Advancing the global public health agenda for NAFLD: a consensus statement

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NAFLD is a potentially serious liver disease that affects around one quarter of the global population, causing a substantial burden of ill health and having wide ranging social and economic implications. A multisystem disease, NAFLD is considered the hepatic component of metabolic syndrome. Unlike other highly prevalent conditions NAFLD has received little attention from the global public health community. Health system and public health responses to NAFLD have been weak and fragmented, and despite the scale of the challenge NAFLD is largely unknown outside of the field of hepatology. There is currently no global public health movement for addressing NAFLD and the disease is absent from nearly all national and global strategies and policies for related conditions. In this global Delphi study, a multidisciplinary set of experts developed consensus statements and recommendations, which a wider collaborator group reviewed over three rounds until consensus was achieved. Covering a wide range of areas, from epidemiology, awareness, care and treatment, to public health policies and leadership, the consensus statements and recommendations are of wide relevance to policymakers, healthcare practitioners, civil society groups, educational institutes and affected populations. These recommendations can provide a foundation for comprehensive public health responses to NAFLD in the years to come.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a potentially serious liver disease that results in substantial healthcare costs and economic losses, and reduced health related quality of life.[1-6] A biologically and clinically heterogenous disease, NAFLD covers a broad spectrum of histological conditions that result in hepatic and non-hepatic morbidity and mortality. Left untreated, NAFL (steatosis) can evolve to non-alcoholic steatohepatitis (NASH) with increasing hepatic fibrosis leading eventually to cirrhosis, liver cancer, end-stage liver disease and death.[7,8] NASH is a leading cause of progression to cirrhosis and hepatocellular carcinoma[9,10] with liver cancer the second leading cause of years of life lost amongst all cancers.[11]

NAFLD is part of a multisystem disease and is often considered in the majority of cases the hepatic manifestation of metabolic syndrome.[12-14] While strongly associated with obesity, NAFLD also occurs in normal weight individuals, especially in Asian populations.[15,16] Cardiovascular disease (CVD) is the leading cause of death in NAFLD patients, followed by extrahepatic malignancies, chronic kidney disease, Type 2 Diabetes Mellitus (T2DM), and liver-related complications.[12,13,17-19] The latter become the leading cause of death in those progressing to the cirrhotic stage.

NAFLD is closely related to other highly prevalent non-communicable diseases (NCDs) with substantial overlap in the public health and health system approaches needed to prevent and manage these conditions. However, NAFLD is currently absent from major NCD strategies and action plans at the global and national level,[20,21] and efforts to integrate NAFLD into the NCD agenda have been limited.

Despite the scale of the challenge and the human, social and economic implications of the disease, NAFLD is largely unknown outside of the field of hepatology and there is currently no global public health movement for addressing the challenge. In this study a global multi-disciplinary set of experts developed consensus statements and recommendations for tacking the burden of NAFLD. Applying a public health lens, the study sets out current thinking on NAFLD across a wide range of themes, from epidemiology, awareness, care and treatment to public health policies and leadership.

The consensus statements and recommendations stemming from this process are of wide relevance to policymakers, healthcare practitioners, civil society groups, educational institutes and affected populations. The overarching goal of this study is to provide a foundation for comprehensive public health responses to this challenge and to outline catalytic actions that will move this agenda forward in the years to come.

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Methods

Delphi consensus expert panel members and topics

A core group (Table 1) of 33 experts were identified by the EASL International Liver Foundation (ILF) to lead a Delphi study to develop consensus statements and recommendations to advance the NAFLD public health agenda. The chair (J.V.L.) and project coordinator (H.E.M.) led this group of clinicians, researchers, advocates, academic, and civil society experts working in 16 countries through the development and implementation of the Delphi process. First, core group members identified experts to be invited to participate in the Delphi consensus-building project; a total of 218 individuals comprise the expert panel including the core group members. The demographic description of the expert panel is summarized in Table 2 and its extensive national diversity in terms of country of origin and where currently based is presented in Supplementary Table 1. The core group drafted the initial statements to be used for the first Delphi survey round (R1), which were grouped in the following categories: 1) human and economic burden; 2) awareness; 3a) defining and implementing models of care; 3b) considerations for children; 3c) considerations for low-resource settings; 4) treatment and care; 5) patient and community perspectives; 6) policy strategies and a whole of society approach; 7) leadership for the NAFLD public health agenda.

Delphi method data collection

The Delphi method design[22] employed consisted of five components of data collection including a first (R1) and second (R2) survey round, an online convening of the core group, a web-based review of draft recommendations, and a third and final (R3) survey. We used the QualtricsXM® platform to develop and distribute the surveys. The data collection periods for each survey round ranged between 1.5 and 3 weeks, allowing for holiday periods. The R1 survey contained 38 draft statements with 4-point Likert-type categories for respondents to indicate their level of agreement/disagreement (i.e., Agree/ Somewhat agree/ Somewhat disagree/ Disagree) with the statements. In this round, responses of agreement led to an open-ended option for respondents to provide comments and/or suggest edits to the statements; responses of disagreement provided an option to include an explanation of or rationale for their disagreement. The revised R2 survey contained 37 statements, which reflected suggestions from R1 including the addition of new and merging of other statements. In the R2 survey, we included text-box summaries of the edits made to each of the statements for respondents to consider as they indicated their level of agreement or disagreement with them. The open-ended comment options were provided to all but those who responded 'Agree' with the statements.

A majority of core group members (27/33) participated in the online World Café following the R2 survey, which permitted in-depth break-out group discussions on issues that had arisen in the previous survey rounds. Concurrent with revising the statements for R3, the core group developed a draft set of recommendations to accompany the consensus statements. Preliminary feedback on these recommendations from the larger expert panel was sought over a 1-week period by way of a shared Google document. Thus, the final set of 37 statements were accompanied by 26 recommendations in R3. Given fairly high levels of agreement in the previous survey rounds, the consensus statements and recommendations in R3 were presented with a binary (Agree/Disagree) response option. A text box at the end of each of the survey domain sections provided respondents with the option to include final open-ended comments.

