Research Article
NAFLD and Alcohol-Related Liver Diseases

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A global research priority agenda to advance public health responses to fatty liver disease

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Background & aims: An estimated 38% of adults worldwide have non-alcoholic fatty liver disease (NAFLD). From individual impacts to widespread public health and economic consequences, the implications of this disease are profound. This study aimed to develop an aligned, prioritised fatty liver disease research agenda for the global health community.
Methods: Nine co-chairs drafted initial research priorities, subsequently reviewed by 40 core authors and debated during a three-day in-person meeting. Following a Delphi methodology, over two rounds, a large panel (R1 n = 344, R2 n = 288) reviewed the priorities, via Qualtrics XM, indicating agreement using a four-point Likert-scale and providing written feedback. The core group revised the draft priorities between rounds. In R2, panellists also ranked the priorities within six domains: epidemiology, models of care, treatment and care, education and awareness, patient and community perspectives, and leadership and public health policy.
Results: The consensus-built fatty liver disease research agenda encompasses 28 priorities. The mean percentage of 'agree' responses increased from 78.3 in R1 to 81.1 in R2. Five priorities received unanimous combined agreement ('agree' + 'somewhat agree'); the remaining 23 priorities had >90% combined agreement. While all but one of the priorities exhibited at least a super-majority of agreement (>66.7% 'agree'), 13 priorities had <80% 'agree', with greater reliance on 'somewhat agree' to achieve >90% combined agreement.
Conclusions: Adopting this multidisciplinary consensus-built research priorities agenda can deliver a step-change in addressing fatty liver disease, mitigating against its individual and societal harms and proactively altering its natural history through prevention, identification, treatment, and care. This agenda should catalyse the global health community's efforts to advance and accelerate responses to this widespread and fast-growing public health threat.

Introduction

Over the past three decades, the fatty liver disease burden has increased drastically. An estimated 38% (95% CI 33.71-42.49) of the global adult population[1,2] and around 13% of children and adolescents,[3] now have the disease. Left unmanaged, the disease can progress through increasing stages of hepatic fibrosis, leading to cirrhosis and associated complications, including hepatocellular carcinoma (HCC) (Box 1).[4,5] Fatty liver disease causes quality of life impairments, which worsen with disease progression and are compounded by comorbidities.[6–8] Fatty liver disease is a leading cause of HCC, which is the second leading cause of years of life lost amongst all cancers.[9] Beyond the human toll, the disease has wide-reaching social and economic implications and yet it remains under-recognised and under-evaluated.[10,11]

Through cardiometabolic risk factors, fatty liver disease shares a complex bi-directional relationship with other common diseases, including cardiovascular disease, the leading cause of death in those with fatty liver disease.[13] Type 2 diabetes mellitus, cancer, sarcopenia, and chronic kidney disease are all commonly associated with fatty liver disease,[14,15] with the risk of extrahepatic complications increasing in parallel with liver disease severity.[15]

The multisystem nature of fatty liver disease has important implications for patient management, including the development of multi-disciplinary care models.[16] A lack of specific

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symptoms often leads to a clinically relevant delay in diagnosis.[17,18] Non-invasive tests (NITs) provide a practical and safe way of assessing fibrosis severity[19] and the risk of future liver-related events.[20,21] NITs have been used in the development of pathways to identify and stratify patients based on care needs,[22–25] yet such pathways are not implemented in the majority of healthcare settings.[16]

Several pharmacological treatments are under development, with some in late-stage clinical trials.[26,27] However, India is the only country where regulators have approved a pharmacological treatment for routine use in fatty liver disease (saroglitazar).[28] In the absence of pharmacological treatments approved for NASH, management is focused on improving insulin resistance and weight loss, when needed, and on attenuating the pro-inflammatory milieu of obesity, which are the predominant disease drivers.[29,30]

Few outside of the liver community recognise the need to deliver whole-of-society public health responses to fatty liver disease.[31–33] In 2021, a global consortium of experts set out consensus recommendations on how to accelerate public health action on this issue.[34] The negative impact of the COVID-19 pandemic on fatty liver disease risk factors[35,36] further reinforces the urgent attention this public health threat requires.

The liver health community (*i.e.*, the people and organisations who are largely working to improve liver health) must now build on past efforts to develop a clear vision and pathway to reduce the burden and address the individual and societal impacts of this growing challenge. Research is the central pivot for these efforts, accelerating the pace of knowledge creation and its translation into policy and practice.[37–39]

Materials and methods

Delphi expert panel member sample

The study's nine co-chairs used an iterative approach involving purposive, snowball, and targeted sampling to generate a large, global panel for this Delphi study. Based on publication record and engagement with the fatty liver disease agenda, the co-chairs identified 31 experts in clinical care (*e.g.*, liver, diabetes, obesity, and nutrition), public health, policy, advocacy, and patient representation, who collectively formed the core author group (n = 40) (Table S1). The proposed survey panel (n = 473) was created by compiling a list of known fatty liver disease experts from around the world with input from the core group (Fig. 1). Through this process, an expert panel diverse in demographic, disciplinary, and geographical characteristics was obtained (Table 1).

Box 1. The evolution of fatty liver disease nomenclature.[12]

The relationship between fatty liver disease, obesity, and diabetes was first described in the mid-1900s. Until then, the distinction between alcohol-related and non-alcoholic fatty liver disease (NAFLD) had been uncommon. In 1980, Ludwig *et al.* coined the term non-alcoholic steatohepatitis (NASH),[12] with NAFLD being a widely used umbrella term describing a histological spectrum ranging from steatosis without inflammation, to steatosis with varying degrees of inflammation and hepatocellular ballooning, which can lead to fibrosis, cirrhosis, and hepatocellular carcinoma. Recently, several proposals have been made to change the disease name, moving away from the construct of 'non-alcoholic' and better reflecting the metabolic foundation of the disease's aetiology. In 2023, a global consensus process is ongoing to reach agreement on the disease nomenclature. In this paper, we refer to fatty liver disease which arises in the absence of heavy alcohol intake and independently of other liver diseases.

