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Research article

JHEP|Reports

European 'NAFLD Preparedness Index' — Is Europe ready to meet the challenge of fatty liver disease?

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JHEP Reports **2021.** https://doi.org/10.1016/j.jhepr.2021.100234

Background & Aims: Non-alcoholic fatty liver disease (NAFLD), which is closely associated with obesity, metabolic syndrome, and diabetes, is a highly prevalent emerging condition that can be optimally managed through a multidisciplinary patient-centred approach. National preparedness to address NAFLD is essential to ensure that health systems can deliver effective care. We present a NAFLD Preparedness Index for Europe.

Methods: In June 2019, data were extracted by expert groups from 29 countries to complete a 41-item questionnaire about NAFLD. Questions were classified into 4 categories: policies/civil society (9 questions), guidelines (16 questions), epidemiology (4 questions), and care management (12 questions). Based on the responses, national preparedness for each indicator was classified into low, middle, or high-levels. We then applied a multiple correspondence analysis to obtain a standardised preparedness score for each country ranging from 0 to 100.

Results: The analysis estimated a summary factor that explained 71.3% of the variation in the dataset. No countries were found to have yet attained a high-level of preparedness. Currently, the UK (75.5) scored best, although falling within the mid-level preparedness band, followed by Spain (56.2), and Denmark (43.4), whereas Luxembourg and Ireland were the lowest scoring countries with a score of 4.9. Only Spain scored highly in the epidemiology indicator category, whereas the UK was the only country that scored highly for care management.

Conclusions: The NAFLD Preparedness Index indicates substantial variation between countries' readiness to address NAFLD. Notably, even those countries that score relatively highly exhibit deficiencies in key domains, suggesting that structural changes are needed to optimise NAFLD management and ensure effective public health approaches are in place.

Lay summary: Non-alcoholic fatty liver disease (NAFLD), which is closely associated with obesity, metabolic syndrome, and diabetes, is a highly prevalent condition that can be optimally managed through a multidisciplinary patient-centred approach. National preparedness to address NAFLD is essential to allow for effective public health measures aimed at preventing disease while also ensuring that health systems can deliver effective care to affected populations. This study defined preparedness as having adequate policies and civil society engagement, guidelines, epidemiology, and care management. NAFLD preparedness was found to be deficient in all 29 countries studied, with great variation among the countries and the 4 categories studied.

Keywords: Non-alcoholic fatty liver disease; Liver health; Multiple joint correspondence analysis; Policy preparedness; Health policy; Metabolic-associated fatty liver disease; Non-alcoholic steatohepatitis; Europe.

Received 13 November 2020; received in revised form 16 December 2020; accepted 28 December 2020; available online 21 January 2021

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent emerging condition[1,2] and the most common chronic liver disease globally.[3] The global prevalence is estimated to be 25% (95% CI: 22–20)[4] and between 2012 and 2017 the disease was the most rapidly growing contributor to liver mortality and morbidity.[5] With an estimated prevalence of 24% (95% CI: 16–34) Europe has a high burden of NAFLD,[4] which is closely associated

with the increasing prevalence of obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM).[6,7] By 2025, obesity in Europe is forecasted to increase in 44 countries, with 33 of the 53 World Health Organization (WHO) European Region countries estimated to have a prevalence of over 20%.[8] Driven by sustained increases in the burden of obesity and T2DM and an ageing population, the NAFLD burden is expected to grow further in the coming years.[2]

NAFLD covers a broad spectrum, from non-alcoholic fatty liver (steatosis) to non-alcoholic steatohepatitis (NASH), which is associated with hepatic fibrosis and can ultimately lead to end-stage liver disease, liver cancer, and death.[3,9,10] Cardiovascular disease remains the leading cause of death in people with NAFLD.[3,10] The disease is also recognised as a leading cause of liver cancer,[11,12] with liver cancer being the second leading cause of years of life lost amongst all cancers.[13] NASH is already a leading cause of liver transplantation in the USA.[14] In Europe, between 2002 and 2016, 4% of all first-time liver transplant recipients were transplanted for NASH, with the proportion of transplants related to NASH increasing from 1.2% in 2002 to 8.4% in 2016.[15]

