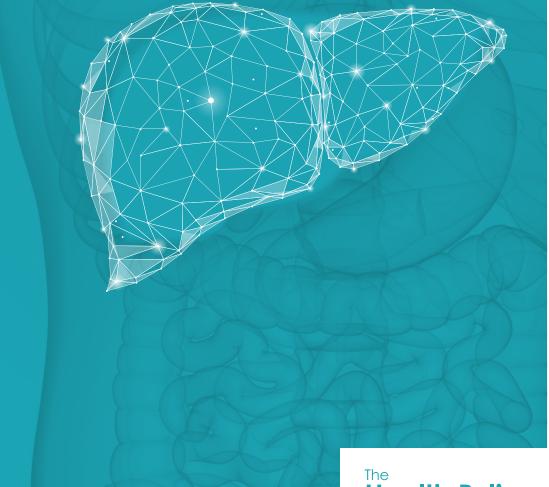
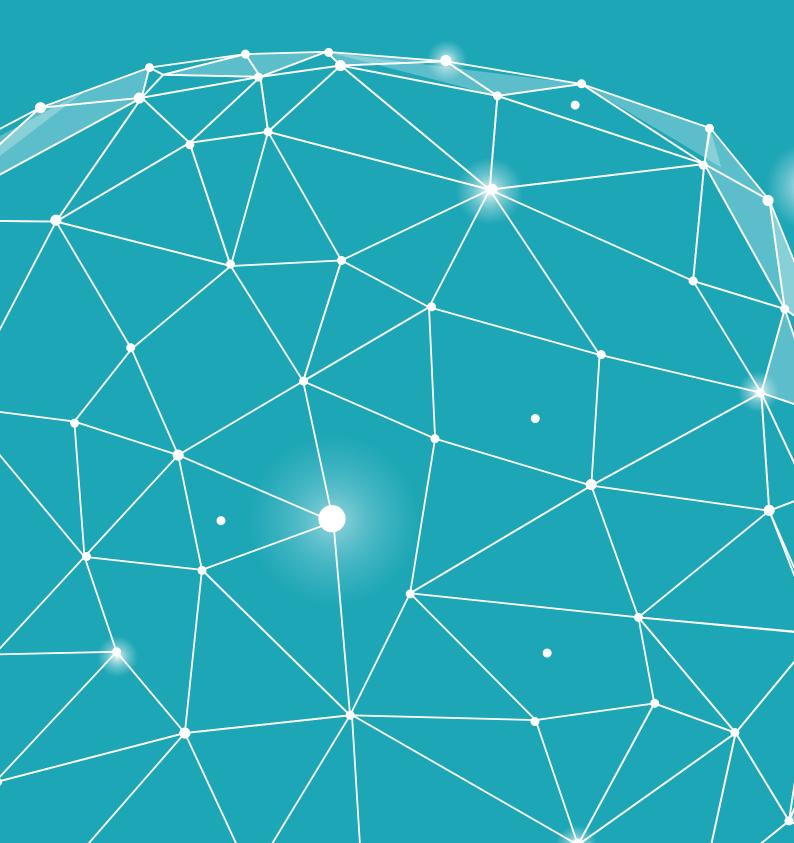
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Health Policy
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[research, people, action]



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Executive summary

The global prevalence of obesity increased almost threefold between 1975 and 2016, affecting 650 million adults in 2016. One aspect of obesity that is often neglected is its impact on the liver.

Non-alcoholic fatty liver disease (NAFLD)

is a chronic progressive liver disease strongly linked to obesity. It affects an estimated one in four people worldwide.² The diagnosis of its more progressive form, known as non-alcoholic steatohepatitis (NASH), is dependent on the availability of liver histology data, therefore its exact prevalence is uncertain.

However, it is estimated that NASH affects up to 20% of people with NAFLD.³⁴ The global prevalence of NASH has increased in the past 15 years and is projected to continue rising parallel to the growth in obesity and type 2 diabetes.⁵

NASH leads to liver-related complications and has a significant public health impact.

