to those with no alcohol consumption (0 g/d).<sup>28</sup> Similar findings were reported from multiple other studies that included patients from various ethnic backgrounds,<sup>29,30</sup> though as would be expected, some other reports did not report such an association.<sup>31</sup> Notably, a recent study of 28 million individuals and 649,000 cases with outcomes from the Global Burden of Diseases, Injuries, and Risk Factors for 195 countries and territories. This suggested that there is no safe limit for alcohol use.<sup>32</sup> Similar conclusions were reached in 6732 Finnish individuals where those without baseline liver disease and an average follow-up of 11 years, demonstrated that a safe limit of alcohol use does not exist.<sup>29</sup>

Another important consideration is that any set threshold of alcohol intake does not consider social realities where there is substantial interindividual variability in response to alcohol consumption based on age, sex, ethnicity, duration of alcohol consumption (short term vs chronic), timing (ongoing vs remote) and genetic susceptibility. This renders setting any absolute threshold of alcohol intake for a given individual unreliable and conceptually flawed. It should also be pointed out that there is no standardization or optimal questionnaires for alcohol intake and patient recall is often flawed with a tendency to under report. Adding to the complexity, recent data suggest some gut bacteria can produce alcohol contributing to liver damage.<sup>33</sup> In addition, there is accumulating evidence suggesting a shared genetic determinants of alcohol-related and metabolic associated fatty liver diseases, with a pivotal role for hepatic lipid accumulation that may be followed by hepatic inflammation in disease progression in both entities.<sup>34-38</sup>

Using the term 'non-alcoholic' to describe all fatty liver un-associated with alcohol consumption also leads to the lumping together of likely a variety of distinct and heterogeneous conditions. Thus, with advancements in our understanding of the metabolic dysfunction that triggers and promotes MAFLD development and progression, it seems appropriate that we eliminate alcohol from both the name and definition. This would open the door to develop and implement a set of 'positive' criteria to define the condition rather than relying on a 'non' or 'negative' definition.

## 2.2 | Renaming: Patients and physicians perspectives

For patients and physicians, the current acronym brings confusion that can negatively impact doctor-patient trust. It is likely that a

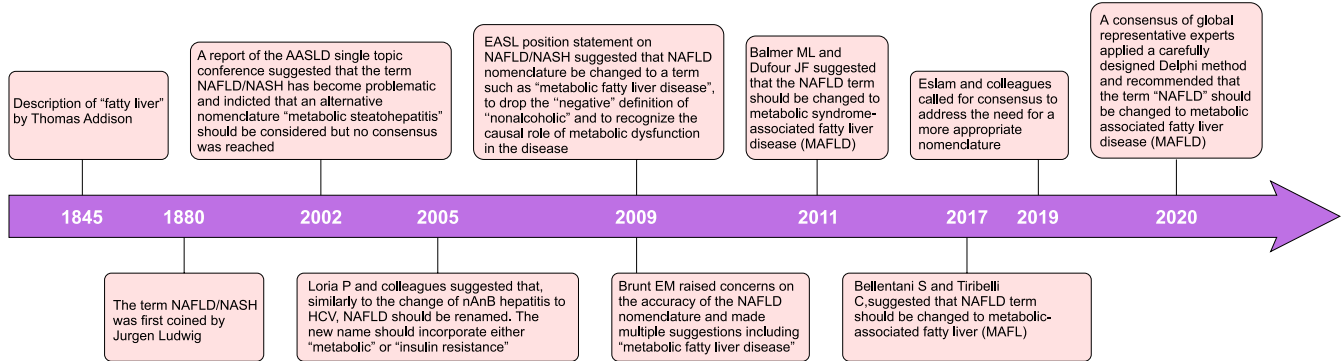
significant number of clinicians have experienced this ambiguous, even confusing conversation with a newly diagnosed NAFLD patient: 'the diagnosis of your liver disease is NAFLD, but it does not really have anything to do with alcohol'. Because it is 'non-alcoholic' that does not mean you can drink whatever you choose. Furthermore, having the term 'non' does not imply that the condition will not progress. Indeed, the term 'non' limits consideration of the clinical and pathological attributes of this complex disease and does not highlight the primary role of metabolic dysfunction in its pathogenesis. The current antidefinition provides no information whatsoever about what characterizes the condition.

