Received: 14 November 2017 | Accepted: 14 November 2017

DOI: 10.1111/liv.13643

REVIEW ARTICLE

WILEY Liver INTERNATIONAL

Global epidemiology of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: What we need in the future

Ana Ruth Araújo[1,2,3] | Natalia Rosso[1] | Giorgio Bedogni[1] | Claudio Tiribelli[1] | Stefano Bellentani[1,4]

[1]Fondazione Italiana Fegato-Onlus, Trieste, Italy

[2]Departamento de Clinica Medica, Faculdade de Medicina, Universidade Federal do Amazonas, Manaus, Brazil

[3]Fundaçao Alfredo da Mata, Manaus, Brazil

[4]Clinica Santa Chiara, Locarno, Switzerland

Correspondence
Dott. Med. Stefano Bellentani, Capo Servizio Gastroenterologia ed Epatologia, Clinica Santa Chiara SA, Locarno, Switzerland.
Email: s.bellentani@clinicasantachiara.ch or bellentanistefano@gmail.com
www.stefanobellentani.com

Funding information
Dr. Araújo was supported by a fellowship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior- CAPES, Brazil. This study was supported in part by an intramural grant from FIF.

Handling Editor: Francesco Negro

Abstract

The estimated prevalence of non-alcoholic fatty liver disease (NAFLD) worldwide is approximately 25%. However, the real prevalence of NAFLD and the associated disorders is unknown mainly because reliable and applicable diagnostic tests are lacking. This is further complicated by the lack of consensus on the terminology of different entities such as NAFLD or nonalcoholic steatohepatitis (NASH). Although assessing fatty infiltration in the liver is simple by ultrasound, the gold standard for the assessment of fibrosis, the only marker of progression towards more severe liver disease is still liver biopsy. Although other non-invasive tests have been proposed, they must still be validated in large series. Because NAFL/NAFLD/NASH and related metabolic diseases represent an economic burden, finding an inexpensive method to diagnose and stage fatty liver is a priority. A translational approach with the use of cell and/or animal models could help to reach this goal.

KEYWORDS

global epidemiology, new definition, non alcoholic fatty liver disease, nonalcoholic steatohepatitis

1 | INTRODUCTION

The "real prevalence" of fatty liver (FL) with its different clinical and histological forms is still to be defined, although the prevalence of obesity and diabetes are booming. What is still lacking is a clear definition of these disorders and non-invasive, reliable and affordable tests to distinguish simply non-alcoholic fatty liver (NAFL) from non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH). The aim of this article is to review critically what we know and what we should do to define the dimension of the problem, the terminology, and how to reduce and prevent this potentially life-threatening disease.

Abbreviations: AFLD, alcoholic fatty liver disease; FL, fatty liver; FLI, Fatty Liver Index; MAFL, metabolic associated fatty liver; MASH, metabolic associated steatohepatitis; NAFLD, non-alcoholic fatty liver disease; NAFL, non-alcoholic fatty liver; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

2 | THE NEED FOR A NEW POSITIVE DEFINITION

Non-alcoholic fatty liver disease is a negative definition based on the presence of FL (or "hepatic steatosis") determined by a surrogate index such as the Fatty Liver Index (FLI),[1] on imaging or histology, in the absence of other causes such as excess alcohol consumption (<20-30 g/day or 14 standard drinks per week in women and 21 standard drinks in men), viral, steatogenic medications or other monogenic hereditary disorders. The most recent EASL (European Association for the Study of the Liver)-EASD (European Association for the Study of Diabetes) – EASO (European Association FOR THE STUDY OF OBESITY) and AASLD (American Association for the Study of Liver Disease) practice guidelines[2,3] did not help clarify the definitions in clinical practice of NAFL, NAFLD and FL. NAFL is characterized by excessive

liver fat that is not due to alcohol consumption, without signs of inflammation or fibrosis. Primary NAFLD/NASH is commonly associated with insulin resistance or metabolic liver diseases such as diabetes, obesity and dyslipidemia,[2,3] and it is now considered to be the hepatic manifestation of the metabolic syndrome (MS). However, there is also a non-insulin resistance primary NAFLD/NASH of either genetic or cryptogenic aetiology (see Table 1) and a secondary NAFLD/NASH.