Delphi statement domains

The development of the research priorities started with the core author group leading the development of evidence notes around seven topics, summarising the current knowledge base, envisioning what 'success' would look like in the next decade, identifying key questions, and suggesting research priorities for: (1) the human and economic burden, (2) defining and implementing models of care, (3) treatment and care, (4) education and awareness, (5) patient and community perspectives, (6) policy strategies and a societal approach, and (7) leadership for the fatty liver disease public health agenda. Twenty-six of the core-group members and 11 co-authors held a three-day meeting at Wilton Park, UK, in October 2022, co-chaired by H.E.M and opened by T.B and J.V.L, as part of the process. The research priorities were subsequently revised by J.V.L and H.E.M to reflect the Wilton Park discussions, and topics 6 and 7 were combined. The full core group received revised priorities for review in December 2022, with further revisions made based on core group feedback ahead of the first Delphi survey round (21 December 2022 to 15 January 2023).

Delphi method data collection and analysis

The study design consisted of an in-person Wilton Park meeting (Table S2) and two survey rounds (R1 and R2) wherein panellists reviewed and voted on the research priorities. The study used the Qualtrics XM platform to develop and distribute the surveys (round duration ranged from 2 to 3.5 weeks), which included four-point Likert-type response categories for measuring the level of agreement with the draft research priorities (*i.e.*, 'agree', 'somewhat agree', 'somewhat disagree', and 'disagree'); the survey included a fifth 'not qualified to respond' option to accommodate the broad range of knowledge and expertise across panel participants. Panellists could provide comments and suggest edits to individual priorities in text boxes, which followed each of the statements. Both R1 and R2 included a text box allowing for overall comments at the end of each survey. Demographic data were collected from participants in R1.

An analytic team comprised of a sub-set of the core group (J.V.L, H.E.M, P.N.B, C.J.K, D.R, D.I.W, and M.V-R) reviewed the R1 data, including 600 open-ended comments from the panellists, and initiated draft revisions. The full core group then reviewed the revised priorities. In R2 (8-21 February 2023), panellists voted on the revised priorities, which were accompanied by text boxes summarising changes made based on panellist and core group input from R1. Panellists also ranked at least half of the priorities within each of the six domains; for domains with only three priorities panellists ranked all three.

Quantitative analysis of the R1 and R2 results included frequencies and proportions of the four response categories spanning 'agree' to 'disagree' for all research priority statements, as well as those selecting 'not qualified to respond'. For the final R2 Delphi results, we assigned each research priority statement with a grade to indicate the level of combined

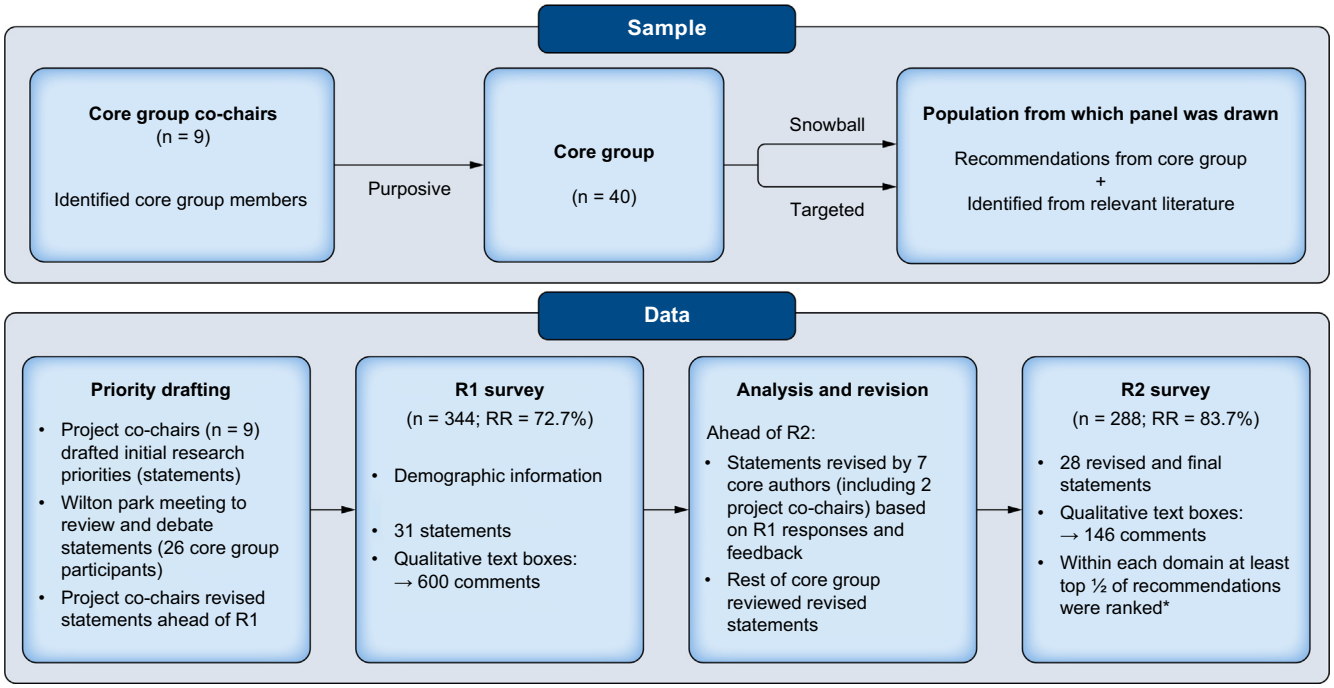

Fig. 1. Delphi panel generation and data collection. Study methodology, including sample and data collection. Top, the iterative sampling approach used to generate a large and diverse Delphi panel (n = 344): nine co-chairs identified a core group of 31 experts in clinical care, public health, policy, and advocacy, who collectively formed the core authorship group (n = 40), working across 20 countries; the core group identified individuals with expertise in the fatty liver disease field. Bottom, the iterative digital data-collection process, including priority drafting (by the study co-chairs) and revision (by the co-chairs and other core authors) of the statements; one survey round (R1) of draft statements; analysis and revision of the statements by the core group; and a revised and final survey round (R2) of the consensus statements. R1 included text boxes for panellists to provide comments and suggest edits to individual statements; the final round (R2) allowed for overall comments at the end of each domain. For the final set of statements in R2, panellists ranked at least the top half of recommendations in each of the six domains. *For domains with three priorities, panellists were required to rank them all. RR, response rate.

agreement ('agree' + 'somewhat agree'), using a system that has been used in other Delphi studies[34,40,41] in which 'U' denotes unanimous (100%) agreement, 'A' denotes 90-99% combined agreement, 'B' denotes 78-89% combined agreement, and 'C' denotes 67-77% combined agreement. The data tables report the proportion who selected 'not qualified to respond', who were removed from the denominator to calculate the levels of agreement/disagreement from the relevant sample.

