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European ‘NAFLD Preparedness Index’ — is Europe ready to meet the challenge of fatty liver disease?

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**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 to AP, 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/.
Abstract:

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 Score 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 four 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 standardized 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 United Kingdom (75.5) scored best, although falling within the mid-level preparedness band, followed by Spain (56.2), and Denmark (43.4), while Luxembourg and Ireland were the lowest scoring countries with a score of 4.9. Only Spain scored highly in the epidemiology indicator category, while the United Kingdom was the only country that scored highly for care management.

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

Lay summary: NAFLD, which is closely associated with obesity, diabetes, and metabolic syndrome, 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 four categories studied.
**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 to 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 United States.\(^14\) 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.\(^22,23\) In morbidly obese patients, bariatric surgery may also result in sustained improvement in liver fat, inflammation, and fibrosis.\(^24\)

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.\(^25\) Furthermore, many of the broad discussions on international health policy, including WHO’s universal health coverage programme\(^26\) and the United Nations’ Sustainable Development Goals,\(^27\) 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.\(^28,29\)
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.

Questions were classified into four 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 categorize countries into one of three levels for each of the four 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. 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 four 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 (Figure 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 hypothesized reference scenarios (Lowest, Middle, and Best preparedness) were included in the analysis to standardize and contextualize responses, such that the minimum possible score was the “Low-preparedness scenario” and the maximum was “Best-preparedness”. Values of the country scores were standardized to range from 0 to 100 (lowest to best preparedness) using the standard min-max transformation technique. We managed, prepared, and analysed all data using R 4.0.2. Microsoft Excel 2017 version 15.31 was used for storage of the data. Data and code to reproduce these analyses can be found at https://osf.io/zek3u/.

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 four indicators (Table 2). For the epidemiology and NAFLD care management indicators, only Spain and the United Kingdom scored in the high-level, respectively. For the guidelines indicator, two countries scored in the middle-level response, with the rest either in the high-level (n= 10) or in the low-level (n= 17). For the policies/civil society indicator, most countries scored in the middle level (n= 13).
From the MCA, we estimated a summary factor that explained 71.7% of the variation in the dataset. The highest contribution to the score were the high response levels for NAFLD care management and epidemiology (Supplemental Figure 1).

The highest scoring country was the United Kingdom (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 (Figure 2). 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.

This analysis, the first of its kind, demonstrates two main results. First, no country was able to approximate to the ‘high preparedness-level’ scenario. Whilst the United Kingdom scored most favourably, demonstrating the importance of addressing all four of the study’s preparedness indicators, its score was primarily driven by a national guideline within a national universal healthcare system\(^\text{33}\) that advocates 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 health-care 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 one 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\(^\text{34}\), 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.\(^\text{35}\) 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”\(^\text{36}\). Within this context public health approaches that place the responsibility on individuals are unlikely to succeed, rather there is need for comprehensive structural responses that create healthy environments that support and promote healthy lives\(^\text{37}\).

The obesogenic environment impacts along a social gradient, with lower-income populations disproportionately affected. In no small part this is due to the availability of cheap ultra-processed, energy-dense, but nutrient poor, high-fat and high-sugar foods.\(^\text{38,39}\) Indeed, in a a cross-sectional analysis of a nationally representative sample of adults from the United States, food-insecure adults were more likely to have NAFLD and advanced fibrosis.\(^\text{40}\) Food insecurity is associated with obesity, diabetes, and hypertension and drives a cardiometabolic risk profile, which are all risk factors for fatty liver development\(^\text{41}\). 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 four 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.

Since 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. 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. There is also an independent role for dietary composition in both obese and lean NAFLD patients. Large prospective observational studies point to an inverse association between NAFLD and the Mediterranean diet, reinforced by clinical trials comparing it to a regular low-fat diet. 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) and the 2019 European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines. However, given the obesogenic environment, adherence to a healthy diet can be challenging, 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.

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 two (Bulgaria and Norway) had a guideline for a known comorbidity like diabetes that mentioned NAFLD. 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 practitioners 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, standardized 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.

