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AP&T Alimentary Pharmacology & Therapeutics WILEY

A sustainable development goal framework to guide multisectoral action on NAFLD through a societal approach

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Funding information This work was supported by the EASL International Liver Foundation who

Summary

Background: Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent condition that requires a comprehensive and coordinated response across sectors and disciplines.

Aims: In the absence of a multisectoral framework to tackle this condition, we developed one using the sustainable development goals (SDGs) as the basis for converging thinking about the design and delivery of public health responses.

Methods: A multidisciplinary group identified the SDG targets and indicators for inclusion in the new framework through a two-stage process. Firstly, a core team of three researchers independently reviewed the 169 targets and 231 indicators of the SDGs to select a shortlist. Over two Delphi rounds, a multidisciplinary group of 12 experts selected which of the shortlisted targets and indicators to include. Respondents also provided written feedback on their selection. Targets and indicators with 75% or greater agreement were included in the final framework.

Results: The final framework comprises 16 targets—representing 9% of all targets and 62% (16/26) of the shortlisted targets—and seven indicators, accounting for 50% (7/14) of the shortlisted indicators and 3% of all indicators. The selected targets and indicators cover a broad range of factors, from health, food and nutrition to education, the economy, and the built environment.

Conclusions: Addressing the challenge of NAFLD will require a re-envisioning of the liver health landscape, with greater focus on joined-up systems thinking and action.

The Handling Editor for this article was Dr Rohit Loomba, and it was accepted for publication after full peer-review.

The complete list of author affiliations are listed in Appendix 1.

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acknowledges funding from Intercept Pharmaceuticals, as well as Bristol Myers Squibb and Merck Sharp & Dohme. The funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

1 | INTRODUCTION

There is increasing recognition of the need to view complex health issues as systems problems, requiring multidisciplinary and multisectoral responses.¹ Non-alcoholic fatty liver disease (NAFLD) is a potentially serious liver condition that affects close to one in four adults globally,^{2,3} causing substantial impairment to health-related quality of life⁴ and significant healthcare costs and economic loss.⁵ Despite the scale of the challenge, NAFLD remains largely unknown outside the field of hepatology and public health responses have been weak and fragmented.⁶

NAFLD is an umbrella term that describes a spectrum of liver damage, with non-alcoholic steatohepatitis (NASH) the most serious form. Part of a multisystem disease, NAFLD shares a complex bidirectional relationship with components of the metabolic syndrome. The disease is a leading cause of cirrhosis⁷ and contributes to cardiovascular disease, type 2 diabetes and non-hepatic cancer morbidity and mortality.^{8,9} NAFLD is strongly–but not exclusively–associated with obesity¹⁰ and is still common in nonobese individuals.¹¹ The disease is largely underdiagnosed in the general population.¹²

NAFLD shares common risk factors with other highly prevalent non-communicable diseases (NCDs), namely those related to food systems and the lived environment. As with NCDs more broadly, addressing NAFLD will require a comprehensive, cohesive, and coordinated response that synergistically acts upon the immediate, underlying and basic influences of the disease at all stages of the life course. The lack of joined-up efforts, including a comprehensive multisectoral framework for addressing NAFLD, is a barrier to the design and delivery of public health responses to this disease.

The Sustainable Development Goals (SDGs) serve as the mainstay of the 2030 Agenda for Sustainable Development with clear priorities, from reducing social and economic inequalities to improving nutrition, health and education.¹³ The 17 goals and 169 targets that make up the SDGs provide a blueprint for cross-sectoral collaboration and action. Previous studies have used the SDGs to develop a conceptual framework for informing policy approaches on sustainable development and urban health¹⁴ and to highlight the importance of addressing obesity for achieving the sustainable development agenda.¹⁵

We set out to develop a NAFLD-SDG framework to help conceptualise the design and delivery of a comprehensive, multisectoral public health response to NAFLD.

2 | METHODS

ers with whom the liver health community needs to engage.

The NAFLD conceptual model developed by Lazarus et al¹⁶ outlines the basic, underlying and direct influences that contribute to the development of the disease. We grouped elements of this model into six domains: (a) economic, political and social context; (b) health; (c) nutrition and food environment; (d) welfare and social services; (e) education; and (f) lived environment, in order to link the elements of the model to specific SDG targets and indicators (Table S1).