The diagnosis and treatment of NAFLD and its common comorbidities requires multidisciplinary patient-centred care; however, awareness of the disease amongst at risk populations, the general public, and non-liver specialist healthcare providers is limited.[16] Diagnosis of NAFLD is further complicated by the difficulties with ruling out liver diseases of other aetiology, namely assessing excess alcohol consumption, and the availability of accurate, inexpensive non-invasive diagnostic tools for identifying and staging the disease, with liver biopsy remaining the gold standard for the assessment of fibrosis.[17]

Despite substantial interest in the development of treatments for NAFLD and some evidence of progress, there is currently no approved pharmacological therapy.[18–20] In the absence of pharmacological treatments, lifestyle interventions aimed at addressing the underlying risk factors of NAFLD and metabolic syndrome, including diet and physical activity, are the cornerstone of clinical management,[21] although patient adherence to lifestyle changes remains a critical issue for successful care.[21,22] In morbidly obese patients, bariatric surgery may also result in sustained improvement in liver fat, inflammation, and fibrosis.[23]

Although NAFLD is a major public health challenge, it remains largely absent in national health policies. A 2019 study of 29 European countries found that none had a national strategy for addressing NAFLD and that NAFLD was mentioned in less than 50% of all national strategies and clinical management guidelines on obesity, diabetes, and cardiovascular disease.[24] Furthermore, many of the broad discussions on international health policy, including the WHO's Universal Health Coverage Programme[25] and the United Nations' Sustainable Development Goals,[26] do not refer to NAFLD or NASH.

Country preparedness to address NAFLD is essential to ensure that health systems can accommodate this growing population while delivering effective prevention and care. To sustainably reduce the burden of NAFLD, improvements in early diagnosis and clinical management need to be accompanied by public health policy actions that comprehensively address the risk factors for NAFLD, obesity, T2DM, and cardiovascular disease in parallel.[27,28]

In this paper, we introduce a newly designed score, which aims to identify priority actions that can be taken to better prepare countries to address the growing challenge of NAFLD.

Materials and methods

In June 2019, expert groups from 29 countries in the European Union/European Economic Area (EU/EEA) completed a 41-item questionnaire about NAFLD by reviewing key documents in their setting and extracting the appropriate data.[24]

Questions were classified into 4 indicators composed of a varying number of survey questions: policies and civil society engagement (9 questions), guidelines (16 questions), epidemiology (4 questions), and NAFLD management and care (12 questions). For each indicator, countries were classified into low-, middle-, or high-preparedness levels based on the definitions in Table 1. The responses to survey questions were used to categorise countries into 1 of 3 levels for each of the 4 indicators (Table 1). The index was created by using the values of the indicators only and not the direct answers from the questions on the survey. The full questionnaire is provided in the Supplementary material.

Next, we applied a multiple correspondence analysis (MCA) to calculate a preparedness score for each country based on their indicator values and the indicator values of all other countries in the study. The purpose of the MCA was to determine the weights for each of the levels of each indicator for the score. In an MCA, the Chi-squared distance is calculated between the response patterns of all the countries and dimensions are fitted to the data to extract the maximum amount of variation. The percentage of the total variation explained is calculated for each of the new dimensions, termed components.[29] MCA helps to determine the relationship among the response pattern in the multidimensional data. This approach enables all of the information in the categorical values for the 4 indicators for all countries to be combined into a single factor that functions as a weighted summary of each possible different level indicator combination. The weighted summary has an assigned weight (Fig. 1) for each individual level of each indicator, which combine to give the full score of the country. In creating this index, we only used the first weighted summary dimension of the MCA as it explained the most variation 71.7% versus 4.0%, 2.8%, and 1.6% variation for the second, third, and forth dimensions, respectively.