Trivialization is another concern with the existing terminology. Many patients link liver disease solely to excess drinking and this can be a substantial barrier to acceptance of their diagnosis and to reluctance in moving through the stages of behavioural change and life-style interventions. This barrier is compounded if alcohol consumption is within the current recommended limits for the current definition of NAFLD.<sup>39,40</sup> Thus, renaming is the first pivotal step in the patient management journey to increase their understanding of, and perceptions of their disease, which then translates to better acceptance of therapeutic strategies.

According to a recent Lancet-EASL commission, patients with liver disease experience stigma resulting in a barrier to disease awareness and inequity in access to proper healthcare.<sup>41,42</sup> Including the word 'alcohol' as in 'NAFLD' is not only a misnomer, but could be harmful for patients because of this risk for active stigmatization. This is even more challenging given the growing prevalence of disease among children and also in many parts of the world, where alcohol consumption is taboo for religious or cultural reasons. In these situations, asking about alcohol intake can be misinterpreted as being provocative and perceived as a moral judgement.<sup>43</sup> Finally, having alcohol in the name will make any attempt at developing 'positive' criteria that is independent of alcohol even more confusing.

## 2.3 | The milestone in renaming

Multiple calls have been voiced by individual experts raising various concerns over the inaccuracies and serious negative consequences of 'NAFLD' as a term to describe fatty liver disease associated with metabolic dysfunction (Figure 1). In 2002, a report by the American Association for the Study of Liver Diseases (AASLD) single topic conference suggested that the inclusive term NAFLD/NASH is problematic and suggested an alternative nomenclature such as 'metabolic steatohepatitis', though this was but not uniformly accepted.<sup>44</sup> In 2005 Loria and colleagues suggested that NAFLD should be renamed.<sup>22</sup> They elaborated that similar to the change from nAnB hepatitis to HCV, the NAFLD acronym should be abandoned<sup>22</sup> and suggested that we incorporate either 'metabolic' or 'insulin resistance'. In 2009, an European Association for the Study of the Liver (EASL) position statement on NAFLD/NASH had clearer recommendations that NAFLD nomenclature should be changed to a term such as 'metabolic fatty liver disease' in order to drop the 'negative' definition and to recognize



**FIGURE 1** A timeline of key suggestions about the revising nomenclature of fatty liver disease

the likely causal role of metabolic dysfunction.<sup>45</sup> In 2011, Balmer ML and Dufour JF suggested that NAFLD should be renamed metabolic syndrome-associated fatty liver disease (MAFLD).<sup>46</sup> In 2017, Bellentani and Tiribelli also raised concerns on the use of 'non' and suggested metabolic-associated fatty liver (MAFL).<sup>47</sup> From a pathological perspective, in 2009, Brunt et al, also raised concerns on the accuracy of this nomenclature and made multiple suggestions including 'metabolic syndrome steatohepatitis' (MESH), 'metabolic fatty liver disease' and 'obesity-related fatty liver disease'. Interestingly, all suggestions used the terms 'metabolic', 'fatty liver' and 'disease'.

In spite of these various calls and initiatives, it has been challenging to change the nomenclature of NAFLD mainly because of the following conundrum: 'OK, then what is the alternative'? In 2019, Eslam and colleagues called for consensus to address this need<sup>48</sup> and later published a consensus of a representative panel of experts after applying a carefully designed Delphi method. The group reached consensus that the term 'NAFLD' should be replaced by metabolic associated fatty liver disease (MAFLD). The striking consistency between experts in the consensus (70%) speaks to the fact that MAFLD means virtually the same thing to different groups. Of interest, a majority of 169 respondents (64%) of a subsequent independent Twitter poll thought that NAFLD should indeed be changed to MAFLD and almost everyone acknowledged the limitations of the current label (<https://twitter.com/HannesHagstrom/status/1229025417203519489>).

Although this change has not been accepted by the major societies, it is to be expected that this will take time. However, the lessons that we can learn from other diseases is that change is a gradual process-pending acceptance by individuals, organizations and countries. The alternative is that we wait another two decades and potentially see no progress. Ultimately, even a partial change may accelerate the need in the field to build consensus, whatever that might look like.