It can lead to liver cirrhosis and liver cancer,⁶⁷ and is also both a consequence of and risk factor for chronic diseases related to obesity, such as type 2 diabetes, cardiovascular disease, cancer and chronic kidney disease.⁸⁻¹⁰

Diagnosis of NASH is complex

as symptoms are non-specific and typically go unrecognised.¹¹ Many people are only identified and diagnosed once cirrhosis or liver cancer has developed.¹¹ There is also a lack of reliable non-invasive diagnostic tests to confirm NASH; definitive diagnosis requires a liver biopsy¹² – an invasive, high cost and sometimes painful procedure.¹³ 14

To date, no medicines have been approved for the treatment of NASH, although many are in development.¹² The current cornerstone of NASH management is the adoption of lifestyle modifications aimed at weight loss.¹⁵ ¹⁶

Sustained weight loss is highly beneficial for NASH and its complications, and also addresses associated comorbidities such as type 2 diabetes.^{9 17} However, many people find it difficult to make and sustain the necessary lifestyle changes.^{14-16 18 19}



As prevalence of NASH continues to rise and its implications place escalating pressure on health systems, there is a clear public health imperative to reduce its burden. As a critical starting point, we need to improve our understanding of NASH – in terms of how many people are affected, what influences disease progression, and how to prevent and effectively manage it. NASH requires a multidisciplinary approach, which should be reflected in the integration of NASH into public health policies and initiatives tackling obesity, and multidisciplinary models of care.

There is also a need for reliable, non-invasive diagnostic tests for NASH, as well as effective treatment options to improve patient outcomes and reduce the burden of disease on health systems and society.

In this context, we have identified five main challenges around NASH and propose recommendations for action for policymakers across Europe.

Challenges and recommendations for NASH

CHALLENGES

1

Limited awareness of the association between obesity and liver health, and disregard for the importance of liver health generally



RECOMMENDATIONS

Create education and awareness campaigns to improve understanding of the importance of good liver health among the general public and healthcare providers outside of the hepatology community

Absence of NAFLD/NASH from health policies focused on obesity, despite their reciprocal impact



Include liver conditions in public health policies and action plans on obesity and other related conditions

2 Lack of a reliable evidence base to guide policymakers, making it difficult to quantify the scale of the problem



Improve data collection efforts to achieve a better understanding of NASH prevalence, economic costs and its impact on quality of life

4

Lack of consensus among existing clinical guidelines, contributing to widespread variation in diagnosis and care



Educate primary care providers on NAFLD and NASH and develop clear care pathways to encourage more effective diagnosis and high-quality care

5

Poor health-system preparedness to provide appropriate multidisciplinary care for people with NAFLD and NASH and to meet growing needs for liver transplantation



Establish new multidisciplinary models of care for NAFLD and NASH, involving all relevant primary and specialist care providers

1 Introduction

The global prevalence of obesity increased almost threefold between 1975 and 2016, affecting 650 million adults in 2016.

This has exacerbated the rise of chronic non-communicable diseases (NCDs)²⁰ and has led to considerable costs for individuals, health systems and society. As a result, substantial attention and efforts have been directed towards preventing and curbing obesity and its impact.

One aspect of obesity that is often neglected, however, is its impact on the liver. Non-alcoholic fatty liver disease (NAFLD) is strongly linked to obesity.

It is one of the leading causes of chronic liver disease worldwide,⁵ ²¹ affecting one in four people.² The diagnosis of its more progressive form, known as non-alcoholic steatohepatitis (NASH), is dependent on the availability of liver histology data, therefore its exact prevalence is uncertain. However, it is estimated that NASH affects up to 20% of people with NAFLD.³ ⁴ The global prevalence of NASH has increased in the past 15 years and is projected to continue rising parallel to the growth in obesity and type 2 diabetes.³⁻⁵

NASH has a significant public health impact that extends beyond the liver. It can lead to liver scarring (fibrosis) that may progress to cirrhosis and liver cancer. 67 11 22-24 It is also a consequence of and risk factor for chronic diseases related to obesity. People with NASH are at high risk of developing and exacerbating type 2 diabetes, cardiovascular disease (CVD), cancer and chronic kidney disease. 8-10