For the ranking, scores were calculated and normalised in Microsoft Excel (v.16.70) to compare rankings within each domain. Demographic data were analysed descriptively, including frequencies and proportions. No data were excluded from any analyses. Instances of missing data were totalled, and denominators were adjusted as applicable, for any calculations involving missing datapoints.

Ethical considerations

As this study does not include patients, patient data, or biological human samples, it received ethical review exemption from the Hospital Clínic of Barcelona, Spain, ethics committee on 19 December 2022. Each participant was asked to consent to participating in the study, prior to their inclusion. Adequate measures to ensure personal data protection and confidentiality have been taken and data were deidentified for all analyses.

Results

A total of 473 individuals were invited to participate in R1 and 344 (72.7%) completed the survey. These 344 respondents were invited to participate in R2, of whom 288 (83.7%) completed the survey. Table 1 details the demographics of all expert panellists involved in the study. The mean age of respondents was 53.8 (standard deviation: 10.1). Most respondents were male (64.8%), worked in high-income countries (69.9%) and in the Europe and Central Asia region (42.2%), were primarily employed in the academic sector (66.6%), and worked in the clinical research field (79.4%). A total of 94 countries were represented in terms of respondent country of origin and 91 in terms of respondent country of work.

In R1, the study presented 31 initial research priorities to the panel. During revisions ahead of R2, three priorities were removed, with key components of these original statements being merged with existing priorities, leaving 28 priorities for the panel to review in R2. Across the two Delphi rounds, consensus increased for all six domains. The mean percentage of 'agree' responses across domains increased from 78.3 in R1 to 81.1 in R2, following the consideration of substantive comments received in R1.

Table 2 presents the final priorities, agreement grades, and rankings for each of the six domains. Within the final priorities in R2 (Fig. 2), the panel reached a unanimous combined agreement ('agree' + 'somewhat agree') with five priorities and >90% combined agreement with the remaining 23; the mean level of combined agreement across all priorities was 97.7%. For 13 priorities, 'agree' answers were below 80%, with higher reliance on 'somewhat agree' to achieve the high rate of overall combined agreement (Table S3).

Table 1. Delphi panel characteristics (n = 344).

Characteristic	n (%)
Gender	
Woman	115 (33.7)
Man	221 (64.8)
Non-binary or gender diverse	3 (0.9)
Prefer not to say	2 (0.6)
No response	3 (0.9)
Age	
All, mean [SD]	53.8 [10.1]
No response	12 (3.5)
Country of origin, by income level (n = 94)	
Low or middle	124 (36.9)
High	212 (63.1)
No response	8 (2.3)
Global region[a] of origin	
East Asia and Pacific	37 (11.0)
Europe and Central Asia[b]	142 (42.3)
Latin America and Caribbean	41 (12.2)
Middle East and North Africa	28 (8.3)
North America	52 (15.5)
South Asia	19 (5.7)
Sub-Saharan Africa	17 (5.1)
No response	8 (2.3)
Country of work, by income level (n = 91)	
Low or middle	102 (30.1)
High	237 (69.9)
No response	5 (1.5)
Global region[a] of work	
East Asia and Pacific	36 (10.6)
Europe and Central Asia[c]	143 (42.2)
Latin America and Caribbean	34 (10.0)
Middle East and North Africa	24 (7.1)
North America	76 (22.4)
South Asia	12 (3.5)
Sub-Saharan Africa	14 (4.1)
No response	5 (1.5)
Primary sector of employment[d]	
Academic	229 (66.6)
Public	62 (18.0)
Private	38 (11.0)
Civil society	9 (2.6)
Other	3 (0.9)
No response	3 (0.9)
Field(s) of employment[d,e]	
Clinical research	273 (79.4)
Non-clinical research	81 (23.5)
Healthcare provider	180 (52.3)
Patient/policy advocacy	36 (10.5)
Education	10 (2.9)
Other	7 (2.0)
No response	3 (0.9)
Years working in fatty liver disease field	
1 to 11	148 (43.7)
12 to 22	132 (38.9)
23 to 33	49 (14.5)
34 to 44	8 (2.4)
45 to 55	2 (0.6)
No response	5 (1.5)
Publications authored focused on fatty liver disease	
<6	103 (30.9)
6 to 25	95 (28.5)
26 to 50	54 (16.2)
51 to 100	42 (12.6)
>100	39 (11.7)
No response	11 (3.2)
International or regional liver association membership(s)[e]	
AASLD	165 (48.0)
APASL	34 (9.9)
ALEH	30 (8.7)
EASL	191 (55.5)
Other	18 (5.2)
No membership	152 (44.2)
Area of national professional association/society membership(s) in country of work[e]	
Liver disease	254 (73.8)
Gastroenterology	184 (53.5)
Obesity	42 (12.2)
Diabetes/endocrinology	45 (13.1)
Heart disease	11 (3.2)
Cancer	15 (4.4)
Primary care	5 (1.5)
Other	26 (7.6)
No membership	25 (7.3)

Percentages may sum to >100 due to rounding. Percentages for 'no response' are based on the total number of participants; all other percentages are calculated after excluding n of no response, unless otherwise indicated. AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; ALEH, Asociación Latinoamericana para el Estudio del Hígado (Latin American Association for the Study of the Liver); EASL, European Association for the Study of the Liver.