## 2.4 | Evolving towards redefining of fatty liver disease

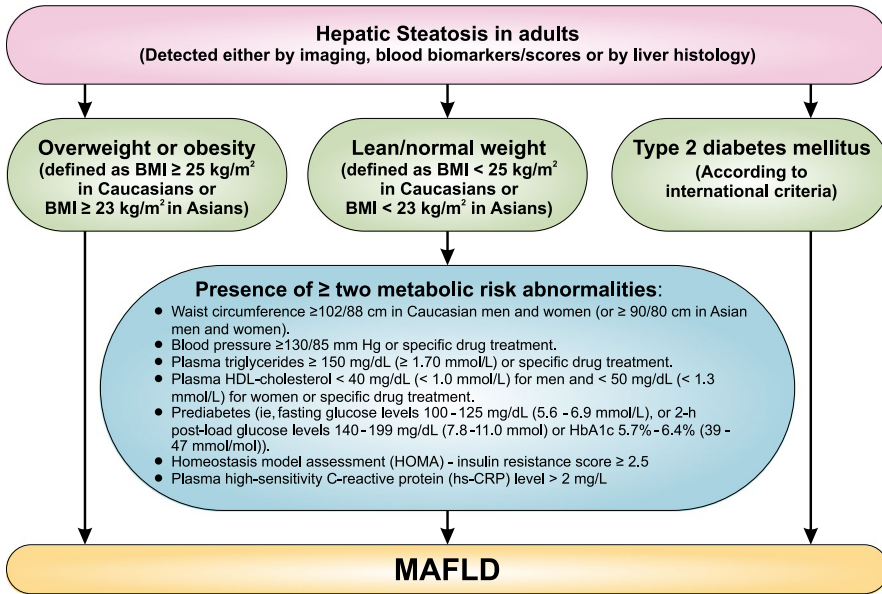
As a consequence to the proposed name change, an international consortium of the 32 experts from 22 countries all over the world was convened to undertake in-depth analyses of accuracy of fatty

liver disease definition and spectrum of heterogeneity. This consortium introduced simplified and easily applicable comprehensive proposal for redefining of fatty liver disease. They suggested a new practical and clinically based definition of MAFLD that incorporates 'positive criteria' for the diagnosis, ensures that MAFLD is a clear, distinct entity and circumvent the serious limitation of the current 'antidefinition'. These criteria are based on detection of steatosis with one of different modalities (imaging, blood biomarker or histology) with the presence one of the three criteria, overweight or obesity, type 2 diabetes mellitus or evidence of metabolic abnormalities<sup>49</sup> (Figure 2).

An intriguing aspect of this new definition, that exclusion of other significant alcohol intake or other chronic liver disease is not prerequisite for the diagnosis of MAFLD anymore. Thus it would be very interesting if future epidemiological studies could evaluate the association between fatty liver and other chronic liver disease and including continuous or ordinal ethanol intake and assess their interaction and the differential prognosis of patients with more than one liver disease.

Another aspect of the proposed redefinition of the disease that merit careful consideration that in order to improve the assessment of patients' disease severity, the simple and falsely dichotomous classification into non-alcoholic steatohepatitis 'NASH' vs 'non-NASH' was proposed to be abandoned. This likely will have broader impact on improving the ongoing effort for discovering non-invasive predictor for NASH, unmet need to date, likely because of the negative implication of this dichotomization. Further studies would be required to address whether we should reconsider the current endpoints for clinical trials that require improvement of NASH. Notably, that the only Phase 3 clinical trial for MAFLD to date that showed significant results, demonstrated a significant effect for obeticholic acid on fibrosis, whereas co-primary endpoint of NASH resolution was not achieved.<sup>50,51</sup> Thus, it would be interesting explore in new proposed definition on this cohort and explore the effect on hepatic inflammation, rather than on NASH.

In addition, with appreciated heterogeneity of the disease, the nomenclature 'MAFLD' is flexible enough to be an overreaching term with several common denominators between potential subtypes. The disease covers a spectrum that extends to lean subjects with MAFLD and those with related cirrhosis that are previously



**FIGURE 2** A recently proposed diagnostic criteria for metabolic associated fatty liver disease (Adopted from Eslam et al<sup>49</sup>)

called ‘cryptogenic cirrhosis’. This proposed definition system will also allow space for further discoveries of these sub-types that had better represent of patient diversity (Figure 3).