Despite their rising prevalence and burden, NAFLD and NASH have not yet featured in public health policies. In 2017, the European Liver Patients' Association (ELPA), in partnership with the European Association for the Study of the Liver (EASL), organised the first European Policy Summit on NAFLD and NASH to raise awareness among policymakers of the public health and economic impact of NAFLD and NASH.25 They called on all stakeholders – European and national policymakers, clinicians, experts and patient advocacy groups to develop concrete actions across Europe in the face of this next major global public health challenge.²⁵ This was followed by the EASL International Liver Foundation's European NAFLD Policy Review, which covered eight countries and was expanded in 2019 to include the entire European Union, Norway and Switzerland.²⁶

This report aims to lay the foundation for a measured policy response to the anticipated rise in NASH in years to come.

Focusing on Europe and the Middle East,* it offers up-to-date estimates of the epidemiology and impact of NASH and highlights major strategic issues to improve clinical management and health-system preparedness. It concludes with key recommendations for action for policymakers.

2 What is NASH?

NASH is the progressive form of NAFLD, a chronic liver disease characterised by excessive fat accumulation in the liver (steatosis).¹² NASH occurs when fat accumulation in the liver is accompanied by liver cell injury (hepatocellular ballooning) and inflammation (steatohepatitis).¹²

The main risk factors for NAFLD and NASH are obesity, type 2 diabetes and metabolic syndrome.^{5 8 21} It is, however, possible for people to have NAFLD and NASH in the absence of these conditions. Lean NAFLD denotes the presence of NAFLD in people with a body mass index below 25kg/m².²⁷ There may also be additional risk factors for NAFLD and NASH related to age, ethnicity and genetics.^{5 21}

2.1 Diagnosis

The progression of NAFLD to NASH is not yet well understood and is variable from person to person. Symptoms of NASH, which may include fatigue, lethargy, abdominal pain and sleeping problems, are non-specific so they can often be misinterpreted as something else. NASH is typically only detected once it has progressed to cirrhosis or liver cancer, therefore most people live with the disease for years without being aware of the damage accumulating in their liver.

Another complicating factor is that definitive diagnosis of NASH can only be made by liver biopsy, 12 an invasive procedure subject to sampling variability, high cost, and possible pain and complications. 13 14 There exist acceptable and relatively accurate non-invasive diagnostic tools to assess for liver fibrosis and to help select people for liver biopsy. 12 However, there are no well validated non-invasive tests for NASH and there is no consensus on thresholds or strategies for use of these tools in clinical practice, hence diagnosis rates vary considerably across practices and regions. 2 29 30

Diagnosis of NAFLD and NASH also requires the exclusion of persistent excessive alcohol consumption as a cause of fatty liver disease, 12 but this criterion is not always simple to exclude. Fatty liver disease primarily caused by persistent excessive alcohol consumption is known as alcoholic liver disease (ALD). Differentiation between ALD and NAFLD is difficult as it relies on patient-reported consumption. As obesity is common, risk factors for NAFLD may be present in individuals who also consume unsafe levels of alcohol. 31 32 Emerging evidence indicates that these two conditions may coexist and interact. leading to an accelerated rate of disease progression.32

2 What is NASH? (continued)

2.2 Prevalence

Estimates of NASH prevalence vary widely and are likely to be under-reported and inaccurate,⁵ making it difficult to quantify the scale of the problem for policymakers.

As mentioned previously, many cases of NASH go undetected until they have progressed to cirrhosis or liver cancer.¹¹ Existing data tend to be derived from people with NAFLD who have been selected for biopsy, and are therefore not representative of the general NAFLD population. Given that liver biopsy is rarely performed outside of a specialist setting, under-reporting of NASH is particularly high in primary care settings.³³

With these caveats in mind, *Figure 1* presents the most up-to-date prevalence figures for NAFLD and NASH.