Definitions of the difference between alcoholic and non-alcoholic fatty liver diseases (AFLD vs NAFLD) are associated with significant methodological limitations including inadequate adjustment for confounding factors, different ways of calculating alcohol consumption, and failure to measure lifetime use or the pattern of alcohol intake. AFLD and NAFLD also have many similarities in pathogenesis, histology and genetic factors since the genes PNPLA3 and TM6SF2 contribute to the progression of both AFLD and NAFLD).[4] Because of these confounding factors the real prevalence and incidence of NAFLD and NASH varies greatly in the general population.

We strongly believe that the nomenclature must be revised. The classification of obesity was also recently changed, and there is an ongoing discussion on the universally accepted definition of so-called Metabolic Healthy Obesity (MHO), an important, emerging phenotype with intermediate risks in between healthy, normal weight and unhealthy, obese individuals, which should include both insulin sensitivity and FL.[5] We recently suggested moving from a negative to a positive definition of primary NAFLD and NASH to call them MAFL (Metabolic Associated Fatty Liver) and MASH (Metabolic Associated SteatoHepatitis)[6] thus revising the old definition and classification (See Table 2).

Key points

- The global prevalence of obesity, metabolic syndrome, and : Type 2 Dabetes Mellitus (T2DM) are high and increasing. Non-alcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are the expression in the liver of this entity. NAFL may be a benign or more severe disease evolving to cirrhosis and HCC.
- The definition and classification of primary NAFLD/NASH must be revised and associated with the metabolic changes in the liver.
- The real prevalence of NAFL, NAFLD and NASH has not been clarified.
- The need for sensitive, affordable, and reliable non-invasive tests to diagnose and stage this disease is urgent. Translational research may provide solutions.

3 | THE DIMENSION OF THE PROBLEM WORLDWIDE

There is a need to better define the current and future burden of NAFLD-related liver disease. Several reports have evaluated the epidemiology of NAFLD/NASH worldwide to allocate healthcare resources and develop national strategies, but because of the many possible confounding factors mentioned above, the real prevalence of primary NAFLD and NASH in the general population is probably **over**estimated. The most accurate estimation of the global prevalence of NAFLD is 24%-25% of the general population, a figure reported for the first time in Italy by the Dionysos study[7] and recently confirmed by Younossi[8,9] who described some regional differences with the highest rates reported in South America and the Middle East, followed by Asia, the USA and Europe.[8]

The increasing prevalence of NAFLD/NASH is in parallel to the pandemic spread of obesity, T2DM and MS, and NAFLD/NASH shall be the leading cause of the progression to cirrhosis and HCC in the next 5 years. A recent study performed from 1975 to 2014 in 19.2 million adult participants, reported that the age-standardized prevalence of obesity increased from 3.2% in 1975 to 10.8% in 2014 in men and from 6.4% to 14.9% in women.[10] The authors claim that if these trends

TABLE 1 Actual classification of non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH)

Primary insulin-resistant NAFLD/NASH	Primary non insulin resistant NAFLD/NASH	Secondary NAFLD/NASH
Metabolically healthy obesity (MHO) (visceral obesity)	Genetic [PNPLA3 and TM6SF2 genes involved]	Associated with endocrine disorders: - Policystic ovary sindrome (PCOS) - Hypothyroidism - GH deficiency
Metabolically obesity normal weight (MONW)	Hypobetalipoprotein syndrome	Environmental (High fructose diet; high fat diet)
Type 2 diabetes mellitus (T2DM)	Metabolically obesity normal weight (MONW) (probably genetic, too)	Drug-related (amiodarone, methotrexate, tamoxifen, corticosteroids)
Congenital lipodistrophy	Unknown causes (Cryptogenic)	Jejunoileal bypass
Lysosomal acid lypase deficiency (LALD or non-obese fatty liver)		Total parenteral nutrition (TPN), Starvation
		Associated with other hepatic diseases [viral, autoimmune, alcoholic steatohepatitis (ASH), etc.]

TABLE 2 New proposed classification of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis

Primary MAFL/MASH	Secondary MAFL/MASH
Metabolically healthy obesity (MHO) (visceral obesity)	Associated with endocrine disorders: - Policystic ovary syndrome (POS) - Hypothyroidism - GH Deficiency
Metabolically obesity normal weight (MONW) (probably genetic, too)	Environmental (High fructose diet; high fat diet)
Type 2 diabetes mellitus (T2DM)	Drug-related (amiodarone, methotrexate, tamoxifen, corticosteroids)
Genetic [PNPLA3 and TM6SF2 genes involved]	Jejunoileal bypass
Hypobetalipoprotein syndrome	Total parenteral nutrition (TPN), starvation
Congenital lipodistrophy	Associated with other hepatic diseases [viral, autoimmune, alcoholic steatohepatitis (ASH), etc.]
Lysosomal acid lypase deficiency (LALD or non-obese fatty liver)	
Unknown causes (Cryptogenic)	

continue, the global prevalence of obesity will reach 18% in men and over 21% in women in 2025. This situation is even more serious if the paediatric population is considered, with the prevalence of obesity increasing from 0.7% in 1975 to 5.6% in 2016 in girls, and from 0.9% to 7.8% in boys.[11] Because the progression from FL to NASH is more rapid and aggressive in children than in adults,[12] this is especially worrisome because obesity in early life increases the risk of both cirrhosis and HCC in adulthood.