The SDGs consist of 17 goals, followed by targets within each goal and indicators within each target. Targets are specific objectives while indicators serve as quantifiable metrics. The selection of targets and indicators for inclusion in the NAFLD-SDG framework followed a two-stage process. Firstly, a core team of three researchers (JVL, HEM, and TTKH) independently reviewed the 169 SDG targets and 231 unique indicators proposed by the Inter-Agency and Expert Group on SDGs,¹⁷ selecting targets and indicators directly or indirectly linked to one of the six domains. Where unanimity was not achieved in the selection, the core team discussed until consensus was achieved. Not all indicators within the selected targets were included as some accompanying indicators were insufficiently specific or relevant to NAFLD. Conversely, if an indicator was included, the target under which it fell had to be included.

The second stage of the selection followed a Delphi process over two rounds of voting (Figure S1). In the first round, a multidisciplinary group of 12 experts were invited to select which of the shortlisted targets and indicators to include in the NAFLD-SDG framework. Respondents also provided written feedback on their selection. Nine of the 12 experts (75%) completed the round 1 survey (three did not respond by the deadline; Table S2). For round 2, the survey included a summary of the written feedback provided by respondents in round 1. Targets which received less than 25% agreement in round 1 were removed (n = 1). In the second round of voting, all 15 individuals completed the survey (the 12 experts and three core team members). The core group members who led the analysis completed the round 2 survey prior to other respondents so as not to be influenced by the selection of others. Targets and indicators with 75% or greater agreement were included in the final NAFLD-SDG framework.

3 | RESULTS

Table 1 reports the final level of consensus achieved for each of the shortlisted targets and indicators. A total of 16 targets across eight

This new framework can help guide this process, including by outlining the stakehold-

TABLE 1 SDGs and associated targets and indicators shortlisted for inclusion in the SDG-NAFLD framework and final level of consensus

Domain related				
to the NAFLD conceptual		Percent agreement		Percent agreement
framework	Targets	for target ^a	Indicators	for indicator ^a
SDG 1. End poverty	in all its forms everywhere			
Economic, political, and social context	1.1 By 2030, eradicate extreme poverty for all people everywhere, currently measured as people living on less than \$1.25 a day	60%	1.1.1 Proportion of the population living below the international poverty line by sex, age, employment status, and geographic location (urban/rural)	60%
Economic, political, and social context	1.2 By 2030, reduce at least by half the proportion of men, women, and children of all ages living in poverty in all its dimensions according to national definitions	73%	1.2.1 Proportion of population living below the national poverty line, by sex and age	67%
Welfare and social protection	 1.3 Implement nationally appropriate social protection systems and measures for all, including floors, and by 2030 achieve substantial coverage of the poor and the vulnerable 	57%	N/A	N/A
Economic, political, and social context	1.4 By 2030, ensure that all men and women, in particular the poor and the vulnerable, have equal rights to economic resources, as well as access to basic services, ownership, and control over land and other forms of property, inheritance, natural resources, appropriate new technology, and financial services, including microfinance	80%	N/A	N/A
SDG 2. End hunger,	achieve food security and improved nutrition, and promote su	ustainable agrio	culture	
Food environment and nutrition	2.1 By 2030, end hunger and ensure access by all people, in particular the poor and people in vulnerable situations, including infants, to safe, nutritious, and sufficient food all year round	80%	N/A	N/A
Food environment and nutrition	2.2 By 2030, end all forms of malnutrition, including achieving, by 2025, the internationally agreed targets on stunting and wasting in children under 5 years of age, and address the nutritional needs of adolescent girls, pregnant and lactating women, and older persons	100%	2.2.1 Prevalence of stunting (height for age <-2 standard deviation from the median of the WHO Child Growth Standards) among children under 5 years of age	40%
			2.2.2 Prevalence of malnutrition (weight for height >+2 or <-2 standard deviation from the median of the WHO Child Growth Standards) among children under 5 years of age, by type (wasting and overweight)	100%
SDG 3. Ensure healt	hy lives and promote well-being for all at all ages			
Health and health systems	3.3 By 2030, end the epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases and combat hepatitis, water-borne diseases, and other communicable diseases	22% ^b	3.3.4 Hepatitis B incidence per 100,000 population	22% ^b
Health and health systems	3.4 By 2030, reduce by one-third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being	100%	3.4.1 Mortality rate attributed to cardiovascular disease, cancer, diabetes, or chronic respiratory disease	100%
Health and health systems	3.5 Strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol	73%	3.5.2 Alcohol per capita consumption (aged 15 years and older) within a calendar year in litres of pure alcohol	73%

TABLE 1 (Continued)