The growing prevalence of NAFLD and NASH in children and young people is particularly concerning. The largest study to date to analyse the prevalence of NAFLD and fibrosis due to NASH in a group of young, largely asymptomatic Caucasians with suspected NAFLD in the UK found that one in five had steatosis, and one in 40 had evidence of fibrosis due to NASH, at only 24 years of age.³⁶ An increased risk of NAFLD and NASH at a younger age may progress and lead to serious ill health in early adulthood.⁵ 37



Figure 1. Prevalence of NAFLD and NASH

2005

NAFLD affected approximately **15%** of the global population.²

2019

Prevalence is estimated at **25%**.²

By 2030

Prevelance is expected to increase to more than **28**%.³

15% > 25% * 28% * 6

NAFLD prevalence is estimated to be **23**% in Europe and **24**% in the United States.²

Data for the Middle East are scarce but prevalence is estimated at **32**%.²



23% Europe



24%



32% Middle East

An estimated 20% of people with NAFLD develop NASH.^{34*}

NAFLD



NASH

20%





Based on US data and a large modelling study, NASH affects 2–6% of the global population.²⁶¹¹

2-6%



In people with obesity and type 2 diabetes, NAFLD prevalence is approximately 50–70% and NASH prevalence is approximately 56%.^{34 35}



NAFLD

50-70%

NASH

56%

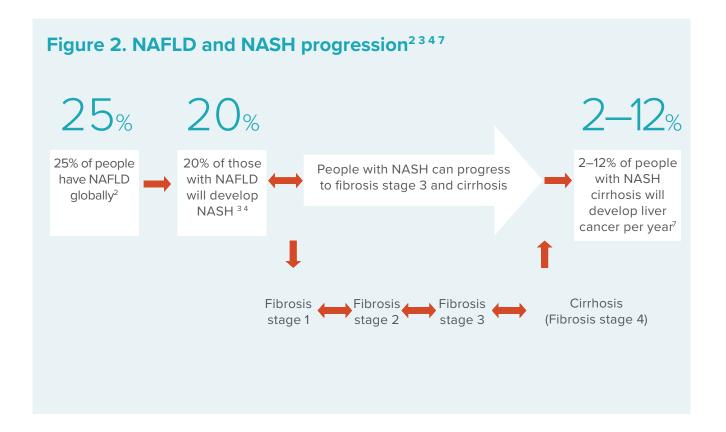
^{*} There exist numerous studies on the prevalence of NASH among people with NAFLD, but estimates may not be reliable due to selection and ascertainment bias, as well as diminished accuracy of diagnostic tests.

3 Public health impact

3.1 Impact of NASH on the liver

NASH can progress to advanced liver fibrosis, cirrhosis and liver cancer (Figure 2). The risk of mortality increases with fibrosis progression; people with NASH have an overall mortality rate of 7.9% within seven years of diagnosis – almost twice that of the general population.³⁶

People with NASH have an increased mortality rate almost 2x that of the general population³⁶



The presence and degree of fibrosis are the main factors determining disease outcome of NASH. 22 23 37 The rate of disease progression is not uniform; some people experience fast fibrosis progression while others follow a much slower course or may even experience regression.²⁸ Several retrospective studies of people with biopsy-proven NAFLD found that the risk of adverse outcomes increases with stage of fibrosis. ^{22 23 37} Estimates vary between studies but suggest that of people with cirrhosis due to NASH, approximately 2–12% develop liver cancer per year.⁷ Recent evidence also suggests that people with lean NAFLD are at higher risk of developing severe liver disease compared to people with NAFLD who are overweight or obese.²⁷

3.2 Broader public health impact of NASH

Beyond their impact on the liver,
NAFLD and NASH may lead to significant
comorbidities. The risk of obesity,
type 2 diabetes, CVD, cancer and chronic
kidney disease is elevated in people with
NAFLD.²⁸³⁸ CVD is the most common cause
of death among people with NASH, followed
by cancer outside the liver and then
liver-related complications (due to cirrhosis
and liver cancer).²²²³³⁹

NASH has a bidirectional relationship with type 2 diabetes, such that once developed, diabetes can promote NASH progression to cirrhosis and liver cancer.⁸ People with type 2 diabetes and other metabolic conditions appear more likely to have more progressive stages of disease compared to people with few or no metabolic conditions.⁴⁰⁴¹



3 Public health impact (continued)

3.3 **Economic costs**

The rise of NASH, its complications and comorbidities carry significant economic costs for health systems and society.