Three hypothesised reference scenarios (lowest-, middle-, and best-preparedness) were included in the analysis to standardise and contextualise responses, such that the minimum possible score was the 'low-preparedness scenario' and the maximum was 'best-preparedness'. Values of the country scores were standardised to range from 0 to 100 (lowest- to best-preparedness) using the standard min-max transformation technique.[30] We managed, prepared, and analysed all data using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Microsoft Excel 2017 version 15.31 (Microsoft Corp., Redmond, WA, USA) was used for storage of the data.

Results

For every indicator, the modal preparedness level was low/middle. The high-preparedness level response was never the most frequent level for any of the 4 indicators (Table 2). For the epidemiology and NAFLD care management indicators, only Spain and the UK scored in the high-level, respectively. For the guidelines indicator, 2 countries scored in the middle-level response, with the rest either in the high-level (n = 10) or the low-level (n = 17). For the policies/civil society indicator, most countries scored in the middle-level (n = 13).

Table 1. Definitions of the categorisation for the different preparedness categories. NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Indicator	N	Low-level preparedness	Middle-level preparedness	High-level preparedness
Policies and civil society	9	Countries that do not meet the definitions for the middle- or high-level	Countries with an obesity, alcohol, cardiovascular disease, diabetes, or health and diet strategy in place with no civil society or government campaign in place	Countries where NAFLD is mentioned in any strategy on obesity, alcohol, cardiovascular disease, diabetes, or health and diet and a civil society or government campaign addressing NAFLD is in place
Guidelines	16	Countries that do not meet the definitions for the middle- or high-level	Countries with one of: diabetes, cirrhosis, dyslipidaemia, alcohol, hypertension, cardiovascular disease, or hepatocellular carcinoma guidelines that include NAFLD	Countries with a NAFLD/NASH guideline in place or diabetes, cirrhosis, dyslipidaemia, alcohol, hypertension, cardiovascular disease, or hepatocellular carcinoma guidelines that all contain NAFLD
Epidemiology	4	Countries that do not meet the definitions for the middle- or high-level	Countries that either have an epidemiologic NAFLD population study in the last 5 years or an ongoing epidemiologic assessment, or a regional NAFLD cohort, or a NAFLD registry	Countries with a population level epidemiological study on NAFLD in the past 5 years or an ongoing NAFLD epidemiological assessment, and a national registry, or a regional NAFLD cohort
NAFLD care management	12	Countries where NAFLD care is only provided by gastroenterologists and hepatologists, primary care providers and multidisciplinary teams are not involved in NAFLD management, and lifestyle programmes are not part of NAFLD care	Countries that are not classified as high- or low-level	Countries where primary care providers and multidisciplinary teams are involved in NAFLD management, lifestyle programmes are part of NAFLD care, and an algorithm is in place to guide referral from primary to secondary care

From the MCA, we estimated a summary factor that explained 71.7% of the variation in the dataset. The highest contributions to the score were the high response levels for NAFLD care management and epidemiology (Fig. S1).

The highest scoring country was the UK (75.5), followed by Spain (56.6), and Germany (43.8), while Luxembourg and Ireland were the lowest scoring countries with a score of 5.0 (Fig. 1). In total, there were 14 countries that scored lower than the mid-level preparedness scenario (20.3; Table 3). No countries scored in the high-level for every indicator.

Discussion

We present a detailed analysis of national readiness to address the public health challenges posed by NAFLD. By assessing four key domains, we encompass not only the response at the level of healthcare provision, but also, crucially, public health responses that may prevent or reduce the burden of NAFLD-related morbidity and/or mitigate future healthcare costs.