Domain related		Demonst		Demonst
to the NAFLD conceptual	Turn t	Percent agreement	la di stano	Percent agreement
framework Health and health systems	Targets 3.8 Achieve universal health coverage, including financial risk protection, access to quality essential healthcare services, and access to safe, effective, quality, and (f) (f)	for target ^a	Indicators 3.8.1 Coverage of essential health services	for indicator ^a
Health and health systems	affordable essential medicines and vaccines for all 3.a Strengthen the implementation of the WHO Framework Convention on Tobacco Control in all countries, as appropriate	27%	3.a.1 Age-standardised prevalence of current tobacco use among persons aged 15 years and older 3.c.1 Health worker density and distribution	20%
Health and health systems	3.b Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Health Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the TRIPS Agreement regarding flexibilities to protect public health, and, in particular, provide access to medicines for all	87%	N/A	
Health and health systems	3.c Substantially increase health financing and the recruitment, development, training, and retention of the health workforce in developing countries, especially in the least developed countries and small island developing states	100%	3.c.1 Health worker density and distribution	100%
SDG 4. Ensure inclu	usive and equitable quality education and promote lifelong lear	ning opportun	ities for all	
Education	4.1 By 2030, ensure that all girls and boys complete free, equitable, and quality primary and secondary education leading to relevant and effective learning outcomes	80%	4.1.2 Completion rate (primary education, lower secondary education, upper secondary education)	80%
Education	4.4 By 2030, substantially increase the number of youth and adults who have relevant skills, including technical and vocational skills, for employment, decent jobs, and entrepreneurship	73%	N/A	N/A
Education	4.5 By 2030, eliminate gender disparities in education and ensure equal access to all levels of education and vocational training for the vulnerable, including persons with disabilities, indigenous peoples, and children in vulnerable situations	80%	N/A	N/A
SDG 10. Reduce in	equality within and among countries			
Economic, political, and social context	10.3 Ensure equal opportunity and reduce inequalities of outcome, including by eliminating discriminatory laws, policies, and practices and promoting appropriate legislation, policies, and action in this regard	100%	N/A	N/A
SDG 11. Make citie	s and human settlements inclusive, safe, resilient, and sustaina	ble		
Built environment	11.2 By 2030, provide access to safe, affordable, accessible, and sustainable transport systems for all, improving road safety, notably by expanding public transport, with special attention to the needs of those in vulnerable situations, women, children, persons with disabilities, and older persons	53%	N/A	N/A

TABLE 1 (Continued)

Domain related to the NAFLD conceptual framework	Targets	Percent agreement for target ^a	Indicators	Percent agreement for indicator ^a		
Built environment	11.6 By 2030, reduce the adverse per capita environmental impact of cities, including by paying special attention to air quality and municipal and other waste management	40%	11.6.2 Annual mean levels of fine particulate matter (e.g. PM2.5 and PM10) in cities (population weighted)	40%		
Built environment	11.7 By 2030, provide universal access to safe, inclusive, and accessible, green and public spaces, in particular for women and children, older persons, and persons with disabilities	93%	11.7.1 Average share of the built-up area of cities that is open space for public use for all, by sex, age, and persons with disabilities	93%		
SDG 12. Ensure sust	ainable consumption and production patterns					
Food environment and nutrition	12.3 By 2030, halve per capita global food waste at the retail and consumer levels and reduce food losses along production and supply chains, including post-harvest losses	47%	N/A	N/A		
SDG 16. Make cities	and human settlements inclusive, safe, resilient, and sustaina	ble				
Economic, political, and social context	16.1 Significantly reduce all forms of violence and related death rates everywhere	87%	16.1.4 Proportion of population that feels safe walking alone around the area where they live	87%		
SDG 17. Strengthen	SDG 17. Strengthen the means of implementation and revitalise the global partnership for sustainable development					
Economic, political, and social context	17.14 Enhance policy coherence for sustainable development	86%	N/A	N/A		
Economic, political, and social context	17.16 Enhance the Global Partnership for Sustainable Development, complemented by multi-stakeholder partnerships that mobilise and share knowledge, expertise, technology, and financial resources, to support the achievement of the SDGs in all countries, in particular developing countries	100%	N/A	N/A		
Economic, political, and social context	17.17 Encourage and promote effective public, public- private, and civil society partnerships, building on the experience and resourcing strategies of partnerships	100%	N/A	N/A		
Economic, political, and social context	17.18 By 2020, enhance capacity-building support to developing countries, including for least developed countries and small island developing states, to increase significantly the availability of high-quality, timely, and reliable data disaggregated by income, gender, age, race, ethnicity, migratory status, disability, geographic location, and other characteristics relevant in national contexts	100%	N/A	N/A		