Findings

Consensus Statements and Recommendations

There was a consistent trend in increased consensus for all statements, such that the R1 mean percent for 'agree' responses was 80.3%, R2 was 90.9%, and R3 was 98.5%. Substantive comments provided in the text boxes were incorporated into the statements resulting in higher levels of agreement in subsequent survey rounds. We present the level of agreement with the consensus statements following a grading system recently used by others in a Delphi project,[23] which denoted unanimous (100%) agreement with a 'U,' 90% to 99% agreement with an 'A,' 78% to 89% agreement with a 'B,' and 67% (a supermajority) to 77% agreement with a 'C.' As summarized in Table 3, there was unanimous agreement with 7 statements and greater than 90% agreement with 30 statements. With regard to the recommendations emanating from the consensus statements, the mean percent agreement for the 26 recommendations was 98%. Applying the same grading system resulted in three recommendations with unanimous agreement, 22 with greater than 90% agreement, and one at greater than 80% agreement (Table 4).

The human and economic burden

The global prevalence of NAFLD amongst adults is estimated to be 23-25%.[24,25] The burden varies between and within regions with the highest prevalence in the Middle East (32%) and South America (30%) and the lowest in Africa (13%).[25] Up to 20% of people with NAFLD are affected by NASH.[25-27] However, reliable epidemiological estimates disaggregated by fibrosis stage, age, gender and geographical location are limited. The need for resource-intensive procedures to accurately assess NAFLD and its severity and the practicalities of conducting population-based surveillance are barriers, as is the variety of diagnostic methods and criteria. The availability of good quality data remains a barrier to concerted action on NAFLD at the national and global levels.

In most populations the burden of NAFLD increases proportionally with increases in body mass index,[28] although the condition is also common in lean and non-obese individuals.[29] In the vast majority of patients, NAFLD emerges in the context of the metabolic syndrome (MetS), with insulin resistance the common pathophysiological mechanism.[13] NAFLD prevalence is higher amongst T2DM patients than in the general population while T2DM incidence is higher in patients with NAFLD.[13,19,30,31] Driven by an increasing prevalence of obesity and T2DM, and an ageing population, the NAFLD burden is projected to grow in the coming decade.[27,32]

Between 1990 and 2017, disability adjusted life years and deaths due to cirrhosis increased globally. In this period the number of prevalent cases of compensated cirrhosis due to NASH more than doubled while for decompensated cirrhosis the figure more than tripled. With the expansion of prevention and treatment measures for hepatitis B and C NASH is expected to overtake these as the leading cause of cirrhosis in the near future.[33]

Epidemiological data on NAFLD in children are scarce. There is marked heterogeneity in the findings of available studies, due in part to variations in study setting, the race and ethnicity of studied populations and the reference method used to define NAFLD. A 2015 meta-analysis estimated the prevalence of NAFLD in children aged 1-19 years olds at 7.6% (95% CI 5.5% to 10.3%),[34] rising to 34.2% (95% CI: 27.8% to 41.2%) based on studies conducted in child obesity clinics. NAFLD prevalence is generally higher in children living with obesity,[34-39] but this is likely to differ by populations group and ethnicity.[40] NAFLD is also a public health problem in normal weight children and adolescents.[39] Driven in part by rising obesity level the burden of childhood NAFLD has increased over the past decade.[41]

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Understanding of the natural history, pathophysiology and phenotypes of childhood NAFLD has advanced in the past two decades including articulating the clinically relevant subtypes of paediatric NASH.[42] NAFLD in children living with T2DM has a unique pathological phenotype which appears more aggressive than the adult form.[43] Further research is still needed to elucidate the pathophysiology, genetics, natural history and responses to treatment in paediatric NAFLD.[42]

There are limited data on the long-term impact of NAFLD in childhood compared with that developed in later life. Weight gain in childhood or late adolescents is associated with a greater risk of NAFLD than weight gain in late adulthood,[16] while weight gain in late adolescence increased the risk of liver related outcomes in adulthood.[44] A Danish study estimated that for every 1 unit increase in BMI Z-score between 7 to 13 years, the risk of cirrhosis increased by 16%.[45] Another study in the same age group showed that a 1-unit increase in BMI increased the risk of liver cancer 30 years later by 20-30%.[46] More data on the long-term consequences of childhood NAFLD, as opposed to NAFLD developed later in life, including the lifetime risk of developing cirrhosis will help to inform strategies for prevention and management.

More recently, NAFLD research has started to explore the impact of the disease on affected populations using patient report outcomes (PROs) data. PROs enable researchers and clinicians to expand beyond clinical and histological outcomes to understand the full impact of the condition. PROs capture a patient's perspective on their health status, from quality-of life (QoL) and health-related quality of life (HRQoL) to work productivity, fatigue and satisfaction. Such information allows for a comprehensive understanding of disease impact at an individual and societal level. PRO tools have been developed and validated for use in people living with NAFLD.[47-49] Overall, QoL worsens with disease progression. People living with NAFLD report worse QoL than those living without the disease, people living with NASH report worse QoL than those with NAFL,[50,51] and patients with cirrhotic-NASH report worse HRQoL than patients with non-cirrhotic-NASH.[2] The association between disease stage and HRQoL varies between countries[3] highlighting the importance of local data. Future research should aim to further our understanding of the outcomes most relevant to people living with NAFLD, such that policies and management strategies can be designed to minimise the impact of the disease on those affected.

In addition to the human burden, NAFLD also has wide-ranging economic implications for affected populations and societies at large,[3,4,6] from direct- and in-direct medical expenses to indirect costs, including those associated with work loss. The majority of economic costs associated with NAFLD are also incurred in the latter stages of the disease.[4] Investment cases should be developed for NAFLD at global, regional and local levels. To support this, toolkits should be prepared to provide guidance on obtaining the requisite economic data and communicating the findings to policymakers, healthcare funders/payers and other relevant stakeholders.

The human and economic impact of NAFLD provide a compelling imperative for action. More and better data on NAFLD, especially in understudied populations such as children, are needed to advance our understanding of the impact of the disease, and to shape health system and public health responses. Data disaggregated by disease stage, gender, age and geographical area will be important. In the absence of population-based and longitudinal studies alternative research methods need to be explored. Electronic health records are one potentially valuable resource.[52] Recent efforts to standardise the administrative codes used to record exposures and outcomes for NAFLD will improve the feasibility of such research and facilitate the comparison between study populations. [53] As understanding advances at the basic science and epidemiological level, it will be important to also explore the effectiveness of operational models on patient outcomes and resource utilisation.

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The lack of data on the human and economic burden of NAFLD not only inhibits our ability to deliver proportionate health system and public health responses, but to raise awareness of the disease and its consequences among key population groups. As we strive to improve our understanding of NAFLD epidemiology, the liver health community will also need to consider how it communicates these findings to different target audiences.