[a]Based on World Bank regions.

[b]n = 3 participants are originally from Central Asia.

[c]n = 3 participants work in Central Asia.

[d]Denominator includes n of no response.

[e]Sum may exceed sample size as participants could choose >1 response.

Patient and community perspectives was one of two domains within the study where more than half of the research priority statements had <80% of the panel 'agree.' Five of six statements (5.1 and 5.3-5.6) illustrated higher reliance on 'somewhat agree' to achieve >90% combined agreement. *Leadership and public health policies* was the second domain where more than half of the research priority statements had <80% of the panel 'agree.' Two of three statements (6.1 and 6.3) illustrated higher reliance on 'somewhat agree' to achieve >90% combined agreement.

The priority rankings are explored in the discussion, alongside a summary of current evidence within each area.

Discussion

This study engaged a multi-disciplinary group of experts and leaders from around the world to develop a consensus research agenda that is ambitious and transformational in nature and can deliver a step-change in how fatty liver disease is prevented and managed. To achieve this change, the study not only puts forward a shared research vision, but also illuminates degrees of agreement within the fatty liver disease community of practice, underscoring the benefit of continued discussion throughout the community. Here, we explore the importance of the research priorities for advancing the field with a focus on the highest ranked priorities across the six fatty liver disease research domains. The high response rates across both survey rounds and the substantial, often near-unanimous agreement of the panellists on all priorities suggests that agreeing on research priorities, for the first time in the fatty liver disease field, was a meaningful and important undertaking that builds on early priority-setting efforts.[42,43]

Building the case for action: a better understanding of the human and economic burden

Knowledge of fatty liver disease has advanced tremendously over the past three decades, including on the predominant risk factors and disease drivers, yet gaps remain in our understanding of its natural history.[44] Most studies on its natural history and clinical progression emerge from tertiary centres, registries, or are based on biopsy availability,[45–47] which introduces disease-spectrum bias, while few are from prospective unbiased cohorts. As the field seeks to advance understanding, the panel specifically prioritised cohort studies that prospectively monitor outcomes in patients with defined liver disease (priority 1.2; ranked 1st in its domain); such cohorts will ideally be sampled from the general population.

In a separate but related priority, the panel unanimously supported the development and validation of risk prediction models to forecast progressive hepatic and extrahepatic outcomes (priority 1.4; ranked 3rd in its domain). The few risk-prediction models currently in use focus on broad risk factors, such as diabetes and body mass index. Future efforts will lead toward more nuanced predictors of outcomes, including novel biomarkers, as part of the quest towards precision medicine.[43,48]

While notable efforts have been made to establish the disease prevalence in both adults and children,[1–3,48] there are critical knowledge gaps in most countries and regions. The panel prioritised additional studies to better quantify the overall burden, including the disease prevalence and the quality of life impairment, in the general population and in high-risk groups (priority 1.1; ranked 2nd in its domain).

The panel almost universally agreed that additional studies are necessary to better quantify both the direct and indirect costs of fatty liver disease (priority 1.3). Available studies, while showing substantial costs associated with the disease,[10,11,49,50] are limited to a small number of high-income countries. Of equal importance to the panel was to advance understanding of the factors driving inequities in fatty liver disease (priority 1.5). The limited data in existence highlight large inequities by social group[51] and mirror what is seen more widely with non-communicable diseases (NCDs).[52] Further elucidating these factors will support the development of more targeted approaches to prevent and manage the burden of fatty liver disease.

Advancing health system responses to fatty liver disease

Defining and implementing multidisciplinary models of care

One of the greatest challenges in clinical practice remains the identification of those with fatty liver disease and subsequent risk-stratification of those needing aggressive intervention and close monitoring by a specialist, from those who can be managed in primary care. Great advances have been made on the use of NITs in the past decades[48,53,54] and there is increasingly robust evidence of the value of current NITs for prognostication,[20,21] yet substantial challenges remain.[55] There is a critical unmet need when it comes to non-invasive approaches for monitoring disease progression and assessing disease resolution or meaningful improvements in fibrosis.[48,56,57] The panel unanimously recognised this imperative and gave a high priority to further validating NITs, with a focus on enabling early diagnosis, prognosis, and monitoring of liver disease progression (priority 2.4; ranked 1st in its domain). Within this, emphasis will be needed on the cost-effectiveness of different approaches within different resource environments[19,58,59] and the appropriate cut-offs to be used in different settings and population groups.[60]

The multisystem nature of fatty liver disease, and the fact that many patients present with a range of comorbidities, requires a multi-disciplinary approach to management and care;[16,61,62] however, multi-disciplinary care models have not been widely adopted in most healthcare settings.[16] The panel unanimously called for further studies to determine the effectiveness of different models of care, including the impact on patient outcomes and their cost-effectiveness (priority 2.1; ranked 2nd in its domain). As this work advances, emphasis should be placed on care models that can be adaptable and implementable based on local resources. Specific considerations are needed around care models for paediatric populations (priority 2.2).[63–66]

Alongside the development of effective care models, the heterogeneity of patient presentation, coupled with the large burden of disease, means that tools are needed to support clinicians to identify those at highest risk of disease progression and adverse outcomes. The panel stressed the need to validate risk prediction models in different population groups, enabling them to be tailored to specific groups (priority 2.3; ranked 3rd in its domain).

The use of digital technologies in healthcare settings holds great potential for supporting service delivery,[67] yet this is a relatively new area of research within the field of fatty liver disease.[68–71] The panel supported the exploration of how novel digital technologies can be utilised within healthcare settings (priority 2.5) and further exploration of the potential for artificial intelligence methods to improve diagnosis of fatty liver disease (priority 2.7). The panel also supported further understanding how digital health approaches can support patients to achieve lifestyle behavioural change (priority 2.6). This work can build upon and complement broader efforts within the NCD and mental health fields.[72,73]

Accelerating advances in fatty liver disease treatment

In advancing treatment and care for affected populations, the panel highly ranked the importance of understanding the role of NITs in guiding treatment indication, response, and discontinuation, as well as predicting outcomes (priority 3.2; ranked 1st in its domain). This priority speaks to the current gap in evidence on the use of NITs to gain information on therapeutic responses.[48,74] As specific therapeutics are approved, NITs which can guide treatment decisions will be critical, especially given the likely long duration and high cost of treatment.