Estimates of the costs of NAFLD and NASH are limited, but existing analyses show increasing costs with increasing severity of disease. 36 42 These costs arise from liver-related morbidity and associated comorbidities that amount not only to healthcare spending but also to indirect costs related to lost work productivity.⁴²

Figure 3 presents available economic data for NAFLD and NASH.

Figure 3. Economic costs for NAFLD and NASH







Based on a 2016 data analysis, the annual costs associated with continues to rise in line with all cases of NAFLD (from simple fatty liver disease to late-stage cirrhosis) were estimated at €35 billion in France, Germany, Italy and the UK together and \$103 billion in the US.42

If prevalence of NAFLD obesity prevalence, associated costs could increase to an estimated €334 billion in Europe and \$1.005 trillion in the US over the next 10 years.42

Recent data revealed total annual hospitalisation costs of people with NAFLD and NASH in Italy were at least 50% higher in those with advanced liver disease compared with those without, after adjusting for individual characteristics and comorbidities such as type 2 diabetes and CVD.36

3.4 Impact on quality of life

The reported impact of NASH on health-related quality of life (HRQoL) is mostly related to fatigue. A recent analysis of data from the European NAFLD registry demonstrated that older age, female gender, the presence of diabetes and detection of lobular inflammation correlate with lower HRQoL. Studies have also found increased impairment of HRQoL and work productivity in people with advanced NASH compared with the general population. Further research is needed on patient-reported outcomes for NAFLD and NASH in future clinical trials, including in marginalised populations.



4 Clinical management

There is a lack of effective treatments that decrease the risk of cirrhosis and liver cancer and mitigate the need for liver transplantation, among people with NASH.

4.1 Treatment

The ultimate aim of treatment for NASH is to reduce progression to cirrhosis or liver cancer and decrease NASH-related mortality. Currently, there are no approved medicines available for NASH, and regulatory authorities have accepted accelerated clinical trials and approval procedures for NASH. Many medicines are in development and some have recently demonstrated effectiveness in treatment of NASH with liver fibrosis. Therefore, there are high hopes that the first approved medicine will become available in the near future

In the absence of approved medicines, lifestyle modifications are the cornerstone of NASH management. As NASH is strongly linked to obesity, sustained weight loss is beneficial for NASH and liver fibrosis; it also addresses associated comorbidities such as type 2 diabetes. 15-17 50 Weight loss through the combination of diet and exercise is the most established approach, demonstrating a clear relationship between the proportion of weight lost and the degree of NASH improvement. 15 16

However, many people find it difficult to make and sustain the necessary lifestyle changes. 14-16-18 For example, a large prospective study found that approximately 85% of people with NAFLD could not achieve a weight loss of 10% or more, which is the threshold shown to induce the highest rates of NASH resolution and fibrosis regression. 15

In people unresponsive to lifestyle modifications, bariatric surgery is an option for reducing weight⁵¹ and thus improving histological features of the liver.^{52 53}
However, in many countries bariatric surgery is currently approved only for managing metabolic complications¹² and not as treatment for NASH.⁵⁴ The procedure's invasiveness and cost, as well as the inherent risks once NAFLD has progressed to cirrhosis, also limit its potential as a widespread treatment modality for NASH.⁵⁴



4.2 Liver transplantation

Liver transplantation is currently the only recourse for people with advanced NASH presenting with late-stage cirrhosis and/or liver cancer.³¹ However, it is not a cure for NASH as it does not address the underlying cause. As long as people exhibit metabolic risk factors, the risk of recurrent NASH remains even after transplantation.⁵⁵ Furthermore, some individuals with NASH may not be eligible for transplantation due to comorbidities related to metabolic syndrome, such as morbid obesity or coexistent CVD.³¹⁵⁵