Awareness, education and terminology

Despite being the most prevalent liver disease in history, NAFLD remains largely unknown outside of the field of hepatology. Knowledge of NAFLD amongst general practitioners [54] and non-liver health specialists is generally poor, with an underappreciation of the scale of the challenge and the potential seriousness of the disease.[55] There is also little awareness of the condition in the general public, including the risk factors and potentially serious health consequences. Patients at higher risks for NAFLD, including people living with T2DM and other metabolic risk factors, are also unaware of the disease, their increased risk of developing it, or how it interacts with other metabolic conditions.[56-58]

Increasing awareness of NAFLD will require simple, effective messages and non-stigmatising terminology that communicates the risk and consequences of the disease. Such messages need to be targeted to specific audiences, from health care professionals–especially the liver and gastroenterology communities, primary care providers and diabetes specialists– to policy makers and the general public. In developing awareness strategies and tools, health communication experts and the media should be engaged. Educational materials should be developed and made available to all relevant professional, especially primary care providers and specialists working in relevant fields, namely diabetes and obesity.

Since the early 2000s, several proposals have been made to change the name NAFLD. The central arguments for change have been to remove the unhelpful confection 'non-alcoholic' and to better reflect the metabolic underpinnings of the disease's aetiology.[59] However, in the absence of widespread consensus, NAFLD has remained the commonly used nomenclature. More recently the term Metabolic Dysfunction Associated Fatty Liver Disease (MAFLD) has gained traction as a possible replacement. An international groups of experts from 22 countries reached consensus on the change to MAFLD,[60,61] with the proposal endorsed by regional liver associations in South America[62] and the Asian Pacific[63] as well as experts in sub-Saharan Africa [64] and the Middle East and North Afirca.[65] However, others have expressed concerns about a premature change of name without full consideration of the broad implications, from diagnostic criteria to trial end-points, calling instead for regional liver societies to jointly work together to reach consensus.[66]

We urge the relevant organisations to engage in a thorough process to reach agreement on the path forward. The current lack of clarity risks fragmentation and confusion within the liver health community that will undoubtably harm efforts to bring much needed attention and action to this public health issue. Beyond the clinical and scientific considerations this process should consider how any name change can positively impact efforts to communicate about the disease to as wide a possible audience.

Defining and implementing models of care

A model of care (MoC) is a setting specific framework that outlines how patients are managed along the cascade of care. A comprehensive MoC outlines what services are provided, where they should be provided, and by whom, and also how services are integrated and coordinated within a healthcare system.[67] Clearly defined, context specific MoCs will be important for managing the burden of NAFLD, yet MoCs have received little attention to date. A recent review identified seven published examples

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of comprehensive MoCs for NAFLD, with only one focused on children.[68] Establishing such MoCs should be a key focus for healthcare decisionmakers and providers.

The majority of NAFLD patients can be managed in primary care. For patients with NAFL or early-stage fibrosis, management focuses on preventing disease progression and the development or exacerbation of metabolic comorbidities. Patients with advanced disease may require the hepatic component of the disease to be managed by a hepatologist or gastroenterologist,[69,70] while a smaller proportion will require tertiary care, such as for transplant surgery.[71,72] The first step in any model of care is to identify a patient's needs and link them to the appropriate service; a process known as risk-stratification. However, in the absence of established care pathways, diagnosing NAFLD remains an enduring challenge, with diagnoses often incidental following the identification of abnormal liver enzymes or steatosis based using imaging technqiues.[73]

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Fibrosis stage is an important indicator for long-term liver and non-liver outcomes.[74] A range of non-invasive tests (NITs) have been validated for detecting advanced fibrosis in clinical practice, from blood-based scores to imaging techniques.[75] The performance of these NITs is strongly influenced by pre-test probability. In primary care settings where the population prevalence of advanced disease is low, the negative predictive value of NITs for advanced fibrosis is generally high, while the positive predictive value is lower.[76,77] NITs can be especially effective at identifying advanced disease when used in sequential algorithms.[78-81] There is also some evidence that certain combinations of NITs can identify patients with significant fibrosis with a high positive predictive value.[82] While several NITs have been investigated for use in paediatric populations, none are currently validated for use in routine clinical practise. Initial screening in children generally relies on alanine liver transferase and ultrasound, with a biopsy required to definitively diagnose and stage the disease. There is hope that combinations of NITs might replace the need for biopsy in paediatric populations the future.[83] Future research should focus on the development of more efficient and effective NITs for risk-stratifying patients in primary care and diagnosing and staging NASH in secondary care.

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A care pathway is a framework to support decision-making, including when to refer to specialist care. There are several published examples of care pathways for identifying advanced liver disease,[84-90] and some evidence of the cost-effectiveness of these approaches.[91-93] Yet in many healthcare settings, formal pathways do not exist and NITs are not routinely used in all healthcare setting where they could be of benefit. While the availability of NITs will vary between healthcare settings, non-commercial blood-based scores could be feasibly implemented in most primary and secondary care settings. To manage the burden of NAFLD locally, feasible care pathways need to be developed and healthcare providers equipped with the tools and knowledge to support the care of people living with NAFLD. This is especially true for primary care providers, as many people living with NAFLD will first present in primary care, yet the condition is widely under diagnosed in primary care settings.[94] Other important settings including diabetes clinics where the prevalence if advanced disease is likely to be higher than in the general population.[14,19] These pathways will also ensure that the necessary healthcare infrastructure is in place when more effective pharmacological treatments become available for NAFLD patients. Such pathways were not adequately addressed prior to all-oral direct-acting antiviral becoming available for hepatitis C, which hampered early efforts to link people with treatment.[67]

Care pathways for children living with NAFLD should also consider the transition from paediatric to adult services to ensure continuity of care. Such a process needs to be designed with full recognition of the differences in clinical management between children and adults and the psychological factors associated with such a transition.[95]

Compensated advanced chronic liver disease (cACLD) is a relatively new term to describe the early phases of severe chronic liver disease covering severe fibrosis and compensated cirrhosis. Adoption of the terminology and concept of cACLD would be helpful for clinical and research purposes as it better reflects the continuum of advanced disease and the increased risk of decompensation than the current usage of fibrosis stages 3 and 4.[96]

There is widespread consensus that certain risk factors increase the chances of developing NAFLD and of the disease progressing to advance stages, namely T2DM and obesity. There is, however, a lack of consensus amongst liver associations on the benefits and cost-effectiveness of active case finding in specific patient groups. Guidance from EASL, EASD and EASO recommends screening for NAFLD in people with obesity, MetS and in particular T2DM.[97] Both the Asia–Pacific Working Party on NAFLD and the Latin American Association for the Study of the Liver recommend screening be considered in certain high-risk populations, including those with T2DM and obesity.[98,99] The American Diabetes Association recommends screening for NASH and advanced fibrosis in patients with elevated liver function testing or hepatic steatosis on ultrasound.[100] In contrast AASLD does not recommend systematic screening in these groups given a lack of data on the cost-effectiveness of such approaches.[101] While appropriate targets for active case findings will be determined locally with consideration for the epidemiology, we recommend that this includes people living with T2DM and those with central adiposity. These approaches should be evaluated for their impact on patient outcomes and for cost-effectiveness.