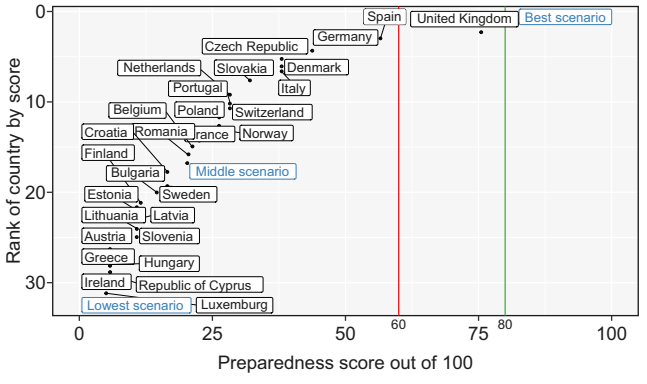

Fig. 1. European NAFLD Preparedness Index and country rank (n = 29). The red line cut-off at 60 denotes countries that are unprepared. Above the green line (80) denotes prepared. NAFLD, non-alcoholic fatty liver disease. The index was calculated using a multiple correspondence analysis.

This analysis, the first of its kind, demonstrates 2 main results. First, no country was able to approximate to the 'high preparedness-level' scenario. Whilst the UK scored most favourably, demonstrating the importance of addressing all 4 of the study's preparedness indicators, its score was primarily driven by a national guideline within a national universal healthcare system[31] that advocates for early detection of NAFLD and associated comorbidities in primary care. Overall, however, with a score of 75.4, the UK can still improve and the presence of guidelines does not imply that they are widely adopted by healthcare professionals in day-to-day practice. Secondly, despite the high disease burden in Europe, the organisation of health systems seems insufficient to address NAFLD, as highlighted by the large number of countries scoring low on the guidelines indicator, including countries with policies addressing liver disease, and only 1 country scoring high on care management. As such, our findings clearly highlight major weaknesses in current preparedness across Europe and support the need for specific policy actions to address these weaknesses.

From a public health perspective attention must be paid to NAFLD prevention owing to the substantial health and economic implications of advanced disease,[32] together with the lack of effective pharmacological therapies. NAFLD is closely related to a range of modifiable risk factors linked to the built environment, sociocultural context, and psychological factors.[33] These include the easy availability of unhealthy food and drinks, including in or near schools, the lack of safe space for undertaking physical activity, or the lack of fiscal policies that incentivise healthy lifestyle choices. Together, these unfavourable conditions lead to what is commonly termed the 'obesogenic environment'.[34] Within this context public health approaches that place the responsibility on individuals are unlikely to succeed, rather there is a need for comprehensive structural responses that create healthy environments that support and promote healthy lives.[35]

The obesogenic environment impacts along a social gradient, with lower-income populations being disproportionality

Table 2. Breakdown of the country (n = 29) responses by the 4 indicators. NAFLD, non-alcoholic fatty liver disease.

	Low-level preparedness	Mid-level preparedness	High-level preparedness
Policies and civil society	6	13	10
Guidelines	17	2	10
Epidemiology	17	11	1
NAFLD care management	5	23	1

affected. In no small part this is as a result of the availability of cheap ultra-processed, energy-dense, but nutrient poor, high-fat and -sugar foods.[36,37] Indeed, in a cross-sectional analysis of a nationally representative sample of adults from the USA, food-insecure adults were more likely to have NAFLD and advanced fibrosis.[38] Food insecurity is associated with obesity, diabetes, and hypertension and drives a cardiometabolic risk profile, which are all risk factors for fatty liver development.[33] Consequently, policies to prevent or provide care for obesity, diabetes, or NAFLD should be developed as a continuum of actions targeting populations at different levels of risk. Such policies represent an opportunity for much needed cross-disciplinary collaboration. However, our findings highlight the lack of sufficient policies, with 19 countries (66%) scoring in the low and middle categories, possibly underlining the lack of this continuum in prevention and care pathways. Seeing as only 4 countries (10%) have NAFLD civil society involvement focused on NAFLD, nations should also strive to work on developing this area so as to help advocate for improved government responses.