Cirrhosis due to NASH is expected to become the leading indication for liver transplantation in Europe within the next decade. ⁵⁶ Currently, the main indication for liver transplantation in Europe is cirrhosis due to viral hepatitis, followed by alcoholic cirrhosis. ⁵⁷ However, data from the European Liver Transplant Registry (ELTR) demonstrate that the proportion of transplants due to metabolic diseases, including NASH, has increased over time, while the proportion due to viral hepatitis is decreasing. ⁵⁸ In the Nordic countries, NASH is the second most rapidly increasing indication for liver transplantation. ⁵⁹



5 Creating a sustainable policy response to NASH: key challenges to be addressed

As the prevalence of NASH increases, challenges around this complex systemic disease are becoming increasingly apparent.

These challenges must be addressed if we are to improve health outcomes for people and decrease the overall toll of NASH on health systems and society.

Figure 4 identifies key challenges which we describe in further detail in this chapter. We propose recommendations to address these challenges in the subsequent chapter.

Figure 4. Key challenges around NASH

- Limited awareness of the association

 between obesity and liver health,
 and disregard for the importance of liver
 health generally
- Absence of NAFLD/NASH from health policies focused on obesity, despite their reciprocal impact
- 2 Lack of a reliable evidence base to guide policymakers, making it difficult to quantify the scale of the problem
- Lack of consensus among existing clinical guidelines, contributing to widespread variation in diagnosis and care
- Poor health-system preparedness to provide appropriate multidisciplinary care for people with NAFLD and NASH and to meet growing demands for liver transplantation

5.1 Limited awareness of the association between obesity and liver health

An underlying challenge to public health efforts focused on NASH is that the general public lacks awareness of the link between obesity and liver health. Most people are unlikely to consider unhealthy diets and sedentary lifestyles as possible causes of liver disease, 18 as they tend to perceive liver disease as being caused either by alcohol or injecting drug use. 18 Because of these associations, liver disease tends to be highly stigmatised. 60

Awareness and knowledge of liver health, and of NAFLD and NASH in particular, is also relatively poor among healthcare providers outside of the hepatology community. Surveys have found that some people with NASH felt their physicians were not adequately informed of the disease's characteristics, prognosis and management, and GPs reported they often lacked adequate knowledge of NAFLD and how to care for it. In one survey, eight out of ten diabetologists, endocrinologists and cardiologists reported the need for increased education on NASH management strategies and emerging therapies.

5.2 Absence of NAFLD/NASH from health policies focused on obesity

Low consideration of the influence of obesity on liver health is reflected in national health policies. According to a recent policy review of France, Germany, Italy, Portugal, Slovenia, Spain, Sweden and the UK, NASH was mentioned little, if at all, in these countries' strategies or action plans for obesity. In addition, none of these countries had a written national NAFLD and NASH strategy or action plan. 162



5 Creating a sustainable policy response to NASH (continued)

5.3 Lack of a reliable evidence base to guide policymakers

To date, there are not enough data on NASH – in terms of either epidemiological or real-world data - to quantify its true prevalence and burden. The absence of routine screening for NAFLD and NASH in primary care, coupled with the lack of reliable, available and easy-to-use non-invasive tests to diagnose NASH, contribute to NAFLD and NASH being substantially underdiagnosed and under-reported.^{2 21 29} This is illustrated by much lower recorded numbers of diagnosed cases of NAFLD in clinical settings compared with prevalence rates obtained from population-level studies.30 For example, the largest real-world study using records for 17.7 million adults from four large European primary healthcare databases (Italy, the Netherlands, Spain and the UK) found that, in all four countries, levels of recorded NAFLD in primary healthcare databases were approximately 1.85%,30 as compared to a prevalence of 25% anticipated from modelling studies.²

Challenges with diagnostic coding also contribute to NASH being under-reported in available health statistics. While NASH has become the second leading cause of liver transplantation in the US,63 this is currently not the case in Europe. The proportion of liver transplants due to NASH in Europe is thought to be largely under-represented because of coding issues.⁶⁴ The proportion of NASH-related deaths in Europe is also under-reported for similar coding reasons.⁶⁵ Evidence suggests that NAFLD coded as the primary cause of death is only starting to appear in countries where obesity prevalence is high, such as Hungary, Ireland, Luxembourg and the UK.65