As a multisystem, comorbid disease, people living with NAFLD will often benefit from multidisciplinary care, especially for those with advanced fibrosis.[102] Establishment of multidisciplinary teams (MDT) can be an effective way to manage the diverse clinical needs of patients.[102] There are several published examples of multidisciplinary secondary care clinics for NAFLD.[87,88,103-105] The composition and structure of the MDT and the services that are provided will reflect what is feasible and appropriate within a given healthcare setting.

Access to high-quality primary care preventive interventions is critical to reducing the burden of NCDs,[106] yet there is little evidence on what approaches work best in primary care for NAFLD patient outcomes. Common risk factors for NAFLD, obesity, T2DM and CVD, including unhealthy diet and physical inactivity,[107] provide an opportunity for integrated chronic disease management approaches. Structured management programmes for other conditions, such as diabetes, can serve as a starting point for more integrated models.[108] In low recourse settings, the World Health Organisation package of essential non-communicable disease interventions for primary healthcare can be used as a basis for integrating NAFLD care into related disease areas, including diabetes management.[109] Technology innovation can also help facilitate collaboration between patients and providers and the coordination of services within a health system.[110]

As the liver community leads efforts to improve the care and outcomes for people living with NAFLD we should prioritise operational research that furthers our understanding of the impact of different MoCs on patient outcomes and the cost-effectives of these approaches in different healthcare settings. This research should consider the structural barriers that make coordination and collaboration within healthcare systems a challenge and how to effectively engage across disciplines.

Treatment and care

The treatment and care of NAFLD patients is highly dependent on the disease stage.[70] Interventions aimed at modifying lifestyle risk factors–namely weight, diet and physical activity–and the management of comorbidities are the cornerstone of treatment of all patients,[70,111,112] and this is reflected in the clinical management guideline from regional liver associations[97,99,101,113] In patients

with more advanced disease addressing components of MetS, liver related pharmacotherapy and management for cirrhosis related complications are important.[70,114] As the number of effective pharmacological treatments for NAFLD increases, programmes aimed at modifying lifestyle risk factors will continue to be a core element of NAFLD disease management.

There is some evidence that lifestyle interventions can prevent disease progression and, in some cases, reverse fibrosis.[115,116] In overweight and obese NAFLD lifestyle interventions aim to achieve a 7–10% weight loss which is associated with the improvement of liver enzymes and histology.[97,99,101] Lifestyle programmes are most effective when behaviour change approaches are incorporated as part of a long-term comprehensive lifestyle modification programme.[117] Dietary guidance for people living with NAFLD generally centres on the reduction of saturated fat, refined carbohydrates, and red and processed meats.[118] The Mediterranean diet and the Dietary Approach to Stop Hypertension (DASH) have proven beneficial in some patients.[118,119] Different forms of physical activity–aerobic, resistance or high intensity intervals–all appear to have a beneficial effect on liver fat.[116,120] Even in the absence of weight loss exercise can result in a 20-30% reduction in intrahepatic lipid.[116] It is important that exercise programmes are tailored to the patient's needs and preferences to support compliance. Further research is needed to identify the most effective interventions, including lifestyle treatments and pharmacological treatments, that can help people living with NAFLD and obesity to achieve and sustain a weight loss of at least 10%. Research is also needed to determine how best to implement lifestyle interventions including how different operational models influence long term complicate and patient outcomes, and the cost-effectiveness of different approaches.

Making effective structured lifestyle treatment programmes available to people living with NAFLD, especially those who are at high risk of advanced fibrosis and/or rapid fibrosis progression, should be a priority of the liver health community. Both public and private funders have a key role to play in ensuring financial support for these services, (e.g. reimbursement). As a first step NAFLD needs to be adequately incorporated into relevant national healthcare policies and guidelines, something that is currently lacking.[121]

While there are currently no pharmacological treatments specifically approved for NAFLD, clinical trials are exploring numerous drug candidates targeting energy intake, energy disposal lipotoxic liver injury, inflammation and fibrosis.[122] The invasive nature of liver biopsy, the inherent variability of histological findings and the lack of an alternative validated surrogate for long-term clinical benefit have complicated the development of efficacious treatments for NAFLD. As the field moves forward it will be beneficial for currently accepted surrogate histological endpoints for conditional NASH drug approval to be standardised, with the goal of eventually replacing them with non-invasive diagnostic and surrogate endpoint biomarkers, including weight loss/BMI.

Patient and community perspectives

People living with NAFLD can provide valuable insights to the design and delivery of interventions to safeguard and improve their health. Actively engaging people with lived experiences and considering their perspectives ensures that interventions are patient-centric, ultimately improving adherence and outcomes.[123,124] Patients and patient organisations should be actively involved in developing policies and strategies to address NAFLD, including the development of clinical practice guidelines. Yet, globally, few NAFLD patients' groups exit, and there is no global platform or coordinating mechanism to support local patient organisations. Financial and technical support is needed to help form NAFLD patient groups, or to establish sub-groups in existing patient organisations focused on other conditions. In the absence of specific groups for NAFLD, professional and patient organisations that address associated conditions including T2DM, obesity, heart disease and cancer will play an important role disseminating information on NAFLD, especially to people in high-risk groups. Medical

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associations should play a central role, supporting patient groups to meet the needs of people living with NAFLD, including developing information products and tools.

The NAFLD community can learn from experiences in the viral hepatitis movement, where patient organisations played a pivotal role, including driving World Health Assembly resolution 67.6, which was passed in May 2014.[125] The World Hepatitis Alliance has been key to this success, providing a platform which united diverse organisations around a common vision. While no global patient organisation exists for NAFLD, there are organisations within the wider NCD community, such as the NCD Alliance, which the liver health organisations, some of which do address NAFLD, can engage with to increase awareness and attention for people living with NAFLD. The meaningful engagement of people with lived experiences is also becoming more mainstream in the NCD space, including within WHO,[126] providing opportunities for the liver health community to engage in and shape this agenda.