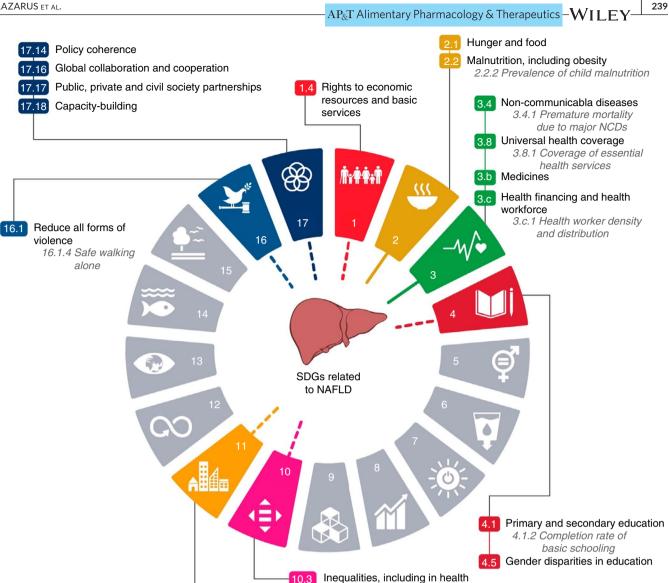
Abbreviations: NAFLD, non-alcoholic fatty liver disease; NCD, non-communicable disease; SDG, Sustainable Development Goal; TRIPS, Trade-Related Aspects of Intellectual Property Rights; WHO, World Health Organization.

^a Final results from round 2 voting among experts (n = 15).

^b Removed after round 1 of voting.

SDGs were included in the framework, representing 9% of all SDG targets and 62% (16/26) of the shortlisted targets. Seven indicators across five SDGs were also included in the framework, accounting for 50% (7/14) of the shortlisted indicators and 3% of all SDG indicators.

Below, we summarise the targets and indicators included within each of the six domains. Figure 1 provides a graphical representation of the NAFLD-SDG framework and differentiates the targets into those having a direct or indirect influence on NAFLD. The indirect



Green public spaces 11.7.1 Open space for public use Directly related to NAFLD Indirectly related to NAFLD

FIGURE 1 NAFLD-SDG framework. The NAFLD-SDG framework shows the SDG targets and indicators most relevant to NAFLD. The eight coloured segments indicate the selected targets, the seven selected indicators are nested within five of these targets. Solid lines indicate targets with a direct link to NAFLD, the dashed line shows those indirectly related. NAFLD, non-alcoholic fatty liver disease; NCD, non-communicable disease; SDG, Sustainable Development Goal

10.3

targets are generally upstream factors that have the potential to influence NAFLD via their impact on downstream elements.

3.1 | Economic, political and social context

Seven targets across four SDGs were included in the economic, political, and social context domain. These seven targets represent the distal factors that have a downstream influence on the development of NAFLD.

SDG 1.4, related to equal access to economic resources and basic services, was the only SDG 1 target included in the framework. Shortlisted targets and indicators related to poverty eradication and social protection systems did not meet the threshold for inclusion. While poverty eradication is of central importance to the global development agenda, this has a relatively indirect influence on the development of NAFLD. Economic growth has a complex relationship with metabolic diseases, including NAFLD. This is in part due to the proliferation of unhealthy diets and sedentary behaviour that are associated with increasingly westernised lifestyles. In low-income settings, increasing socio-economic status may be accompanied by changes in diet and lifestyle associated with the risk of developing NAFLD. Through a NAFLD lens, the focus should be placed on reducing inequalities and improving health literacy while ensuring that economic development is accompanied by appropriate public health measures and improved access to health services. SDG 10.3, which is included in the framework, specifically relates to reducing inequities of outcomes, including health.

SDG 16.1 on reducing violence was included in the framework along with indicator 16.1.4 on public perception about feeling safe when walking near home. While the association to NAFLD is indirect, this target and its related indicator provide important insights on people's ability to exercise near their homes freely and safely, which is a prerequisite for increasing levels of physical activity.

Four SDG 17 targets addressing cross-cutting factors around governance, partnerships, and knowledge were included in the framework. While indirectly related to NAFLD, these factors provide a foundation for integrated and collaborative approaches to sustainable development, which are central to addressing major global health challenges.