Currently, the central focus of treatment for fatty liver disease has been lifestyle interventions (*e.g.*, nutrition, exercise, and weight loss), pharmacological treatment of comorbidities such as obesity and diabetes, and liver-directed therapies. The panel acknowledged that the prevention of fatty liver disease-related cirrhosis or HCC will require multi-pronged strategies which address an array of risk factors (*e.g.*, social, environmental, behavioural, biological, and genetic) and called for studies to assess the efficacy and cost-effectiveness of such strategies (priority 3.1; ranked 2nd in its domain). As fatty liver disease treatment options expand, patient-centred decision

Table 2. Consensus statements for a fatty liver disease research priorities agenda.

Statement		Grade	Rank	A (%)	SA (%)	A+SA (%)	SD (%)	D (%)	NQ (%)	N
Domain 1: The human and economic burden										
1.1	Implement studies to better quantify the fatty liver disease burden, including health-related quality of life, in the general population and in specific high-risk groups.	A	2	92.7	6.3	99.0	0.7	0.3	0.0	288
1.2	Conduct cohort studies to prospectively monitor outcomes in patients with defined liver disease phenotypes (*e.g.*, NASH, NASH with fibrosis, cirrhosis, hepatocellular carcinoma).	U	1	93.0	6.6	99.7	0.3	0.0	0.3	287
1.3	Conduct additional studies on the socio-economic costs of fatty liver disease, capturing direct and indirect costs.	A		84.3	13.2	97.6	1.7	0.7	0.3	287
1.4	Develop and validate risk prediction models to forecast progressive hepatic and extrahepatic outcomes, to inform clinical decision making.	U	3	91.6	8.4	100.0	0.0	0.0	0.7	286
1.5	Report all data disaggregated by sex, race, ethnicity, age, socioeconomic status, education level, and other variables related to inequities.	A		74.2	23.3	97.6	2.1	0.3	0.3	287
Domain 2: Defining and implementing models of care										
2.1	Determine the effectiveness of different models of care for fatty liver disease, including their impact on patient outcomes and their cost-effectiveness.	U	2	90.6	9.0	99.7	0.0	0.3	0.0	288
2.2	Validate multidisciplinary models of care for fatty liver disease in paediatric populations.	A		80.7	17.9	98.6	1.4	0.0	2.8	280
2.3	Evaluate how risk prediction models for fatty liver disease perform in different populations, so that they can be tailored to specific populations and groups.	A	3	85.1	12.8	97.9	1.7	0.3	0.0	288
2.4	Validate non-invasive tests to enable early diagnosis, prognosis, and monitoring of liver disease progression.	U	1	93.4	6.3	99.7	0.3	0.0	0.0	288
2.5	Explore how novel digital technologies (*e.g.*, artificial intelligence, data-based analytics, digital health applications and therapeutics) can be utilised within healthcare settings.	A		73.2	21.3	94.4	4.9	0.7	0.3	287
2.6	Assess how digital health (*e.g.*, applications, interventions, therapeutics) can support patients to achieve lifestyle behavioural change.	A		69.8	26.7	96.5	2.8	0.7	0.0	288
2.7	Further explore the use of artificial intelligence to improve diagnostics for fatty liver disease.	A		63.9	31.2	95.1	3.5	1.4	1.0	285
Domain 3: Treatment and care										
3.1	Assess the efficacy and cost-effectiveness of multi-faceted strategies (*e.g.*, social, environmental, behavioural, biological) to prevent fatty liver-related cirrhosis and hepatocellular carcinoma.	A	2	84.7	14.3	99.0	0.7	0.3	0.3	287
3.2	Study the role of non-invasive tests in guiding treatment indication, response, and discontinuation, as well as predicting outcomes.	A	1	94.1	5.2	99.3	0.3	0.3	0.0	288
3.3	Evaluate patient-centred decision making in relation to fatty liver disease treatment and care outcomes.	A		79.5	16.3	95.8	3.5	0.7	0.0	288
3.4	Evaluate the efficacy and cost-effectiveness of the optimal management of related diseases (*e.g.*, diabetes, obesity) on fatty liver disease and other liver-related outcomes.	U	3	90.3	9.4	99.7	0.3	0.0	0.0	288
Domain 4: Education and awareness										
4.1	Conduct comparative population-based surveys to understand fatty liver disease knowledge amongst the general population and high-risk groups specifically, to inform the development of awareness-raising approaches.	A	2	82.2	14.6	96.9	2.1	1.0	0.3	287

(*continued on next page*)

Table 2. (*continued*)