5.4 Lack of consensus among existing clinical guidelines

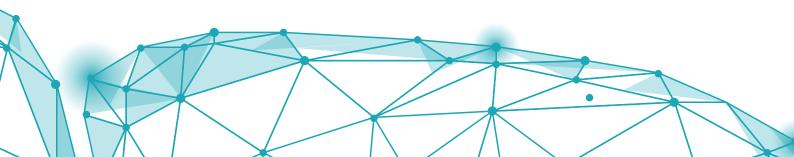
In addition to limited data on NASH, there is also a lack of consensus on standardised care pathways. International guidelines, such as those from the World Gastroenterology Organisation (WGO)⁶⁶ and those produced from the collaboration between the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO),12 differ in respect to recommendations for NAFLD and NASH screening, diagnosis, treatment and follow-up, among other areas. There is also extensive variation in national, and nationally endorsed, clinical practice guidelines for NAFLD, such as those from Italy,67 Germany,⁶⁸ Spain⁶⁹ and the UK.⁷⁰

In the absence of clear, consensus-driven guidelines, management of people with NAFLD and NASH in clinical practice is highly variable. GPs and specialists other than hepatologists may not consider the overlap between NAFLD and metabolic risk factors, and may therefore overlook a high proportion of individuals at high risk of NAFLD and NASH.⁷¹ This may lead to missed opportunities for early diagnosis when treatment may be most effective.

5.5 Poor health-system preparedness

The high level of comorbidities in people with NASH calls for a multidisciplinary approach to care. Studies demonstrate the beneficial impact of this approach on liver disease, metabolic conditions and CVD in people with NAFLD and type 2 diabetes.^{72 73} However, lack of professional ownership for NASH outside of the hepatology community means that multidisciplinary NASH care is not widely available in practice. 62 Ideally, multidisciplinary teams with experts in hepatology, gastroenterology, diabetology, nutrition and exercise therapy, as well as primary care providers, should be involved in managing people with NAFLD and NASH.7475

As NASH is expected to become a leading cause of liver transplantation in Europe within the next decade, ⁵⁶ health systems may face increasing challenges in terms of meeting organ demand. There is already a dramatic shortage of available livers for transplantation. ³¹ As a result, transplant waiting times have been extended, leading to increased morbidity and mortality among potential recipients. ³¹ The high prevalence of obesity in people with NASH also makes transplants more resource-intensive and costly for this population. ⁵⁵



6 Conclusions and recommendations

As the rise of NASH places escalating pressure on health systems, there is a clear public health imperative to reduce its burden. As a critical starting point, we need to improve our understanding of NASH in terms of who and how many people are affected, what influences disease progression and how to effectively prevent and treat it. A multidisciplinary approach to NAFLD and NASH is needed and should be reflected in the integration of NAFLD and NASH into public health policies on obesity and multidisciplinary models of care. The intrinsic links between NAFLD, NASH, obesity, type 2 diabetes, CVD and other NCDs should also be underlined in health promotion initiatives, professional education and policy efforts.

We also need to improve the diagnosis and management of NASH in clinical practice.

The lack of reliable, non-invasive diagnostic tests for NASH hinders early diagnosis and misses opportunities to prevent disease progression. It also complicates the discovery of potential treatments for NASH: as long as people with NASH remain undiagnosed, clinical trials will struggle to recruit participants and will thus remain unable to test potential new medicines.



With these challenges in mind, we offer the following recommendations for policymakers across Europe:

RECOMMENDATIONS

HOW TO DRIVE CHANGE

Create education and awareness campaigns to improve understanding of the importance of good liver health



Launch health promotion campaigns in non-clinical settings on healthy eating, physical activity and other factors contributing to good liver health.

Educate healthcare providers outside of the hepatology community on NAFLD and NASH.