> **Commented [MT27]:** Please provide some brief description of this resolution

A challenge for engaging people living with NAFLD is the stigma associated with the condition. Liver disease in general is commonly associated with unhealthy alcohol use, while NAFLD is associated with obesity; both of these associations are with highly stigmatised conditions.[23,127-129] People living with multiple chronic conditions may also experience multiple, interacting forms of stigma.[130] The implications of stigma needs to be acknowledged and addressed when developing prevention and treatment approaches for NAFLD. High-profile individuals living with NAFLD can be especially useful in creating awareness and advocating for greater action on prevention and treatment, as well as reducing the stigma associated with the condition.

Policy strategies and a whole of society approach

Despite being a highly prevalent liver disease, there has been very little attention on the policies and strategies needed to prevent, management and treat NAFLD. A review of 29 European countries examining the existence of policies for NAFLD found large variations in national responses with all countries poorly prepared to address the challenge.[121,131] A recent globally study of 102 countries painted a similar picture, highlighting an overall lack of attention on NAFLD within national health agendas with no country reporting having a written NAFLD strategy. NAFLD is also explicitly mentioned in very few national strategies or clinical guidelines for related conditions such as obesity or diabetes. These findings highlight the extremely low priority the condition has in diseases specific and national health agendas – and the need for a concerted effort to shape and deliver a robust public health response.

> **Commented [HM28]:** Note to cite new global policy paper

At a health system level, chronic disease management is driving the need for the re-orientation of health systems away from siloed disease-centric models to multidisciplinary patient-centred care.[132,133] The liver community, through collaboration with others working on metabolic disease management, can help lead this process in the years to come for the betterment not only of liver disease patients but all people living with NCDs.

At both a public health and clinical management level, there is substantial overlap in the measures required to address NAFLD and the other major NCDs. Common risk factors–such as unhealthy diets, physical inactivity and unhealthy alcohol consumption–provide an opportunity for collaborative approaches to improve public health. Policies, fiscal measures and legislation that address common risk factors for NCDs in a coordinated, simultaneous way have the potential to be highly impactful. One such example is taxes on sugar sweetened beverages.[134-136] Yet despite the common approaches needed to address NAFLD and other NCDs, NAFLD is not mentioned by name in the majority of key global or national NCD strategies; most notably it is absent from the WHO action plan on the prevention and control of NCDs.[137] Liver health organisations must engage with WHO and other national and international organisations to ensure that measures to prevent and treat NAFLD are fully

integrated within a broader package of cost-effective interventions that holistically address NCD risk factors. A World Health Day dedicated to liver health, for example, would provide a platform for advocacy and awareness raising within and beyond the global health field.

Complex health issues require us to rethink systems and go beyond the immediate causes of a disease to consider underlying and basic influences of disease requiring multidisciplinary and multisectoral responses.[138] The liver health field must now expand its horizons to look beyond the health sector as it seeks to address the challenge of NAFLD. We can take lessons from other fields such as obesity, where over the past two decades thinking has evolved beyond individual-level factors underlying energy imbalance to considering biological, social, environmental and policy drivers of health behaviours and outcomes[139] and the interconnections across these levels of influence in a systems approach.[140,141] Such an approach calls for coordinated actions from all stakeholders and requires improving policies and practices across multiple sectors as well as shifting social norms on health.[142,143]

To address NAFLD, collective action is required across disciplines and sectors. Existing frameworks such as the United Nations Sustainable Development Goals (SDGs) can usefully inform and guide the development of multisectoral efforts to address NAFLD. A recently developed NAFLD-SDG framework can help conceptualise thinking about the design and delivery of such responses, as we look to tackle the direct, underlying and cross-cutting causes of the disease. The NAFLD prevention agenda should include the creation of healthier, more equitable and sustainable societies as one of its core goals. As a first step, the NAFLD-SDG framework can be used as a strategic advocacy tool to build the case for closer collaboration within and between sectors.

> **Commented [HM29]:** Note to cite new SDG paper

Leadership for the NAFLD public health agenda

To move the NAFLD public health agenda forward, national and regional liver associations, in collaboration with governments and other stakeholders, will need to lead the way. Multilateral organisations, such as WHO, will have a key role to play in shaping and delivering responses to NAFLD, firstly by recognising the condition as a major health issue, and secondly by supporting nationally-led efforts to deliver public health responses.

There are a number of existing policy levers and movements that can support efforts to deliver responses to NAFLD. Global efforts to expand universal health coverage (UHC) and ensure that health systems are people-centred provide useful mechanisms for holistically addressing NCDs, including NAFLD and associated diseases such as diabetes and obesity.

Medical societies that provide care for any and all aspect of metabolic syndrome are well positioned to help lead this change. The develop of joint plans of actions, guidelines, policy briefs and educational tools is should be exploited.

Further, a global coalition of organisations and individuals should lead the development of a NAFLD public health roadmap and to support the global health community in following it. This coalition should actively engage with those outside of the liver health space by growing and nurturing a broad network of individuals and organisations with a common vison and goals.

Conclusions
NAFLD is a highly prevalent disease which represents a major global public health challenge. In this study, a global group developed a set of consensus statements and recommendations which can help to guide the field as it works to shape and implement adequate health systems and public health responses. By applying a public health lens, the statements and recommendations derived from this study are of relevance to a wide audience, from researchers and practitioners to policy

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makers and funders. The liver health community must now actively engage in the development of a roadmap to translate these recommendations into action.