As no NASH-specific pharmacological treatment is currently available, lifestyle interventions, coupled with comorbidity management, remain the cornerstone of treatment for all patients across the disease spectrum.[21] Policies need to reflect that weight reduction achieved by caloric restriction, with or without increased physical activity, leads to improved serum liver enzymes, liver fat, degree of hepatic inflammation, and fibrosis.[39–41] There is also an independent role for dietary composition in both obese and lean NAFLD patients.[42] Large prospective observational studies point to an inverse association between NAFLD and the Mediterranean diet,[43,44] reinforced by clinical trials comparing it to a regular low-fat diet.[45] For this reason, the Mediterranean diet has been recommended for the treatment of NAFLD in the joint Clinical Practice Guidelines from the European Association for the Study of the Liver – European Association for the Study of Diabetes, and European Association for the Study of Obesity (EASL–EASD–EASO)[39] and the 2019 European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines.[46] However, given the obesogenic environment,

Table 3. Combined indicator responses for 29 EU/EEA countries and their NAFLD preparedness scores. The preparedness score ranges from 0 (lowest) to 100 (best). EEA, European Economic Area; EU, European Union; NAFLD, non-alcoholic fatty liver disease.

Country	Policy/civil society	Guidelines	Epidemiology	NAFLD care management	Preparedness score
Best preparedness scenario	High	High	High	High	100.00
UK	High	High	Middle	High	75.49
Spain	Middle	High	High	Middle	56.56
Germany	High	High	Middle	Middle	43.76
Czech Republic	High	High	Low	Middle	38.01
Denmark	High	High	Low	Middle	38.01
Italy	High	High	Low	Middle	38.01
Slovakia	Middle	High	Middle	Middle	32.06
The Netherlands	High	Low	Middle	Middle	28.28
Portugal	High	Low	Middle	Middle	28.28
Switzerland	High	Low	Middle	Middle	28.28
Poland	Middle	High	Low	Middle	26.28
Norway	High	Middle	Low	Middle	26.25
France	High	Low	Middle	Low	22.53
Belgium	Low	High	Low	Middle	21.26
Romania	Middle	High	Low	Low	20.52
Middle scenario	Middle	Middle	Middle	Middle	20.29
Croatia	Middle	Low	Middle	Middle	16.54
Sweden	Middle	Low	Middle	Middle	16.54
Bulgaria	Middle	Middle	Low	Middle	14.54
Finland	Low	Low	Middle	Middle	11.53
Estonia	Middle	Low	Low	Middle	10.79
Latvia	Middle	Low	Low	Middle	10.79
Lithuania	Middle	Low	Middle	Low	10.79
Slovenia	Middle	Low	Low	Middle	10.79
Austria	Low	Low	Low	Middle	5.78
Greece	Low	Low	Low	Middle	5.78
Hungary	Low	Low	Low	Middle	5.78
Republic of Cyprus	Low	Low	Low	Middle	5.78
Ireland	Middle	Low	Low	Low	5.04
Luxembourg	Middle	Low	Low	Low	5.04
Lowest scenario	Low	Low	Low	Low	0.00

adherence to a healthy diet can be challenging,[38] emphasising the urgent need for supportive policies that address the underlying systems issues. For morbidly obese individuals with NAFLD, bariatric surgery is another management option that can result in improvements in liver fat, inflammation, and fibrosis.[23]

Despite the existence of international NAFLD guidelines, most countries scored low for the clinical guidelines indicator. Of the countries without a specific NAFLD guideline only 2 (Bulgaria and Norway) had a guideline for a known comorbidity such as diabetes that mentioned NAFLD.[24] Countries should consider revising current national guidelines for common comorbidities, including diabetes and cardiovascular disease, to include NAFLD. This will require close engagement and collaboration between professional associations and practicians from across disciplines. NAFLD can be a serious condition requiring multidisciplinary care, and it will be critical for all countries to have guidelines specific to their health system to ensure that care management is well guided, standardised and culturally appropriate. It is worth noting that the presence of guidelines is no guarantee of their full and proper implementation, and further research should investigate the implementation of guidelines and the impact on clinical outcomes.