4 | NATURAL HISTORY AND DISEASE BURDEN

To better understand the natural history and disease burden of this entity, NAFLD may be classified into two groups: NAFL or NASH with steatosis accompanied by inflammation, fibrosis and other changes. The odds of progression to advanced liver disease, including hepatic decompensation and hepatocellular carcinoma (HCC), are higher in patients with NASH than those with NAFL.[13] Progression to cirrhosis is characterized by the progression of the stages of fibrosis, and the stage of fibrosis has been linked to long-term clinical outcomes.[14] Most liver-related outcomes occur once cirrhosis has developed, except for HCC, which can occur without cirrhosis.[15,16] The healthcare resources necessary to manage NAFLD increase markedly with the worsening of fibrosis, and especially once cirrhosis has developed. NASH is now one of the main causes of end-stage liver disease and HCC requiring liver transplantation in the US.[17,18] Increasing age, obesity and DM have been clearly identified as risk factors for the progression to cirrhosis.[19] Patients with

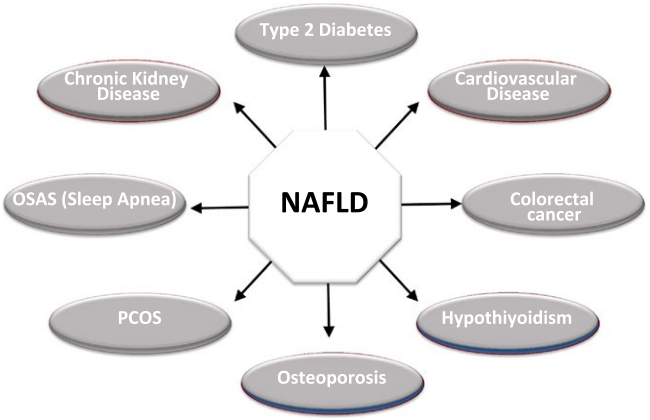

FIGURE 1 Extrahepatic complications of non-alcoholic fatty liver disease

NASH have a high risk of both liver-related morbidity and mortality as well as metabolic comorbidities (10 × higher than the general population), cardiovascular disease and mortality (2 × higher than the general population), and cancer (particularly bowel and breast cancer).[8,9] All potential extrahepatic complications are reported in Figure 1.

Although there are no exact models to estimate the incidence and the disease burden of NAFLD in the next few years, the changing trends of obesity and diabetes (DM), suggest that this problem is increasing worldwide and might place a growing strain on healthcare systems.

5 | THE NEED FOR RELIABLE BIOMARKERS

Although the research on NAFLD biomarkers has advanced in the last two decades, there are still no reliable non-invasive markers for the diagnosis or the staging of this disease (NAFLD vs NASH). As mentioned above, the FLI[1] is probably the most popular score to diagnose FL in the literature. However, it was not designed to predict changes in FL status, and cannot be used to diagnose NASH.

Effective screening is essential due to the extensive number of NAFLD patients with potentially,[9] and there is an urgent need to develop a non-invasive method, particularly for large-scale NAFLD screening.[20] Non-invasive monitoring of hepatocyte apoptosis in the blood of patients with NAFLD has been proposed as a noninvasive biomarker and may help predict progression to cirrhosis and HCC.[9,21]

In addition, there is also a need to develop and validate a simple, reproducible and non-invasive test(s) that can accurately distinguish NASH from NAFL and determine the stage of disease. This "ideal test" would help clinicians identify and follow-up patients with NASH, predicting the response to therapy and the risk of disease progression.[4] Many studies have identified potential biomarkers to predict disease activity for the whole spectrum of NAFLD[22-29]: a) cell death and apoptosis biomarkers, including caspase-generated CK-18 fragment (CK-18)[23,24]; b) the fibroblast growth factor 21

(FGF21); c) insulin-like growth factor 2 (IGF-2) and the epidermal growth factor receptor (EGFR).[25-29] These biomarkers are expected to improve the ability to stratify disease severity in NAFLD and may identify additional pathways to target for treatment.[28] However, despite several available studies, an accurate and reproducible non-invasive method to diagnose NAFLD/NASH, which could be used for screening in the general population or for patient follow-up has still not been identified.