Statement		Grade	Rank	A (%)	SA (%)	A+SA (%)	SD (%)	D (%)	NQ (%)	N
4.2	Conduct research to identify the educational needs of healthcare providers in key areas, such as primary care, diabetes/endocrinology, obesity medicine, and cardiology, about fatty liver disease.	A	1	89.6	9.4	99.0	0.7	0.3	0.0	288
4.3	Study the effectiveness of strategies to impact fatty liver disease knowledge, attitudes, beliefs, and practices (KABPs), prioritising KABPs among healthcare professionals and high-risk groups.	A	3	72.8	25.4	98.3	1.0	0.7	0.3	287
Domain 5: Patient and community perspectives										
5.1	Conduct research to understand the needs and experiences of fatty liver disease patients and at-risk communities (*e.g.*, perspectives around prevention, treatment, and care, i ncluding mental health).	A	2	78.0	19.2	97.2	2.4	0.3	0.3	287
5.2	Study the impact of treatment and care on overall quality of life, including functional status (physical, psychological, social), in fatty liver disease patients.	A	1	81.9	17.4	99.3	0.7	0.0	0.0	288
5.3	Assess if published patient guidelines result in patients having an improved understanding of fatty liver disease and taking a more active role in their disease management.	A		71.9	25.7	97.6	2.1	0.3	0.0	288
5.4	Evaluate the efficacy of patient-led self-care programmes in improving fatty liver disease outcomes.	A		74.6	22.0	96.5	3.5	0.0	0.3	287
5.5	Explore the potential of new technologies (*e.g.*, digital health applications and therapeutics, mobile interventions) to foster patient engagement in treatment and care.	A	3	75.5	21.3	96.9	2.4	0.7	0.7	286
5.6	Evaluate the effect of interventions to reduce liver disease stigma among patients, the public, and healthcare providers.	A		74.7	21.2	95.8	2.8	1.4	0.0	288
Domain 6: Leadership and policies for the fatty liver disease public health agenda										
6.1	Conduct periodic studies of national and sub-national policies and guidelines for the prevention and management of fatty liver disease, to identify trends and gaps, and assess their implementation.	A	1	79.4	18.8	98.3	1.0	0.7	0.3	287
6.2	Analyse policy successes and failures in addressing non-communicable diseases, to inform the development of fatty liver disease-specific strategies.	A	2	82.6	14.6	97.2	2.4	0.3	0.3	287
6.3	Monitor, study, and report mentions of fatty liver disease within patient groups and professional societies outside of the field of hepatology (*e.g.*, at events, in publications).	A	3	66.8	28.0	94.8	3.8	1.4	0.7	286
Mean % agreement				81.1	16.6	97.7				

Percentages may add up to >100 due to rounding. Grades are based on the percentage of combined agreement ('agree' + 'somewhat agree'). U, unanimous (100%) agreement; A, 90–99% agreement. Responses to each statement are presented as percentages of the total responses. A, agree; SA, somewhat agree; SD, somewhat disagree; D, disagree; NQ, the percentage of participants that indicated that they were not qualified to respond; N, total number of responses; NASH, non-alcoholic steatohepatitis.

making will also become increasingly important (priority 3.3), as seen more broadly in the NCD field.[75,76]

Recognising the shared metabolic risks inherent in both fatty liver disease and other highly prevalent co-morbidities, the panel unanimously highlighted the importance of further evaluating the efficacy and cost-effectiveness of optimal management of related diseases (*e.g.*, diabetes and obesity) on liver-related outcomes (priority 3.4; ranked 3rd in its domain). These factors increase risk of fibrosis progression, which in turn increases all-cause mortality, with the majority of patients succumbing to cardiovascular disease and solid organ malignancy,[46,77] but further evidence is needed that optimal management of these comorbidities has a beneficial impact on hepatic outcomes.[78] This evidence will be critical in ongoing efforts to engage and involve primary care and non-liver specialities within the multidisciplinary management of fatty liver disease.

Improving knowledge and awareness

Despite fatty liver disease being highly prevalent, awareness is generally low amongst non-liver health specialists – most importantly primary care physicians and diabetologists – with critical knowledge gaps around risk-factors, diagnosis, and management approaches[79–81] and a lack of tools to support clinical decision making.[79] While important progress is being made in this area,[82] the panel gave prominence to research

aimed at identifying the educational needs of healthcare providers in key areas, including primary care, diabetes, and obesity (priority 4.2; ranked 1st in its domain), to inform targeted educational strategies. Studies will also be needed to assess the effectiveness of such strategies to impact knowledge, attitudes/beliefs, and practices, starting with key healthcare professionals (priority 4.3; ranked 3rd in its domain).

Many people living with fatty liver disease are unaware of their fibrosis stage, which has important implications for adherence to management approaches.[83] Equally, within population groups at high risk of disease progression, including people with type 2 diabetes mellitus and other metabolic diseases, awareness of fatty liver disease, the health risks posed by it, or how it interacts with their other diseases, is low.[84,85] To inform the development of awareness-raising approaches, the panel suggests that comparative population-based surveys are implemented to understand knowledge amongst the general population and high-risk groups (priority 4.1; ranked 2nd in its domain).

Delivering whole-of-society responses

Patient and community perspectives

The large prevalence of fatty liver disease and the less severe effects of steatosis potentially masks that, in advanced stages, the disease causes substantial impairment in quality of life which is often compounded in those with multiple morbidities.[6–8] Alongside liver-related outcomes, fatigue and depression are important contributors to reduced quality of life in people living with fatty liver disease.[86,87]

While combined agreement on patient-centred orientations was high, the study's results noted above suggest that further discussion within the liver health community on research priorities for patient and community engagement is warranted. The panel felt strongly about the need to study the impact of treatment and care on overall quality of life, including functional status (priority 5.2; ranked 1st in its domain). Knowledge gaps remain about patient needs and experiences,[88] including perspectives around prevention, treatment, and care. The panel prioritised studies that can advance this understanding (priority 5.1; ranked 2nd in its domain).

In chronic disease management, engaged patients are shown to have better outcomes,[89] while lower engagement levels are associated with more adverse events.[90] Digital approaches have proven effective at improving patient engagement in NCD management[91,92] and initial efforts have been made to understand the role of technologies in fostering patient engagement in fatty liver disease treatment and care.[93,94] The panel prioritised further exploration in this novel area of research (priority 5.5; ranked 3rd in its domain). In the area of patient engagement, the panel also agreed that assessing the impact of patient care guidelines[95] will be important (priority 5.3).

In other areas, the panel agreed on further evaluating the efficacy of patient-led self-care programmes in improving fatty liver disease outcomes (priority 5.4) and evaluating the effect of interventions to reduce liver disease stigma among patients, the public, and healthcare providers (priority 5.6).