3.2 | Food environment and nutrition

Target 2.1 (ending hunger), target 2.2 (ending all forms of malnutrition), and indicator 2.2.2 (prevalence of malnutrition) were included in the framework. Ending hunger and childhood undernutrition can have a downstream preventive impact on NAFLD and other metabolic conditions given how early life undernutrition is associated with chronic disease in later life. Overweight and obesity are major risk factors for NAFLD and tackling obesity in all ages will be critical for efforts to prevent and manage the disease. The liver health community should directly engage with actors in the obesity space to identify areas for collaboration from health system responses to broader public health measures.

3.3 | Health and health systems

Four of the SDG3 targets and three indicators were included in the framework. Three of these targets provide mechanisms for addressing NAFLD, from increasing access to healthcare services through universal health coverage (3.8) and growing and training the health workforce (3c), to research and development of medicines for NCDs (3b). Within these targets, the liver health community can lead on a range of specific activities, from advancing the understanding of how best to deliver health services to people living with chronic metabolic conditions, to increasing the awareness, knowledge, and capacity of the health workforce to meet the needs of people living with NAFLD. The remaining target (3.4) is focused on reducing premature mortality from NCDs by one-third. NAFLD contributes directly to this target as NASH is an increasing cause of end-stage liver disease. NAFLD also has an indirect impact, being an early sign of the metabolic dysregulation that leads to cardiovascular disease—a leading cause of death in people living with NAFLD. Addressing NAFLD will be important for the attainment of target 3.4, providing further rationale for addressing this condition as part of broader efforts to prevent and manage NCDs.

3.4 | Education

Two education targets (4.1 primary and secondary schooling completion and 4.5 reducing gender disparities in education) and one indicator (4.1.2 primary and secondary school completion rates) were included in the framework. Equitable and consistent access to education is indirectly related to NAFLD, with childhood education level being associated with health outcomes in adulthood, including NCDs. While the liver health community has no direct involvement in schooling, we can support wider calls within the global public health community to ensure equal access and attainment of basic schooling for all, recognising this as a foundation for health and well-being.

3.5 | Built environment

The built environment can have a marked effect on health through its role in recreation, exercise, and mental well-being. SDG 11.7 (universal access to safe, inclusive, and accessible, green and public spaces) and its associated indicator 11.7.1 (share of open space for public use in cities) were included in the framework. Access to green spaces was selected as a proxy for the liveability of urban spaces. Related to green spaces are the issues of air pollution and re-pedestrianising streets and improving the walkability and cyclability of roads also fall within this domain.

4 | DISCUSSION

Despite affecting 23%-25% of the global adult population,^{2,3} NAFLD remains largely unknown within the global public health community, with little appreciation of the relationship between NAFLD and other highly prevalent diseases nor the need for multisectoral responses to address the challenge.¹⁸ We applied a NAFLD lens to the SDGs, creating a framework to help stakeholders envisage the comprehensive, multisectoral strategies required to address NAFLD.

The NAFLD conceptual model that provided the initial starting point for this paper outlined basic influences at the socio-economic and political levels, underlying influences related to social systems and direct influences such as nutrition. Critically, because the SDGs encompass all these levels of influence and are used and measured¹⁹ worldwide to guide national and international action, they provide a foundational framework for considering the interdependence of different sectors and systems.

The NAFLD-SDG framework can serve several purposes for the liver health and public health communities. Firstly, at a conceptual level, it can support a shift in thinking around NAFLD, from a narrow understanding of the immediate causes of the disease to considering the broader systems and structures that have enabled this to become the most prevalent liver disease in history. Secondly, it can help stakeholders map out strategic priorities across different sectors, including where the liver health community needs to lead the agenda and the many more areas where the community needs to engage in and support ongoing efforts.

Our framework outlines how NAFLD is implicitly captured in the SDGs through its association with many existing goals, targets, and indicators. Nonetheless, there is currently no explicit NAFLD target or indicator; this presents several challenges. The SDGs are used to inform decisions at national and global levels, including which areas to prioritise and fund. NAFLD remains largely obscure outside the liver heath community; specific mention of the disease within the SDGs would be a powerful way to increase awareness and drive action. We would propose that NAFLD be explicitly mentioned in indicator 3.4.1 on NCD mortality rates; this indicator currently includes cardiovascular disease, cancer, diabetes, and chronic respiratory disease.