Tables

Table 1. Core Group Members (N=33)

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Name	Affiliation	Countries where currently based
Quentin Anstee	Newcastle University	United Kingdom
Juan Pablo Arab	Pontifical Catholic University of Chile	Chile
Rachel Batterham	University College London	United Kingdom
Laurent Castera	University of Paris	France
Helena Cortez-Pinto	University of Lisbon	Portugal
Javier Crespo	Universidad de Cantabria.	Spain
Kenneth Cusi	University of Florida	United States
Mae Dirac	University of Washington	United States
Sven Francque	Antwerp University Hospital	Belgium
Jacob George	University of Indonesia	Indonesia
Hannes Hagstrom	Karolinska University Hospital	Sweden
Terry Huang	City University of New York Graduate School of Public Health and Health Policy	United States
Mona H. Ismail	King Fahad University Hospital	Saudi Arabia
Achim Kautz	Kautz[5] gUG	Germany
Shiv Sarin Kumar	Institute of Liver and Biliary Science	India
Jeffrey V. Lazarus (Chair)	Barcelona Institute for Global Health	Spain
Rohit Loomba	University of California, San Diego	United States
Henry Mark	EASL International Liver Foundation	United Kingdom
Veronica Miller	University of California Berkeley	United States
Phil Newsome	University of Birmingham	United Kingdom
Michael Ninburg	Hepatitis Education Project	United States
Ponsiano Ocama	Makerere University College of Health Sciences	Uganda
Vlad Ratziu	Sorbonne University	France
Mary Rinella	Northwestern University Feinberg School of Medicine	United States
Diana Romero (non-voting)	City University of New York Graduate School of Public Health and Health Policy	United States
Manuel Romero-Gómez	Virgen del Rocío University Hospital	Spain
Jörn Schattenberg	University Medical Center Mainz	Germany
Emmanouil Tsochatzis	UCL Institute for Liver and Digestive Health	United Kingdom
Luca Valenti	University of Milan	Italy
Vincent Wong	The Chinese University of Hong Kong	China
Yusuf Yilmaz	Marmara University	Turkey
Zoabair Younouss	Inova Fairfax Medical Campus	United States
Shira Zelber-Sagi	University of Haifa School of Public Health	Israel

Table 2. Expert Panel Demographic Composition and Level of Engagement (N=218)

CHARACTERISTIC	% (n)
Gender	
Man	67.0 (146)
Woman	30.7 (67)
Prefer not to say/no response	2.3 (5)
Primary sector of employment	
Academic	71.1 (155)
Civil society	4.1 (9)
Public	15.1 (33)
Private	4.6 (10)
Other/no response	5.0 (11)
Primary field of employment	
Healthcare provider	21.1 (46)
Clinical research	62.8 (137)
Non-clinical research	3.2 (7)
Advocacy	5.0 (11)
Other/no response	7.8 (17)
Geographical representation	
Countries of origin (n)	89
Countries currently based in (n)	91
*Delphi process engagement**	
Round 1 survey	87.6 (191)
Round 2 survey	88.1 (192)
World Café core group meeting	81.8 (27)
Round 3 survey	84.9 (185)
Participation in 1 or more components	218
Mean # surveys engaged in	2.05
*Numbers sum to >218 due to engagement in multiple components of the Delphi process.	

Table 3. Consensus Statements for a NAFLD Public Health Agenda

STATEMENT		GRADE
1. The human and economic burden		
1.1	According to current estimates, 20%–25% of the global adult population is affected by NAFLD, and an estimated 20% of people with NAFLD will develop NASH. However, robust epidemiological estimates, disaggregated by fibrosis stage, age, gender, risk profile and geographical area, are limited. Incomplete data hinder concerted action at the national and global levels.	A
1.2	Data from central registries, electronic healthcare records or official statistics are available for certain countries and can be useful sources of information. However, differences in reporting, including the use of different administrative codes (e.g. the International Classification of Disease (ICD) codes), limit comparability.	A
1.3	Data on paediatric NAFLD are scarce. Prevalence estimates vary widely, while there is limited information on long-term health outcomes in paediatric NAFLD patients. However, available data indicate that NAFLD is an increasing problem in paediatric populations and is especially prevalent in children with obesity.	U
1.4	A wide range of factors needs to be considered in developing prevention and treatment approaches for NAFLD. These factors extend from metabolic risks, including insulin resistance, to genetic, social and environmental influences that may play a role in the development and progression of the disease.	U
1.5	NAFLD shares a bidirectional relationship with other metabolic conditions. Addressing NAFLD will likely reduce the prevalence and severity of these conditions.	A
1.6	There are both economic and social arguments for taking action on NAFLD. Evidence shows that NAFLD progression is associated with substantial healthcare costs, socioeconomic losses and reduced quality of life, most notably in patients with advanced fibrosis and cirrhosis. Early intervention could help reduce the burden of disease, associated healthcare costs and economic losses.	U
2. Awareness and education		
2.1	Communicating about NAFLD and its consequences has proved to be a major challenge for the liver health community.	A
2.2	Raising the profile of NAFLD as a public health issue will require clear messages about the condition, its consequences and what action is required. These messages should be tailored to specific audiences, including the liver and gastroenterology communities, primary care providers, specialists from other relevant disciplines, as well as stakeholders such as at-risk groups, the media and policymakers.	A
2.3	Primary care providers and diabetes specialists can play a critical role in identifying and referring patients with advanced fibrosis to liver specialists. Raising the awareness of these medical providers would improve their ability to play this role	A
3. Defining and implementing models of care		
3.1	Given the broad disease spectrum of NAFLD and the different levels of care required by patients across this spectrum, having clearly defined, context-specific models of care will be important for addressing the disease burden	A
3.2	The majority of people living with NAFLD can be managed in primary care; only patients with advanced disease need referral to a liver specialist. NAFLD care pathways can guide care decisions, including decisions on when to refer a patient to specialist care.	A
3.3	People living with NAFLD, especially those with advanced fibrosis, commonly require the management of multiple comorbid conditions, including diabetes, obesity and cardiovascular disease.	A
3.4	There is limited evidence on the impact of different NAFLD models of care on patient outcomes and cost-effectiveness. The lack of evidence and of investment in implementation research continues to impede the design and delivery of good care in different healthcare settings and contexts.	A
3.5	Fibrosis stage is an important predictor of long-term liver-related outcomes and overall mortality in NAFLD patients. Evidence of advanced fibrosis is an adequate indicator of a patient's need for referral to specialist liver care.	A