At present, the majority of those diagnosed with NAFLD are followed up in the community by general practitioners but, unless specific guidelines and actions are implemented, patients at risk of advanced fibrosis who might benefit from intervention will remain largely underdiagnosed and untreated. Conversely, patients with mild disease may unnecessarily be referred from primary care to liver health specialists for review, when appropriate preventative lifestyle changes and other preventative interventions could instead be delivered in primary care or the community including through treatment education approaches delivered by nutritionists, nurses, or expert-patients.

The critical concern remains the detection of significant liver fibrosis in patients with NAFLD, which can be associated with progression to cirrhosis and associated complications. Prediction rules based on a combination of serological biomarkers, such as FIB-4, are slowly paving the way to more acceptable and affordable indicators for the identification of patients at high-risk of progressive disease, which could be successfully used in primary care for diagnosis and adequate referral to specialised services.[47,48]

Unfortunately, patients with NAFLD, including those with NASH-associated advanced fibrosis or cirrhosis, often remain undetected until an incidental diagnosis or decompensation of liver cirrhosis, which contributes to increasing trends in NAFLD-related morbidity and mortality. This ineffective 'filter' at the primary care level, attributable in part to inadequate knowledge of non-invasive surrogate markers of fibrosis,[49] could be improved by the use of defined care pathways which utilise a NAFLD-specific stepwise algorithm to guide clinical decisions and improve referral to specialised services.[50] The effectiveness of this approach is indirectly revealed by our analysis as out of 29 European countries only the UK scored high in the NAFLD care management indicator. This is not surprising considering the policy implemented in the UK for NAFLD and NASH, which helps to put liver disease diagnosis and management on the primary care physicians' agenda. There remains, however, a need for reinforcement with adequate education and training on tools (*e.g.* non-invasive markers, specific intervention algorithms, etc.) that can facilitate the early detection of NAFLD[51] and timely referral to appropriate NAFLD care.[52]

Indices

Indices provide benchmarks in health policy and public health and enable systematic assessment over time in and among countries. A prominent example in global health is the Human Development Index,[53] which is widely used by international organisations and governments. Indices have the capacity to change how progress in a specific disease field is monitored at national and international levels, and support the development of clear practical targets that can be used to improve outcomes in an evidence-based manner.[54,55] The NAFLD Preparedness Index provides a clear framework for policy-makers to assess national weaknesses in specific domains and a pathway for these weaknesses to be addressed by specific interventions. For example, if a country in this study wants to go from the low- or middle-level in epidemiology to the high-level they would need to implement one or more of the following interventions: a population level study on NAFLD, an epidemiological assessment of NAFLD, a national registry, or a national or regional cohort.

Limitations

The main limitation of the NAFLD Preparedness Index is that it summarises actions taken and recommendations provided, at a particular point in time, equally, and so it cannot measure the extent to which a health system and its components adhere to each recommendation. For this reason, even a well-prepared country may be less able to act and improve early diagnosis of NAFLD if there is poor adherence to guidelines and policies, for example. Additionally, as the stability of the scores from MCAs is not always reliable, we have included standardised countries to help contextualise the results. Data were extracted by a small group of experts in each country, which can lead to a certain degree of subjectivity; however, data were fact-checked and discussed with the experts to improve quality.

Finally, the Preparedness Index does not capture all elements that are important in being prepared for NAFLD/NASH and how well a country can address this public health challenge. The main component that was not included in the index was a country's disease burden and the amount invested towards fighting NAFLD and associated conditions. Our index is unable to capture the joint effect of the disease burden and policy landscape on preparedness, and other techniques would be needed to combine the two. However, we found that only 1 country scored high in the epidemiology indicator. A lack of good epidemiological data means that few countries have the information required by decision-makers when considering if and how to respond to NAFLD.