Leadership and public health policies

From the local to the global level, public health policy responses to fatty liver disease have, to date, not stemmed the increase in fatty liver disease morbidity or mortality.[31,34,96] A global review of policies, strategies, and guidelines conducted in 2020 found that of 102 countries assessed, around one-third

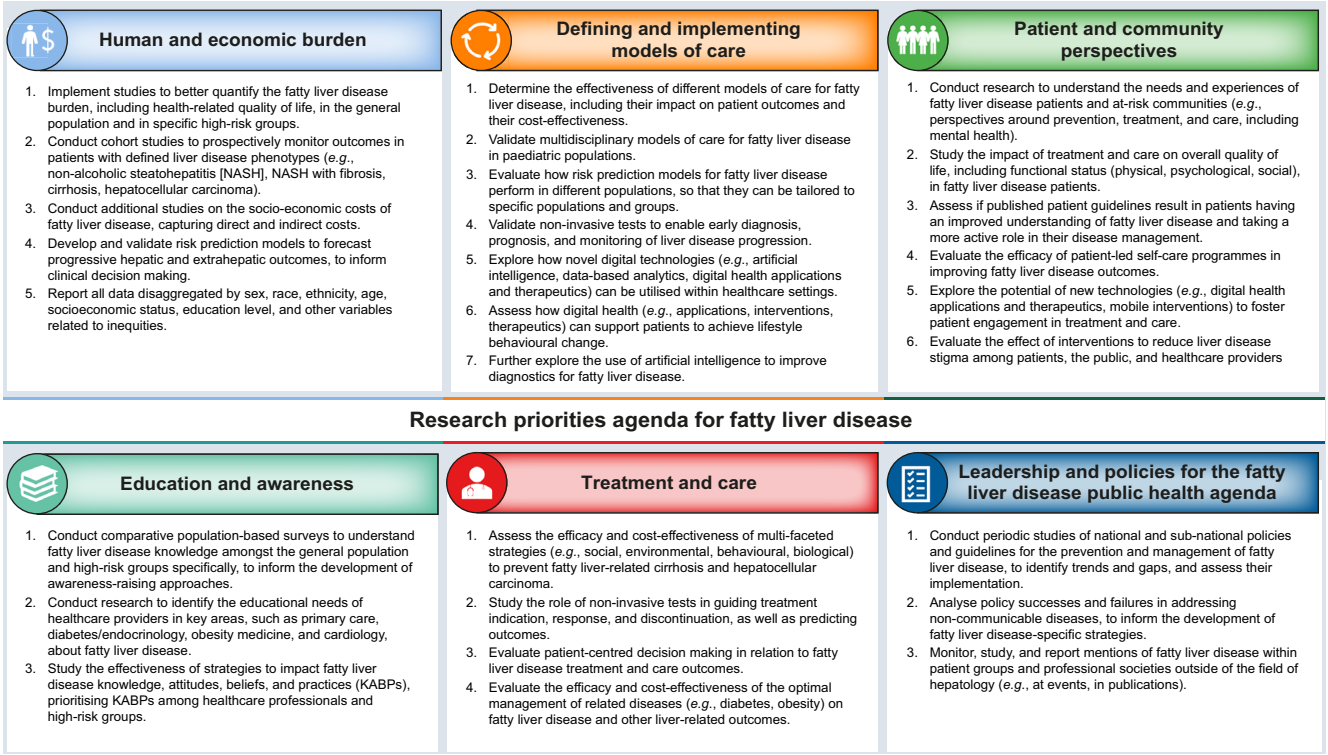

Fig. 2. Research priorities agenda for fatty liver disease.

of countries scored zero on an associated preparedness index.[96] Fatty liver disease is also absent in otherwise broad, global strategies and guidelines, including the World Health Organization's NCD strategies.[97,98] Building on past efforts, the panel near unanimously called for periodic studies to assess national and sub-national policies and guidelines for the prevention and management of fatty liver disease, to identify trends and gaps and assess their implementation (priority 6.1; ranked 1st in its domain).

Agreement was also reached on the need to analyse policy successes and failures in addressing NCDs, to inform the development of fatty liver disease-specific strategies (priority 6.2; ranked 2nd in its domain). This will require a greater focus within the liver heath community on the commercial determinants driving the increasing burden of fatty liver disease.[99]

The multidisciplinary and multi-sectoral nature of the public health responses to fatty liver disease require further engagement and collaboration with those outside of the field of hepatology. In an effort to guide and inform such engagements, and assess their impact, the panel recommends efforts to monitor, study, and report mentions of fatty liver disease within patient groups and professional societies (priority 6.3; ranked 3rd in its domain).

Study strengths and limitations

The major strength of this study is its novelty as the first global effort to propose a comprehensive research agenda for fatty liver disease utilising the rigorous Delphi consensus methodology. Additionally, within this methodology, the ability to illustrate degrees of agreement by breaking-out 'agree' and 'somewhat agree' responses may assist decision makers and researchers. We suggest that the breadth of issues covered, combined with the relatively focused priorities, makes the outcome both aspirational and practical. While this process did not consider how to operationalise these research priorities, including the resource requirements to do so, the findings can guide the investment decisions of research funders.

The Delphi methodology used in this study is an effective approach in consensus building, yet building consensus is not without challenges. In this study we used purposive sampling to develop a core group. To mitigate the biases of purposive sampling, we used snowballing and targeted sampling to yield a panel of 344 people diverse in both expertise and geographical representation. We do, however, acknowledge that the characteristics of the final group (*e.g.*, predominantly based in high-income countries and employed in the academic sector), will have been reflected within the agreement levels of the research priorities. For instance, the lower levels of agreement on the more patient centric and policy-oriented priorities likely reflects the smaller proportion of the panel working in patient/policy advocacy. While 10.5% (n = 36) of the panel reported some engagement in patient/policy advocacy, this was the primary area of work for only 4.7% (n = 16). Conducting the survey in the English language may have also influenced who accepted the invitation to contribute.

Conclusions

Delivering comprehensive health system and public health responses to fatty liver disease will require the global health community to re-envision the landscape, grow the fatty liver disease community of practice, and place greater emphasis on collective and collaborative thinking and action. This global multidisciplinary effort has, for the first time, developed a consensus fatty liver disease research agenda that can serve as the foundation for turning the tide on this silent public health threat.