3.6	Non-invasive tests (NITs) can be effective at excluding advanced fibrosis and the need for further assessment or referral to specialist liver care, especially when combinations of NITs are used sequentially.	A
3.7	The availability and use of different NITs vary among healthcare settings. Non-commercial blood-based scores could be feasibly implemented in most primary and secondary care settings, such as diabetes clinics, if they were more readily available and widely known.	A
3.8	People living with type 2 diabetes mellitus (T2DM) and/or obesity are recognised as being at high risk for NAFLD-related complications. Collaboration and coordination across the different components of the healthcare system will be needed to care for these patients most effectively.	A
3b. Defining models of care: considerations for children (less than 18 years of age)		
3.9	The natural history of paediatric NAFLD is poorly understood, due to a lack of prospective studies and the complex nature of the disease, including pathologies that are unique to children living with NAFLD. Better data on the natural history, pathophysiology and risk factors for disease progression would improve the care of this population.	U
3.10	Models of care for children should address all care needs, including the provision of psychological support, and be designed to facilitate the smooth transfer of care from paediatric to adult services.	A
3.11	The lack of validated NITs for use in children is a barrier to timely diagnosis and linkage to care.	A
3.12	Available data show that paediatric NAFLD is associated with both hepatic and non-hepatic morbidity and mortality. Children living with NAFLD may benefit from multidisciplinary management approaches tailored to their unique healthcare needs.	A
3c. Defining models of care: considerations for low-resource settings		
3.13	In low-resource settings, the availability of diagnostic tools – including NITs – is likely to be limited, especially the more expensive imaging-based tests. Diagnosis in these settings will often require practitioners to make pragmatic choices and resort to low-cost solutions.	A
3.14	NAFLD is not mentioned in the current guidelines from the World Health Organization (WHO) on the detection, diagnosis and treatment of major non-communicable diseases (NCDs) in primary care in low-resource settings. Inclusion of NAFLD in such guidance would help to improve care for affected populations in these settings.	A
4. Treatment and care		
4.1	Interventions aimed at modifying lifestyle risk factors are the cornerstone of NAFLD treatment. There is some evidence that these interventions can prevent disease progression and can, in some cases, reverse fibrosis, yet more data will help to identity the most effective approaches and how to implement them in clinical practice	A
4.2	As the number of effective pharmacological treatments for NAFLD increases, programmes aimed at modifying lifestyle risk factors will continue to be a core element of NAFLD disease management.	A
4.3	Access to treatment programmes for NAFLD requires that they be incorporated into relevant national healthcare policies and guidelines and be adequately funded. Private and public payers/funders have a key role to play in ensuring financial support (e.g. reimbursement) for these services.	A
4.4	The invasive nature of liver biopsy, the inherent variability of histological findings and the lack of an alternative validated surrogate for long-term clinical benefit have complicated the development of efficacious treatments for NAFLD.	A
5. Patient and community perspectives		
5.1	People living with NAFLD can provide valuable insights into the design and implementation of interventions to safeguard and improve their health. Patients and patient organisations should be actively involved in developing policies and strategies to address NAFLD; however, few such groups currently address NAFLD.	A

5.2	Given that NAFLD is a largely invisible public health issue, high-profile patients can be especially useful in creating awareness and advocating for greater action on prevention and treatment.	A
5.3	Professional and patient organisations that address NCDs, including T2DM, obesity, heart disease and cancer, can play an important role in raising the profile of NAFLD, including by providing information to at-risk groups	U
5.4	Stigma can be a major barrier when seeking to address health issues. Liver disease in general is commonly associated with unhealthy alcohol use, while NAFLD is associated with obesity. Both of these associations are with highly stigmatised conditions, and the implications of such stigma need to be acknowledged and addressed when developing prevention and treatment approaches for NAFLD.	A
6. Leadership		
6.1	National and regional liver associations, in collaboration with governments and other stakeholders, have a leading role to play in responding to NAFLD, including in developing public health strategies and guidelines and in collaborating with other disease associations and organisations.	U
6.2	Multilateral organisations such as WHO also have a key role to play in shaping and helping lead the response to NAFLD, firstly by recognising the condition as a major health issue, and secondly by supporting nationally led efforts to deliver public health responses.	A
6.3	Global efforts to expand universal health coverage (UHC) and ensure that health systems are people-centred provide a useful mechanism for holistically addressing NCDs, including not only NAFLD, but also associated diseases such as diabetes and obesity.	A
7. Policy strategies and a whole-of-society approach		
7.1	A national strategy for NAFLD is lacking in almost every country in the world, while NAFLD is explicitly mentioned in very few national strategies or clinical guidelines for related conditions such as obesity or diabetes. This fact highlights the extremely low priority the condition has in national health agendas – and the need for a concerted effort to shape and deliver a robust public health response.	A
7.2	Several highly prevalent NCDs share common risk factors – such as unhealthy diets, physical inactivity and unhealthy alcohol consumption – with NAFLD. Policies, fiscal measures and legislation could address many of these diseases in a coordinated, simultaneous way.	A
7.3	Addressing NAFLD will require collective action that spans diverse disciplines and sectors. Existing frameworks such as the United Nations Sustainable Development Goals (SDGs) can usefully inform and guide the development of multi-sectoral efforts to address the direct, underlying and cross-cutting causes of NAFLD.	U

Table 4. Consensus Recommendations for a NAFLD Public Health Agenda

	RECOMMENDATION	GRADE
	The human and economic burden	
1	Investment is needed in research that will improve understanding of NAFLD epidemiology, especially in understudied population groups such as children, and people without overt metabolic risk factors	A
2	In the absence of population-based and prospective longitudinal studies, alternate research methods should be considered, such as those employing electronic health records.	A
3	Investment cases should be developed for NAFLD at global, regional and local levels. To support these cases, toolkits should be prepared to provide guidance on obtaining the requisite economic data and communicating the findings to policymakers, healthcare funders/payers and other relevant stakeholders.	A
	Awareness and education	
4	Professional societies and other relevant stakeholders, such as patient organisations, should collaborate on a transparent process to carefully reconsider the nomenclature of fatty liver diseases, with special attention to the benefits of and barriers to changing the name of non-alcoholic fatty liver disease.	A
5	The liver health community should engage health communication experts to jointly develop effective strategies and practical tools to increase awareness in key audiences, including the media and policymakers.	A
6	Professional bodies should develop simple knowledge products and educational courses targeting the liver and gastroenterology communities, primary care providers and specialists from other disciplines, as well as at-risk populations, the media and policymakers. The courses should include medical school and continuing medical education activities.	A
	Defining and implementing models of care	
7	Healthcare planners and providers should design and implement locally feasible NAFLD care pathways, utilising available tests to efficiently determine a patient's care needs and link them to appropriate services.	U
8	Healthcare providers – especially primary care providers, diabetes specialists and those caring for people living with obesity – should be equipped with the tools and knowledge needed to support the care of NAFLD patients. At a minimum, providers should be able to identify which patients require referral to a liver specialist.	A
9	Multidisciplinary care models should form the basis for managing NAFLD patients, especially those with advanced fibrosis.	U
10	Research should focus on developing more-effective and -accurate NITs for risk-stratifying patients – including children – in primary care, and for staging fibrosis and diagnosing NASH in secondary care.	U
11	Implementation research should be undertaken to better understand the barriers to uptake of currently available NITs.	A
12	Active case finding should be considered in population groups at high risk for advanced fibrosis. The specific target populations ought to be determined locally but should include patients with T2DM and patients with central adiposity.	A
13	The terminology and concept of 'compensated advanced chronic liver disease' should be adopted, as it better reflects the continuum of advanced disease and the increased risk of decompensation than the current usage of fibrosis stages 3 and 4.	B
14	Implementation research is needed to identify the core elements of effective NAFLD care models in different healthcare settings – including low-resource settings – and to provide generalisable findings that can inform the development of models of care in different contexts.	A
15	Preventing and treating childhood NAFLD should be a priority, both as a means of improving child health and as a way of reducing the burden of disease in later life.	A
	Treatment and care	
16	Research should focus on identifying interventions, including lifestyle treatments (e.g. diet and physical activity regimens) and pharmacological treatments that can help people living with NAFLD and obesity to achieve and sustain a weight loss of at least 10%.	A