6 | FUTURE PERSPECTIVES

Despite the alarming numbers of patients, real therapeutic options are still limited for NAFLD because of its complexity and the high individual variability. At present, drug therapies are based on the association of several compounds in an attempt to reverse the comorbidities of the metabolic syndrome. The molecular mechanisms leading to fat accumulation, oxidative imbalance, and liver fibrosis are the targets of the main classes of drugs. The potential pharmacological benefits of existing clinically available drugs, those in phase II trials as well as drugs under evaluation in preclinical studies, have been extensively reviewed. Unfortunately, to date, none of the pharmacological approaches have provided a real, long-lasting benefit. Thus, the cornerstones to the management of this disease are still lifestyle modifications and weight loss. Interestingly, histological improvement in liver biopsies is associated with the extent of weight loss. A reduction of ≥5%-10% in body weight is needed to obtain a beneficial effect in the reversion of NASH (and fibrosis). Unfortunately, low patient compliance to this approach (even in highly motivated subjects) is the most difficult obstacle.[30,31]

Recent studies on bioactive food compounds are an interesting approach.[32-34] Although nutritional interventions are one of the most successful strategies for the management of NAFLD and NASH, more research is still needed to develop suitable treatment with high impact against these diseases. Thus, there is an urgent need to develop highly effective and safe therapeutic strategies for NASH.

Several experimental models have been characterized in the field of translational research to study the molecular mechanisms involved in the onset and progression of the disease. These cover a wide spectrum of variables, from a single cell to more complex systems such as ex-vivo or in-vivo *models*. In the past few years the latter have played an important role in the understanding of the pathophysiological mechanisms of the disease, and provided useful and detailed information on the cellular response to fatty acid overload and the cross-talk of injured hepatocytes with other hepatic cells, such as stellate cells.[35-37] However, it must be remembered that although the models may mimic the clinical scenario, any results obtained in the lab need to be validated and translated in the much more complex human system.

7 | WHAT NEXT?

Although it is clear that FL (either NAFLD or NASH) is significantly increasing in all the regions of the world, a precise estimation of the denominator of the equation clinically diagnosed FL/undiagnosed subjects is still lacking. This is mainly due to the lack of non-invasive, affordable tests that can be used worldwide to precisely define the number of affected individuals and to the confusing terminology which prevents reliable comparisons of series from different countries and institutions. As previously reported, FL is one element of the much more complex metabolic syndrome and it will probably be encountered in consultations for T2DM or cardiovascular diseases. Thus, FL and all related diseases should be managed by multidisciplinary teams. This coordinated effort will help determine the "denominator" of the equation and provide more focused and effective prevention.

CONFLICTS OF INTEREST

The authors do not have any disclosures to report.

ORCID

Stefano Bellentani http://orcid.org/0000-0003-2836-8870

REFERENCES

1. Bedogni G, Bellentani S, Miglioli L, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol*. 2006;6:33-40.
2. EASL–EASD–EASO. Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol*. 64:1388-1402.
3. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2017. https://doi.org/10.1002/hep.29367.
4. AJmera VH, Terrault NA, Harrison SA. Is moderate alcohol use in nonalcoholic fatty liver disease good or bad? A critical review *Hepatology*. 2017;65:2090-2099.
5. Roberson LL, Aneni EC, Maziak W, et al. Beyond BMI: the "Metabolically healthy obese" phenotype & its association with clinical/subclinical cardiovascular disease and all-cause mortality – a systematic review. *BMC Public Health*. 2014;14:14-26.
6. Bellentani S, Tiribell C. Is time to change NAFLD and NASH nomenclature? *Lancet Gastroenterol Hepatol*. 2017;2:547-548.
7. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology*. 2005;42:44-52.
8. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol*. 2017. https://doi.org/10.1038/nrgastro.2017.109. Published online 20 September 2017.
9. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64:73-84.
10. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet*. 2016;387:1377-1396.
11. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet*. 2017;17:32129-32133.