4.1 | Re-visioning the liver health landscape

Historically, the liver health community has rarely considered multidisciplinary approaches, focusing instead on increasing access to treatment. However, this began to change with the advent of new curative treatments for viral hepatitis C in 2013. Despite the availability of new treatments, the prevalence of hepatitis C infection did not decline.²⁰ It became clear that a whole-of-systems approach would be needed to address hepatitis C, including engaging with atrisk populations, patient groups, addiction specialists, and general practitioners, both to prevent infection and to diagnose and treat it.²¹

The liver health field must now further expand its horizons to look beyond the health sector as it seeks to address the challenge of NAFLD. This will require a re-visioning of the liver health landscape for the years to come and embracing systems thinking. The liver health community can draw inspiration from other fields that have had some success in recent years, including the obesity field. In the past two decades, popular thinking on obesity has shifted from a focus on individual-level factors underlying energy imbalance to considering biological, social, environmental, and policy drivers of health behaviours and outcomes.²² More recently, research has gone one step further to emphasise the interconnections across these levels of influence in an integrated, systems approach.²³ 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.²⁴ For NAFLD, we need a similar paradigm shift. The NAFLD-SDG framework provides the guidance for this.

4.2 | Integrating NAFLD within the NCD agenda and ongoing public health efforts

At both public health and clinical management levels, there is substantial overlap in the measures required to address NAFLD and the other major NCDs. However, NAFLD is not mentioned by name in almost any key global or national NCD strategy, most notably the WHO Global Action Plan on the Prevention and Control of NCDs.²⁵

At a health system level, chronic disease management is driving the need for the reorientation of health systems away from siloed disease-centric models to multidisciplinary patient-centred care. This transition will be critical for enabling health systems to deliver the care required by people across the life course. The liver community, through collaboration with others working on metabolic disease management, can help lead this process in the years to come.

Given the relationship between NAFLD, obesity, and other highly prevalent NCDs, namely, type 2 diabetes and heart disease, integration of NAFLD within the NCD agenda makes sense from both strategic and operational perspectives. By doing so, the liver health community can become a powerful ally for the NCD community. Significant efforts are underway to establish alliances across organisations dedicated to NCDs, both to increase political clout and drive multisectoral action. It is now time for the liver community to join in these efforts.

4.3 | Strengths and limitations

Our paper has several strengths and limitations. The selection of targets and indicators is a somewhat subjective process. In the shortlisting phase, we reduced the risk of individual bias by having three researchers independently review all of these before unanimously agreeing on the targets and indicators to be put forward for voting. The diversity of the panellists also has a substantial impact on the outcome of the Delphi process. To ensure that a breadth of perspectives was considered, we engaged with experts from a range of disciplines, from liver health and NCDs, to food and nutrition, and the SDGs. We do acknowledge the limited geographical diversity in the group as a limitation; future work in this area will benefit from engaging with experts in all global regions. One of the major strengths of the paper lies in the use of the SDGs. Developed through a collaborative multi-stakeholder process, the SDGs are a widely known and utilised framework, thus making our findings applicable to a wide audience.

5 | CONCLUSION

NAFLD and its risk factors have an impact across all life-stages with complex interactions between biological, environmental, and social

determinants, which calls for a comprehensive whole-of-society response. The NAFLD-SDG framework can act as a strategic advocacy tool to build the case for closer collaboration within and between sectors seeking to address NAFLD and other NCDs. The liver health community needs to champion the cause of NAFLD and should seek to engage with existing efforts within other relevant sectors. A NAFLD public health roadmap, developed through broad engagement with key stakeholders, can help guide this process and translate the NAFLD-SDG framework from concept to action.

ACKNOWLEDGEMENTS

Declaration of personal interests: All authors declare no relevant completing interests, ICMJE forms for all authors have been made available to the journal.

AUTHORSHIP

Guarantor of the article: Jeffrey V. Lazarus.

Author contributions: JVL and HEM conceptualised the study. JVL, HEM, and TTKH shortlisted the targets and indicators. JVL, HEM, SD, JG, SH, NL, MER, MRG, JBS, JMS, LV, SZS, MAD, and TTKH participated in the Delphi rounds. HEM and JVL led the data collection and analysis. HEM, JVL, and TTKH developed the first draft of the manuscript, all authors provided input and feedback on the manuscript drafts and reviewed and approved the final version prior to submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Lazarus JV, Mark HE, Colombo M, et al. A sustainable development goal framework to guide multisectoral action on NAFLD through a societal approach. *Aliment Pharmacol Ther*. 2022;55:234–243. doi:<u>10.1111/</u> apt.16720

APPENDIX 1

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