**2.5 | Promises of the change: Lessons can be learned from other diseases**

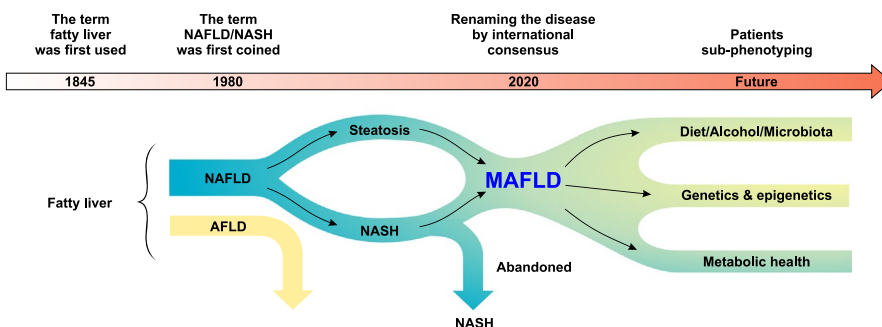
The renaming of NAFLD to MAFLD holds great promise to circumvent the inappropriate and inadvertent consequences of the older term NAFLD, such as stigmatization, trivialization and lack of patient awareness and can serve as a catalyst to increase funding and health policy action. There is a precedent for changing the name of other spectrum-like diseases (such as, epilepsy, autism and schizophrenia) and lessons can be learned from their experiences.<sup>5,52</sup>

**2.6 | Impact on health plans**

NAFLD is under-represented in the national health plans of developed countries. For example, in 2018/2019, experts from 29 European countries reported that none of these countries had written strategies or action plans for NAFLD. Only two countries had

any mention of NAFLD/NASH in relevant existing strategies such as for obesity.<sup>53</sup> Similarly, while many countries such as Egypt have very effective action plans for viral hepatitis, there are no similar policies to combat the growing burden of MAFLD.<sup>54</sup> In addition research outputs related to MAFLD have been disproportionately low.<sup>55</sup> The consequences are that it undermines progress towards improvements in human capital and the goal of universal health coverage.

The low levels of national and international attention paid to NAFLD in terms of health strategies, action plans and funding might at least partly be attributable to the inappropriate nomenclature. In the end, anything that begins with ‘non’ may be considered a ‘non-issue’ or a ‘non-starter’ and insinuates ‘not important’.<sup>2,56</sup> A name that is a longwinded non-definition and that only informs us what this group of diseases is not, does not befit a disease that now constitute the world's most common liver disease. An analogy is the ongoing effort to rename and reframe non-communicable diseases to get rid of the ‘non’ for the same reason.<sup>57-59</sup> In this regard, while the expected global economic burden of non-communicable diseases over the next two decades is US \$47 trillion and cause 30 times more deaths than human immunodeficiency virus (HIV), it receive 17 times less funding. Furthermore, NCDs receive the lowest development assistance per disability-adjusted life-year.<sup>57-59</sup> Thus, renaming NAFLD to MAFLD will help give the



**FIGURE 3** Past, present and future perspectives of redefining fatty liver disease



disease an appropriate name that reflects its pathophysiology and will lead to simple messages that can ultimately help raise funds to combat it.

## 2.7 | Impact on stigma and awareness

Recent analysis of data from the National Health and Nutrition Examination Survey (NHANES) 2001-2016, suggested that awareness of NAFLD was 1.5%, 2.4%, 2.2% and 3.5%, across the chronological surveys from 2001- 2004, 2005-2008, 2009-2012 and 2013-2016 respectively.<sup>60</sup> Similar results were obtained from 'Continuum Clinical', a global patient recruitment and retention company which suggested that only 6% of patients at high risk of developing steatohepatitis are aware of the disease.<sup>61</sup> Another recent survey by The NASH Education Program™ suggested that just 4% of respondents had heard about NAFLD,<sup>62</sup> whereas another work has suggested that a majority of patients with NAFLD have a poor understanding of the disease.<sup>63</sup> Worryingly, there is substantial under appreciation of NAFLD by primary care clinicians and under-recognition of the spectrum of the disease and how it can be assessed.<sup>64</sup> Similarly, a recent study indicated that NAFLD is under-recognized and commonly discovered incidentally at an advanced stage with cirrhosis.<sup>65</sup> A recent study of real-world data for 17,669,973 adults also revealed that in spite of the growing incidence, there is substantial under-diagnosis and under-recording for NAFLD.<sup>66</sup>