12. Marin V, Rosso N, Dal Ben M, et al. An animal model for the juvenile non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. *PLoS ONE*. 2016;11:e0158817.
13. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol*. 2015;13:643-654.e1-9; quiz e39-40.
14. Adams LA, Lymp JF, St Sauver J, et al. The natural history of non-alcoholic fatty liver disease: a population-based cohort study. *Gastroenterology*. 2005;129:113-121.
15. White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clin Gastroenterol Hepatol*. 2012;10:1342-1359.e2.
16. Piscaglia F, Svegliati-Baroni G, Barchetti A, et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. *Hepatology*. 2016;63:827-838.
17. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology*. 2015;148:547-555.
18. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. *Hepatology*. 2014;59:2188-2195.
19. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology*. 2007;45:846-854.
20. Sherif ZA, Saeed A, Ghavimi S, et al. Global epidemiology of nonalcoholic fatty liver disease and perspectives on US minority populations. *Dig Dis Sci*. 2016;61:1214-1225.
21. Feldstein AE, Wieckowska A, Lopez AR, Liu YC, Zein NN, McCullough AJ. Cytokeratin-18 fragment levels as noninvasive biomarker for nonalcoholic steatohepatitis: a multicenter validation study. *Hepatology*. 2009;50:1072-1078.
22. Joka D, Wahl K, Moeller S, et al. Prospective biopsy-controlled evaluation of cell death biomarkers for prediction liver fibrosis and nonalcoholic steatohepatitis. *Hepatology*. 2012;55:455-464.
23. Cusi K, Chang Z, Harrison S, et al. Limited value of plasma cytokeratin-18 as a biomarker for NASH and fibrosis in patients with nonalcoholic fatty liver disease. *J Hepatol*. 2014;60:167-174.
24. El Bassat H, Ziada DH, Hasby EA, Nagy H, Abo Ryia MH. Apoptotic and anti-apoptotic seromarkers for assessment of disease severity of non-alcoholic steatohepatitis. *Arab J Gastroenterol*. 2014;15:6-11.
25. Shen J, Lik-YuenChan H, Wong GL, et al. Non-invasive diagnosis of non-alcoholic steatohepatitis by combined serum biomarkers. *J Hepatol*. 2012;56:1363-1370.
26. Giraudi PJ, Gambaro SE, Arroyo SO, et al. A simple in silico strategy identifies candidate biomarkers for the diagnosis of liver fibrosis in morbidly obese subjects. *Liver Int*. 2017. https://doi.org/10.1111/liv.13505.
27. Hagstrom H, Stal P, Hultcr antz R, Brismar K, Ansurudeen I. IGFBP-1 and IGF-I as markers for advanced fibrosis in NAFLD – a pilot study. *Scand J Gastroenterol*. 2017;19:1-8.
28. Ajmera V, Perito ER, Bass NM, et al. Novel plasma biomarkers associated with liver disease severity in adults with nonalcoholic fatty liver disease. *Hepatology*. 2017;65:65-77.
29. Qi S, Xu D, Li Q, et al. Metabonomics screening of serum identifies pyroglutamate as a diagnostic biomarker for nonalcoholic steatohepatitis. *Clin Chim Acta*. 2017;473:89-95.
30. Townsend SA, Newsome PN. Review article: New treatments in non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2017;46:494-507.
31. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 2015;149:367-378, e5; quiz e14–15.
32. Marin V, Gazzin S, Gambaro SE, et al. Effects of oral administration of silymarin in a juvenile murine model of non-alcoholic steatohepatitis. *Nutrients*. 2017;9:e1006.
33. Lavine JE, Schwimmer JB, Van Natta ML, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. *JAMA*. 2011;305:1659-1668.
34. He XX, Wu XL, Chen RP, et al. Effectiveness of omega-3 polyunsaturated fatty acids in non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *PLoS ONE*. 2016;11:e0162368.
35. Van Herck MA, Vonghia L, Francque SM. Animal models of non-alcoholic fatty liver disease – a starter's guide. *Nutrients*. 2017;9:1072.
36. Chavez-Tapia NC, Rosso N, Tiribelli C. In vitro models for the study of non-alcoholic fatty liver disease. *Curr Med Chem*. 2011;18:1079-1084.
37. Giraudi PJ, Becerra VJ, Marin V, Chavez-Tapia NC, Tiribelli C, Rosso N. The importance of the interaction between hepatocyte and hepatic stellate cells in fibrogenesis induced by fatty accumulation. *Exp Mol Pathol*. 2015;98:85-92.

How to cite this article: Araújo AR, Rosso N, Bedogni G, et al. Global epidemiology of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: What we need in the future. *Liver Int*. 2018;38(Suppl. 1):47–51. https://doi.org/10.1111/liv.13643