Include liver conditions in public health policies and action plans on obesity and other related conditions



Integrate NAFLD and NASH into existing policies and initiatives aimed at preventing and reducing obesity, especially among children and young people. Emphasise the reciprocal relationship between NAFLD/NASH, type 2 diabetes and other NCDs linked to obesity.

Improve data collection to achieve a better understanding of NASH prevalence, economic costs and impact on quality of life



Invest in the collection of relevant epidemiological and real-world data to better understand the natural history of NAFLD and NASH and their impact.

Incorporate these data into workforce planning and public health plans to ensure health systems are well prepared to manage people with NAFLD and NASH from diagnosis all the way to long-term monitoring.

Educate primary care providers on NAFLD and NASH and develop clear care pathways to encourage more effective diagnosis and high-quality care



Provide continuing medical education to primary and secondary care providers on the impact of obesity on the liver, and the impact and risk of NAFLD and NASH in people with type 2 diabetes and other NCDs linked to obesity.

Encourage screening of high-risk individuals for NAFLD in primary care and non-hepatology settings, with appropriate referral for assessment for NASH – through development and implementation of consensus-driven guidelines.

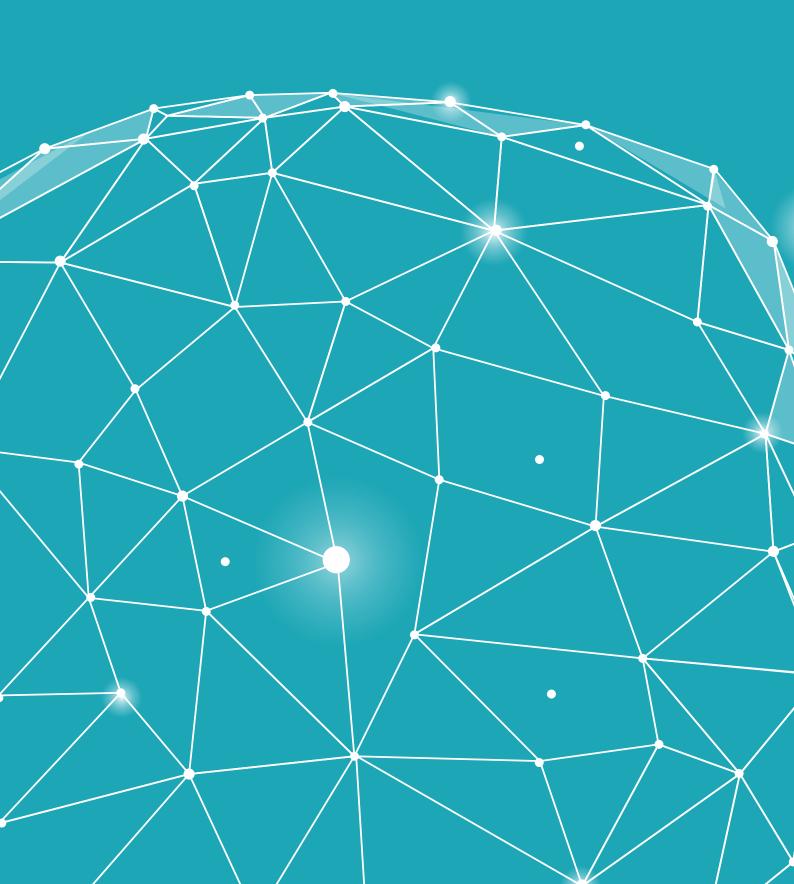
Encourage public—private partnerships between academia, industry, health professionals and patient groups to develop non-invasive and easy-to-access diagnostic tools and effective treatment options for NASH.

Establish new multidisciplinary models of care for NAFLD and NASH



Foster and provide specific funding for the establishment of multidisciplinary teams for metabolic syndrome and NAFLD/NASH management, consisting of primary care providers, hepatologists, gastroenterologists, endocrinologists, cardiologists, diabetologists, nutritionists and physical therapists.

Encourage the development of cross-specialty guidelines to help implement multidisciplinary care in practice.



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