17	Effective structured lifestyle treatment programmes should be made available to people living with NAFLD, especially those who are at high risk of advanced fibrosis and/or rapid fibrosis progression.	A
18	Currently accepted surrogate histological endpoints for conditional NASH drug approval should be standardised, with the goal of eventually replacing them with non-invasive diagnostic and surrogate endpoint biomarkers.	A
Patient and community perspectives		
19	Medical associations and other stakeholders should support patient groups in meeting the needs of people living with NAFLD. Where possible, NAFLD-specific groups should be formed. Patient groups focused on related conditions – including diabetes and obesity – should be provided with relevant information on NAFLD to share with their members.	A
20	Patient groups for liver disease and related NCDs should be involved in the development of clinical practice guidelines for NAFLD. Medical associations should also support these patient groups in developing relevant materials on NAFLD for their members.	A
6. Leadership		
21	A global coalition of organisations and individuals should lead the development of a NAFLD public health roadmap and support the global health community in following it.	A
22	Medical societies that provide care for any aspect of metabolic syndrome should formally collaborate to address NAFLD, including by jointly developing guidelines, policy briefs and plans of action.	A
7. Policy strategies and a whole-of-society approach		
23	Efforts to detect, prevent and treat NAFLD should be integrated within a broader package of cost-effective interventions that holistically address NCD risk factors, focusing specifically on unhealthy diets, physical inactivity and unhealthy alcohol consumption.	A
24	Global health organisations – including WHO – and national institutions should incorporate NAFLD into their technical materials on NCDs and include NAFLD among their priority NCDs.	A
25	The WHO should dedicate a World Health Day (7 April) to liver health to highlight the global prevalence of NAFLD and its significance for public health.	A
26	The NAFLD prevention agenda should include the creation of healthier, more equitable and sustainable societies as one of its core goals. One way to do that should be to emphasise the SDG targets that are relevant to preventing and treating NAFLD.	A

Supplementary Table 1. Expert Panel National Representation (N=218)

Country of origin (89 countries)		Country Where Currently Based (91 countries)	
Country name	n	Country name	n
Algeria	1	Algeria	1
Argentina	2	Argentina	2
Armenia	1	Armenia	1
Australia	6	Aruba	1
Austria	2	Australia	7
Azerbaijan	1	Austria	1
Bahrain	2	Azerbaijan	1
Bangladesh	1	Bahamas	1
Barbados	1	Bahrain	2
Belgium	3	Bangladesh	1
Benin	1	Belgium	3
Brazil	1	Benin	1
Bulgaria	1	Brazil	1
Burkina Faso	1	Bulgaria	1
Cabo Verde	1	Burkina Faso	1
Canada	3	Cabo Verde	1
Central African Republic	1	Canada	3
Chile	2	Central African Republic	1
China	4	Chile	2
Costa Rica	1	China	4
Croatia	1	Colombia	1
Cuba	1	Costa Rica	1
Czech Republic	1	Croatia	1
Denmark	2	Cuba	1
Dominican Republic	2	Czech Republic	1
DRC	1	Denmark	2
Ecuador	3	Dominican Republic	2
Egypt	5	Democratic Republic of the Congo	1
Estonia	1	Ecuador	1
Ethiopia	1	Egypt	5
Finland	2	Estonia	1
France	5	Ethiopia	1
Germany	5	Finland	2
Ghana	1	France	6
Greece	3	Germany	5
Hong Kong	1	Ghana	1
Hungary	1	Greece	2
India	5	Hong Kong	1
Indonesia	2	Hungary	1
Iran	2	India	2
Ireland	1	Indonesia	2

Israel	2	Iran	1
Italy	13	Ireland	1
Japan	5	Israel	2
Kazakhstan	1	Italy	11
Kuwait	1	Japan	5
Latvia	1	Jordan	1
Lebanon	1	Kazakhstan	1
Lithuania	1	Kuwait	1
Malawi	1	Latvia	1
Malaysia	2	Lebanon	1
Mexico	4	Lithuania	1
Mongolia	1	Malawi	1
Nepal	1	Malaysia	2
Netherlands	2	Mexico	5
New Zealand	1	Nepal	1
Nigeria	1	Netherlands	2
Not provided	8	New Zealand	1
North Macedonia	1	Nigeria	1
Norway	1	Not provided	8
Oman	1	North Macedonia	1
Pakistan	1	Norway	1
Philippines	1	Oman	1
Poland	2	Pakistan	1
Portugal	4	Philippines	1
Republic of Moldova	1	Poland	2
Saudi Arabia	3	Portugal	4
Serbia	1	Qatar	1
Singapore	2	Republic of Moldova	1
Slovakia	1	Saudi Arabia	3
Slovenia	1	Serbia	1
South Africa	3	Singapore	2
South Korea	3	Slovakia	1
Spain	7	Slovenia	1
Sri Lanka	1	South Africa	3
Sudan	1	South Korea	4
Sweden	3	Spain	7
Switzerland	2	Sri Lanka	1
Taiwan	4	Sudan	1
Thailand	1	Sweden	3
Tunisia	1	Switzerland	1
Turkey	3	Taiwan	3
Uganda	1	Thailand	1
United Kingdom	15	Tunisia	1
Ukraine	1	Turkey	2
United Arab Emirates	1	Uganda	1
United States	20	United Kingdom	14

Uzbekistan	2	Ukraine	1
Venezuela	1	United Arab Emirates	1
		United States	28
		Uzbekistan	2

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Highlighted references

Acknowledgements

Key points: (4-6 bullet points (30 words each) summarizing the main findings)

Author contributions