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Abbreviations

HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NCD, non-communicable disease; NIT, non-invasive test; R, round.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

This study was led by a core group of 40 co-authors. J.V.L led the core group and provided regular updates by email. Twenty-six core group members and 11 co-authors participated in a three-day in-person meeting hosted by Wilton Park, UK, in October 2022, which informed the development of the research priorities included in the Delphi study. Seven co-chairs (A.M.A, J.P.A, P.C, M.N, J.M.S, V.W-S.W, and Z.M.Y) led the drafting of seven evidence notes, including key priorities and challenges, ahead of the Wilton Park meeting and were supported by core group members (R.B, T.B, H.C-P, K.C, N.D, A.D, T.T-K.H, Al.K, V.M, P.N.N, M.E.R, M.S, E.T, and S.Z-S). The evidence notes were reviewed by J.V.L and H.E.M and informed the drafting of the research priorities statements and actions. D.R and J.V.L. led the methodology. J.V.L, H.E.M, P.N.B, C.J.K, D.R, D.I.W, and M.V-R reviewed comments submitted as part of the two survey rounds. J.V.L., H.E.M, and M.V-R reviewed all comments sent directly by email. All panel members provided two rounds of comments through Qualtrics XM. H.E.M, M.V-R, and J.V.L wrote the first draft of the manuscript, which was reviewed by the core group. Those fulfilling authorship criteria are named.

Data availability statement

De-identified source data for all analyses will be made available by contacting the corresponding author (Jeffrey.Lazarus@sph.cuny.edu), with appropriate ethical approval and for fair use.

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Supplementary data

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Supplemental information

A global research priority agenda to advance public health responses to fatty liver disease

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Supplementary materials

A global research priority agenda to advance public health responses to fatty liver disease

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The list above is of core authors. For the full authorship list, please refer to the manuscript.

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Table S1. Core group members (n=40).

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Shira Zelber-Sagi	School of Public Health, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel

Table S2. Wilton Park meeting delegates.

First Name	Last Name	Position	Institution	Country
William	Alazawi	Professor of Hepatology	Queen Mary University of London	UK
Naim	Alkhouri	Chief Medical Officer and Director of the Fatty Liver Program	Arizona Liver Health	USA
Alina M.	Allen	Director, NAFLD Clinic	Mayo Clinic	USA
Saleh A.	Alqahtani	Chairman, Board of Directors and Executive Director	King Faisal Specialist Hospital & Research Centre	Saudi Arabia
Juan Pablo	Arab	Associate Professor of Medicine	Western University	Canada
Marco	Arrese	Professor of Medicine	Pontificia Universidad Católica de Chile	Chile
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Jacqueline	Bowman-Busato	Policy Lead	European Association for the Study of Obesity	Belgium
Paul N.	Brennan	Clinical Lecturer and Specialist Registrar in Hepatology	University of Dundee	UK
Patrizia	Burra	Head of Multivisceral Transplant Unit	Padua University Hospital	Italy
Massimo	Colombo	Chair of the International Liver Foundation	EASL	Italy

Kenneth	Cusi	Professor of Medicine	University of Florida	USA
Nikos	Dedes	Chair	Greek Patients Association	Greece
Davide	Fortin	Post Doc	Aix Marseille University	France
Sven M.	Francque	Professor	Antwerp University Hospital	Belgium
Alexander	French	Head of Education and Capacity Building	World Obesity Federation	UK
Amalia	Gastaldelli	Research Director	Institute of Clinical Physiology	Italy
Hannes	Hagström	Consultant hepatologist	Karolinska Institutet	Sweden
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Maria Paula	Macedo	Professor	NOVA Medical School	Portugal

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Shira	Zelber-Sagi	Head of School of Public Health, Faculty of Social Welfare and Health Sciences	University of Haifa	Israel

Table S3. Research priorities that achieved less than 80% agreement.

Statement		A (%)	SA (%)
Section 1: The human and economic burden			
1.5	Report all data disaggregated by sex, race, ethnicity, age, socioeconomic status, education level, and other variables related to inequities.	74.2	23.3
Section 2: Defining and implementing models of care			
2.5	Explore how novel digital technologies (e.g., artificial intelligence, data-based analytics, digital health applications and therapeutics) can be utilised within healthcare settings.	73.2	21.3
2.6	Assess how digital health (e.g., applications, interventions, therapeutics) can support patients to achieve lifestyle behavioural change.	69.8	26.7
2.7	Further explore the use of artificial intelligence to improve diagnostics for fatty liver disease.	63.9	31.2
Section 3: Treatment and care			
3.3	Evaluate patient-centred decision making in relation to fatty liver disease treatment and care outcomes.	79.5	16.3
Section 4: Education and awareness			
4.3	Study the effectiveness of strategies to impact fatty liver disease knowledge, attitudes, beliefs, and practices (KABPs), prioritising KABPs among healthcare professionals and high-risk groups.	72.8	25.4
Section 5: Patient and community perspectives			

5.1	Conduct research to understand the needs and experiences of fatty liver disease patients and at-risk communities (e.g., perspectives around prevention, treatment, and care, including mental health).	78.0	19.2
5.3	Assess if published patient guidelines result in patients having an improved understanding of fatty liver disease and taking a more active role in their disease management.	71.9	25.7
5.4	Evaluate the efficacy of patient-led self-care programmes in improving fatty liver disease outcomes.	74.6	22.0
5.5	Explore the potential of new technologies (e.g., digital health applications and therapeutics, mobile interventions) to foster patient engagement in treatment and care.	75.5	21.3
5.6	Evaluate the effect of interventions to reduce liver disease stigma among patients, the public, and healthcare providers.	74.7	21.2
Section 6: Leadership and policies for the fatty liver disease public health agenda			
6.1	Conduct periodic studies of national and sub-national policies and guidelines for the prevention and management of fatty liver disease, to identify trends and gaps, and assess their implementation.	79.4	18.8
6.3	Monitor, study, and report mentions of fatty liver disease within patient groups and professional societies outside of the field of hepatology (e.g., at events, in publications).	66.8	28.0
A, agree; SA, somewhat agree.			