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 due in part to inadequate knowledge of non-invasive surrogate
markers of fibrosis could be improved by the use of defined care pathways which utilise a NAFLD-specific stepwise algorithm to guide clinical decisions and to improve referral to specialised services. The effectiveness of this approach is indirectly revealed by our analysis as out of 29 European countries, where only the United Kingdom scored high in the NAFLD care management indicator. This is not surprising considering the policy implemented in the United Kingdom 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 and timely referral to appropriate NAFLD care.

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, which is widely used by international organizations 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. 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 score is that it summarizes 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 standardized countries to help contextualize 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 score 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 one country scored high in the epidemiology indicator. A lack of good epidemiological data means that few countries have the information required by decisionmakers when considering if and how to respond to NAFLD.

Conclusions
In this study, we calculated a NAFLD preparedness score 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; EEA, European Economic Area; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; 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.

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Table 1: Definitions of the categorization for the different preparedness categories

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Low-level Preparedness</th>
<th>Middle-level Preparedness</th>
<th>High-level Preparedness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policies and civil society</td>
<td>Countries that do not meet the definitions for the middle- or high-level</td>
<td>Countries with an obesity, alcohol, cardiovascular disease, diabetes, or health and diet strategy in place with no civil society or government campaign in place</td>
<td>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</td>
</tr>
<tr>
<td>Guidelines</td>
<td>Countries that do not meet the definitions for the middle- or high-level</td>
<td>Countries with one of: diabetes, cirrhosis, dyslipidaemia, alcohol, hypertension, cardiovascular disease, or hepatocellular carcinoma guidelines that include NAFLD</td>
<td>Countries with a NAFLD/NASH guideline in place or diabetes, cirrhosis, dyslipidaemia, alcohol, hypertension, cardiovascular disease, or hepatocellular carcinoma guidelines that all contain NAFLD</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Countries that do not meet the definitions for the middle- or high-level</td>
<td>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</td>
<td>Countries with a population level epidemiological study on NAFLD in the last 5 years or an ongoing NAFLD epidemiological assessment, and a national registry, or a regional NAFLD cohort</td>
</tr>
<tr>
<td>NAFLD care management</td>
<td>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</td>
<td>Countries that are not classified as high- or low-level</td>
<td>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</td>
</tr>
</tbody>
</table>

Notes: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Table 2: Breakdown of the country (n=29) responses by the four indicators

<table>
<thead>
<tr>
<th></th>
<th>Low-level preparedness</th>
<th>Mid-level preparedness</th>
<th>High-level preparedness</th>
</tr>
</thead>
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<td>10</td>
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Note: NAFLD, non-alcoholic fatty liver disease.
<table>
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<th>Country</th>
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<th>Guidelines</th>
<th>Epidemiology</th>
<th>NAFLD care management</th>
<th>Preparedness score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best preparedness scenario</td>
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<td>High</td>
<td>High</td>
<td>High</td>
<td>100·00</td>
</tr>
<tr>
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<td>High</td>
<td>High</td>
<td>Middle</td>
<td>High</td>
<td>75·49</td>
</tr>
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<td>Spain</td>
<td>Middle</td>
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<td>High</td>
<td>Middle</td>
<td>56·56</td>
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<tr>
<td>Germany</td>
<td>High</td>
<td>High</td>
<td>Middle</td>
<td>Middle</td>
<td>43·76</td>
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<tr>
<td>Czech Republic</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Middle</td>
<td>38·01</td>
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<td>Denmark</td>
<td>High</td>
<td>High</td>
<td>Low</td>
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<td>Slovakia</td>
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*Preparedness score ranging from 0 (Lowest) to 100 (Best).

Notes: EEA, European Economic Area; EU, European Union; NAFLD, non-alcoholic fatty liver disease.
Figure 1: European NAFLD Preparedness Score and country rank (n=29).

Notes: 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.
Highlights

NAFLD is a highly prevalent condition associated with obesity, diabetes, and metabolic syndrome.
NAFLD can be optimally managed through a multidisciplinary patient-centred approach.
National preparedness is essential to allow for effective public health measures aimed at preventing disease.
NAFLD preparedness means having adequate policies and civil society engagement, guidelines, epidemiology, and care management.
NAFLD preparedness was found to be deficient in all 29 countries studied.