It has been demonstrated that stigma is common among patients with liver disease and unfortunately this is linked to adverse behaviours and attitudes such as decreased healthcare seeking actions.<sup>67</sup> It was found that liver disease is commonly associated with stigma because of its link with alcohol.<sup>68</sup> This is an even more challenging issue in sub-populations such as in children where alcohol consumption is usually not a relevant concern, and in parts of the world where is a prohibition of alcohol intake for religious and social reasons.

The change to MAFLD holds promise to aid in increasing awareness of the disease and decreasing its stigma. Lessons can be garnered from other fields that passed through the process of changing the nomenclature. For example, in 2002 in multiple East Asian countries including Korea and Japan, schizophrenia has been revised from 'split-mind disorder' (the translation of 'schizophrenia') to 'attunement disorder' as the original term was linked to high social stigma.<sup>5</sup> Notably, subsequent studies and a systematic review have demonstrated that in countries where schizophrenia has been renamed, it was accompanied by significant reductions in stigma, more accurate knowledge about disease, and improvements in attitudes towards patients.<sup>69</sup> Furthermore, in a study that included 150 mental health practitioners reasons for not informing patients and guardians about a schizophrenia diagnosis in 38% was that the name had a negative meaning.<sup>52</sup> Interestingly, it was shown that name change leads to significantly increased disease notification rates by mental health practitioners.<sup>70</sup> Thus, social stigmatization by inappropriate terminology can and does delay diagnosis, appropriate treatment and lead to poorer outcomes.<sup>70</sup>

## 2.8 | Challenges and the way forwards

Renaming fatty liver disease requires careful deliberation of societal and medical ramifications, but the revision is well worth the effort considering the benefits. Some have suggested that changing the old label may be cumbersome with no guarantees of either wide recognition by the community or achieving the predicted promises, particularly for the identification of patients and their overall perception of the disease. Further research will be required to assess the positive and negative consequences of renaming NAFLD to MAFLD. However, we also need to accept that in a world of 7 billion, achieving universal consensus and approval from all organizations does take time and will evolve naturally to greater (or lesser) extent. It seems that a feasible approach is encouraging gradual change, which can be followed by acceptance by learned societies if the change have widespread acceptance. In this context, a recent study that included 482 gastroenterologists and hepatologists mainly from academic centres, indicated that clinical practice patterns for the management of steatohepatitis frequently diverges substantially from published practice guidelines.<sup>71</sup> Hence, wide acceptance of the name change to MAFLD will be even more crucial.

## 3 | CONCLUSION REMARKS

Since the initial description by Ludwig and colleagues in 1980 to describe fatty liver disease arising in the absence of significant alcohol intake,<sup>72</sup> there have been major conceptual advances in our understanding of the pathophysiology of the disease. The term NAFLD is a poor fit and the time has come for a change to a more accurate one 'MAFLD'. Renaming fatty liver disease is not about being pedantic, but calling the world's most common liver disease 'non-alcoholic' propagates confusion, undermines efforts to spur a sense of urgency, and deflects attention from effective system-wide interventions. In spite of various initiatives to update disease nomenclature, previous attempts have not received much traction. Now, with the recent consensus, it is the perfect time to consolidate the growing support for change and then beyond this, to refocus efforts by reframing the disease, to develop more effective and durable treatments and cures. As a corollary, the name change has the potential to increase patient awareness and understanding and to garner funding more effectively for research efforts to mitigate the impacts of the disease.

### CONFLICT OF INTEREST

The authors have nothing to disclose.

### AUTHOR CONTRIBUTIONS

YF, IW, SB, AG, YA and DA contributed to conceptualization and the writing of the manuscript.

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