Conclusions

In this study, we calculated a NAFLD Preparedness Index for 29 European countries. Countries that received higher scores are more prepared to respond to the NAFLD epidemic than countries with lower scores. The index highlights key gaps in policies, civil society engagement, guidelines, epidemiology, and care management. These findings can initiate critical discussions as countries seek to improve their state of preparedness to address the NAFLD pandemic.

Abbreviations

EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; EEA, European Economic Area; ESPEN, European Society of Clinical Nutrition and Metabolism; EU, European Union; MCA, multiple correspondence analysis; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus; WHO, World Health Organization.

Financial support

The original data collection was funded by the EASL International Liver Foundation with support from Gilead Sciences Europe Ltd., Allergan Pharmaceutical International Ltd., Bristol-Myers-Squibb Company, Pfizer Inc., and Resoundant Inc. The statistical analysis was funded by the EASL International Liver Foundation with support from Bristol-Myers-Squibb Company, Intercept, and Genfit. JVL is supported by a Spanish Ministry of Science, Innovation and Universities Miguel Servet grant (Instituto de Salud Carlos III/ESF, European Union [CP18/00074]) and further acknowledges institutional support from the Spanish Ministry of Science, Innovation and Universities through the 'Centro de Excelencia Severo Ochoa 2019–2023' Programme (CEX2018-000806-S), and support from the Government of Catalonia through the CERCA Programme. QMA and VR are members of the EPoS (Elucidating Pathways of Steatohepatitis) consortium funded by the Horizon 2020 Framework Program of the European Union under Grant Agreement 634413. QMA, VR, HCP, ME, and MRG are members of the LITMUS (Liver Investigation: Testing Marker Utility in Steatohepatitis) consortium funded by the IMI2 Program of the European Union under Grant Agreement 777377. QMA is a Newcastle NIHR Biomedical Research Centre investigator. AP, PC, GM, KN, FT, and SZS have no financial support statements to disclose.

Conflicts of interest

The authors declare no conflicts of interest that pertain to this work. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

JVL conceived of the article, developed the preliminary outline, and led the development of the questionnaire with QMA and HCP. JVL, QMA, and HCP led the data collection with input from ME, GM, KN, VR, MRG, and FT while AP led the development of the methods and analysis. In addition, AP and JVL verified the data. JVL wrote the first draft with input from AP, QMA, SZS, and PC. All authors contributed to and reviewed the full draft of the article, subsequent revisions, and approved the final version for submission.

Data availability

Data and code to reproduce these analyses can be found at https://osf.io/zek3u/.

Acknowledgements

The authors would like to thank the national experts for their contribution, which included reviewing documents and confirming results: Michael Trauner (Austria), Sven Francque (Belgium), Lyudmila Mateva (Bulgaria), Ivana Mikolasevic (Croatia), Emmelia Vounou (Cyprus), Radan Brůha (Czech Republic), Maja Thiele (Denmark), Riina Salupere (Estonia), Hannele Yki-Järvinen (Finland), Vlad Ratziu (France), Frank Tacke (Germany), Georgios Papatheodoridis (Greece), Bela Hunyady (Hungary), Suzanne Norris (Ireland), Giulio Marchesini (Italy), Ieva Tolmane (Latvia), Jonas Valantinas (Lithuania), Joseph Weber (Luxembourg), Mette Vesterhus (Norway), Robert Flisiak (Poland), Helena Cortez-Pinto (Portugal), Liana Gheorghe (Romania), Marek Rac (Slovak Republic), Katja Novak (Slovenia), Manuel Romero-Gómez (Spain), Mattias Ekstedt (Sweden), Jean-François Dufour (Switzerland), Ger Koek (The Netherlands), and Quentin M Anstee (UK).

Supplementary data

Supplementary data to this article can be found at https://doi.org/10.1016/j.jhepr.2021.100234.

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Author names in bold designate shared co-first authorship

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